On the harmonious meeting of visual perception and memory circuitries

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Preface

In the late eighties I started to think about memory and the brain, inspired by my father’s stories at Sunday morning’s breakfast table about the limbic system, my mother’s fascination about human electrophysiology, and lots and lots of SF literature on artificial intelligence, to name only “I, robot” by Isaac Asimov. I came up with something that I called the “fuik theorie”, which means trap theory in Dutch. It was a metaphor on the perceptual input (the fishes) falling into the trap entrance (the visual perceptive system). The perceptual input was supposed to be trapped “for ever” into the very deep of the trap (the memory system). In order for fishes to get into the trap some incentive should be responsible, such as the intrinsic properties of the fish and the trap. In terms of perceptual information, I expected that the compatibility between the system and the percept were responsible for possible uptake, whereas other factors such as the emotional valence or selective attention represent the speed of information uptake, and the flow of fishes and surrounding water represent the perceptual load and context. The condition of the trap can be reflected by lesions and clinical or developmental state of the human being. After proposing these ideas to my parents and friends the responses were diverse and moderate, including shaking heads, and motivational support and disbelieve that such a primitive idea could be true. Yet glutting with self confidence it was at that stage that I decided to pursue this idea and began to gather evidence to proof this. Since then, I learnt a lot about the brain, about memory and its interaction with the visual system, about role of different areas, the medial temporal lobule, the dorsal and ventral stream, the frontal-parietal network, hierarchical and top-down processing, and synchronization as a binding neural mechanism. For all of these learning processes I am most grateful to my colleagues and mentors in Bonn and Zurich who supported me scientifically and financially. Especially Guillén Fernández and Jürgen Fell sharpened my thinking about memory, electrophysiology, neuroimaging, and publishing. In this team, a physician, physicist and psychologist, I felt the sense and necessity of multidisciplinary science utterly vivid. I thank Fred Mast and Lutz Jäncke at the University of Zurich, and Ernst Martin at the Children’s University Hospital who supported me in my pursuit to understand learning and perception. I thank all volunteers, patients and children who sacrificed their time and effort for science. Last but not least, I am most thankful for the support of my family and friends who had the patience in good and bad times. I thank you all very much!

Peter Klaver

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Synopsis

Classical theories of memory often postulate the existence of multiple memory systems, based on the duration with which information can be held in memory (short-term and long-term memory), the type of information that is held in memory (procedural or declarative memory), or the effort with which information can be encoded or retrieved (low effort in priming, high effort in working memory). Usually, based on lesion studies with amnesic patients these theories allocate different memory systems to different brain structures (see Figure 1 for a schematic illustration). A prominent role in this framework plays the medial temporal lobe (MTL). The MTL as often been seen as a unitary system that enables formation of novel memories, consolidation, and conscious recollection of past events and facts (Squire & Zola, 1998). Alternatives to a unitary account have been proven difficult to validate, although recent attempts have been made to allocate visual perceptual functions to the MTL (Murray, Bussey, & Saksida, 2007).

This cumulative habilitation demonstrates that it is possible to directly differentiate mechanisms within the human MTL and validate interactions between memory and visual perception. I consider this interaction invaluable for the formation and retrieval of memory, because memory systems are in constant interaction with perceptual input from the surrounding world. These perceptions may change representations stored in memory, some perceptions may form novel memories, others may be ignored, forgotten memories may be restored, and changing memories may adjust the way in which we perceive the world. This cumulative habilitation postulates that the MTL enables “selection for declarative memory”, in analogy to the “selection for action” and “selection for perception” hypotheses about the role of the dorsal and ventral streams in visual processing (Goodale & Milner, 1992). Its anatomical predisposition and localization at the confluence of the sensory and limbic system features an ideal bridge between visual processing and memory (Figure 2). Here, I will present functional evidence that in humans the MTL is at least one of the structures where visual perception and memory operations meet. In addition, evidence is provided that functional connectivity between the MTL and the parietal lobule is used for “selection for working memory”, that visual perception and accompanied associative processing during the first encounter provides a template for subsequent recognition, and that different mechanisms are responsible for memory formation enabling subsequent item recognition by visual familiarity or recollection of study context information.
Figure 1: A schematic illustration of memory functions and associated brain regions according to Gabrieli and Baddeley (Baddeley, 1992; Gabrieli, 1998).

My contributions to science

This cumulative habilitation assembles a selected sample of my studies (see publication list in the Appendix for a complete register). My endeavor to contribute to the field of psychology and cognitive neuroscience is focused on the question where and how in the brain visual processes and memory operations meet. None of my study collaborators had this specific motivation to work on the projects. I explicate my methodological choices and theoretical achievements that summarize what I think are my most important contributions to the field of cognitive science and cognitive neuroscience. These theoretical considerations have not been published before, or only in parts.

My methodological choices

1. **Intracranial EEG recordings within the MTL were used to investigate the interaction between visual processing and memory operations.** Intracranial EEG was recorded in patients with intractable epilepsy during a seizure free period in a preoperative diagnostic procedure. The patients had depth electrodes placed in left and right medial temporal lobe, because physicians were uncertain about the origin of the epileptic seizures. I analyzed task related EEG signal from the seizure free hemisphere and localized the electrical source based on MR images and electrophysiological characteristics. The precise localization at the end of the ventral visual stream (rhinal cortex) and within the memory related hippocampus, as well as the high temporal resolution of the electrophysiological signal provided a unique
window to memory operations in the human brain. I used two ways of signal analysis. One is the traditional averaging technique time locked to a known event (event-related potentials, ERP). This procedure was used in articles 4 and 8 to separate rhinal cortex and hippocampus contributions to memory operations (Fernández, Klaver, Fell, Grunwald, & Elger, 2002; Klaver et al., 2005). The second technique is based on the idea that cognition related brain activity can be associated with changes in neural activity (power) and changes in temporal variance (phase) of neural activity (increased variance blurs the signal and reduces the ERP amplitude). To perform such an analysis the EEG signal is segmented in frequency bands (e.g. gamma (>30 Hz) and theta (5-7 Hz) bands) followed by extraction of amplitude and phase information in different time windows time following a known event. Next, phase coupling between MTL structures, phase locking across trials, and power changes within rhinal cortex and hippocampus were analyzed. Thus, communication between MTL structures and phenomena such as a temporal reset associated with a cognitive event could be separately observed (Fell et al., 2006; Fell et al., 2001; Mormann et al., 2007). This technique goes beyond EEG coherence analyses in which general changes in neural coherence between electrode positions are analyzed, without separating the EEG signal in power and phase information. In another article we correlated coherence and synchronization values in low (theta) and high (gamma) frequency bands (Fell, Klaver et al., 2003) to verify earlier proposed relevance of interactions between these frequency bands in memory (Buzsáki, 1996; Jensen, Idiart, & Lisman, 1996). Jürgen Fell developed the tools of coherence and synchronization signal analysis. I helped to develop these tools further, performed the ERP analyses, and guided the analyses to make theoretical inferences about the transfer of information between visual perception and memory. Both ERPs and power/phase analysis proved to provide invaluable information about the timing and localization in which brain regions related to visual perception and memory were active and began to communicate to form memories. The ERP studies were cited 46 times, the latter four articles were cited 275 times.

II. Functional MRI was used to investigate neural activity in brain areas related to memory and visual processing. The advantage of functional MRI above intracranial (or scalp recorded) EEG is that it can be used to detect co-activation or coherent neural activity in far distant neural networks as well as near brain regions in both healthy volunteers and patients. For example, the contribution of visual processing related brain areas to memory operations can be detected. I used fMRI to detect visual processes in memory (Fliessbach, Weis, Klaver, Elger, & Weber, 2006; Klaver et al., 2007; Weis, Klaver, Reul, Elger, & Fernández, 2004; Weis, Specht et al., 2004) and used fMRI to detect memory processes in perception (Klaver et al., 2004). For Klaver et al. (2004, 2007) I completely developed the study design, analyzed and interpreted the data and wrote the papers. For the other three articles I
III. Stimulus-onset asynchrony between prime and probe stimuli was varied to obtain hemodynamic interactions between memory and perception in the order of tenths of a second. Functional MRI is stigmatized as compared to ERPs that it has very limited temporal resolution, since the hemodynamic response is a low frequency signal that peaks after six seconds, while EEG samples neural activity in the range of milliseconds. I challenged this view by modifying the delay time between prime and probe stimulus in small steps of temporal asynchrony (150, 450 and 750 ms). Results demonstrated that hemodynamic responses varied with prime-probe stimulus onset asynchrony and that this method is effective in artificially enhancing the temporal resolution of fMRI to investigate specific transfer between memory (prime) and visual recognition (target) (Klaver et al., 2004). This tool can be used to investigate other cognitive domains as well.

IV. Task instruction was modified to investigate the role of cognitive control over implicit memory in visual processing and semantic processing related areas. I developed a novel experimental design to separate the role of attention on neural repetition effects in visual and
memory related areas. The two task conditions differed only in task instruction not in the perceptual features (Klaver et al., 2007). Results demonstrated that directing attention by task instruction, in combination with brain imaging, can be used to investigate differential contribution of cognitive control on the role of visual and semantic processing related areas in memory.

V. *Stimulus properties were manipulated to investigate the effect of different levels of visual and semantic processing on memory.* In several tasks I varied single stimulus attributes to investigate the role of visual processing in memory. For example, word types were used that differed only in the associative strength between visual and verbal information (word imagery) (Fliessbach et al., 2006; Klaver et al., 2005) or stimulus familiarity (word frequency) (Fell et al., 2006; Fernández et al., 2002; Klaver et al., 2005). The results showed that word frequency affected lower levels of memory operations than word imagery. In another example I modulated stimulus modality and semantic congruency to investigate if visual or semantic processes affected neural repetition priming (Klaver et al., 2007). All these examples demonstrated that memory operations are dominated by high level visual and semantic processes.

VI. *The contrast between correctly detected repeated items (hits) and incorrectly repeated items (misses) can be used to detect separate contributions of stimulus familiarity (misses > hits) and successful memory retrieval (hits > misses) to memory.* There has been a long debate about whether stimulus familiarity contributes to memory. Primate and human electrophysiology studies found that stimulus repetition reduced neural activity in rhinal cortex, which may contribute to memory and reflects stimulus familiarity, whereas stimulus repetition enhanced neural activity in the hippocampus reflecting retrieval of stored information from memory (Brown & Aggleton, 2001; Fernández et al., 2001). In fMRI the reversed old/new effect is biased by repetition suppression effects that may not contribute to memory. To solve this problem Guillén Fernández developed the idea that comparing misses and hits may differentiate memory retrieval (hits > misses) from stimulus familiarity (misses > hits), since both hits and misses are repeated items, but discriminate true from false recognition (Weis, Klaver et al., 2004; Weis, Specht et al., 2004). I transferred the idea to study the memory effect of word imagery during an encoding/recognition task (Fliessbach et al., 2006). I contributed to the development of the three study designs, data analysis and interpretation of the data.

VII. *Subsequent recording of neural activity during study and test can be used to detect distinct and common contributions of memory formation and retrieval to memory success.* Behavioral study designs, let alone lesion studies, cannot truly distinguish whether differences in memory performance are caused by encoding or retrieval operations. To overcome this problem study designs were developed in which neural activity was recorded
during both study and test. This allowed for the analysis of neural activity related to successful memory formation or successful retrieval. Additionally, shared neural mechanisms during encoding and recognition can be detected. I contributed to the development of these novel study designs (Fliessbach et al., 2006; Weis, Klaver et al., 2004; Weis, Specht et al., 2004). These studies could effectively show that memory related processes are repeated during encoding and recognition, without participation of low level visual processes. In Klaver et al. (2007) I chose not to analyze the study phase because study and test phase differed strongly in perceptual information. I also used a continuous recognition paradigm in which study words were intermixed with repeated words during a recognition task (Klaver et al., 2005). Although in this type of task, successful memory formation cannot be clearly distinguished from successful recognition operations, common word imagery related neural activity during processing of novel and repeated words could be observed. These results suggest that this procedure is more generally applicable in memory research.

VIII. \textit{Intranasal administration of hormone oxytocin was used to investigate the interaction between human visual processing and memory.} Prior knowledge about the unique features of the hormone oxytocin in social behavior of humans and social recognition in rodents led me to predict that oxytocin administration might be helpful in human memory research. Indeed, oxytocin was demonstrated to improve human social memory performance, which proved that a transfer between basic neural mechanisms and human behavior is possible (Rimmele, Hediger, Heinrichs, & Klaver, 2009). In a recently submitted novel grant proposal I plan to use the same procedure while recording fMRI to investigate if visual processing (in fusiform face area) contributes to the oxytocin effect on social memory.

IX. \textit{Focal lesions in well circumscribed regions within the memory system were used to detect mutual dependencies between visual perception and memory.} Prior knowledge about focal lesions can be used to investigate neural connectivity between impaired and healthy brain areas, especially when intact neural connectivity is available on the contralateral (nonfocal) side within the same participants. We demonstrated that rhinal cortex still provides synchronized neural activity into the hippocampus, even when the hippocampus is sclerotic (Mormann et al., 2007). I was involved in the development of the study idea and interpretation of the data in terms of neural connectivity between rhinal cortex and hippocampus. In an ongoing project I currently use a similar logic to investigate neural connectivity (fMRI) in preterm born adolescents during visual perception and memory formation.

X. \textit{Prior knowledge about regional differences in maturation rate within the visual system was used to detect distinct and dependent influences on neural activity of visual processing.} Cortical thickness and white matter connectivity show regional maturation differences as
has been demonstrated repeatedly in longitudinal and cross-sectional studies of human development (Giedd et al., 1999; Paus et al., 1999). I compared different age groups in a cross-sectional study design and showed that even very young children can be scanned to investigate changes in neural networks related to visual perception (Klaver et al., 2008; Lichtensteiger, Loenneker, Bucher, Martin, & Klaver, 2008). Particularly interesting for the interaction between visual perception and memory is the age dependent functional rearrangement between neural activity in dorsal and ventral visual streams. I recently started a project in which I use this knowledge to investigate connectivity between these pathways and hippocampal structures.

XI. **Ambiguous interpretation about neural activity differences between groups with different abilities can be solved.** Neural activity differences between groups can often not be uniquely attributed to group differences or performance differences. Schlaggar and colleagues acknowledged this problem and argued that performance between groups should be equalized (Schlaggar et al., 2002). Their solution, however, brings along unwanted problems that tasks have to be specifically designed, task features differ between groups, or groups achieve ceiling level of performance. I used a similar method as Schlaggar and colleagues and found neural activity differences despite ceiling level in both groups (Rotzer et al., 2009). In another study, I used a passive viewing task, which has the advantage that all participants, even 5 year old children, can perform the task, but has the disadvantage that no behavioral control can be obtained (Klaver et al., 2008). In a different, and to my opinion, more elegant approach I separated each group in good and bad performers on the basis of median performance and analyzed independent and dependent contributions of performance and group to neural activity. The results demonstrated that this method can effectively separate performance and age dependent neural activity (Lichtensteiger et al., 2008). This method is more generally applicable and can be done on almost any data set in which groups differ in performance.

XII. **Applying cognitive neuroscience to a clinical setting.** I used prior knowledge about neural mechanisms of working memory in primates to transfer this in a novel clinical neuropsychological diagnostic tool. I used the idea that working memory is characterized by its resistance to interfering stimuli (Desimone, 1996) to predict that the Corsi test for spatial working memory can be extended by letting participants memorize every second item in a sequence. The suppression technique increased working memory load in both verbal and spatial working memory. The so called “block suppression test” (BST) proved to be an effective diagnostic tool of extended spatial working memory and showed that it is possible to adapt knowledge from cognitive neuroscience to clinical setting (Beblo, Macek, Brinkers, Hartje, & Klaver, 2004).
Neural coupling between visual processing and memory related brain areas is associated with declarative memory formation: a “selection for declarative memory” hypothesis. This statement reflects upon formation of declarative memories by interaction between visual and memory operations, and the limitations of connectionist and information processing approach.

1. **Finding that high frequency synchronous oscillatory neural activity between brain areas plays a role not only in perception, but also in human memory formation.** A classic learning hypothesis is that high frequency synchronous firing between neurons provides a transient and flexible neural mechanism to bind visual features during perception and strengthen associative connectivity between concepts (Hebb, 1949). This hypothesis inspired connectionist theories in cognitive science (McClelland & Rumelhart, 1988). Temporary binding was shown in human visual perception (Tallon-Baudry & Bertrand, 1999) and associative learning between long distance cortical areas (Miltner, Braun, Arnold, Witte, & Taub, 1999). We could show for the first time that gamma synchronization supports memory formation in humans (Fell et al., 2006; Fell, Klaver et al., 2003; Fell et al., 2001; Mormann et al., 2007). I was involved in the development of the study ideas, data acquisition, analysis, and interpretation, and in writing the manuscripts.

2. **Finding that memory formation is associated with a stimulus induced reset of oscillatory neural activity in high frequency bands (ca. 40 Hz) between rhinal cortex and hippocampus in such a way that phases of two brain areas are transiently synchronous after the reset.** Although many studies showed that the rhinal cortex and hippocampus support memory formation, direct evidence for an interaction between these areas failed (Brown & Aggleton, 2001). The same articles mentioned above demonstrated that subsequently recalled words yield different neural synchronization values as compared to subsequently forgotten words (Fell et al., 2006; Fell, Klaver et al., 2003; Fell et al., 2001; Mormann et al., 2007). Both increases and decreases in neural synchronization were found suggesting that temporal neural coupling and decoupling between rhinal cortex and hippocampus contribute to memory formation.

3. **Finding that neural activity in the rhinal cortex represents the input of visual information.** The hippocampus represents the output during memory formation, suggesting a feedforward mechanism between visual and memory system during memory formation. In contrast to previous findings supporting neural synchronicity in learning paired associations, we found temporal coupling in a chain of information processing between visual processing and memory. Specifically, the finding that phase locking is still present when hippocampal regions are sclerotic suggests that neural coupling is not triggered by hippocampal neurons (Mormann et al., 2007). The finding that increased neural activity in the rhinal cortex...
(Fernández et al., 2002) is associated with an increase in neural coupling (Fell et al., 2006) suggests that neural coupling is primarily triggered by neural activity generated in the rhinal cortex. Thus, temporal neural synchronization in the gamma band range can be seen as a feedforward mechanism in learning.

4. **Finding that neural coupling between areas provides a time-window in which transfer of information can take place between two brain regions in a functional network, not transfer itself.** Subsequently remembered as compared with forgotten items induce enhanced neural coupling shortly after stimulus onset (100-300 ms), followed by an ERP (AMTL-N400) (300-600 ms) that is generated by the rhinal cortex, a positive ERP wave (600-1000 ms) that is generated by the hippocampus (Fernández et al., 1999; Fernández et al., 2002) and finally desynchronization between rhinal cortex and hippocampus (1000-1100 ms). Taking this temporal sequence and previous knowledge about the information transfer through the ventral stream into account (Fernández et al., 2001), I would argue that neural synchronization between rhinal cortex and hippocampus “selects” to-be remembered information for memory to transfer any information provided by the rhinal cortex into hippocampal structures, followed by a “selection closure” so that only information is memorized during the limited period in which rhinal cortex and hippocampus transfer information (Fell et al., 2006; Fell et al., 2001). I was involved in the development of the study ideas, analysis and interpretation of the data, and writing the manuscripts. Similar ideas have been proposed by Jürgen Fell, Guillén Fernández and myself in review papers (Fell, Klaver, Elger, & Fernández, 2002a; Fernández & Tendolkar, 2006). A different and more physiological view has been proposed by Axmacher and colleagues (Axmacher et al., 2006), who suggest that synchronized gamma oscillations induce long term potentiation (LTP) and depression (LTD) of postsynaptic neurons in CA3 subregions of the hippocampus. These are thought to support Hebbian learning mechanisms. Important for cognitive science, the “selection for declarative memory” hypothesis corresponds to a traditional information processing account whereas the “Hebbian learning” hypothesis corresponds more to a connectionist framework (Posner, 1990). I favor a hybrid hypothesis because the findings that late rhinal cortex and hippocampus activity contributes to memory success (Fernández et al., 2002; Klaver et al., 2005) cannot be explained by the latter hypothesis, while temporary coupling cannot be explained by the former.

5. **Finding that coherence of neural activity in low frequency bands modulates high frequency coupling, and thus the efficacy of memory formation.** Previous studies proposed that interactions between hippocampal theta and gamma rhythms may contribute to learning and memory in rodents (Chrobak & Buzsáki, 1998b; Jensen et al., 1996). For the first time we found evidence of coupled contribution of slow and high frequency EEG activity during memory formation within the human MTL (Fell et al., 2006; Fell, Klaver et al., 2003). The
role of these slow waves in transfer of information or building Hebbian assemblies within the hippocampus is still unclear (Fell et al., 2006).

**Visual familiarity and associative processing with stored information support different types of memory formation.** This statement reflects upon the dual process and dual code account, and dissection of memory operations within the MTL.

1. **Finding that item properties distinguish memory formation within hippocampus and rhinal cortex.** The unitary account of the MTL states that both rhinal cortex and hippocampus support similar mechanisms in memory, i.e. both regions are necessary and cannot be separated functionally (Squire & Zola, 1998). Previous intracranial studies showed that neural activity support memory formation in both MTL regions (Fernández et al., 1999). Here, we demonstrated that word frequency and word imagery differentially affect memory formation operations in rhinal cortex and hippocampus (Fernández et al., 2002; Klaver et al., 2005). Thus, item properties can distinguish memory formation within the MTL. I was involved in the development of the study ideas, data acquisition, analysis and interpretation, and writing the manuscripts.

2. **Finding that hippocampus and rhinal cortex supports different recognition operations.** Dual process models of recognition memory propose that recognition of an item can be based on recollection, i.e. recognition accompanied by contextual information (true episodic memory), or on a sense of familiarity (Yonelinas, 1994). We demonstrated that retrieval operations distinguish mnemonic operations within the MTL. While a hippocampal signal increase of neural activity was associated with successful retrieval of context information an activity decrease provided a familiarity signal that is sufficient for successful item recognition (Weis, Specht et al., 2004). The findings extend electrophysiological findings that show a neural decrease and increase in rhinal cortex, respectively hippocampus during recognition (Klaver et al., 2005), and divide two processes contributing to memory recognition within closely associated regions in the MTL. I was involved in the development of the study idea, data analysis and interpretation of the data and writing the manuscript.

3. **Finding that signal decrease in rhinal cortex supports implicit memory and familiarity recognition but not all neural repetition suppression in visual cortex supports familiarity recognition.** We found differences in neural activity between new and old items in occipital cortex and between misses (repeated items incorrectly identified as new) and hits (repeated items correctly identified as old) in the MTL (Weis, Klaver et al., 2004). This indicated that visual perception related neural activity may be associated with repetition effects but these do not contribute to correct identification of repeated items.
4. Finding that memory benefit for high frequency and high imagery words are supported by different neural mechanisms. Word familiarity and word imagery both benefit from the associative strength to other words in semantic memory (Rubin & Friendly, 1986). This may facilitate recall, since more cues are thought to be available for successful retrieval. Here, we demonstrated that memory formation (not retrieval) related neural activity supports better recall for high as compared to low frequency words (Fernández et al., 2002). The localization in the rhinal cortex suggests that neural activity supports familiarity based item recognition, but not associative memory. We also showed that memory formation and retrieval related neural activity support memory benefit of high imagery words (Fliessbach et al., 2006; Klaver et al., 2005). The localization in the hippocampus (Klaver et al., 2005) suggest that this supports associative rather than familiarity based processing in memory. These results extend recent findings about the role of word frequency and imagery in item recognition and recollection (Gregg, Gardiner, Karayianni, & Konstantinou, 2006; O'Neill, 2005).

5. Finding that oxytocin improves memory formation for subsequently known stimuli but not remembered stimuli. The dual process hypothesis was strengthened by showing that intranasal oxytocin administration during study improves subsequent recognition of known stimuli, but not remembered stimuli on the day after study. The twenty-four hours delay between study and test is sufficient for oxytocin to reach baseline concentrations during recognition, so that memory improvement after intranasal oxytocin administration can be related to memory formation. It is known that oxytocin attenuates neural activity in amygdala in response to face stimuli (Domes et al., 2007), and that oxytocin receptors are present in rodent MTL (Winslow & Insel, 2004), but it is not known whether oxytocin affects neural activity in different subregions within the MTL during memory formation. In a recently submitted project grant I proposed to test the hypothesis whether oxytocin influences different MTL subregions during memory formation.

What is perceived during the first encounter forms the template in memory with which repetitions are compared. This statement reflects upon the importance of making a good first impression.

1. Finding that attended and ignored words leave different semantic traces in implicit memory. Several researchers claimed that semantic information of words automatically leaves a memory trace, even when the words are not consciously perceived (Dehaene et al., 1998; Kiefer, 2002). Those results have lead to the assumption that there is no cognitive control over semantic processing in implicit memory. I tested this view and showed that 1) semantic information of previously ignored words affected neural repetition suppression of previously attended pictures, and that 2) there was an effect of selective attention on implicit memory.
of semantic information. These results are partially incompatible with the view that semantic processing of words is impenetrable by cognitive control and rather suggest that semantic information leave different memory traces when words are attended or ignored (Klaver et al., 2007).

2. **Finding that a semantic processing related area discriminates perceptual priming from conceptual priming.** Repetition priming is thought to be constrained by perceptual priming and conceptual priming (Roediger & McDermott, 2003). Whereas conceptual priming is thought to share common mechanisms between words and pictures (Price, Noppeney, Phillips, & Devlin, 2003; Vandenbergh, Price, Wise, Josephs, & Frackowiak, 1996), perceptual priming is thought to be located in the visual system (Dehaene et al., 2001). I found that most priming sensitive areas, including visual processing related areas, are sensitive to conceptual priming and respond similarly to top-down modulations (Klaver et al., 2007). The only area differentially sensitive to stimulus type and top-down control was the left inferior prefrontal cortex that yielded stronger neural repetition suppression for word repetitions than for picture-word repetitions, particularly when words were previously attended to. This suggests that a semantic processing area discriminates perceptual priming from conceptual priming and contributes to perceptual priming. These results strongly contrasts with the view that perceptual priming is generated by visual processing areas (Dehaene et al., 2001) and that the left prefrontal cortex is only sensitive to semantic/mnemonic processing (Demb et al., 1995; Hagoort, 1997; Wagner, Desmond, Demb, Glover, & Gabrieli, 1997).

4. **Finding that neural activity at memory formation is reactivated during retrieval, which supports the reinstatement hypothesis.** An influential theory in memory research is that neural activity during memory formation is reactivated during recognition: the reinstatement hypothesis (Desimone, Albright, Gross, & Bruce, 1984). We found support for this hypothesis using fMRI and intracranial ERPs. Successful memory formation was found to overlap with successful retrieval in rhinal cortex (positive recognition: hits > misses) and with familiarity recognition (negative memory effect: misses > hits) in the rhinal cortex/hippocampus (Weis, Klaver et al., 2004). These fMRI results indirectly supported our findings that rhinal cortex activity increases during successful memory formation (Fernández et al., 2002) and decreases during repetition (Klaver et al., 2005), while hippocampal activity increases during both first and second presentation contributing to memory success (Klaver et al., 2005). Hence, neural activity in visual and memory related areas differentially contribute to successful memory formation and recognition, which extends earlier findings using primate electrophysiology (Brown & Aggleton, 2001)

5. **Finding that reinstatement of neural activity during retrieval may be content rather than modality specific.** Dual code hypothesis presumes visual and verbal representations of high
imagery words and predicts activation of verbal and visual related areas during memory (Paivio, 1986). In two studies I could show that word imagery related neural activity during study (high imagery words more than low imagery words) reoccurred during repetition. This was found in hippocampal electrodes (Klaver et al., 2005) and in parietal cortex using fMRI (Fliessbach et al., 2006). The reinstatement effects were not modality specific but reflect reoccurrence of semantic processes in memory. The findings were in line with content rather than modality sensitive processes in neural repetition priming (see Finding 1 and 2) and do not support the dual code hypothesis.

6. Finding that hormone oxytocin facilitates processing of the first encounter of social information. Oxytocin was administered intranasally during study and positively influenced recognition of faces on the day after study (Rimmele et al., 2009). Since only familiarity recognition of repeated faces improved I concluded that oxytocin can only strengthen memory formation of social information. Memory formation is thus category specific and dependent on endocrine status at study.

Functional connectivity between MTL and posterior parietal lobule may play a role in transferring memories into visuospatial working memory: a “selection for working memory” hypothesis. This statement reflects upon the ambiguous role of the parietal cortex in episodic and working memory.

1. Finding that immediate use of a recent memory is associated with enhanced neural activity in the left posterior parietal lobule. I found that selecting valid prime information to facilitate visual recognition is associated with an increase in neural activity within the left parietal lobe. This process requires matching the prime information with information stored in memory. Since parietal neural activity was found to be dependent on cue information (only relevant primes induced neural activity), not target information (parietal activity also occurred when non-targets followed a relevant cue), I could demonstrate that parietal neural activity was associated with memory processing rather than visual processing or motor processing (Klaver et al., 2004).

2. Finding that ventral neural activity precedes parietal neural activity in the use of primes. In contrast to prime information that induced parietal activity and target information that was associated with neural activity in motor system, I found that delay time between prime and probe was associated with an increase in neural activity within ventral visual stream. Enhanced ventral stream neural activity occurred in shorter delay times than actual use of cues, suggesting that ventral stream occurred earlier than parietal activity (Klaver et al., 2004).

3. Finding that structural impairment in parahippocampal region and posterior parietal lobule relates to aberrant parietal neural activity during spatial working memory and acquisition
of spatial representations of numbers during development. We demonstrated that children with developmental dyscalculia show reduced brain structure in parietal lobule and parahippocampal gyrus ((Rotzer et al., 2008), not included in this cumulative habilitation). Neural networks supporting spatial working memory were found to be impaired (Rotzer et al., 2009), thus suggesting that development and learning of spatial number representations depend on a cooperation between neural structures in the parietal lobule and MTL.

4. Finding that left posterior parietal lobule plays a role in memory retrieval, left inferior frontal cortex with memory formation, and hippocampus with both successful memory formation and retrieval. Retrieval (old > new) and retrieval success (hits > misses) related activity was associated with an increase in left parietal lobule activity, but the amount of neural activity during retrieval actually predicted successful memory retrieval in the MTL (Fliessbach et al., 2006). By contrast, successful memory formation was associated with neural activity in frontal cortex and MTL (Weis, Klaver et al., 2004). These findings support the idea that the MTL is closely related to successful memory formation and retrieval success, whereas the posterior parietal lobule is related to retrieval per se and inferior frontal cortex supports successful memory formation indirectly. Since parietal and frontal cortex have been traditionally related to working memory functions (Wager & Smith, 2003), such findings contribute to the understanding of the interaction between working memory and episodic memory. I was recently acknowledged a grant for a project proposal that aims to investigate this interaction further.

5. Finding that ventral neural activity maturation precedes parietal neural activity during visual perception. There has been an extensive debate about different maturation rates of visual perception related to visual motion or identity recognition. These perceptual functions have been attributed to dorsal respectively visual ventral stream functions. I found that neural activity of high order visual perception differed between adults and school aged children. Only age related differences were found in parietal lobule but not in ventral stream, suggesting delayed functional maturation of dorsal stream areas (Klaver et al., 2008; Lichtensteiger et al., 2008). In respect to memory processing I would therefore predict that memory operations associated with dorsal stream functioning mature later that memory processes associated with ventral stream functioning. These include episodic memory retrieval and working memory. This issue will be investigated in a recently acknowledged project proposal.

Outlook
My professional aims for the near and intermediate future are two folded. First, I aim to develop a research work group and improve my skills as a group leader and lecturer at the University of Zurich. Second, I continue studying the interaction between the memory and visual system. In a
recently approved grant proposal I test the “selection for working memory” hypothesis of hippocampal-parietal connectivity in memory. That project examines the overlap of parietal neural activity in episodic memory and working memory of adults, normally developing children and atypically developing children (preterm born adolescents with very low birth weight and children who were born with congenital heart disease and corrected for this heart failure shortly after birth). I also submitted a grant proposal to modulate the memory network by hormone administration (oxytocin). This project aims to test whether oxytocin supports and post-traumatic stress disorder impairs memory formation by influencing neural activity in emotional (amygdala), memory (hippocampus) and visual (fusiform gyrus) processing areas. These projects take advantage of recent development in brain imaging techniques that allow for investigating networks of structurally (diffusion tensor imaging, voxel based morphometry) and functionally connected brain regions (functional connectivity). Finally, in an ongoing project, in cooperation with Prof. Fred Mast at the University of Bern, I investigate the influence of visual perception on memory, by suppressing visual processing during vestibular stimulation in memory tasks. Further projects in this line of research will follow.
Included articles


Overview of Articles

In the following overview of articles I took the liberty of sorting the articles thematically, rather than applying a strict chronological order. Footnotes are added to leverage the summaries into a contemporary discussion comprising novel data and hypotheses in the field and to link the studies with each other. I start with articles about the neural communication between the visual and memory system (1, 2), followed by studies about the influence of hippocampus sclerosis (3) and stimulus properties (4, 5) on neural activity within the MTL, about functional dissociations within the memory system (6, 7), about interactions between the visual and memory system by example of the word concreteness effect (8, 9), about the relevance of oxytocin in declarative memory (10), about top-down processing in neural repetition priming of words and visual advance information processing (11, 12), about mechanisms of spatial working memory (13, 14) and about the role of dorsal and ventral stream development in visual perception (15, 16). All data from epilepsy patients (1, 2, 3, 4, 5, 8) were collected at the Department of Epileptology, University Hospital Bonn (Germany). Functional brain imaging data were collected at the Medical Center Bonn (6, 7, 11, 12), Life & Brain Center Bonn (9), or at the MR Center of the University Children’s Hospital Zurich (14, 15, 16). Data from the oxytocin study (10) was collected at the Psychological Institute of the University of Zurich. Data from a working memory study (13) was collected at the Gilead Hospital, Bethel in Bielefeld.

On the harmonious meeting of visual perception and memory circuitries

The first two articles use similar methods in the same experiment to investigate contributions of the rhinal cortex and hippocampus, and their cooperation by synchronous neural activity to declarative memory formation. In both articles we hypothesized that memory formation is supported by synchronization of neural activity between input from the visual ventral stream and output to the memory network. In the first article we investigate the role of gamma synchronization in memory formation. The second article examines the role of theta coherence and its interaction with gamma synchronization. To further investigate the properties of neural activity in the MTL we examined if MTL pathology (hippocampus sclerosis) affects neural activity in the MTL during memory formation. In a review paper we also explored theoretical issues related to the formation of memories through synchronous activity (Fell et al., 2002a). In two review papers we elaborated if synchronous neural activity might contribute to visual feature binding under the influence of selective attention (Fell, Fernández, Klaver, Elger, & Fries, 2003) and if slow wave neural activity might contribute to the attentional blink (Fell, Klaver, Elger, & Fernández, 2002b). The review papers are not included in this cumulative habilitation.
The **first** article investigates the role of synchronous neural activity in the gamma frequency range to the formation of memories by MTL structures.

Although many studies showed that the rhinal cortex and hippocampus support memory formation, direct evidence for an interaction between these areas failed (Brown & Aggleton, 2001). Based on earlier studies about visual object recognition (Engel & Singer, 2001), we hypothesized that synchronous neural activity in the gamma frequency range (around 40 Hz) might be optimal for the communication of neural structures. We examined the contribution of neural activity in the gamma frequency to memory formation by reanalyzing data from a study that reported event-related potentials in intractable epilepsy patients who were implanted with bilateral depth electrodes in MTL (Fernández et al., 1999). The patients memorized word lists and subsequently recalled as many items as possible\(^1\). The study was a follow-up on the data published by Fernández and colleagues who reported that the AMTL-N400 was larger for subsequently recalled words compared with subsequently forgotten words. ERPs recorded from hippocampal electrodes showed a slow positive deflection for subsequently remembered words as compared with forgotten words\(^2\). In this article, to further investigate memory formation, single-trial EEG epochs were segmented for subsequently recalled and forgotten items in periods before and after word presentation. The comparison of subsequently remembered and forgotten items revealed an increase of phase locking in the gamma range (32-48 Hz) between rhinal and hippocampal electrode sites shortly after word presentation (100-300 ms) followed by a decrease of synchronization (1000-1100 ms). We could additionally show that gamma activity decreased during memory formation in both parahippocampal region and hippocampus in approximately the same time windows. These findings demonstrated for the first time that rhinal cortex and hippocampus cooperate during memory formation. We suggested that gamma synchronization support a transient connection between both MTL structures initializing memory formation. The following decoupling may terminate transfer between rhinal and hippocampal structures. Such synchronization and desynchronization requires highly accurate timing of neural discharges within a time range of just a few hundred milliseconds. We considered it unlikely that semantic information would be available at the early time point of synchronization and rather suggest that directed attention might, as a first step, allocate specific

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\(^1\) In between the encoding and free recall phase patients performed a working memory task (counting backwards) to prevent rote rehearsal of learned items.

\(^2\) The intracranial recordings are highly specific to investigate contributions of MTL structures, because they have limited volume conduction effects. Based on the location of the electrodes, steep potential gradients towards neighboring electrode positions, and polarity reversal on temporal basal electrodes, the AMTL-N400 neural generator could be localized in the rhinal cortex (McCarthey, Nobre, Bentin, & Spencer, 1995), while the hippocampus is shielded towards the outside by the radial cylindrical arrangement of hippocampal pyramidal neurons (Klee & Rall, 1977).
connections necessary for memory formation, before actual information transfer takes place\(^3\). In principle, cortical regions like the frontal cortex or superior temporal sulcus, might influence rhinal-hippocampal synchronzation. The early timing, however, suggests that coupling might be initiated by a top-down process mediated directly by the thalamus (LaBerge, 1997)\(^4\). The alternative hypothesis that a third pacemaker may drive phase-locked gamma activity in both structures could not fully be excluded. However, the close relationship and anatomical connections between these two MTL structures support the role of cortical-hippocampal interaction through gamma synchronization during memory formation (Buzaški, 1996; Fernández et al., 1999).

My contribution to the article was the conceptual development of the study, interpreting the results and writing the manuscript. Jürgen Fell, Guillén Fernández and I primarily developed the concept for the study. Guillén Fernández recruited all patients, designed the stimuli and experiment, and collected all of the data. Jürgen Fell analyzed all data. Carlo Schaller was the neurosurgeon who implanted the electrodes of the epilepsy patients. Klaus Lehnertz helped with the data analysis. Thomas Grunwald was leading epileptologist. Christian Elger was head of the department and provided the infrastructure for the study.

The second article investigates the contribution of coherent neural activity in the theta frequency range on synchronous neural activity in the gamma frequency range to the formation of memories in MTL structures.

Theta activity has been shown to play an important role in memory encoding. Rodent studies linked hippocampal theta activity with memory processes, and emphasized a direct link between theta and gamma activity\(^5\). Based on such findings the so called theta-gamma phase coding hypothesis was postulated for declarative memory formation (Jensen, 2001). This model postulates that memory storage of multiple items is coded by distinct cycles of gamma oscillations and the position of these cycles with respect to the theta phase. Since human evidence for these mechanisms were unknown we examined neural collaboration in the MTL during memory formation and reanalyzed the data of the previous study (Fell et al., 2001).

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\(^3\) Rhinal-hippocampal gamma oscillations were recently proposed to support the establishment of Hebbing assemblies. The precise timing was argued to induce LTP and LTD based learning within the CA3 of the hippocampus (Axmacher et al., 2006).

\(^4\) Previous studies showed in vitro gamma oscillations in the CA1 field of hippocampal slices that followed within the first second after stimulation that were associated with a prolonged elevation of excitatory postsynaptic potentials (Bliss & Lomo, 1973; Traub, Whittington, Stanford, & Jefferys, 1996). Although both data sets underline the role of gamma oscillations in memory formation within the MTL, our macroscopic EEG field recordings clearly cannot be directly compared with the in vitro data since we were not able to differentiate between hippocampal subregions.

\(^5\) It was reported that theta waves may modulate hippocampal gamma activity (Chrobak & Buzaški, 1998a) and that firing of hippocampal place cells in the gamma range during movement through a labyrinth the depends on the phase of the theta rhythm (O'Keefe & Recce, 1993).
Spectral power and coherence in the delta (1-4 Hz), theta (4-7 Hz), alpha1 (7-10 Hz), alpha2 (10-13 Hz), beta1 (13-16 Hz) and beta2 (16-19 Hz) were calculated for successful as opposed to unsuccessful remembered items. Subsequently remembered items yielded higher spectral coherence values than for forgotten items, but no difference between frequency bands. Differences, however, seemed to be specifically large in low frequency range of theta and delta band. To examine the relation of the EEG coherence with the previously reported gamma synchronization, we correlated the change in EEG coherence and spectral power bands with individual signal change in gamma synchronization. This was done for the two phases in which gamma synchronization increased (100-200 ms) and decreased (1000-1100 ms) after word presentation. We found that only the theta band correlated with gamma synchronization values for the early increase in gamma synchronization. These data support the hypothesis that gamma synchronization is modulated by theta coherence. The findings also extend scalp EEG recordings that coherence in lower frequency bands support memory encoding (Weiss, Müller, & Rappelsberger, 2000). These studies revealed a role of neocortical structures in memory formation, where it was proposed that they may be initiated by hippocampal-neocortical loops (Buzsáki, 1996). Together, we propose that theta oscillations initiate an encoding state. Within this state gamma synchronization may open the gate for information transfer into the hippocampus (Fernández & Tendolkar, 2001).

My contribution to the article was the conceptual support for the study, interpreting the data and writing the manuscript. Jürgen Fell, Guillén Fernández and I developed the idea for the study. Guillén Fernández recruited all patients, designed the stimuli and experiment, and collected all of the data. Jürgen Fell analyzed all data. Hakim Elfadil helped with the data analysis. Carlo Schaller was the neurosurgeon responsible for implanting the electrodes of the epilepsy patients. Christian Elger was head of the department and provided the infrastructure for the study. The same pool of data was used in the first article. The tool uses slightly different selection criteria of electrodes, so that a different final set occurred as in Fell et al. 2001 and Fernández et al. 1999.

The third article investigates the effect of hippocampus sclerosis on neural activity in the MTL during memory formation

Hippocampal sclerosis is a frequent cause of temporal lobe epilepsy that is characterized by gliosis and severe neuronal degeneration in CA1, CA3 and hilus of the hippocampus (Wyler, Dohan, Schweitzer, & Berry, 1992). It is a major cause of memory disturbance. Here, we

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6 Based on recent hypotheses about the role of theta/gamma oscillation interaction during memory formation one might argue that theta phase reset allows for an entrainment of gamma activity inducing hippocampal LTP during this period. This may enable the establishment of Hebbian assemblies (Axmacher et al., 2006).
investigated the effect of hippocampal sclerosis on memory formation within the MTL using intracranial EEG recordings from patients with hippocampal sclerosis. We reanalyzed our previous reported data (Fell et al., 2001; Fernández et al., 1999) and now compared pathological (ipsilateral) and healthy (contralateral) EEG. Conventional ERPs, AMTL-N400 and late positive component, showed a decrease on the pathological compared with the contralateral side. Changes in power and phase information were analyzed in the sub-gamma range ranging from 0.5 to 30 Hz. No effect on power changes was found, except that power reduced in the delta/theta band (1-7 Hz) on the pathological side. Phase clustering was more pronounced in rhinal cortex than in hippocampus. Surprisingly, no evidence was found for a contribution of power or phase clustering to memory formation, suggesting that these ERPs are caused by a mixture of phase and power changes. Thus, the reduction of conventional ERPs on the focal site adds to the previous studies using different paradigms, such as recognition memory or oddball P3 tasks (Grunwald, Elger, Lehnertz, Van Roost, & Heinze, 1995; Puce, Kalnins, Berkovic, Donnan, & Bladin, 1989). The reduction seemed to be caused by a reduction of delta/theta power that even drops below pre-stimulus baseline. This decrease in power may be caused by the reduced availability of neural assemblies associated with hippocampus sclerosis. The findings suggest that these available neurons are not used during memory formation, or that EEG power in this frequency range require reciprocal connections between hippocampus and rhinal cortex. The finding that phase clustering is not affected by hippocampus sclerosis suggests that network functions remain unaffected and that timing of recruitment of the available neurons remains intact. Given our previous findings this means that the rhinal cortex keeps projecting on the sclerotic hippocampus.

My contribution to the article was in helping with the data analysis and interpretation of the data and writing the manuscript. Florian Mormann and Jürgen Fell had the idea for the study. Florian Mormann primarily analyzed the data and wrote the manuscript. Guillén Fernández recruited all patients and collected all of the data. Christian Elger was head of the department and provided the infrastructure for the study. Jürgen Fell helped with the data analysis and interpretation of the data and writing the manuscript. All data were previously published in the first and second article of this cumulative habilitation as well as in Fernández et al. (1999).

On memory of common and uncommon words

These articles investigate word frequency dependent memory operations in the MTL. The first article applies conventional ERPs to show that hippocampus and rhinal cortex process high frequent words differently than low frequent words during memory formation. The second article examines neural synchronization, thus resolving information transfer between rhinal cortex and hippocampus.
The fourth article investigates characteristics of declarative memory in MTL in dependence of item characteristics.

The goal of this study was to differentiate MTL contributions to mere mnemonic processing and processing that is supported by item properties. High frequency words have richer semantic contexts (Gregg, 1976) and are more meaningful (Noble, 1963) than low frequency words. They may associate more easily with each other and possess more associations with semantic memory, which may enhance free recall. To examine this hypothesis we recorded EEG from MTL in intractable epilepsy patients who were implanted with depth electrodes during presurgical evaluation. Nine patients memorized lists of high and low frequency words, followed by a distractor task and subsequent free recall. As expected we found that memory performance for high frequency words was greater than for low frequency words. There were no dependencies on the position in word lists for high and low frequency words. A subsequent memory effect was found on the AMTL-N400. Moreover, the subsequent memory effect was restricted to high frequency words. The hippocampal subsequent memory effect was reflected by a late positive ERP component between 600 and 2000 ms. There was no difference between low and high frequency words on this ERP wave and no interaction with memory was found. We thus argued that the rhinal cortex MTL-N400 may support memory formation indirectly by increased semantic processing, while hippocampus supports an exclusive mnemonic operation, independent of item properties. These findings support a dissociation of MTL functions in which item properties differentially affect neural activity in the rhinal cortex and hippocampus. The hippocampus seems to play a more general role in memory formation. These findings oppose against the unitary hypothesis of the MTL (Squire & Zola, 1998), but strengthens the hypothesis that the parahippocampal region enables semantic processing (Chan et al., 2001).

The data are also congruent with Otten and colleagues (2001) who found that the anterior MTL supports both semantic processing and memory formation, while the posterior MTL activation was sensitive to memory formation only (Otten, Henson, & Rugg, 2001). The anterior part might reflect the ATL-N400, the posterior part the hippocampal subsequent memory effect. Alternatively, one might argue that the AMTL-N400 memory effect reflects word-to-word

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7 A similar design was used as Fernández et al. 1999 and Fell et al. 2002, but with different sets of word frequencies and smaller total amount of words.
8 Depending on the type of memory task, order of words and distinctiveness of low frequency words, the pattern of memory performance for high and low frequency words can be reversed (Glanzer & Adams, 1990).
9 This effect may be specific for a free recall paradigm, because a later study applying a different memory paradigm (continuous recognition paradigm) with high and low imagery words (Klaver et al., 2005) reported a concreteness effect within hippocampus. We found no ERP differences between high and low frequency words. The results of that study are presented in this cumulative habilitation.
10 Otten and colleagues (2001) used a levels of processing account which takes advantage of the effect that deeply encoded items (e.g. in a semantic decision task) are more effectively memorized than shallow encoded items, e.g. in a perceptual decision task (Craik & Lockhart, 1972)
associations, while the hippocampus reflects word-to-context associations\textsuperscript{11}. Thus, the data support distinct processing of the rhinal cortex and hippocampus, which differentially contribute to memory formation.

My contribution to the article was the recruitment of the patients and the collection of the data. I analyzed all data and wrote parts of the manuscript. Guillén Fernández had the main idea for the study, he designed the stimuli and experiment and mainly wrote the manuscript. Guillén Fernández, Jürgen Fell and I interpreted the data. Thomas Grunwald was leading epileptologist. Christian Elger was head of the department and provided the infrastructure for the study.

The fifth article investigates the effect of item characteristics (word frequency) on neural synchronicity in MTL structures during memory formation.

In this study we reexamined the findings from Fernández and colleagues (2002) by applying the techniques described by Fell and colleagues (2001). We now analyzed the data in a frequency band between 2 and 48 Hz, thus both including gamma frequency (Fell et al., 2001) and slow wave activity (Fell, Klaver et al., 2003). Due to the low time resolution for the slow waves, phase and power synchronization values were averaged in time windows of 100 ms for the frequency bands delta (2 Hz), theta (4-6 Hz), alpha (8-12 Hz), lower beta (14-20 Hz), higher beta (22-30 Hz) and gamma (32-48 Hz). Delta, theta and alpha synchronization did not differ for high and low frequency words. Delta synchronization was higher for subsequently remembered than forgotten words. High frequency words increased gamma synchronization between rhinal and hippocampal electrodes between 300 and 500 ms, but low frequency words elicited no such effect. Late desynchronization was found for high frequency words and for low frequency words between 1000 and 1300 ms, respectively between 600 and 900 ms. Beta activity seems to be broader distributed across the trial. Differences between this and earlier studies could be due to the slightly different use of filtering, and to the smaller number of words that were memorized in each category making the present findings less reliable. The data support the hypothesis that gamma synchronization between rhinal and hippocampal electrodes occurs only when sufficient information is to be processed as is the case for high frequency words. Based on previous findings we suggested that gamma synchronization enables a temporary time window for the transfer of information (Fernández & Tendolkar, 2001). Others, however, argued that Hebbian assemblies can be formed due to the precise timing of action potentials (Axmacher et al., 2006). This alternative hypothesis cannot be excluded.

\textsuperscript{11} This hypothesis seems concordant with our findings on word concreteness in the MTL, since concrete words are more easily to remember and to embed in a context than abstract words, and elicit hippocampal activation ((Klaver et al., 2005) in this cumulative habilitation).
My contribution to the article was the recruitment of the patients and collection of data. I helped with the interpretation of the data and writing of the article. The same pool of data was used in the seventh article. For this article data analysis was done by Jürgen Fell. The tool uses slightly different criteria, so that a different number of subjects were included in the final data set. The motivation to perform this analysis was made by Fell, Fernandez and I. Nicolai Axmacher, Florian Mormann and Stephan Haupt help to interpret the results. Christian Elger was head of the department and provided the infrastructure for the study.

On functional dissociations in the memory system

These articles use functional MRI to dissociate declarative memory operations. The findings suggest that a signal decrease supports a familiarity signal in memory that can be dissociated from an increase in neural activity supporting successful recollection. The first article also indicates a role for visual areas that do not support memory processing and provides evidence for the reinstatement hypothesis by reoccurrence of encoding activity during recognition. The second article emphasizes different characteristics for source and item memory processing in the MTL.

The sixth article investigates networks of declarative memory during encoding and retrieval.

Functional brain imaging in healthy adults was used to investigate contributions of signal increase and decrease to successful memory formation and recognition. Successful memory formation is associated with both enhanced and decreased neural activity (Otten & Rugg, 2001). A classic recognition memory comparison in imaging studies, the old/new effect, contrasts correctly identified old items with correctly identified new items. A problem with the reverse contrast is that brain activity for new more than old items cannot be clearly associated with recognition memory success, since it might be contaminated with a neural repetition priming effect that does not support conscious recognition (Donaldson, Petersen, & Buckner, 2001). On the other hand, neural decreases have been shown to contribute to recognition memory in electrophysiological studies (Brown & Aggleton, 2001; Smith, Stapleton, & Halgren, 1986). To separate neural repetition priming from neural decreases that contribute to recognition memory, we compared brain activity to correctly identified old items (hits) and old items misclassified as new (misses). The reverse comparison is not contaminated with repetition priming and is closer to actual memory status. Hence, the aims of this study were 1) to examine neural correlates of encoding and recognition in a single study-test experiment, 2) to disentangle

12 Grunwald and colleagues reported no differences in the AMTL-N400 between hits and misses, while the hippocampal recognition effects (late negative component, LNC) differentiated between correctly and incorrectly identified old items (Grunwald et al., 2003). The authors suggested that the repetition effect on the AMTL-N400 may not support conscious recognition. This hypothesis is not in line with the negative recognition effect.
positive and negative repetition effects supporting recognition memory, 3) to uncover brain areas that support both memory encoding and recognition, thus resolving neural mechanisms in which some areas are reused during recognition. Sixteen healthy adults were examined using fMRI during encoding and recognition task in which photographs were repeated from the encoding phase and were intermixed with novel photographs. Participants judged for each presented photograph if it was a landscape or building and memorized the items. Positive subsequent memory effects (subsequently remembered more than forgotten items) were associated with activity in left prefrontal cortex, left angular gyrus bilateral fusiform gyrus and parahippocampal cortex. This finding emphasizes the role of these areas in the effort to memorize information (frontal), or actual memory formation (hippocampus), or semantic association building within the parahippocampal region (Kirchhoff, Wagner, Maril, & Stern, 2000). Negative subsequent memory effects were found in posterior cingulate gyrus and precuneus, which may reflect task related processing and directs resources away from memory formation (Otten & Rugg, 2001). Next, neural activity was investigated during recognition. The old/new effect was found in several areas of the prefrontal cortex, anterior cingulate, bilateral inferior parietal cortex, left insula, and cerebellar areas. The right prefrontal activity (in accord with the left prefrontal activity during encoding) is in line with the prefrontal hemispheric encoding/retrieval asymmetry (HERA) model (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). The positive recognition effect partly overlapped with the old/new effect with small differences in location. These differences were interpreted to be partly due to statistical variance by the different number of included items in the different analyses. Together the frontal, parietal and cerebellar areas were thought to support successful recovery of declarative memories during recognition memory. Neural repetition priming effects (new > old) were found primarily in bilateral occipital areas, indicating that visual processing areas reveal repetition effects which do not directly contribute to declarative memory recognition. The negative recognition effect was small and centered in anterior parahippocampal gyrus. In line with human and primate electrophysiological studies (Brown & Aggleton, 2001; Smith et al., 1986) we argued that the negative recognition effect contributes to a familiarity based decision rather than an actual recollective experience (Henson, Cansino, Herron, Robb, & Rugg, 2003). However, alternative explanations that priming may contribute cannot be fully excluded. Yet, since the priming effect as measured by the new > old contrast resulted in different pattern of neural activity, this interpretation seems unlikely. Masking the subsequent memory effect with the positive recognition effect showed overlap in the inferior and anterior MTL, probably in the collateral sulcus that is covered with the rhinal and perirhinal cortex. Masking the subsequent memory effect with the negative recognition effect showed overlap in the MTL. This confirmed the hypothesis that the MTL plays a role in both encoding and recognition (Fernández et al., 1999; Smith et al., 1986). We also found overlap with the positive recognition effect in the lateral
anterior temporal cortex, left fusiform activity\textsuperscript{13}, vermis of the cerebellum and pons. Taken together, we found evidence that several brain areas support successful memory formation and recognition, which is in line with the reinstatement hypothesis.

My contribution to the article was primarily in designing the study, supporting the data analysis and interpreting the results. Susanne Weis recruited all participants and collected all of the data. She programmed the stimuli and experiment, analyzed the data and primarily wrote the manuscript. Guillén Fernández had the idea for the study design and supervised the analysis, interpretation of the data and writing the manuscript. Jürgen Reul provided access to the scanner facilities. Christian Elger was head of the department.

The seventh article investigates networks of declarative memory during contextual retrieval and item recognition.

Dual process models of recognition memory distinguish qualitative distinct forms of memory (Yonelinas, 2002). Recognition of items that is accompanied by recollection of contextual information represents true episodic memory, while recognition unaccompanied by contextual information can rely upon a sense of familiarity (Mandler, 1980)\textsuperscript{14}. The current study elicits these distinctions by elaborating on Weis and colleagues and compares recognition of item information without recollection of context with recollection of source information. The subjects were now asked to memorize the buildings and landscapes together with its color in which greyscale photographs were transformed in red/blue/yellow/green-scale images. In the recognition phase grey-scale photographs were repeated together with new photographs, and old/new decisions were required, followed by indication of the color in which the picture was presented during study. Imaging data for positive source memory (correctly identified old pictures with its correct source judgment (correct color) more than correctly identified old pictures with incorrect source recognition) yielded activation in the bilateral anterior hippocampus. Negative source memory (the reverse contrast) yielded no significant activation. Negative item recognition (less activity for hits with incorrect source judgment as opposed to misses) revealed a decrease of activity in the right anterior MTL. Both hits without contextual retrieval and false alarms show similar decrease of activation. Thus, contextual retrieval of color was accompanied with hippocampal activation, while recognition without contextual retrieval was associated with deactivation in the right MTL. These data support the dual-memory model. The hippocampal

\textsuperscript{13} Encoding and retrieval related activity in the fusiform gyrus was not further discussed in the article. However, in the context of the cumulative habilitation and reinstatement hypothesis, this region plays a role in object recognition. This area is also closely related to other studies identifying fusiform/parahippocampal gyrus activity to support declarative memory formation during an implicit memory repetition task (Turk-Browne, Yi, & Chun, 2006). These studies showed that larger difference of neural activity between initial encoding and repetition predicted subsequent memory success.

\textsuperscript{14} See also Rimmele and colleagues (2008) in this cumulative habilitation.
activation by reciprocal connections with association cortex may link an item to contextual information during retrieval. The deactivation may support a sense of familiarity that could also occur for novel items incorrectly identified as old (false alarms). The data are also in line with animal studies showing that visual recognition in the anterior temporal lobe at the end of the visual ventral stream is associated with a deactivation by repetition (Murray & Bussey, 1999). This deactivation may support familiarity in humans (Brown & Aggleton, 2001; Henson et al., 2003).

My contribution to the article was to support designing the experiment and interpreting the data. Susanne Weis was Ph.D. student and recruited all participants, designed the stimuli, and collected all of the data. She primarily analyzed the data and wrote the manuscript. Karsten Specht helped with the data analysis. Guillén Fernández had the main idea for the study design and primarily supervised the interpretation of the results and writing the manuscript. Indira Tendolkar helped interpreting the results. Jürgen Ruhlmann provided access to the MR facilities. Klaus Willmes was official supervisor of Susanne Weis. Christian Elger was head of the department.

**On the memory of high and low imagery words**

In the eighth and ninth article I pursued the question, which neural mechanisms support the memory benefit of high imagery words above low imagery words and whether visual processes contribute to this benefit. The eighth article tests whether central memory areas of the MTL (rhinal cortex and hippocampus) contribute to the word imagery effect during continuous recognition using intracranial ERPs. The ninth article investigates the neural network underlying the concreteness effect in a word encoding and recognition task using functional MRI.

The **eighth** article investigates networks of declarative memory in MTL in dependence of word imagery.

Memory operations on high imagery words are known to exceed that of low imagery words. High imagery words are assumed to convey both a verbal and pictorial representation, whereas low imagery words only engage a verbal representation (Kieras, 1975). This is elaborated in the dual-code theory (Paivio, 1986). Recent memory theories, however, attribute the memory advantage of high above low imagery words to the stronger semantic associations and the property of high imagery words to be easily embedded in contexts. Evidence from lesion studies and imaging studies suggested the contribution of anterior temporal cortex in word imagery, and partially in memory processing (Bussey & Murray, 1999; Wise et al., 2000). Yet, no study tested the role of word imagery in MTL regions. We used data from a continuous recognition paradigm.
(Rugg & Nagy, 1989) that was applied in a presurgical evaluation setting to identify abnormalities in memory processing of the left or right MTL (Grunwald et al., 1999). Fourteen patients were tested. In an independent test, all words were rated for word imagery. Only clearly identified high and low imagery words were analyzed. These words were also separated in high and low frequent words to test if ERPs were affected by items properties other than word imagery. Recognition memory performance was greater for high above low imagery words, but did not depend on word frequency. In concordance with earlier studies a reduced AMTL-N400 was found in response to repeated words as compared with new words. In hippocampal electrodes a positive ERP was found between 300 and 600 ms (P600) followed by a late negative component (LNC 600-900 ms). The LNC was enhanced for old as compared with new items. Word imagery affected only the P600. Thus, memory effects and word imagery could be differentiated. We suggested that the word imagery effect on the P600 reflects an integration of words with semantic knowledge including both conceptual and pictorial information, which is in line with other studies on conceptual processing of pictures (Vannucci et al., 2003). We also discussed that the P600 may underlie the same process supporting memory formation (Fernández et al., 1999; Fernández et al., 2002). Grunwald and colleagues also reported the P600 to occur for consciously recognized items as opposed to missed items. Since the number of trials allowed for no reliable analysis depending on memory success, we could not verify its role in memory conclusively (Grunwald et al., 2003). The absence of concreteness effect on AMTL-N400 is not in line with scalp recorded N400 studies that showed enhanced activity for concrete words. Very low frequency words may attract attention and improve memory, while high frequency words elicit richer semantic processing and sometimes improve memory. The absence of word frequency effect contrasts with other memory studies (including Fernández et al. 2002 in this cumulative habilitation) and may be due to the small difference between high and low frequency words as caused by the stimulus selection that was limited by the clinical setting. In sum, the findings support a distinction between hippocampal and rhinal cortex memory functions on word imagery that has not previously been observed.

15 High and low imagery words are in literature often referred to as concrete, respectively abstract words.
16 Mormann and colleagues showed in the same experiment (without separating concrete and abstract words) that between 190 and 500 ms post-stimulus a phase reset is taking place for all frequency bands between 4 and 50 Hz (Mormann et al., 2005). Based on recent hypotheses about the role of theta/gamma oscillation interaction during memory formation one might argue that theta phase reset allows for an entrainment of gamma activity inducing hippocampal LTP during this period (Axmacher et al., 2006). Following this reset starts a period in which increased theta/delta activity in rhinal cortex and hippocampus accompanies the P600.
17 A recent study analyzed a larger number of patients (n=31) with the same paradigm in which they separated subsequently remembered and forgotten items. They reported a similar pattern of memory formation as in the free recall paradigms, in which subsequently remembered items accompanied a greater AMTL-N400 and a greater hippocampal P600 compared with forgotten words. Memory formation also accompanied between trial phase locking and synchronous activation between hippocampal and rhinal cortex (Fell, Ludowig, Rosburg, Axmacher, & Elger, 2008). These data lead to the prediction that high imagery words engage hippocampal processes involved in memory formation.
My contribution to the article was the idea of the study. I analyzed the data and I wrote the manuscript. The patients and experiment were part of an ongoing clinical diagnostic program. Thomas Dietl collected all of the data. Simone Schür helped piloting and selecting the stimuli. Carlo Schaller was the neurosurgeon who implanted the depth electrodes for the epilepsy patients. Christian Elger was head of the department and provided infrastructure of the study. Guillén Fernández and Jürgen Fell helped writing the manuscript and interpreting the data.

The ninth article investigates circuitries of memory formation and recognition memory in dependence of word imagery.

The study investigates the neural basis of the word imagery effect during encoding and recognition memory using fMRI. The experimental design is similar to Weis and colleagues (2004 in this cumulative habilitation). Participants were presented with high and low imagery words, and were requested to memorize the words. In the following recognition memory task they were presented with repeated and novel words. Subsequent memory effects during encoding phase yielded left inferior frontal activity for low and high imagery words. Word imagery effects (low > high imagery words) overlapped with the subsequent memory effect, suggesting that low imagery word processing during successful memory formation share a common process associated with effortful retrieval of semantic knowledge (Binder, Westbury, McKiernan, Possing, & Medler, 2005; Noppeney, Phillips, & Price, 2004). This is both in line with the hypothesized facilitated access for concrete words to semantic knowledge (Schwanenflügel, Akin, & Luh, 1992) and with the image-based code processing of concrete words that does not require semantic processing (Paivio, 1986). For recognition we found similar enhanced frontal activity for low imagery words and bilateral angular gyrus and left inferior parietal lobule activity for high imagery words, both effects replicating previous studies (Binder et al., 2005). The old/new effects yielded activation in precuneus, cerebellum, angular and supramarginal gyrus, anterior cingulum, rolandic operculum, bilateral ventral caudate, and inferior triangular gyrus. A similar pattern was found for the positive recognition effect (old hit > miss). These findings are in line with Weis and colleagues as well as other studies (Henson, Hornberger, & Rugg, 2005). Priming effects (new>old) and negative recognition (old miss > hit) were not found. The left inferior parietal and angular activity overlapped with the concreteness effect (concrete more than abstract words) and old/new effect. Since the parietal activation was also found to support recollection more than recognition based on mere familiarity memory (Wheeler & Buckner, 2004), this finding suggested that concrete words might be better suited to evoke contextual retrieval, which supports recollection. The old/new effect for concrete words overlapped with the concreteness effect during encoding in bilateral precuneus, left cerebellum...
bilateral posterior and anterior cingular cortex. The posterior precuneus activation may support retrieval of imageable material (Lundstrom et al., 2003)\textsuperscript{19}. The precuneal overlap for encoding and retrieval suggested a content specific reinstatement of neuronal activity from the encoding period while successfully retrieving this information (Nyberg, Habib, McIntosh, & Tulving, 2000)\textsuperscript{20}. Finally, the behavioral concreteness effect \textsuperscript{21} with different memory contrasts yielded a positive correlation with the activation for the old/new-contrast during recognition in the left MTL (fusiform gyrus/hippocampus) indicating that subjects activating this region stronger during correct recognition showed a larger benefit from high imagery words. These findings were interpreted to support retrieval of object information from words, as indicated by the common activation during processing of picture and high imagery words (Wheeler & Buckner, 2004; Woodruff et al., 2005)\textsuperscript{22}. Taken together, we found strong evidence for the reinstatement hypothesis of concrete and abstract words, but no clear support for the dual-code hypothesis.

My contribution to article was the initial idea for the study design. I provided the stimuli and developed the experimental design. Klaus Fliessbach primarily collected the data, analyzed the data and wrote the manuscript. Susanne Weis helped with data collection and data analysis. Christian Elger was head of the department and provided infrastructure for the study. Bernd Weber helped with the data analysis and writing of the manuscript.

On the role of oxytocin in declarative memory

The tenth article investigates how oxytocin affects declarative memory of faces.

Oxytocin is a highly preserved neuropeptide that is known to improve social recognition and binding in non-human mammals (Winslow & Insel, 2004). Oxytocin is both sufficient and necessary in the medial amygdala of rodents for establishing a social memory (Ferguson, Aldag, Insel, & Young, 2001). The medial amygdala projects to the bed nucleus of the stria terminalis and via the lateral septum to the hippocampus. In humans the role of oxytocin in memory is not clear. Some studies reported an improvement of face memory (Guastella, Mitchell, & Mathews, 2008), while other studies showed impaired memory after intranasal administration of oxytocin (Heinrichs, Meinschmidt, Wippich, Ehlert, & Hellhammer, 2004). Oxytocin may also affect

\textsuperscript{19} Participants judged whether these were certainly or probably old, certainly new or probably new. Only confident responses were analyzed because previous studies showed that insecure responses do not support memory operations.

\textsuperscript{19} Anterior precuneus activation has been suggested to accompany retrieval of more abstract information (Lundstrom et al., 2003; Woodruff, Johnson, Uncapher, & Rugg, 2005).

\textsuperscript{20} The activation may also be a consequence of retrieval success rather than being necessary for successful recollection (Woodruff et al., 2005).

\textsuperscript{21} Recognition memory for concrete words is better than for abstract words.

\textsuperscript{22} The hippocampal activation reported by Klaver et al. 2005 was also interpreted similarly. The contrasts, however, differ. In Klaver et al. both new and old words show hippocampal differences. In Fliessbach et
face processing less specifically. We pursued the hypothesis that oxytocin might only affect memory of faces but not of non-social stimuli, and examined whether the effect on memory might be different between different aspects of memory. Therefore, the study was designed as a double blind placebo-controlled remember-know paradigm. This paradigm allows for a dissociation of conscious retrieval of a certain event in memory, and remembering the presence of the repeated stimuli without full recollection of the context (Yonelinas, 2002). Oxytocin administered subjects remembered the face stimuli better than placebo control subjects. This was not the case for non-social stimuli. Several control variables like arousal differences between subjects or valence and gender of stimuli did not influence the findings. A closer look on the results revealed that higher recognition for faces could be explained by the lower false alarm rate for know responses, rather than by higher remember responses. These indicated an improvement of the signal-to-noise ratio for discriminating new faces from old ones.

Recollection memory of faces was unaffected by oxytocin. Recollection “remember” judgments reflect the conscious effortful retrieval of qualitative information of a study event. Familiarity “know” judgments are largely dependent on the strength of a memory trace that can be described by signal detection theory (Yonelinas, 2002). Thus, oxytocin seems to improve the immediate strengthening of neural circuitry selectively representing social memories. As an alternative, oxytocin may shift the threshold of familiarity in other brain areas of the face processing network. However, given the potential role of the amygdala in memory and its high density of oxytocin we considered it likely that the amygdala plays at least partial role in the effect of oxytocin on social memory.

My contribution to the article was the supervision for the idea, the stimuli and the experimental design. I supervised interpretation of the data and writing of the manuscript. Ulrike Rimmele had the initial idea for the study and primarily wrote the manuscript. Katrin Hediger recruited all participants and collected all of the data. Ulrike Rimmele and Katrin Hediger analyzed the data. Markus Heinrichs supported the whole study.

23 Faces provide strong social cues that are almost automatically detected in visual scenery, and faces are known to yield enhanced activity more than other stimuli, like houses, or inanimate objects. This neural network includes areas in the ventral stream of the fusiform gyrus (fusiform face area) and occipital faces area (OFA) that are thought to process invariant aspects of faces contributing to face perception (see also our study by Lobmaier and colleagues that is not discussed in this cumulative habilitation (Lobmaier, Klaver, Loenneker, Martin, & Mast, 2008)), as well as in the dorsal stream (posterior superior temporal sulcus, pSTS) that process variable aspects of faces, like eye gaze and biological motion (see also Lichtensteiger et al. 2008 in this cumulative habilitation discussing the development of the pSTS) and amygdala that processes emotional aspects of faces (Haxby, Hoffman, & Gobbini, 2000; Vuilleumier & Pourtois, 2007).

24 The results do not directly support the exclusive contribution of the amygdala in memory. Previous studies showed that lesions in the amygdala disrupt emotional memory. However, some studies suggested an involvement of the amygdala in emotional judgments, suggesting that the amygdala supports a more general function than memory (Gabrieli, 1998).
On top-down control over neural priming

Two articles pursue the question what kind of neural mechanisms underlie top-down processing of primes. The eleventh article uses a repetition priming paradigm in which words are superimposed with pictures during encoding and words or picture names are repeated that were previously attended or ignored as words or pictures. The twelfth article uses primes that provide fully predictive information about an upcoming probe. I call this advance information cues. Subjects match cues information with memory to facilitate visual recognition of the upcoming probe.

The eleventh article investigates neural repetition priming of words in dependence of selective attention, stimulus type and semantic congruency during study.

Word repetitions lead to response facilitation (“priming”) and reduced neural responses in the brain and are a powerful tool to investigate verbal representations (Henson, 2003). Priming is a form of memory that is given under implicit memory instructions and led to the decomposition of word processing into a perceptual, word identification, and conceptual level of processing (Roediger & McDermott, 2003). This article investigates if these levels of word processing can be modulated by top-down processing. Literature is ambiguous on this issue. On the one hand, word repetition priming was found to occur without conscious awareness of the lexical information (Dehaene et al., 2001). On the other hand, when attention is directed to simultaneous presented pictures, word information may not interfere with picture categorization (Glaser & Düngelhoff, 1984) and words may not leave a memory trace (Rees, Russell, Frith, & Driver, 1999). To test whether word repetition priming can be modulated by top-down processing I used a variation of the Stroop paradigm, in which words and pictures are superimposed during two study phases and subjects were requested to make a natural/man-made

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25 By contrast with declarative memory in the previously described studies or cueing studies with visual advance information cues as discussed next (Klaver et al., 2004), priming is often thought not to contribute to declarative memory formation (Donaldson et al., 2001). Recent studies, including those in this cumulative habilitation, showed that neural decrease accompanied with priming may impair subsequent memory formation (Wagner, Maril, & Schacter, 2000) or positively contribute to memory formation (Turk-Browne et al., 2006). In explicit recognition tasks the same neural deactivation may contribute to recognition memory by a familiarity signal (Brown & Aggleton, 2001; Henson et al., 2003; Weis, Klaver et al., 2004).

26 In the typical Stroop interference effect color naming is affected by the congruency of the word information with the color information. In the reversed Stroop effect reading the word is not affected by the congruency of color information with the word information (Glaser & Düngelhoff, 1984; Stroop, 1935). Similarly, picture naming may be affected by the congruency of a simultaneously presented word, while congruency of picture information with a word does not affect word reading. In the categorization task this pattern is reversed. Here, word categorization is affected by the congruency of a simultaneously presented picture, while picture categorization is not affected by the congruency of a simultaneously presented word (Glaser & Düngelhoff, 1984).

27 The Stroop paradigm depicts attentional conflict processing, in which two types of information compete for a response (Roelof, 2003). The paradigm is often used in neuropsychology to test if patients can effectively select the preferential response and suppress the irrelevant information.
semantic categorization judgment for either words or pictures. The words and pictures could be either semantically compatible or incompatible\(^{28}\). During test, the words were repeated that were previously attended or ignored. Additionally, picture names were presented that were previously attended or ignored as pictures. Novel words were intermixed for comparison with the repeated stimuli. Behaviorally larger priming was found for words than for pictures, and only attended words yield significant priming. This finding is in line with our prediction that directing attention away from the word information reduced word processing, and that directing attention away from pictures does not affect picture processing (Glaser & Düngelhoff, 1984)\(^{29}\). Several questions were addressed for the brain imaging data. First, language processing areas were expected to reveal reduced neural repetition suppression\(^{30}\) when attention was directed away from the words during study. Imaging results showed reduced neural repetition priming within the visual word form processing related left fusiform gyrus and semantic processing related left inferior frontal cortex for ignored words during study. This finding extends spatial attention studies on neural priming for objects (Eger, Henson, Driver, & Dolan, 2004). The second question was if neural priming is generally absent by a semantic decision to pictures (Glaser, 1992). We found no support for this hypothesis. First, neural priming for previously ignored words was not significant, but semantic compatibility enhanced neural repetition suppression during presentation of a semi-\(^{31}\)cantly incompatible picture in the anterior inferior prefrontal cortex. Secondly, picture names yield reduced neural priming when they were presented with semantically incompatible ignored words compared to compatible ignored words. Thus, both types of evidence indicate that ignored words induce neural priming at a semantic level, even when they are not inducing behavioral priming\(^{32}\). A third question was whether cross-modal neural priming could be found and if this was sensitive to attention. Evidence was found for cross-modal neural priming, particularly in the left fusiform gyrus. Here, repeated picture names yielded neural repetition suppression similar to repeated words\(^{33}\). By contrast, left anterior

\(^{28}\) In compatible conditions words and pictures were both man-made or both natural. In incompatible conditions study words and pictures belonged to different response categories.

\(^{29}\) In compatible conditions study words and pictures were both man-made or both natural. In incompatible conditions study words and pictures belonged to different response categories.

\(^{30}\) In compatible conditions study words and pictures were both man-made or both natural. In incompatible conditions study words and pictures belonged to different response categories.

\(^{31}\) Neural repetition suppression is the common neural correlate of repetition priming, in which novel stimuli induce a larger neural response than repeated stimuli (Buckner et al., 1998), see also Weis et al. 2004 in this cumulative habilitation. It was argued that neural repetition suppression reflects tuning of neural responses leading to enhanced efficacy of stimulus processing (Grill-Spector, Henson, & Martin, 2006). The behavioral correlate of repetition priming, however, may be limited to restricted areas within the left frontal cortex (Wig, Grafton, Demos, & Kelley, 2005).

\(^{32}\) When incompatible pictures were presented, the ignored words required a different response during study and repetition. Dobbins and colleagues reported that response switches reduced neural priming. Hence, the response switch cannot explain our findings (Dobbins, Schnyer, Verfaellie, & Schacter, 2004).

\(^{33}\) This interpretation contrasts with Rees and colleagues who showed that words are not processed when attention is directed to pictures, but their task was more demanding for the pictures (Rees et al., 1999).

\(^{34}\) Repetition suppression for picture names was not significantly different from repeated words, indicating that cross-modal priming was similarly strong as repetition priming in the left fusiform gyrus. These findings support the criticism on the unique role of the left fusiform gyrus in visual word form processing.
inferior frontal cortex (LIPFC) showed an interaction between attention and stimulus type, indicating selective neural priming for previously attended words more than for the other stimuli. Thus, cross-modal neural priming seems to differ between brain areas in dependence of attention, where only the semantic processing related area LIPFC showed effects of perceptual priming. The fourth question was whether semantic compatibility affects neural repetition priming and cross-modal priming. We found evidence that semantic compatibility during study affects neural repetition effects for word-word and picture-word repetitions in a similar way in some areas. For example, a main effect of semantic compatibility was found in the lateral extrastriate cortex. Other areas showed an interaction between attention and semantic compatibility, for example in the left fusiform gyrus and frontal cortex. The anterior LIPFC yielded similar increase in neural priming for ignored stimuli when they were combined with semantically incompatible attended stimuli. The left fusiform gyrus conveyed reduced neural priming for previously attended stimuli when they were combined with incompatible stimuli during study. Neural priming for previously ignored stimuli was smaller and not sensitive to the compatibility between attended and ignored stimuli. Thus, common representations between words and pictures underwent similar top-down modulations in language related areas. Other areas showed a different neural repetition suppression effects for words and picture names depending on semantic compatibility. We found strong effects of semantic interference on neural priming in bilateral middle occipital gyrus (lateral occipital complex), particularly when incompatible attended pictures during study were repeated as picture names. These findings support the role of semantic interference in the top-down control of priming. Possibly, semantic processing of words may intervene with semantic processing of pictures. Taken together, neural repetition priming of words is sensitive to top-down modulation at different levels of and emphasize a role of this area in attention dependent conceptual word processing (Price & Devlin, 2003). Our results are inconsistent with some specialization accounts of the left fusiform area, which state that this area supports mere visual word processing or even pre-lexical word processing (Dehaene, Le Clec, Poline, Le Bihan, & Cohen, 2002).

The paper did not discuss that these areas showed a general neural increase for all types of stimuli. The neural enhancement was even stronger for stimuli that were previously incompatible with the superimposed words or pictures. One might argue that these areas were involved in reactivation of repeated material, which may be more pronounced when the stimulus was semantically incompatible. One might relate this effect to negative priming. Previous studies, however, reported negative priming effects in retrieval related areas such as the right frontal cortex and parahippocampal gyrus (Egner & Hirsch, 2005; Gazzaley, Cooney, McEvoy, Knight, & D’Esposito, 2005). More consistent with our findings are reports of lingual repetition enhancement for both repeated ignored and attended pictures, where the studied pictures were superimposed with different pictures (Vuilleumier, Schwartz, Duhoux, Dolan, & Driver, 2005). Yet, in contrast to that study we found no difference between attended and ignored stimuli. We found a difference between compatible and incompatible stimuli during study, in which incompatible stimuli induced a larger enhancement than compatible stimuli.

The finding that repeated picture names induced neural enhancement, particularly when they were incompatible and attended during study suggests that object information is retrieved during repetition in the case of a semantic conflict during study. This interpretation is in line with the negative priming account (Fox, 1995; Tipper & Driver, 1988; Vuilleumier et al., 2005) and reinstatement hypothesis (Nyberg et al., 2000). Surprising, however, is that Weis and colleagues (2004, in this cumulative habilitation) found neural repetition suppression effects in these areas that were not related to successful recollection of picture information.
processing, even though semantic processing occurs. Furthermore, neural repetition priming is
dominated by conceptual priming, common to words and pictures, whereas perceptual priming
only occurred in a semantic processing related area.

My contribution to the article was the development of the idea, designing the experiment and
stimuli. I mainly analyzed and interpreted the data and wrote the manuscript. Malte Schnaidt
recruited all participants and collected all of the data and helped with the data analysis. Jürgen
Fell and Guillén Fernández helped with writing the manuscript and statistical analysis. Jürgen
Ruhlmann provided access to the MR scanner facilities. Christian Elger was head of the
department.

The twelfth article investigates characteristics of neural networks during the use of visual
advance information.

Visual advance information is a type of prime that is given under explicit memory instructions. These cues can facilitate behavior, and reduce stimulus/response uncertainty. It is, however,
unclear if this facilitation is due to changing parameters at the domain in which the cue is given
(Rosenbaum, 1980), or in a more general domain (Goodman & Kelso, 1980). Cueing studies
like priming or visual attention tasks have provided contradictory evidence in the visual domain.
Visual priming is usually not given under explicit memory instructions, but has been shown to
decrease neural activity in higher-order processing areas within the cued domain (Buckner et al.,
1998). Visual advance information tasks have not been previously documented using functional
imaging. One of the main aims for the study was to identify areas that are activated by means of
advance information processes that were assumed to occur at different stages in time that are
only a few hundred milliseconds apart (Laarni & Häkkinen, 1994). The main challenge was to
use functional MRI that allowed for a high spatial resolution of neural activation, but was low in
temporal resolution due to the slow hemodynamic response. I hypothesized that domain

36 Visual advance information contrasts with usual priming tasks in the task instruction, in which cues are
processes explicitly (visual advance information) or implicitly (priming). Priming is usually classified
under procedural memory, while visual advance information is not listed in usual memory theories. Both
types of cues, however, result in similar response facilitation. Both types of cues can be given in short-
term memory conditions or long-term memory conditions, although usually visual advance information is
given in short-term memory tasks.

37 The idea for the study design was inspired by ERP and mental chronometry experiments designed by
Dick Smid at the time when I was in Magdeburg for my PhD thesis. The design specifically builds upon
the unpublished MD doctoral thesis of Susanne Köhler. In that study ERP data were collected to
investigate visual and motor processing related potentials in dependence of visual advance information.
The experiment used a go-no-go force choice paradigm, in which a response had to be made to a
multidimensional object with certain shape and color. Prior to each stimulus a cue was presented that
provided advance information of the shape or color of the probe. The cue could also represent a neutral
feature. The color cue (“red”/ “blue”) was identical with the color of the probe, thus providing full
advance information of the probe. The shape cue had the same global shape features as the probe (“two
vertical bars”/ “one vertical bar”). Local shape features of the probe, however, were not predicted by the
cue, so that the subjects always needed to differentiate targets and non-target probes on the basis of these
specific modulation by visual advance information would be mediated by occipital and temporal areas in the ventral stream, while the domain general processes should be mediated by areas outside the occipital cortex and visual ventral stream. To investigate this hypothesis, event-related fMRI was applied while cues (visual advance information) and probes were presented under a go/no-go task instruction. The probes were multidimensional stimuli with a color (“red”/“green”) and motion direction (“up”/“down”). The imperative target stimulus was a red stimulus moving upwards and the other three conjunction possibilities were nontargets assigned to a no-go response. Three types of cues were given. A full advance information cue (FAI, “arrow pointing downward”) predicted full motion direction of the probe and reduced response probability to 0%. Partial advance information (PAI) cue (PAI, “arrow pointing upward”) increased the target probability to 50%, because subjects needed to discriminate only for the color. A neutral cue (NAI, “uninformative picture”) provided no advance information over the motion direction and retained response probability at 25%. The temporal lag (stimulus onset asynchrony, SOA) between cue and probe was varied (150, 450 and 750 ms) to be able to distinguish between conditions in which the cues could and could not be used. Behavioral results showed that subjects facilitated their response decision by advance information more than after neutral cues when SOA between cue and probe was 450 or 750 ms. At 150 ms a smaller response facilitation was detected. Increasing SOA enhanced neural activity in visual ventral stream and occipital cortex, independently of advance information or response. This result probably reflects general preparation mechanisms in the visual system with augmenting available time. The finding that cue information did not affect ventral activity is not in line with local shape features. Local shapes were a connecting diagonals for the bars with different angles (“/”/“\”), or two horizontal bars crossing the vertical at different heights (“\=”/“\=”). The results of the study indicated that processing of the probe selectively responded to the cue information and showed feature specific neural decrease after cue with a relevant color or shape feature. Furthermore, event-related potentials also indicated the occurrence of central processes. For example, a slow wave (current negative variation, CNV) occurred in advance to the probe which might reflect central preparation processes. In addition, ERPs indicating selective motor preparation (lateralized readiness potential) supported the idea that certain motor preparation processes were selectively shortened by the visual cues. Together these results suggested that cues both affected selective visual processes of the probe, visuomotor integration and motor preparation.

38 I chose these features because motion processing is known to be mediated by areas in the dorsal occipital cortex that could be more easily distinguished from the color processing areas (Van Essen & Drury, 1997), see also Klaver et al 2008 in this cumulative habilitation for motion sensitive processing.

39 This way I could circumvent disadvantages of the fMRI technique that the slow hemodynamic properties of fMRI would not be able to differentiate processes that were only a few hundred milliseconds apart. I assumed that the cue itself would not be differentially processes depending on the stimulus that followed the cue, so that all hemodynamic responses distinguishing trials with different SOAs could be primarily dedicated to the processes that followed the cue or were related to the processing of the probe. Recent studies have, however, indicated that the general linear model that is used to model neural activity of hemodynamic responses may not appropriate when two neural processes are initiated in such short intervals. Short repetitions may induce interfering or non-linear effects of the hemodynamic response, for which SPM made a Voltera kernel available. I therefore cannot completely ignore that the findings may be hampered by non-linear effects in the hemodynamic response.
priming studies that show neural activation reduction after cues\textsuperscript{40}. Outside the ventral stream, neural activity depended on cue and probe information and on SOA, indicating that activity increased with available time and information. This finding is in line with visual search paradigms\textsuperscript{41}, and supports the hypothesis that nonspatial cues do not influence the fast processes of stimulus identification, but rather the processes that follow perceptual identification, such as slow attention based search and response preparation processes (Yantis, 2000). Specifically, areas in the motor and pre-motor cortex as well as parietal lobule showed enhanced neural activity after partial advance information more than after neutral cues. Nontarget probes after full advance information reduced activation more than after neutral cues in bilateral parietal lobule, inferior frontal cortex, motor areas and SMA. The absence of advance information (after a neutral cue) seemed to induce greater stimulus/response uncertainty, as indicated by the enhanced neural activity in bilateral parietal cortex and by the reduced accuracy (particularly when an irrelevant motion direction was combined with a relevant color). Two hypotheses were tested next. The response preparation hypothesis predicts more activity with higher likeliness of a response (PAI more than NAI more than FAI). The perceptual processing hypothesis predicts enhanced activity with less advance information about the probe, since (NAI more than PAI more than FAI). There was no area showing more activity for NAI as compared with PAI, thus rejecting the perceptual processing hypothesis. Evidence for the response hypothesis was found. There was a stepwise increase in activity in response related areas as well as in right inferior parietal lobule in dependence of advance information and SOA, with enhanced activity if response probability and time available to process a cue was higher. The left inferior parietal lobule was sensitive to advance information independent of the probe features. Taken together I found evidence that advance information processing is associated with visuomotor preparation processing, rather than with domain specific processing. This emphasizes the importance of cue processing on action and visuomotor integration, rather than perception\textsuperscript{42}. The data are not in line with priming studies which showed reduced neural activity after cue presentation.

\textsuperscript{40} The findings are also not in line with an unpublished study by Köhler and colleagues in which ERPs responding selectively to relevant features were reduced after presentation of a cue with that feature. An explanation for this controversial finding may be that ERPs are more sensitive to differentiate cue and probe specific processing by their temporal dynamics. For example a cue with relevant advance information may enhance processing of the cued feature, while the probe itself may yield reduced neural responses. In the functional MRI results cue and probe processing may not be differentiated so that enhanced processing upon a relevant cue may be covered by neural reduction when a probe was presented.

\textsuperscript{41} Usually, these target objects are conjunctions of features (color, shape, etc.) within an array of objects with different combinations of object features. Such object detection demands slow visual search processes (Treisman & Gelade, 1980). These studies showed that the perceptual quality of an upcoming event was not influenced by cues facilitating the search for an object (Moore & Egeth, 1998).

\textsuperscript{42} Memory studies reported similar areas during recollection more than during mere familiarity (Henson et al., 2005). In those studies, the left parietal activation was interpreted to support restoring information from memory. Our cueing findings are in line with this alternative hypothesis, which suggests that the left parietal lobule restores cue information in memory after cue identification, which then provides the basis for a response.
Furthermore, providing neutral cues may enhance readiness to give a response, but reduce processing of the feature for which otherwise a cue would be expected.

My contribution to the article was the idea for the study, the design of the stimuli and experiment. I recruited all participants and collected all of the data. I analyzed and interpreted the data and wrote the manuscript. Jürgen Fell helped with writing the manuscript. Susanne Weis provided support on the data analysis. Armin de Greiff introduced me in the scanning procedure and data analysis techniques. Jürgen Reul and Jürgen Ruhlmann offered access to the MR scanner. Guillén Fernández was my employer and helped writing the manuscript. Christian Elger was head of the department.

On the features and functions of spatial working memory

Article thirteen and fourteen are based upon the assumption that spatial working memory conveys a parietal-frontal neural network, and that the parietal areas are part of the dorsal stream. The articles investigate how spatial working memory is organized and if spatial working memory contributes the development of long term representations of numbers.

The thirteenth article introduces a novel diagnostic tool for spatial working memory.

This study provided the background and motivation to support the next study on neural correlates of spatial working memory in children with developmental dyscalculia. The study also taps upon mechanisms that differentiate storage and manipulation processing in working memory, and separates working memory from declarative memory functions43. Spatial working memory is known to engage a network including frontal and parietal areas. While parietal areas, being part of the dorsal stream were found to be sensitive to working memory load, the frontal areas are thought to both support retention and manipulation of information online (Courtney, Ungerleider, Keil, & Haxby, 1997)44. Unfortunately, classical diagnostic tests of working memory applied the digit and spatial spans forward and backward like the Corsi block tapping test for spatial working memory. Since working memory is mainly characterized by the ability to manipulate retained information several studies tried to add this to the diagnostic tests. In verbal working memory, working memory demands could by be effectively increased by

43 Classic memory theories of memory separated short-term memory from long-term memory storage and retrieval (Atkinson & Shiffrin, 1968). More recent accounts suggest that working memory capacity limits long term learning of novel material (Baddeley, Papagno, & Vallar, 1988). Recent studies argue that working memory and declarative memory are supported by common neural mechanisms. These studies imply an important role for the hippocampus in both types of memory (Axmacher, Schmitz, Weinreich, Elger, & Fell, 2008). The commonality, however, seems to be based on the storage mechanisms, rather than typical executive functions that support working memory operations.

44 Several studies found executive components, particularly selectivity processing, being a central feature of working memory to be associated with dorsolateral prefrontal cortex activation, whereas spatial
backward rehearsal. In spatial working memory this manipulation did not work. Other approaches like rotating the spatial configuration were proven unpractical, since this task was often too difficult for patients. To accommodate for this problem we adapted the Corsi block tapping test by requesting participants to memorize only every second block (and ignoring the blocks in between). We called this the block suppression test (BST). The results indicated that this manipulation enhanced processing load in spatial working memory. A similar requirement on the verbal counterpart, the digit suppression test (DST), induced similar processing load on verbal working memory capacity. The BST and DST correlated with working memory components, executive functions, but not with learning and memory. Results from a principal component analysis distinguished a verbal and nonverbal working memory component, as well as a verbal and nonverbal memory component. By testing additional neurological patients with miscellaneous pathology, we could prove that the test was suitable for clinical practice. The patients understood the task and showed no disproportional floor effect. The findings thus indicated that the test effectively manipulated executive aspects of working memory and that it is applicable as a diagnostic tool.

My contribution to the article was the development of the experimental design, supervision of the data analysis, interpretation of the data and writing the manuscript. Thomas Beblo required the diagnostic tool, programmed the experiment, and primarily wrote the manuscript. Cornelia Macek and Ina Brinkers recruited all participants and collected all of the data. They primarily analyzed the data. Wolfgang Hartje was head of the department.

The fourteenth article investigates neural networks in children with developmental dyscalculia related to spatial working memory.

We investigated neural development underlying spatial working memory in children with developmental dyscalculia. These children have selective deficits in calculation, but the cause of impairment is far from clear (Mix & Sandhofer, 2007). Some studies suggested developmental dyscalculia is caused by a single impairment of a basic “number sense” (Dehaene, Molko, Cohen, & Wilson, 2004). Other studies argued that a more general cognitive impairment may inflict developmental dyscalculia (von Aster & Shalev, 2007). Anatomically, children with developmental dyscalculia have reduced grey matter in the right parietal lobule as well as in several other areas (Rotzer et al., 2008). We hypothesized that these structural deficits may affect working memory, rather than only specific number processing deficit and scanned these working memory capacity is also associated with parietal activity (Bor & Owen, 2006; Todd & Marois, 2004).

45 A recent study, applying the test in patients with Alzheimer disease showed that the tool could be effective in early diagnosis of the disease (Toepper, Beblo, Thomas, & Driessen, 2008). Our next study on spatial working memory in children with dyscalculia applied this test (Rotzer and colleagues in this cumulative habilitation).
children while they performed a spatial working memory task. Outside the scanner we tested the children on general intelligence, calculation abilities, verbal and spatial working memory. The working memory tasks were the spatial Corsi block tapping task and verbal digit span task. We also used the Block Suppression Test of spatial working memory that adds an executive component to the storage in the Corsi test (see Beblo et al. 2004 in this cumulative habilitation). We found differences between participants on the calculation scale (ZAREKI-R) and all working memory tasks, but not on general intelligence. These findings are in line with previous studies who showed working memory deficits in this population (Camos, 2008). Differences in neural activity were found in the right intraparietal sulcus, as well as in the right inferior frontal gyrus and right insula. Neural activity in the right intraparietal sulcus correlated with both spatial working memory capacity and digit span forward. We found no correlation with the Block Suppression Test, suggesting that intraparietal sulcus is involved in working memory storage, but not manipulation of the stored information. Previous studies suggested that children with dyscalculia have impaired parietal functions (Price, Holloway, Rasanen, Vesterinen, & Ansari, 2007)\(^{46}\). Furthermore, our findings support the hypothesis that intact functioning of the right parietal lobule contributes to both spatial working memory and long term building of spatial number representations (von Aster & Shalev, 2007)\(^{47}\).

My contribution to the article was support for the development of the experimental design, supervision of the data analysis, interpretation of the data and writing the manuscript. Stephanie Rotzer had the main idea for the study. She recruited all participants and collected all of the data. She primarily programmed the experiment, analyzed the data and wrote the manuscript. Thomas Loenneker and Karin Kucian supported the study. Ernst Martin was head of the department and provided infrastructure to the study. Michael von Aster was official supervisor of Stephanie Rotzer.

On the development of the dorsal and ventral visual streams

Two articles follow the hypothesis that the visual system develops differently in the dorsal and ventral stream. We know from earlier studies that visual brain areas that are responsible for low order visual processing (e.g. the primary visual cortex) mature earlier than areas that are

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\(^{46}\) The right parietal cortex is part of the dorsal visual stream. However, these findings are also in line with the hypothesis that neural activity increases in this area depending on the amount of items that need to be stored in short term memory (Klaver, Smid, & Heinze, 1999; Todd & Marois, 2004; Vogel & Machizawa, 2004). The findings are also in line with studies showing a relation between neural activity and individual short term memory capacity (Todd & Marois, 2005).

\(^{47}\) These finding support the hypothesis that working memory supports building long term representations (Baddeley et al., 1988). Conventionally declarative memory and working memory are distinct forms of memory, as also indicated in Beblo et al. 2004 (in this cumulative habilitation) who reported functional independence. Recent studies, however, identified common neural correlates. Both memory operations seem to be supported by hippocampal functioning (Axmacher et al., 2008; Jensen & Lisman, 1996).
responsible for high-order visual processing. Yet, several studies suggested that cortical visual processing streams that are responsible for processing different properties of visual information (such as motion in the dorsal stream and shapes in the ventral stream), mature at different rates. One article tested and confirmed the hypothesis that higher order visual perception (structure-from-motion) in the dorsal stream processes are not fully mature in pre-school and school aged children. A second article investigated neural development of biological motion perception that is processed at the junction of the dorsal and ventral stream in adults.

The fifteenth article investigates typical maturation of neural networks related to high-order visual perception.

One of the main aims for the article was to dissociate visual development in the ventral and dorsal stream. The ventral stream is prone to process visual identity based on shapes, color and texture, while the dorsal stream is inclined to process motion, spatial relations and integrates visual information with motor processing (Milner & Goodale, 1995). Visual perception of shapes that are perceived by coherent motion thus relies on dorsal stream processing (Murray, Olshausen, & Woods, 2003). Based on theories of visual development we argued that higher visual constructive processing, as in shape-from-motion perception that depends on the dorsal stream is not fully developed at school aged children (Braddick, Atkinson, & Wattam-Bell, 2003). We tested five to six year-old children during passive visual perception task in which they perceived randomly moving point-light dots and coherently moving dots that formed 3D rotating objects (structure-from-motion). Static dots were presented as a control stimulus. Functional brain images of the children were compared with those of adults. Randomly moving dots induced similar brain activity in children and in adults, but region of interest analysis revealed maturational differences in motion sensitive area V3a that was more active for adults than for children. This suggested that even motion processing areas are not fully mature at age 6. Structure-from-motion additionally induced activity in parietal areas in adults, but not in children. These findings support the hypothesis that high order visual processing in the dorsal stream is not fully mature in six year-old children. However, children showed increased activity in the ventral stream and in other areas of the occipital cortex such as area V3a. We asserted that reduced maturation is substituted by increased neural activity in areas involved in feature specific perception, whereas adults engage higher order processing areas in the dorsal stream.

48 The ventral stream provides input for memory operations, whereas the parts of the inferior parietal lobule and precuneus are functionally connected the hippocampus (Vincent et al., 2006). These studies provide the basis for my current research on development of memory operations in the dorsal and ventral stream.

49 Note that these areas may not be purely visual as also suggested by Braddick and colleagues (Braddick et al., 2001). The local maxima of these effects are very close (less than 1 cm) to our memory related effects, such as memory retrieval in the old/new effects (e.g. Fliessbach et al. 2006, Weis et al. 2004 in this cumulative habilitation) and advance information processing (Klaver et al. 2004 in this cumulative habilitation).
stream. Yet, these interpretation needs to be taken with caution, since the task had very low cognition demands50.

My contribution to the article was the complete analysis of the data, the interpretation of the results and writing of the manuscript. Janine Lichtensteiger helped developing the paradigm, recruited all participants and collected all of the data. Thomas Dietrich helped setting up the experiment. Thomas Loenneker provided technical support for the whole study. Ernst Martin was head of the department, initiated the project and provided infrastructure for the study.

The sixteenth article investigates typical maturation of neural networks related to biological motion perception.

The article investigated the neural development underlying visual processing of biological motion. In contrast to the first study this article focuses on a type of visual stimulus that is evolutionary important for human beings as a social being. Our brains are programmed to detect coherent motion and derive contours of shapes and body, so that children can already detect human motion based on point-light moving dots (Pavlova, Krageloh-Mann, Sokolov, & Birbaumer, 2001)51. In contrast to the first study, the focus was not on dorsal stream areas in the parietal lobule, but on an area that was assumed to be a pivotal point of the dorsal and ventral stream, namely the posterior part of the superior temporal sulcus (pSTS). This area receives input from motion area in the middle temporal cortex (hMT+) and from areas in the parietal lobule (Giese, 2004)52. Children and adults were presented with point-light moving dots representing a moving person or scrambled motion. Both stimuli were also masked with scrambled motion to assert increased difficulty and participants were required to detect a “man in the snowstorm” by button-press. As expected we found activity for biological motion more than scrambled motion (independent of snow) in the pSTS of adults (Vaina, Solomon, Chowdhury, Sinha, & Belliveau, 2001). Children showed no such activity, which is in line with age related differences found in 7-10 year-old children (Carter & Pelphrey, 2006). By contrast children yielded activity in the right fusiform gyrus, probably the fusiform face area, more than adults. To account for performance differences between adults and children, who were less accurate, we separated both groups in good and poor performers. The analysis revealed that pSTS activity was age but not performance dependent, whereas fusiform activity in response to biological motion occurred only in poor performing children. These findings confirmed our

50 If we consider the results of Lichtensteiger and colleagues (discussed below), one might hypothesize that particularly children with lower performance levels may be responsible for the increase in occipital brain activity (Lichtensteiger et al., 2008).

51 Adults are even able to detect subtle motion differences that identify specific individuals, or differences between man and women, and more difficult masked motion by scrambled motion (Freire, Lewis, Maurer, & Blake, 2006).
previous findings (Klaver et al., 2008) that functional segregation in dorsal stream is not mature at age 6. In addition to the previous study we could for the first time allocate ventral stream activity to performance differences in children.

My contribution to the article was the development of the experimental design and stimuli, supervision of the data analysis and interpretation, and writing the manuscript. Janine Lichtensteiger and Ernst Martin had the main idea of the study. Janine Lichtensteiger recruited all participants and collected all of the data. She primarily analyzed the data and wrote the manuscript. Kerstin Bucher helped setting up the design and supported the data analysis. Thomas Loenneker helped programming the stimuli. Ernst Martin was head of the department and provided infrastructure for the study.

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52 The same area is also dedicated to process changeable aspects in face recognition such as eye gaze (Haxby et al., 2000).


Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling

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In humans, distinct processes within the hippocampus and rhinal cortex support declarative memory formation. But do these medial temporal lobe (MTL) substructures directly cooperate in encoding new memories? Phase synchronization of gamma-band electroencephalogram (EEG) oscillations (around 40 Hz) is a general mechanism of transiently connecting neural assemblies. We recorded depth-EEG from within the MTL of epilepsy patients performing a memorization task. Successful as opposed to unsuccessful memory formation was accompanied by an initial elevation of rhinal–hippocampal gamma synchronization followed by a later desynchronization, suggesting that effective declarative memory formation is accompanied by a direct and temporarily limited cooperation between both MTL substructures.

Results

Lesions of certain MTL substructures, most notably of the hippocampus and the parahippocampal region, disturb the declarative memory system, the system that makes memory accessible to conscious recollection. Neuroimaging studies suggest that both these MTL substructures participate in memory formation. A process in the rhinal cortex, which consists of the histologically distinct entorhinal and perirhinal cortices and is part of the parahippocampal region, precedes a hippocampal process. Anatomically, the entorhinal and rhinal cortices provide most of the neocortical input to the entorhinal cortex, which in turn provides the predominant cortical input to the hippocampus via the perforant path. However, there is no stringent evidence for a direct interaction between rhinal cortex and hippocampus during declarative memory formation in humans. Moreover, the exact time when such a presumed interaction might take place is unknown.

Phase synchronization of gamma oscillations (electrical brain activity of around 40 Hz) is a general mechanism of transiently connecting neural assemblies. This mechanism provides an explanation for the flexibility and specificity of functional associations between brain modules. Evidence has accumulated that phase coupling of induced (that is, not stimulus-locked) gamma activity is essential in object representation. Different object features processed by distinct neural assemblies are bound together to one coherent percept by syn-association of cortical modules via induced gamma-band coupling. From this perspective, the evoked (stimulus-locked) gamma response seems not to be involved in assembly coupling, and its functional role is still unclear. Thus, we analyzed induced gamma synchronization of depth-EEG activity, which was recorded simultaneously from rhinal and hippocampal electrodes in epilepsy patients during a word memorization task. We found successful declarative memory formation to be associated with a transient reduction of gamma power in rhinal and hippocampal recordings together with an initial enhancement of gamma synchronization between both MTL substructures, followed by a later desynchronization.

We took EEG recordings from nine patients with unilateral temporal lobe epilepsy while they performed a single-trial word-list learning protocol with a free recall test after a distraction task. We implanted multicontact depth electrodes bilaterally along the longitudinal axis of each MTL during presurgical evaluation because the zone of seizure onset could not be determined unequivocally by noninvasive investigations. Depth electrodes had a cylindrical surface area of 10 mm². Sensitivity is maximal for field potentials generated within the adjacent brain tissue and, in general, decays with the inverse square of the distance. For example, compared to adjacent brain tissue 0.1 mm away from the recording electrode (0.1 mm is the order of magnitude of the thickness of hippocampal layers), a source 1 cm away only contributes 0.01% to the recorded signal. The placement of electrode contacts within the hippocampus and the anterior parahippocampal gyrus, which is covered by rhinal cortex, were ascertained by magnetic resonance images in each patient (Fig. 1). Only EEG recordings from the MTL contralateral to the zone of seizure origin were analyzed to reduce poorly controllable effects introduced by the epileptic process. Moreover, none of the MTLs investigated here showed any pathology, such as hippocampal atrophy, on clinical MR scans performed during the presurgical work-up. Within these non-epileptic MTLs, we analyzed rhinal and hippocampal recordings with the best signal-to-
noise ratio, assessed by amplitudes of event-related potentials (ERPs) recorded during the same task. The average distance between the selected rhinal and hippocampal locations was 1.6 ± 0.25 cm (mean ± s.e.m.; range, 0.8–2.6 cm).

Each patient participated in 20 study test blocks plus 2 training blocks immediately before the experiment, each containing 12 semantically unrelated German nouns. Patients were instructed to memorize each word presented sequentially on a computer monitor. To prevent ongoing rehearsal, a distraction task was conducted after each block. Thereafter, patients were asked to recall freely the previously displayed words in any order (mean recall rate, 29.7%; range, 20.0–54.6%).

In subjects performing a similar task, was poorer in the patients investigated here than in healthy controls. ERP recordings during the same task showed a delay of the early enhancement in gamma synchronization, a second increase was detected from 500 to 600 ms (main effect of memory, 100–200 ms, and unrecalled words starting within the first 100 ms after stimulus onset (Fig. 2), main effect of time, \( F_{14,1008} = 3.47, p < 0.001, \epsilon = 0.60 \) and interaction of memory × time, \( F_{14,1008} = 3.20, p < 0.01, \epsilon = 0.50 \). Average gamma synchronization between rhinal and hippocampal recordings was increased by up to 16% for subsequently recalled as opposed to subsequently forgotten words. Finally, synchronization and power values were averaged for consecutive 100-ms time windows from 100 ms to 1500 ms relative to stimulus onset.

The time course of phase synchronization between rhinal cortex and hippocampus averaged over all frequencies between 32 and 48 Hz shows a dissociation between subsequently recalled and unrecalled words starting within the first 100 ms after stimulus onset (Fig. 2). Phase synchronization values between electrode contacts within the rhinal cortex and the hippocampus were calculated from the individual wavelet-transformed EEG segments. The higher the synchronization value, the more constant is the phase difference between the two electrodes over all trials. Additionally, averaged power values were determined separately for rhinal and hippocampal recordings for subsequently recalled and unrecalled words. Finally, synchronization and power values were averaged for consecutive 100-ms time windows from 100 ms to 1500 ms relative to stimulus onset.

The early synchronization effect is most pronounced in the frequency range from 36 to 40 Hz and for these frequencies reach 30% (Fig. 3). The second synchronization increase (500–600 ms) and the later desynchronization are prominent in the frequency range from 32 Hz to 40 Hz. Phase lag distributions for both conditions (subsequently recalled and unrecalled words) have a Gaussian shape and are centered around zero (Fig. 4). The difference in synchronization for successful and unsuccessful encoding thus arises from a narrowing of the phase lag distribution caused by an increased amount of phase differences close to zero.
zero. This finding indicates that rhinal and hippocampal neurons oscillate together in a more synchronous rhythm when encoding leads to successful memory formation.

To explore the possibility that the subsequent memory effects identified here could be related to general, ubiquitous effects found throughout the brain, we examined the synchronization between rhinal cortex and a temporolateral location (gyrus temporalis superior). For identification of the zone of seizure onset, EEG recordings were made from this location with subdural strip electrodes in seven of the nine patients. The two remaining patients had no electrodes outside the MTL. The analysis of rhinal-temporal synchronization values revealed neither a memory effect \( (F_{1,54} = 1.20, p = 0.28) \), nor a memory \( \times \) time interaction \( (F_{1,72} = 1.15, p = 0.33, \varepsilon = 0.63) \). Moreover, none of the individual time windows showed a statistically significant memory effect \( (\text{each } p > 0.05) \).

Absolute gamma power values at hippocampal sites were about threefold larger than values from rhinal contacts (average over all frequencies, time windows and conditions, for hippocampus, \( 39.6 \pm 39.8 \mu V^2 \); for rhinal cortex, \( 14.2 \pm 12.2 \mu V^2 \); paired two-tailed t-tests for each individual frequency, condition and time window; all \( p < 0.05, T_B > 2.35 \)). The time course of gamma power at rhinal cortex and hippocampus (Fig. 5) dissociated significantly between conditions (ANOVA effects, for rhinal cortex, time \( (F_{14,1008} = 16.4, p < 10^{-12}, \varepsilon = 0.41) \) and memory \( \times \) time \( (F_{14,1008} = 4.64, p < 0.0001, \varepsilon = 0.54) \); for hippocampus, time \( (F_{14,1008} = 4.68, p < 0.0001, \varepsilon = 0.62) \) and memory \( \times \) time \( (F_{14,1008} = 6.37, p < 10^{-3}, \varepsilon = 0.59) \)). In the rhinal cortex, a gamma peak was observed for both conditions at around 100 ms. However, gamma power was reduced for subsequently recalled compared to unrecalled words (significant reductions from 600 to 800 ms and 1300 to 1400 ms). Similarly, in hippocampal recordings, gamma power was significantly diminished in EEG segments related to successful as opposed to unsuccessful memory formation. This difference was detected between 100 and 400 ms after stimulus onset.

Finally, we compared absolute synchronization and power values for subsequently recalled and unrecalled words during the prestimulus baseline window (-100 to 0 ms) to examine whether EEG changes before word presentation are responsible for our findings, which would have suggested a slowly modulated encoding state rather than transient processes. However, we did not find significant baseline differences between subsequently recalled and unrecalled trials for either rhinal–hippocampal synchronization values \( (F_{1,72} = 0.28, p = 0.60) \), or for gamma power from rhinal \( (F_{1,72} = 1.85, p = 0.18) \) or hippocampal \( (F_{1,72} = 1.05, p = 0.31) \) recordings.

**Discussion**

Our results show EEG activity in the gamma frequency range in field recordings from within the human MTL during a memory task. A previous study revealed a generally higher gamma power in parahippocampal than neocortical recordings in humans. We extend this knowledge by showing that gamma power in hippocampal recordings is even threefold higher than in the parahippocampal region, suggesting that high-frequency oscillations of around 40 Hz have a prominent involvement in medial temporal and especially hippocampal information processing.

Intracranial EEG recordings allow the reliable separation of synchronization and power effects. In view of the anatomical proximity of the inspected areas (mean distance, 1.6 cm), such a separation would be impossible with surface EEG recordings. Previous ERP data indicate that there is no detectable correlation between EEG recorded from within the
hippocampus and the rhinal cortex, even with electrode distances of less than 1 cm. The large anterior medial temporal lobe N400 component, for instance, which reflects word processing and can be recorded with an amplitude of up to 70 µV from rhinal cortex, is usually not observable in recordings from within the hippocampus\textsuperscript{11,27}. On the other hand, hippocampal activity is shielded toward the outside by the radial cylindrical arrangement of hippocampal pyramidal layers\textsuperscript{33}. Thus, it is highly unlikely that our results are biased by correlated EEG recordings. We found successful memory formation to be accompanied by two factors: an early increase and a later decrease in gamma synchronization between rhinal and hippocampal recording sites, and a transient reduction of gamma power at both locations partly within the same time window.

The enhancement of gamma-band synchronization observed here between the rhinal cortex and the hippocampus occurs at zero-phase lag. Such a synchronization requires highly accurate timing of neural discharges within a time range of just a few milliseconds\textsuperscript{34}. By achieving this, gamma synchronization enables a precise functional association between specific brain regions over short as well as longer distances\textsuperscript{16,17}. Thus, gamma-band coupling between rhinal cortex and hippocampus is likely to establish a transient connection between both MTL structures initializing declarative memory formation.

The time course of modulation of gamma synchronization found here is consistent with reports of altered firing rates of single anterior rhinal neurons within 200 ms after visual object presentation\textsuperscript{35}. However, it remains unclear whether semantic information provided by each stimulus is already available during the initiation of rhinal–hippocampal coupling or not. If not, directed attention might, in a first step, allocate specific connections necessary for memory formation before actual information transfer takes place. Attention–driven enhancement of gamma-band phase synchronization has been shown in several studies\textsuperscript{36–38}. In principle, cortical regions like the prefrontal cortex and the superior temporal sulcus, which are anatomically connected with the MTL, could influence rhinal–hippocampal interaction. The early timing, however, suggests that the observed coupling might be initiated by a top-down process mediated directly by the thalamus\textsuperscript{39}. The later decrease in synchronization (1000–1100 ms) may occur following information transfer from the parahippocampal region to the hippocampus\textsuperscript{11} and terminate the communication between both structures. Such a functional decoupling has been found in a visual face perception task and has been termed active desynchronization\textsuperscript{21}.

The timing of rhinal–hippocampal coupling and decoupling fits well with the sequence of processes as monitored by ERPs recorded separately from the rhinal cortex and hippocampus during the same task\textsuperscript{11}. Rhinal ERPs in response to subsequently recalled words start to differ from ERPs in response to subsequently forgotten words about 300 ms after stimulus onset. This subsequent memory effect in the rhinal cortex is followed by a hippocampal effect some 200 ms later that lasts until about 2000 ms after stimulus onset. Assuming that rhinal–hippocampal information transfer occurs between the onset of the rhinal and the hippocampal ERP effects, the early beginning of gamma phase coupling revealed here would allow the preparation for and the actual transfer of information. The decoupling observed follows the end of the rhinal subsequent memory effect at about 900 ms after stimulus onset, the time point when information transfer to the hippocampus might be accomplished.

Fig. 5. Changes of EEG gamma power (%) averaged over all frequencies (32–48 Hz) relative to prestimulus baseline for subsequently recalled versus unrecalled words. Mean ± s.e.m. is plotted. The x-axis depicts the time with respect to stimulus onset (word presentation).
Gamma oscillations induced in the CA1 field of hippocampal slices within the first second following stimulation are associated with a prolonged elevation of excitatory postsynaptic potential, suggesting a crucial involvement in synaptic plasticity, the synaptic correlate of memory formation. These in vitro data and our findings underline the importance of medio temporal gamma activity in memory formation. A direct link linking these two sets of data, however, cannot be drawn, as we recorded macroscopic field potentials summing up hippocampal mass activity and were not able to distinguish oscillations generated specifically by distinct hippocampal subregions like the CA1 field.

Our analysis of macroscopic field potentials revealed that efficient medio temporal information processing, leading to successful memory formation, correlates with reduced gamma power at both recording sites. The transient reduction of gamma oscillations might be explained by the necessity to suppress noise-like ambient gamma activity unrelated to specific study items. One might speculate that in an event of unsuccessful encoding, ongoing background gamma activity interferes with item related activity and distorts the process of memory formation. Thus, reduced gamma power, as assessed here during successful item related activity and distorts the process of memory formation. A direct line linking these two sets of data, however, cannot be drawn, as we recorded macroscopic field potentials summing up hippocampal mass activity and were not able to distinguish oscillations generated specifically by distinct hippocampal subregions like the CA1 field.

EEG recording. Depth electrocorticograms were referenced to linked mastoids, bandpass-filtered (0.03 to 85 Hz, 6 dB/octave), and recorded with a sampling rate of 173 Hz (12-bit analog-digital conversion). To determine the anatomical positions of electrode contacts, MRI scans were acquired in sagittal and adjacent coronal planes, perpendicular to the longitudinal axis of the hippocampus. Electrode contacts were mapped by transferring their positions from M1R to standardized anatomical drawings (Figure 1). EEG trials and corresponding power spectra were visually inspected for artifacts in the gamma frequency range and 4.9% of all trials were excluded from analysis.

Measuring phase synchronization and power. EEG trials were filtered in the gamma frequency range from 32 Hz to 48 Hz (2-Hz steps) by wavelet transforms implementing Morlet wavelets of 7 cycles length. The filtered signals \( w_{jk}(t) \) (time window in each trial; \( k \), trial number) hereby result from the time convolution of original signals and the complex wavelet function. From the wavelet transformed signals \( w_{jk} \), the phases \( \phi_{jk} = \arctan(\Re(w_{jk})/\Im(w_{jk})) \) and the power values \( p_{jk} = |w_{jk}|^2 \) were extracted for each time point \( t \) of each trial \( k \). Power values were averaged separately for trials corresponding to subsequently recalled and unrecollected words. For each time point of each trial, phase differences \( \Delta \phi_{jk} \) between hippocampal and rhinal electrode contacts were determined. Phase synchronization values \( S_k \) were calculated based on the definition of circular variance, \( S_k = \frac{1}{N} \sum_{k=1}^{N} e^{i \Delta \phi_{jk}} \) where \( N \) is the number of trials; \( S_k \in [0,1] \).

Different numbers of trials for subsequently recalled and unrecollected words would cause a bias in the absolute values of the synchronization measure. Therefore, trial numbers were adjusted between conditions using randomized trial lists for the condition with the originally larger trial number. Finally, power and phase synchronization values were averaged for non-overlapping successive time windows of 100 ms duration from -100 to 1500 ms (16 windows in total).

Statistical analysis. Synchronization and power values were normalized with respect to prestimulus values (window 1) separately for each subject and each filter frequency. For statistical evaluation, we conducted three-way ANOVAs with time (15 windows) and memory (subsequently recalled versus unrecollected) as repeated measures, and frequency (9 levels) as independent variable. p-values were Bonferroni corrected for inhomogeneities of covariance when necessary. The notation of the F-values \( F_{(y,x)} \) with \( x \) being the model degrees of freedom, that is, the number of adjustable parameters in the model, and \( y \) being the residual degrees of freedom, that is, the number of degrees of freedom that are not taken up by the model. In a subsidiary analysis, each time window was tested separately by two-way ANOVAs. Effects for time windows with p-values less than 0.05/15 (Bonferroni correction) and for doublets of neighboring time windows each with a p-value less than 0.05/15 (Bonferroni correction) were regarded as statistically significant.

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Rhinal–hippocampal theta coherence during declarative memory formation: interaction with gamma synchronization?

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Keywords: EEG, hippocampus, medial temporal lobe, memory encoding, rhinal cortex

Abstract

The hippocampus and the rhinal cortex, two substructures of the medial temporal lobe, together play a crucial role in human declarative memory formation. To investigate in detail the mechanism connecting these two structures transiently during memory formation we recorded depth EEG in epilepsy patients from within the hippocampus and the rhinal cortex. During this recording, patients performed a single-trial word list-learning paradigm with a free recall memory test following a distraction task. Rhinal–hippocampal EEG coherence and spectral power at both locations in the time interval up to 2 s after onset of word presentation were analysed in the frequency range 1–19 Hz. Successful as opposed to unsuccessful memory formation was associated with a general rhinal–hippocampal coherence enhancement, but without alterations in spectral power. Coherence increases in the theta range were correlated with the previously reported memory-related changes in rhinal–hippocampal gamma phase synchronization. This correlation may suggest an interaction of the two mechanisms during declarative memory formation. While theta coherence might be associated with slowly modulated coupling related to an encoding state, rhinal–hippocampal gamma synchronization may be more closely related to actual memory processes by enabling fast coupling and decoupling of the two structures.

Introduction

The integrity of the medial temporal lobe (MTL) is essential for declarative memory, the ability to remember consciously past events and facts (Scoville & Milner, 1957). Neuroimaging studies have shown that the MTL participates in declarative memory formation, an operation transforming perceptual or internally generated representations into declarative memories (Brewer et al., 1998; Fernández et al., 1998, 1999b; Wagner et al., 1998; Otten et al., 2001; Strange et al., 2002). Memory formation is associated with the sequential activation of the rhinal cortex and the hippocampus, two substructures of the MTL (Fernández et al., 1999a, 2002a). Transient coupling of the two structures by phase synchronization of induced gamma activity accompanies this mnemonic operation (Fell et al., 2001). It has been asked (Wagner, 2001; Otten & Rugg, 2002) whether the same data show evidence for memory-related coherent theta activity that additionally might functionally bind the two MTL structures together.

A significant function of theta oscillations in declarative memory formation has been suggested by previous scalp EEG studies, showing an increase in theta power as well as inter- and intrahemispheric theta coherence in the case of successful word encoding (Klimesch et al., 1996, 1997; Weiss & Rappelsberger, 2000; Weiss et al., 2000; Mölle et al., 2002). Subdural recordings in epilepsy patients and magnetoencephalography (MEG) studies have, moreover, indicated that occurrence of theta activity is related to spatial learning and working memory tasks (Jensen & Tesche, 2002; Kahana et al., 1999; Tesche & Karhu, 2000; Caplan et al., 2001; Raghavachari et al., 2001). Experimental animal literature provides multiple lines of evidence connecting hippocampal theta activity with declarative memory (for review: Vertes & Kocsis, 1997; Berry & Seager, 2001; Kahana et al., 2001; Lisman & Otmakhova, 2001). However, human data on hippocampal theta during a declarative memory task have not been reported yet.

Thus, in a first step we investigated whether rhinal and hippocampal theta oscillations contribute to human declarative memory formation (theta hypothesis). We reanalysed recordings of intracranial EEG activity recorded directly from within the rhinal cortex and the hippocampus in epilepsy patients performing a word memorization task. The previous study on memory-related phase synchronization within the gamma band (Fell et al., 2001) was based on the same data set. Rhinal–hippocampal EEG coherence and spectral power at both locations were evaluated for six frequency bands between 1 and 19 Hz including theta and neighbouring frequency bands. EEG characteristics corresponding to subsequently remembered words were compared with subsequently not-remembered items.

A close interaction between MTL gamma and theta oscillations has been observed in rodents (Chrobak & Buzsáki, 1998a,b). It has been reported that the firing of hippocampal neurons during movement through place fields depends on the phase of the theta rhythm (O’Keefe & Recce, 1993; Skaggs et al., 1996). Based on these observations it has been proposed that the interaction between MTL gamma and theta rhythms plays an important role in coding declarative memories (Lisman & Idiart, 1995; Jensen et al., 1996; Jensen, 2001; Lisman & Otmakhova, 2001). To investigate this ‘theta–gamma hypothesis’, we evaluated in a second step correlations between memory-related coherence effects in the lower frequency range, as analysed here, and the previously reported changes in gamma synchronization (Fell et al., 2001).
Materials and methods

Patients and EEG recording

During presurgical evaluation, the EEG was recorded from nine patients (six women, three men; mean age 34.1 ± 8.3 years) with pharmacoresistant temporal lobe epilepsy, mean duration of illness 26.4 ± 9.1 years; same data as in Fell et al. (2001). Multicontact depth electrodes had been implanted stereotactically along the longitudinal axis of each MTL (Van Roost et al., 1998), because the zone of seizure onset could not be specified unequivocally by noninvasive investigations. In all nine patients a unilateral seizure origin within one MTL was diagnosed (six patients, right side; three patients, left side). Because of a technical artifact in the low frequency range, the EEG data from one patient were excluded from further analysis. Informed consent was obtained from all patients and the study was approved by the local institutional ethics committee.

Depth electroencephalograms were recorded, referred to linked mastoids, with a sampling rate of 173 Hz (12-bit analogue–digital conversion; bandpass filter 0.03–85 Hz). To reduce poorly controllable effects introduced by the epileptic process only EEG recordings from the MTL contralateral to the zone of seizure origin were analysed (Puce et al., 1989; Paller et al., 1992; Grunwald et al., 1995; Guillemin et al., 1995; Elger et al., 1997). Within these nonepileptic MTLs, recordings from one position within the rhinal cortex and one position within the hippocampus were analysed. Selection criterion for both positions was the best individual signal-to-noise ratio, assessed by amplitudes of event-related potentials (ERPs) recorded during the same task (Fernández et al., 1999a).

Electrode localization

The individual placement of electrode contacts within the hippocampus and the anterior parahippocampal gyrus, which is covered by rhinal cortex, was ascertained by magnetic resonance images. For this purpose MRI scans were acquired in sagittal, axial and coronal planes, adjusted to the longitudinal axis of the hippocampus (see also Fig. 1). MRI was performed on a 1.5-T scanner (Gyrosan ACS-II, Philips Medical Systems, Best, the Netherlands) using a standardized protocol: a T1-weighted echo sequence (repetition time 650 ms, echo time 16 ms, number of slices 19, slice thickness 5 mm, interslice gap 0.5 mm), an axial T2-weighted fast spin echo sequence (2876/120/ 21/5/1), and a coronal T2-weighted fast spin echo sequence (3719/120/ 29/2/0.3). Electrode contacts were mapped by transferring their positions from MRI to standardized anatomical drawings (van Roost et al., 1998). Only electrode contacts which could be localized unequivocally within rhinal cortex or hippocampus were selected for further analysis.

Paradigm

Patients performed a word list memorization paradigm with a free recall test during EEG recording. Each patient participated in 20 study test blocks, which consisted of a study, a distraction and a test phase. Twelve semantically unrelated German nouns were sequentially presented during each study phase in uppercase letters for a duration of 400 ms. Interstimulus intervals were randomized and ranged from 2.3 to 2.7 s (mean 2.5 s). Patients were instructed to memorize each word presented on a computer monitor using a rote strategy avoiding memory aids such as making rows, sentences, stories or pictures. To prevent ongoing rehearsal, a distraction task (counting backward by threes) was conducted after each study phase (duration 30 s). Then, patients were asked to recall freely the previously displayed words in any order. To ensure that each patient had understood the task, two training blocks were conducted immediately before the experiment.

Coherence analysis

EEG recorded during the study phase was partitioned offline into segments of 2 s duration starting with stimulus onset (word presentation). To compare successful and unsuccessful memory encoding, EEG segments were separated into two classes corresponding to subsequently recalled and unrecalled study items. Power and spectral coherence were calculated for the following frequency bands: delta (1–4 Hz), theta (4–7 Hz), alpha1 (7–10 Hz), alpha2 (10–13 Hz), beta1 (13–16 Hz) and beta2 (16–19 Hz). Spectral coherence quantifies the frequency-specific degree of linear relationship between two signals (e.g. Challis & Kitney, 1991). It is given by the average cross-power spectrum of two signals divided by the average powers of both signals. The values of spectral coherence range between 0 and 100%. Two factors may contribute to a high value of spectral coherence: (i) Rather constant phase differences between the two signals across trials (phase synchronization), and (ii) parallel variations of signal amplitudes of both signals across trials (amplitude synchronization). Evenly
dispersed phase differences or uncorrelated amplitude variations result in low values of spectral coherence. To exclude a bias in absolute values, trial numbers were adjusted between the two subsequent memory classes (recalled vs. unrecalled) for coherence analysis. This was done by applying randomized trial lists to the class with the originally larger trial number, i.e. trials for this class (e.g. unrecalled words) were randomly selected so that trial number was equal to that for the class with the originally smaller trial number (e.g. recalled words). Coherence values cannot be expected to comply with Gaussian distributions. For statistical analysis coherence values were thus Fisher-z transformed and normal distribution was subsequently checked by Kolmogorov–Smirnov tests. A significant deviation from the null hypothesis of normally distributed Fisher-z-transformed coherence values was found for none of the combinations of statistical factors Memory and Frequency (each $P > 0.15$).

**Synchronization analysis**

In contrast to spectral coherence, phase synchronization analysis implementing wavelet methods is specific to phase effects and allows a higher time resolution suitable for high frequency activity in the gamma range (see also Fell et al., 2001). EEG trials were filtered in the range 32–48 Hz (2-Hz steps) by wavelet transforms implementing Morlet wavelets of 7 cycles length. The filtered signals $w_{jk}(j, k)$ (time point within a trial; $k$, trial number) hereby result from the time convolution of original signals and the complex wavelet function. From the wavelet transformed signals $w_{jk}$ the phases $\phi_{jk}$ [where $\phi_{jk} = \text{arctan}(\text{Im}(w_{jk})/\text{Re}(w_{jk}))$] were extracted for each time point $j$ of each trial $k$ (Im and Re are the imaginary and real parts). For each time point of each trial, phase differences $\Delta \phi_{jk}$ between hippocampal and rhinal electrode contacts were determined. Phase synchronization values $S_j$ were calculated based on the definition of circular variance (Mardia, 1972).

$$S_j = \frac{1}{N} \sum_{k=1}^{N} e^{i\Delta \phi_{jk}}$$

(1)

where $N$ is the number of trials; $S_j \in [0;1]$. Similar to coherence analysis, trial numbers were adjusted between conditions using randomized trial lists for the condition with the originally larger trial number. Finally, phase synchronization values were averaged for nonoverlapping successive time windows of 100 ms duration from −100 to +1500 ms (16 windows in total).

**Results**

**Performance**

Mean recall rate of the previously displayed words was 29.7%. Individual recall rates ranged between 20.0 and 54.6%.

**Spectral power**

A three-way ANOVA of power values with the factor of Memory (recalled vs. unrecalled) as repeated measure and the factors of Frequency (six levels) and Position (rhinal cortex vs. hippocampus) as independent variables yielded no main effects of Memory ($F_{1,83} = 0.09$, n.s.) or Position ($F_{1,83} = 3.01$, n.s.). In spite of a weakly reliable Memory × Position interaction ($F_{1,83} = 4.24$, $P = 0.043$), subsidiary two-way ANOVAs for rhinal and hippocampal recordings did not show any significant main effect of Memory for spectral power (rhinal cortex $F_{1,42} = 3.28$, n.s.; hippocampus $F_{1,42} = 1.82$, n.s.). Also, paired-sample t-tests for the individual frequency bands did not show any significant main effect of Memory.

**Spectral coherence**

Coherence between the rhinal cortex and the hippocampus, however, exhibited a significant main effect of Memory ($F_{1,42} = 8.27$, $P < 0.01$) as evaluated by a two-way ANOVA on Fisher-z-transformed coherence values with the factor of Memory as repeated measure and the factor of Frequency as independent variable. Mean coherence values were found to be increased for all analysed frequency bands in case of successful memory encoding (see Fig. 2). No significant Memory × Frequency interaction and thus no frequency-specific subsequent memory effect was detected ($F_{5,42} = 0.48$, n.s.). However, because our aim was to take a stand with respect to the theta hypothesis, we further performed individual paired-sample t-tests for each frequency band separately. These analyses revealed a significant coherence enhancement (mean difference $54.0 \pm 56.1\%$) only for the theta range ($t_7 = 2.67, P < 0.05$).

Because we had to use randomized lists to account for different trial numbers (see Materials and methods), we calculated rhinal–hippocampal coherence values for another sample of randomized trial lists to re-check the robustness of the observed coherence changes (see Fig. 3). Again, memory-related increases of the average coherence values were observed for all frequency bands (main effect of Memory: $F_{1,42} = 17.26$, $P < 0.001$). Moreover, in this sample a significant Memory × Frequency interaction was detected ($F_{5,42} = 8.48$, $P < 0.001$). A band-specific significant coherence enhancement was found for the delta range (mean difference $71.5 \pm 75.2\%$; $t_7 = 2.48$, $P < 0.05$), as well as a statistical trend for an enhancement for the theta range (mean difference $50.0 \pm 45.9\%$; $t_7 = 2.25$, $P = 0.059$) (see Fig. 3). As in sample 1, individual delta and theta coherence values for recalled compared to unrecalled words were found to be increased in each subject.

Replacement of the EEG data of each subject by Gaussian white noise revealed average coherence values of $\approx2\%$ (see Fig. 4). Thus, the estimated coherence between hippocampus and rhinal cortex in the case of both successful and unsuccessful memory formation (average values between 12 and 19%) was substantially larger (each $P < 10^{-5}$).

![Sample 1](image.png)

**FIG. 2.** Spectral coherence (%) between EEG recordings from within rhinal cortex and hippocampus for subsequently recalled vs. unrecalled words (sample 1). Mean values and their SEM are plotted. Statistical values were calculated in the Fisher-z-transformed domain and afterwards backtransformed.

be related to general, ubiquitous effects found throughout the brain, we examined spectral coherence between a temporolateral location (gyrus temporalis superior) in the vicinity of Wernicke's area and, separately, hippocampus and rhinal cortex. At this location a negative ERP component had been observed under the memorization paradigm, which was attributed to semantic and not to mnemonic processing (Fernández et al., 1999a). For identification of the zone of seizure onset, EEG had been recorded from this location with subdural strip electrodes in six of the eight patients. The two remaining patients had no electrodes outside the MTL. Results for rhinal–temporolateral (RH–TI) and hippocampal–temporolateral (HI–TI) theta coherence as compared to rhinal–hippocampal theta coherence are shown in Fig. 4. For all frequency bands, average RH–TI and HI–TI coherence (values ≈4%) was 3–8× smaller than rhinal–hippocampal coherence (each \( P < 0.002 \)), pointing to a specifically enhanced connectivity between rhinal cortex and hippocampus. Neither an overall Memory effect \( (RH–TI F_{1,30} = 0.25, \text{n.s.}; HI–TI F_{1,30} = 1.47, \text{n.s.}) \), nor Memory effects within the delta or theta band were detected for RH–TI or HI–TI coherence estimates (paired-sample \( t \)-tests, delta: \( RH–TI t_{5} = 0.85, \text{n.s.}; HI–TI t_{5} = 2.02, \text{n.s.}; \theta : RH–TI t_{5} = 0.06, \text{n.s.}; HI–TI t_{5} = 0.55, \text{n.s.}) This result supports the notion that the observed rhinal–hippocampal coherence enhancement is associated with memory-related interaction specifically between the two MTL substructures.

To investigate whether phase or amplitude coupling caused the coherence increases in the theta range observed in the case of successful encoding, spectral coherence was reanalysed with the following modifications of the algorithm. (i) Amplitudes of Fourier-transformed EEG segments were all set to 1. This meant that changes in the coherence measurement incorporated only phase information (phase-based coherence). (ii) Phases of Fourier-transformed EEG segments were set to 0. In this case changes in coherence values were based on amplitude information only (amplitude-based coherence). Paired-sample \( t \)-tests (recalled vs. unrecalled) revealed subsequent memory effects of similar reliability for both modifications (phase-based theta coherence, \( t_{5} = 2.43, P = 0.050; \) amplitude-based theta coherence, \( t_{5} = 2.11, P = 0.070 \)). Hence, both phase and amplitude synchronisation appear to contribute to the enhancement of theta coherence in the case of successful memory encoding.

Finally, we analysed whether there was a connection between the previously reported memory-related transient gamma synchronization changes (Fell et al., 2001) and the present findings. In the previous study, a significant early enhancement of rhinal–hippocampal gamma band phase synchronization (100–300 ms and 500–600 ms after word presentation) and a later phase desynchronization (1000–1100 ms) had been observed in the case of successful memory formation. The synchronization enhancement within the gamma band resulted from an increased amount of rhinal–hippocampal phase difference close to zero. Here, we extracted phase synchronization values from the time and frequency range which had shown the most prominent subsequent memory effect, i.e. from 100 to 200 ms after word presentation and between 36 and 40 Hz.

We examined whether relative changes in the synchronization and coherence values in the case of successful as opposed to unsuccessful encoding might be correlated. For this purpose, correlation coefficients between normalized coherence changes (percentage of the mean coherence for recalled and unrecalled items) and baseline normalized synchronization changes were calculated. A positive correlation was detected between memory-related alterations of theta coherence and gamma synchronization \( (r = 0.80, P = 0.018, \text{see Fig. 5}) \), but not for any of the other frequency bands (each \( P > 0.25 \)). This correlation was, moreover, robust with respect to a jackknife procedure, i.e. when theta–gamma correlations were recalculated dropping one case each time.
exclusively within the theta band. Thus, our results do not specifically support the theta hypothesis in humans but rather speak in favour of a general memory-related coherence effect spreading across the lower frequency bands.

One might wonder whether our results are confounded by volume conduction between the two MTL recording sites. Previous ERP findings indicate (e.g. McCarthy et al., 1995; Fernández et al., 1999a) that there is no detectable correlation between EEGs recorded from within the hippocampus and the rhinal cortex, even with electrode distances of >1 cm. The large anterior medial temporal lobe N400 component, for instance, which reflects word processing and can be recorded with an amplitude of up to 70 μV from rhinal cortex, is usually not observable in recordings from within the hippocampus (e.g. Fernández et al., 1999a). On the other hand, hippocampal activity is known to be shielded towards the outside by the radial cylindrical arrangement of hippocampal pyramidal neurons (Klee & Rall, 1977).

Weiss & Rappelsberger (2000) reported that theta synchronization exhibits topographical differences between encoding of concrete compared to abstract nouns. Encoding of concrete nouns was mainly correlated with intrahemispheric, encoding of abstract nouns mainly with interhemispheric theta coherence increases. These data suggest that besides rhinal–hippocampal interaction neocortical connections are established during memory formation through coupling in the theta range which, however, might be initiated by hippocampo-neocortical loops (Buzsáki, 1996). Enhanced scalp recorded theta coherence between frontal and posterior areas has also been observed during working memory tasks (Sarntheim et al., 1998). Thus, similar to the occurrence of cortical theta, increased cortical theta synchronization might not be a specific correlate of declarative memory formation but might also subserve working memory operations or attention (Kahana et al., 1999; Caplan et al., 2001; Raghavachari et al., 2001). These processes on the other hand come along with declarative memory encoding and might hereby correlate with subsequent recall (Wagner, 1999). However, due to the relevance of the rhinal cortex and hippocampus for declarative memory formation (Gabrieli, 1998), rhinal–hippocampal theta synchronization may support a more specific function.

The present finding of a frequency band-selective correlation between relative rhinal–hippocampal theta coherence and gamma synchronization changes (Fell et al., 2001) may confirm the theta–gamma hypothesis postulating that the two mechanisms interact in the process of storing representations into declarative memory (Lisman & Idiart, 1995; Jensen et al., 1996; Chrobak & Buzsáki, 1998a,b). However, it should be noted that the correlation analysis is based on the data of only eight subjects, so that the generality of this finding is uncertain. In contrast to the rather nonspecific memory-related coherence enhancement across the lower frequency bands, this result tentatively supports the hypothesis of a specific function of theta oscillations in declarative memory formation. A cooperation of hippocampal gamma and theta activity in memory encoding has been proposed in the framework of the theta–gamma phase coding model (Jensen, 2001; Lisman & Otmakhova, 2001). It has been hypothesized that memory storage of multiple items is coded by distinct cycles of hippocampal gamma oscillations, as well as by the position of these cycles with respect to the theta phase. This model is based on the observation that the firing of hippocampal pyramidal cells during movement through place fields depends on the phase of the theta rhythm (O’Keefe & Recce, 1993; Skaggs et al., 1996). Independent of task requirements, the hippocampal theta and gamma rhythm are known to be interwoven, because hippocampal gamma is amplitude-modulated by theta waves (Chrobak & Buzsáki, 1998a,b). The

(mean $P$-value 0.024 ± 0.026; range of $P$-values 0.004–0.085). A stepwise regression analysis (thresholds $P = 0.05$ for inclusion and $P = 0.1$ for exclusion) with the six coherence measures as independent variables and gamma synchronization as a dependent variable confirmed this result. Under the given thresholds the variance of gamma synchronization values was explained best when only theta coherence was included into the model ($F_{1,6} = 10.48$). Hereby, theta coherence accounted for 57.5% of the variance of gamma synchronization changes. However, when gamma synchronization values were extracted from the interval (1000–1100 ms), where previously a desynchronization effect had been observed, no significant correlation with gamma synchronization changes was detected for any of the coherence bands (each $P > 0.15$).

Discussion

The present findings provide additional experimental evidence for an MTL memory model in which the hippocampus and the rhinal cortex cooperate closely with each other in the generation of new memories which are afterwards consciously accessible (Eichenbaum et al., 1996; Chrobak & Buzsáki, 1998a; Aggleton & Brown, 1999; Fernández & Tendolkar, 2001). In the case of successful encoding, both structures appear to be functionally linked by increased phase synchronization of induced gamma activity (Fell et al., 2001) as well as increased phase and amplitude coupling in lower frequency ranges. In contrast to scalp EEG data, intracranial recordings allow a reliable separation of synchronization and power effects (e.g. Bullock et al., 1995). Our results suggest that, within the MTL, enhanced rhinal–hippocampal coherence is a neural correlate of successful memory encoding but increased event-related EEG power is not. In accordance with the scalp EEG findings of Weiss et al. (2000), we observed a coherence increase during successful compared to unsuccessful word encoding, not only for the theta band but also for neighbouring frequency bands. Although rhinal–hippocampal coherence changes in the delta and theta band were the most reliable ones, as revealed by hypothesis-based subanalyses, memory-related rhinal–hippocampal phase and amplitude coupling appears to occur within a broad frequency range and not
present study extends this knowledge by indicating that rhinal–hippocampal synchronization processes of the two oscillations are interrelated.

As previously reported, successful memory formation is accompanied by an early phase coupling in the gamma range between 100 and 300 ms after onset of word presentation and a later decoupling between 1000 and 1100 ms (Fell et al., 2001). Information transfer between rhinal cortex and hippocampus is assumed to occur following the onset of the memory encoding-related effect on rhinal event-related potentials, i.e. between ≈300 and 800 ms (Fernández et al., 1999a, 2002b). Thus, rhinal–hippocampal gamma phase coupling and decoupling have been interpreted as initiating and later concluding information transfer between the two structures. The precise timing of neural firing in the millisecond range accompanying phase synchronized gamma activity (e.g. Engel & Singer, 2001) may, moreover, accomplish Hebbian synaptic modifications and thus provide an initial step of declarative memory formation on the synaptic level (Fernández et al., 2002a). Due to their large wavelength, low frequency oscillations are not capable of enabling transient phase coupling within a time range of about 100 ms and precise timing of neural firing, as can gamma oscillations (Varela et al., 2000; Engel & Singer, 2001). However, coherent low frequency activity might accomplish a slowly modulated connectivity between rhinal cortex and hippocampus and thereby support an encoding state (Fernández et al., 1999b).

We suggest that theta-mediated rhinal–hippocampal synchronization may escort the fast coupling and decoupling processes in the gamma range, which possibly are more closely related to the actual operation of declarative memory formation. In conclusion, our data suggest that rhinal–hippocampal theta coherence interacts with gamma synchronization during declarative memory formation. However, due to the small group size the present findings and interpretations have to be regarded as tentative until they have been confirmed in a larger sample.

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Abbreviations


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Declarative memory formation in hippocampal sclerosis: an intracranial event-related potentials study

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Introduction

Hippocampal sclerosis is the most frequent pathological finding associated with temporal lobe epilepsy. Histopathologically, hippocampal sclerosis is characterized by gliosis and severe neuronal degeneration, particularly in the CA1 and CA3 region and the hippocampal hilus [1]. Apart from the clinical manifestation of seizures, the main neuropsychological correlate of hippocampal sclerosis is an impairment of long-term memory functions [2]. To date, there is no study directly investigating the influence of hippocampal sclerosis on memory formation by means of intracranial event-related potentials (ERPs).

The waveforms observed in ERPs, such as the N400 of the anterior medial temporal lobe (AMTL-N400) or the hippocampal P300, can be caused either by stimulus-evoked increase in electroencephalogram (EEG) power or by increased intertrial coherence (phase clustering) of the ongoing EEG activity [3–7]. Stimulus-evoked power changes are thought to correspond to the event-related activation of neural assemblies distinct from ongoing background dynamics. On the other hand, stimulus-related phase entrainment of ongoing oscillatory activity can produce an ERP component without additional recruitment of activated neurons.

In this study, we therefore apply wavelet-based time-frequency analysis and circular phase statistics to event-related EEG signals recorded intracranially from the medial temporal lobes of epilepsy patients to resective surgery performing a long-term memorization task. By separating effects of power (amplitude) and coherence (phase), we aim to shed light on the mechanisms involved in the functional deficits of the structures involved in the epileptic process.

Methods

Subjects
Nine patients (six women; mean age 34.1 ± 8.3 years) with pharmacoresistant unilateral temporal lobe epilepsy participated in the experiment. In six patients, seizures originated exclusively from the right medial temporal lobe; in three patients, exclusively from the left medial temporal lobe. After resection of the epileptic medial temporal lobe, all patients remained seizure-free (follow-up, 6–15 months). In all patients, histopathological examination of resected tissue revealed hippocampal sclerosis. The EEG study was approved by the local medical ethics committee. Each patient gave written informed consent.

Experimental paradigm
Patients performed a word list memorization paradigm with a free recall test during EEG recording [8]. Each patient participated in 20 blocks, consisting each of a study, a distraction, and a test phase. During each study phase, 12 words were sequentially presented in uppercase letters on a
computer screen for a duration of 400 ms. Interstimulus intervals were randomized and ranged from 2.3 to 2.7 s (mean 2.5 s). To prevent ongoing rehearsal, a distraction task (counting backwards by threes) was conducted after each study phase (duration 30 s). Immediately after this distraction task, patients were asked to recall freely and in any order the 12 words previously displayed. Stimuli consisted of 240 semantically unrelated nouns with a mean length of six letters (range: 4–11) and a mean word frequency of 75 per million (range: 15–175 per million).

**Intracranial electroencephalogram recording**

Bilateral depth electrodes, each equipped with 10 contacts, were inserted along the longitudinal axis of the hippocampal formation using a computed tomography-based stereotactic insertion technique [9], with the anterior contacts located in the anterior parahippocampal gyrus, which is covered by rhinal cortex, and the posterior contacts located within the hippocampus (cf. [8]). Depth electrode recordings were necessary before resective surgery because the seizure onset zone could not be determined unequivocally from surface recordings. The location of electrode contacts was ascertained by MRI in each patient. MRI scans were acquired in sagittal and adjusted coronal (perpendicular to the longitudinal axis of the hippocampus) and axial (parallel to this axis) planes, and anatomical boundaries were ascertained according to Insausti et al. [10].

Depth electroencephalograms were referenced to linked mastoids, band-pass filtered (0.03–85 Hz, 6 dB/octave), and recorded at a sampling rate of 173 Hz (12-bit analog–digital conversion). EEG data for the 240 trials were scanned for artifacts in each patient; 14.4% of trials (range: 1.3–46.7%) were discarded for the focal side (the side containing the seizure-generating focus) and 5.3% (range: 1.7–10.0%) for the nonfocal side. In each hemisphere, one rhinal and one hippocampal electrode contact were selected for further analysis. Selection criterion was highest amplitude of the rhinal AMTL-N400 and the hippocampal late positive component (LPC), respectively [11].

**Analysis of power changes and phase clustering**

EEG trials were filtered in the frequency range from 0.5 to 30 Hz (0.5 Hz steps) by continuous Morlet wavelet transforms [12–14]. The number of cycles of the Morlet wavelet governs the bandwidth of the wavelet filter around a given center frequency and was adapted to yield a constant band width of 1 Hz at full-width at half-maximum for each of the 30 bands, so frequency bands overlapped by 50%. From the wavelet-transformed signals, the phases and power values were extracted for each time point of each trial and were subsequently used to calculate intertrial phase clustering (phase locking) and power changes as described in [7]. Power and phase locking values were normalized with respect to a prestimulus time window of 200 ms separately for each participant and each filter frequency. For the graphical depiction, normalized power and phase-locking values were averaged over patients and then transformed into decibel scale.

**Fig. 1** Medial temporal lobe depth recordings in a memorization paradigm for the focal (grey) and nonfocal (black) side. Left: grand average of event-related potentials (ERPs) from within the rhinal cortex (with the AMTL-N400 as most prominent component) for remembered and forgotten words, respectively. Right: grand average of ERPs from within the hippocampus (with the late positive component as most prominent component).
Statistical analysis
We extracted the peak amplitudes of the ERPs for the rhinal AMTL-N400 (time range: 200–600 ms) and for the hippocampal LPC (500–1200 ms). We averaged the normalized power and phase-clustering values for each patient over the same time range and a frequency range from 1 to 7 Hz. We then conducted a three-way analysis of variance with locus (rhinal vs. hippocampal), memory (subsequently remembered vs. forgotten words), and pathology (focal vs. nonfocal) as repeated measures. Dependent variables were power, phase clustering, and absolute values of ERP peak amplitudes, respectively.

Results
Performance
Mean recall rate of the previously displayed words was 29.7%. Individual recall rates ranged between 20.0 and 54.6%.

![Fig. 2](image-url)

**Fig. 2** Grand average of power changes (left panel) and changes in phase clustering (right panel) in the rhinal cortex (upper part) and hippocampus (lower part) for subsequently remembered (rows 1 and 3) and forgotten words (rows 2 and 4) for event-related potentials recorded from the ipsilateral (focal, columns 1 and 3) and contralateral (nonfocal, columns 2 and 4) temporal lobes. The plots show color-coded power values and phase-locking values, which have been normalized with respect to a prestimulus baseline of 200 ms and transformed into decibel scale (10*log10). The different frequencies (0.5–30 Hz) are represented on the ordinate, whereas time relative to the onset of stimulus presentation is depicted on the abscissa.
Average event-related potential waveforms

We observed a decrease in ERP amplitudes on the pathological vs. the contralateral side for AMTL–N400 and to a lesser extent for the hippocampal LPC (Fig. 1). Statistical analysis revealed a main effect for memory \( P<0.012; F(1,8)=10.22 \) with increased amplitudes for subsequently remembered vs. forgotten words and a statistical trend for pathology \( P=0.057; F(1,8)=4.93 \). No significant interactions were observed.

Power changes

Figure 2 (left panel) depicts the grand average of power changes [remembered vs. forgotten words, ipsilateral (focal) vs. contralateral (nonfocal) side, rhinal cortex vs. hippocampus]. Note an increase in power in the \( \delta/\theta \) band (1–7 Hz) on the nonfocal side during memory formation, which appears more pronounced in the rhinal cortex than in the hippocampus. In contrast, averaged \( \delta/\theta \) power dropped below the prestimulus baseline on the focal side, although this effect was not statistically significant. Statistical evaluation yielded a significant effect only for pathology \( P<0.003; F(1,8)=11.25 \), whereas no significant effects were found for memory and locus. In particular, there was no significant interaction of locus*pathology \( P>0.225; F(1,8)=1.73 \), which confirms that a significant decrease in power was observed both in the hippocampus and the rhinal cortex.

Phase clustering

Figure 2 (right panel) depicts the phase clustering averaged over patients. Note the increase in phase clustering in the \( \delta/\theta \) range, which is more pronounced in the rhinal cortex than in the hippocampus. Statistical evaluation yielded a main effect for locus \( P<0.003; F(1,8)=18.05 \). No significant effects were found for memory and pathology, and no significant interactions were observed.

Discussion

In this study, we analyzed power/phase effects in rhinal and hippocampal ERPs recorded from the epileptic and contralateral medial temporal lobe in epilepsy patients with unilateral hippocampal sclerosis during declarative long-term memory formation. Although in healthy humans with typical language dominance declarative memory is considered to be a predominant function of the left hippocampus, this assumption is not valid for patients with left hippocampal sclerosis, who exhibit an increased incidence of atypical language lateralization [15]. We therefore did not distinguish between right- and left-hemispheric pathology in this study. Successful memory formation is accompanied by a significant increase in the rhinal AMTL–N400 and the hippocampal LPC [11]. Interestingly, this effect is not accompanied by a significant increase in either power or phase clustering, suggesting that a combination of phase clustering and power changes produces the amplitude effect observed in the average ERP.

As the main finding we observed a statistical trend for decreased ERP amplitudes on the focal side in comparison with the nonfocal side, which is reminiscent of findings reported using other cognitive paradigms [16–18]. Phase/power analysis revealed that this reduction of amplitudes in the pathologial temporal lobe is caused by a significant decrease in \( \delta/\theta \) power. After stimulus presentation, the power on the pathological side even tends to drop below the prestimulus baseline.

This decrease in power probably reflects a lower number of neural assemblies that are being recruited into the memorization task. The most likely reason for this is a decreased availability of neural assemblies owing to the neuronal degeneration associated with hippocampal sclerosis [1]. Interestingly, this effect is not restricted to the hippocampus, but is equally present in the rhinal cortex. The latter finding is in disagreement with a recent neuropathological examination of entorhinal cortical tissue that did not confirm a stereotypical neuronal loss pattern in patients with hippocampal sclerosis [19]. Our findings thus indicate that although principal neurons may still be present in the rhinal cortex, they may not necessarily be available any more for memory processing or may require reciprocal hippocampal interaction for this process.

The missing influence of the side of pathology on the phase clustering, on the other hand, indicates that the network functions of the remaining neuronal assemblies are not impaired and that the timing of their stimulus-related recruitment remains rather accurate. As hippocampal phase locking is considered to depend on external input to the stimulus appear to be preserved.

Network functions related to the timing of neural responses to the stimulus appear to be preserved.

Conclusion

Power/phase analysis of intracranial ERPs in hippocampal sclerosis indicates a reduced availability of recruitable neural assemblies not only in the hippocampus, but also in the rhinal cortex during declarative memory formation. Network functions related to the timing of neural responses to the stimulus appear to be preserved.

References


RAPID COMMUNICATION

Human Declarative Memory Formation: Segregating Rhinal and Hippocampal Contributions

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ABSTRACT: The medial temporal lobe (MTL) is the core structure of the declarative memory system, but which specific operation is performed by anatomically defined MTL substructures? One hypothesis proposes that the hippocampus carries out an exclusively mnemonic operation during declarative memory formation that is insensitive to content, whereas the rhinal cortex carries out an operation supporting memory formation indirectly. To explore the interaction between a salient item feature and memory formation, we contrasted neural correlates of memory formation of high- and low-frequency words. Event-related potentials (ERPs) were recorded via depth electrodes from within the MTL in nine epilepsy patients while they memorized single words. To assess memory formation, ERPs to words subsequently recalled in a free recall test were contrasted with ERPs to forgotten words. More high- than low-frequency words were remembered. High-frequency words led to distinct ERP subsequent memory effects in rhinal cortex and hippocampus. Low-frequency words, however, were only associated with the hippocampal ERP effect. The anatomically restricted interaction between word frequency and memory formation might indicate a semantically affected operation in the parahippocampal region supporting memory formation indirectly. By contrast, the missing interaction in hippocampal recordings might suggest a direct correlate of declarative memory formation that is insensitive to item properties. Hippocampus 2002;12:514–519.

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KEY WORDS: episodic memory; semantic memory; memory encoding; event related potential; medial temporal lobe

INTRODUCTION

Declarative memory is what most people mean when they use the term “memory.” It enables conscious recollection of past events and facts (Cohen and Squire, 1980). Evidence for the crucial contribution of the medial temporal lobe (MTL) to declarative memory was initially offered by the pervasive and severe amnesia that occurs after bilateral damage to this region of the brain (Scoville and Milner, 1957). Functional neuroimaging and electrophysiological studies have now confirmed the importance of the human MTL in declarative memory formation (e.g., Brewer et al., 1998; Wagner et al., 1998; Fernández et al., 1998, 1999a,b; Otten et al., 2001; Fell et al., 2001; Strange et al., 2002). However, the MTL is an anatomically heterogeneous region with distinct cytoarchitectonic substructures (Amaral and Insausti, 1990). The question of which specific kind of operation each of these MTL substructures performs remains to be clarified conclusively (e.g., Fernández et al., 1998, 1999a). A recent imaging study has, for the first time however, dissociated and initially specified perirhinal, hippocampal and parahippocampal roles during verbal encoding by showing that perirhinal and hippocampal activity is associated with encoding success while posterior parahippocampal and right anterior hippocampal activity is associated with an enhanced attentional orientation to positionally distinctive items at the beginning of each study list (Strange et al., 2002).

Models describing the MTL as a rather unitary memory system (Squire and Zola, 1998) are in contrast to modular models in which different MTL substructures contribute behaviorally different operations (Mishkin et al., 1997; Eichenbaum, 2000; Brown and Aggleton, 2001; Fernández and Tendolkar, 2001). One hypothesis regarding the formation of new memories is that the hippocampus carries out an exclusively mnemonic operation in a serially organized declarative memory system which is insensitive to item properties and modality. According to this hypothesis the subordinate parahippocampal region feeds the hippocampus with information and supports memory formation by semantic processes, thus indirectly facilitating the transformation of experiences.
into enduring memories (Fernández and Tendolkar, 2001).

To explore further the specific contribution of the rhinal cortex and the hippocampus to declarative memory formation, we contrasted brain activity associated with the memorization of words with high and low frequency of usage. Word frequency is a powerful determinant of the efficiency of its processing in a range of laboratory tasks (Gregg, 1976). For instance, previously memorized high-frequency words are less easily distinguished from unlearned high-frequency words in simple item-recognition memory tests than are low-frequency words. In contrast, high-frequency words show an advantage over low-frequency words in subsequent free recall tests under certain circumstances. Although this frequency paradox in recognition memory and free recall is well established, the high-frequency advantage in free recall is not stable across different task designs. It is usually found in pure lists of only high- or only low-frequency words. However, in mixed lists, where high- and low-frequency words are intermixed within each study list, no or even opposite frequency effects are obtained (e.g., DeLosh and McDaniel, 1996; Gillund and Shiffrin, 1984). It has not been clarified conclusively whether factors such as the specific word frequency, the test expectancy, the length of the study lists, or the modality of word presentation influence the frequency effect in free recall. Regardless of the bases for the contradicting findings, however, the high-frequency advantage in a free recall test has been found in a previous study employing a similar design as used here, short mixed lists with an expected free recall test (Balota and Neely, 1980).

In general, accounts of word frequency effects in free recall have assumed that they largely reflect the relative ease with which words of differing frequencies access their stored lexical representation (Gordon, 1983). Common words, as opposed to uncommon words, have richer semantic contexts (Gregg, 1976) and are more meaningful (Noble, 1963), hence give rise to more associative responses with shorter response times (Cofer and Shevitz, 1952; Noble, 1963). During memory encoding, high-frequency words are easy to associate with one another, because they tend to possess more associations to other words in semantic memory (Rubin and Friendly, 1986). This relationship between word frequency and semantic associative processing may lead to the free recall advantage of high-frequency words (Gregg, 1976). Hence, a neural correlate of successful memory formation in a study with a free recall advantage that occurs for high- but not for low-frequency words would suggest a support operation related to item properties but which is not an exclusively mnemonic operation. A subsequent memory effect unrelated to word frequency, however, suggests a difference in the quality of encoding, rather than a difference in item properties. It may thus indicate an exclusively mnemonic operation of declarative memory formation which is insensitive to item content.

We investigated nine patients (four women, mean age 35.7 ± 13.6 years) with drug-resistant unilateral temporal lobe epilepsy who were undergoing evaluation for possible epilepsy surgery. Each patient was right hand dominant and a native German speaker. Each had normal or fully corrected vision and received anticonvulsant treatment with carbamazepine as the only centrally acting drug. Carbamazepine plasma levels were within the so called therapeutic range (6–12 μg/ml). No clinical signs of intoxication were observed, and no seizure occurred in the 24 h before the investigation. Each patient gave written informed consent, and the study was approved by the local medical ethics committee.

Brain activity associated with encoding of high- and low-frequency words was assessed by event-related potentials (ERPs) recorded via depth electrodes from within the hippocampus and the anterior parahippocampal gyrus, which is covered by rhinal cortex (perirhinal and entorhinal cortices) (Amaral and Insausti, 1990). The depth electrodes were inserted using a previously described technique (Van Roost et al., 1998), because the seizure onset zone could not be determined unequivocally for resective surgery by noninvasive means. The location of electrode contacts was ascertained by magnetic resonance images (MRI) in each patient. Contacts were mapped by transferring their positions from MRI to standardized anatomical drawings (Jackson and Duncan, 1996). MRI scans were acquired in sagittal and adjusted coronal planes, perpendicular to the longitudinal axis of the hippocampus (repetition time = 3719 ms, echo time = 120 ms, flip angle = 90°, Field of view = 22 cm; thickness: 2.0 mm; gap: 0.3 mm; 1.5 T) (ACS-II, Philips, Eindhoven, Netherlands). Only EEG recordings from the MTL contralateral to the zone of seizure origin were analyzed to reduce poorly controllable effects introduced by the epileptic process (Grunwald et al., 1995). If seizures are proved to originate unilaterally, electrodes in the healthy MTL enable recordings of normal human brain activity unrelated to epilepsy (Paller et al., 1992). Unilateral seizure onset was indicated in each patient by at least three seizures originating exclusively in depth recordings of one MTL (right MTL in five, left in four patients) and proved by complete seizure control after resection of this MTL (mean follow-up: 9.6 ± 3.4 months).

Each patient participated in a direct single-trial word list learning paradigm similar to the paradigm used previously (Fernández et al., 1999b) with 20 study-test blocks. After the procedure was explained to each patient, two training blocks were conducted immediately before the investigation, to ensure that each patient had understood the task. During each block, patients were initially asked to memorize nine words presented sequentially on a computer monitor. Words were presented in uppercase letters (white against black background), in central vision (horizontal visual angle 3.0°), and for a duration of 400 ms (randomized interstimulus interval: mean, 2.5 s; range, 2.3–2.7 s). Patients were instructed to memorize each word for a later memory test. Thereafter, a distraction task was conducted to prevent ongoing rehearsal maintaining working memory: Patients were asked to count backward in series of threes for 30 s, starting at a number between 81 and 99 displayed on screen. During the following 90-s test phase, participants were instructed to freely recall previously presented words in any order. The stimuli consisted of 180 German nouns, 90 with high frequency (mean frequency: 415.2 ± 80.1/million (Baayen et al., 1995), mean word length: 5.98 ± 1.16 letters) and 90 with low frequency (mean frequency: 4.1 ± 1.0/million (Baayen et al., 1995), mean word length: 6.13 ± 1.19 letters). The order of words was pseudorandomized across subjects under the constraints that each list of nine words contained four or five high-frequency words intermixed with four or five low-frequency words. Word length
was balanced between lists, and neither semantic nor phonological similarities occurred within lists.

High-frequency words were better recalled than low-frequency words (mean recall rates 38.44 ± 12.4 vs 27.33 ± 11.96; t(8) = 2.35, P < 0.05). To analyze the interaction between study list position and recall probability we compared recall probabilities of the initial, middle, and final three words of each study list. Although list position had a significant effect on recall probability (F(2,7) = 8.44, P < 0.05), the factor of word frequency did not interact with this effect (F(2,7) < 1.26, n.s.). Moreover, to explore whether certain items were consistently remembered or forgotten across subjects, we compared, by χ² tests, the observed distribution of recall probabilities of high- and low-frequency words and their expected Binomial distributions, which were calculated under the assumption of individual (item and subject) recall probabilities equal to the observed mean recall rates. Expected and observed distributions for either high- or low-frequency words were highly similar and not reliably different (high-frequency words: χ² = 1.295, n.s.; low-frequency words: χ² = 1.007, n.s.), indicating there were no systematic item differences between words later recalled and forgotten.

Turning to the ERP data, high-frequency words tended to be accompanied by a larger negativity with a peak latency of about 400 ms in the rhinal cortex, as compared with low-frequency words (Fig. 1). This potential, which is called anterior medial temporal lobe N400 (AMTL-N400), is always obtained in studies using visually presented words (e.g., McCarthy et al., 1995; Nobre and McCarthy, 1995; Grunwald et al., 1995; Fernández et al., 1999b). The word frequency effect at the AMTL-N400 just failed to reach significance (F(1,8) = 3.91, P < 0.1). The subsequent memory effect, the difference between ERPs to subsequently recalled and ERPs to subsequently forgotten words at the AMTL-N400, however, was significant (main effect of memory: F(1,8) = 6.77, P < 0.05). Moreover, there was a reliable interaction between the factors of memory and word frequency at the AMTL-N400 (Fig. 2; F(1,8) = 6.03, P < 0.05). Post hoc analyses, performed separately for ERPs associated with either high- or low-frequency words, confirmed at the AMTL-N400 a subsequent memory effect for high-frequency words (t(8) = −2.92, P < 0.05), but not for low-frequency words (t(8) < 1, n.s.). In line with previous descriptions, the AMTL-N400 and its subsequent memory effect exhibited a steep voltage gradient over the neighboring electrode contacts. Four patients had additional subdural strip electrodes over the basal surface of the parahippocampal gyrus, anterior to the hippocampus, revealing an inferior positive component (Fernández et al., 2001) with a positive subsequent memory effect that is a phase-inverted AMTL-N400 (McCarthy et al., 1995; Fernández et al., 1999b). Both characteristics—steep voltage gradient and phase reversal—indicate a local generator within the anterior parahippocampal gyrus, probably within the perirhinal cortex (McCarthy et al., 1995).

In hippocampal recordings, subsequently recalled words were accompanied by a more positive ERP component in the late time window (600–2000 ms after stimulus onset) as opposed to forgotten words (Fig. 1; main effect of memory: F(1,8) = 39.79, P < 0.001). This component exhibited neither a main effect of word frequency (F(1,8) < 1, n.s.) nor an interaction with this factor (F(1,8) < 1, n.s.) (Figs. 1, 2). It was detectable within, but not immediately outside, the hippocampus. Hippocampal neurons are arranged cylindrically (Amaral and Insausti, 1990). Hence, they produce a radially symmetric field that is closed in the sense of being isopotentially zero outside the hippocampus (Klee and Rall, 1977). Thus, this positive component was generated within the hippocampus proper. Finally, to test directly whether the effects generated in the rhinal and the hippocampus were dissociated, we calculated a three-way analysis of variance (ANOVA) with the factors of region (rhinal cortex versus hippocampus), word frequency (high- versus low-frequency words), and memory (subsequently recalled versus forgotten words). This calculation revealed a reliable interaction between all three factors (F(1,8) = 9.25, P < 0.05), indicating a regional dissociation and allowing separate analyses for recordings from the rhinal cortex and the hippocampus as reported above.

The ERPs associated with high-frequency words recorded in this study replicate our initial findings, also using common words (Fernández et al., 1999b) with fewer items (90 vs 240) and fewer subjects (9 vs 12). High-frequency words elicited two subsequent memory effects: a negativity at the AMTL-N400, probably generated in the rhinal cortex, and a positivity later on, probably generated within the hippocampus. The newly introduced manipulation of word frequency, however, broke up the positive correlation between the sizes of the rhinal and the hippocampal subsequent memory effects. Low-frequency words did not trigger a subsequent memory effect at the AMTL-N400. Nevertheless, they were accompanied by a hippocampal subsequent memory effect in the same way as high-frequency words. The interactions between word frequency and recall rates as well as between word frequency and the rhinal subsequent memory effect at the AMTL-N400 indicate that an operation executed by the rhinal cortex facilitates declarative memory formation indirectly. All words, irrespective of word frequency, appear to undergo this operation, because all words were accompanied by an AMTL-N400. However, high-frequency words with a rich semantic context appear to stimulate more elaborate processing in rhinal cortex, which leads to more effective memory formation. In contrast, the hippocampal subsequent memory effect did not interact with word frequency. Hence, it might be a correlate of an exclusively mnemonic operation within the declarative memory system that uses rhinal input for memory formation, but that is not influenced by stimulus properties such as word frequency or resulting processes.

Our findings are not only in accord with the results of a previous depth ERP study investigating declarative memory formation (Fernández et al., 1999b), but also with an earlier priming study revealing a larger AMTL-N400 for words with rich semantic content than for words serving only grammatical function (Nobre et al., 1995). Although selective damage to the parahippocampal region is rare in humans, the role of the parahippocampal region in the semantic domain seems to be supported by lesion data in patients with semantic dementia (Chan et al., 2001; Galton et al., 2001) and imaging data showing anterior parahippocampal activations in relation to semantic violations and recognition of semantic associations (Ricci et al., 1999; Newman et al., 2001).
FIGURE 1. Grand average event-related potentials (ERPs). Electroencephalogram was referenced to linked mastoids, bandpass-filtered (0.03–85 Hz, 6 db/octave), and sampled with 173 Hz. Averaging epochs lasted 2.2 s (0.2-s prestimulus baseline). Data from a contact in the anterior parahippocampal gyrus as ascertained by magnetic resonance imaging (MRI) with the maximal AMTL-N400 and from a contact in the hippocampus as ascertained by MRI with the maximal late positive component (600–2,000 ms) were averaged separately. Data shown is smoothed with a moving average filter of three data points. ERPs were quantified by mean amplitudes of an early time window (200–600 ms) for rhinal and a late one (600–2,000 ms) for hippocampal recordings. Data were subjected separately to two-way ANOVAs (memory: recalled / unrecalled and word frequency: high / low frequency).
Our findings are congruent regarding the direct hippocampal contribution to declarative memory formation with the results obtained by Strange et al. (in press), using event-related functional MRI. Although Strange and colleagues were able to make further inferences about the MTL contribution to declarative memory formation, we are unable to support these inferences about the posterior parahippocampal contribution (no posterior parahippocampal electrodes), the interhemispheric interaction (seizure onset zone in the contralateral MTL), and the primacy effect (too small number of recalled-primacy trials). Nevertheless, we have extended the knowledge about the rhinal contribution to declarative memory formation by revealing the clear-cut interaction between encoding success and word frequency. This finding might be in line with an other event-related functional MRI study (Otten et al., 2001), using the so-called levels of processing task (Craik and Lockhart, 1972) leading to two MTL activations: An anterior MTL activation that was sensitive to subsequent memory and semantic processing, and that the hippocampal subsequent memory effect is related to semantic processing necessary for word-to-word associations, which seem to be more readily induced by high-frequency words, and that the hippocampal subsequent memory effect is related to word-to-context associations, which are formed irrespective of word frequency for all words. Without identifying conclusively the specifics of the underlying operations, our findings provide evidence for a behaviorally relevant dissociation between rhinal and hippocampal contributions to declarative memory formation in humans. Such a functional dissociation was initially suggested on the basis of experimental data in animals (Brown and Aggleton, 2000; Eichenbaum, 2000) and humans with selective lesions within the MTL (Aggleton and Shaw, 1996; Vargha-Khadem et al., 1997). More recently, functional imaging studies employing functional imaging techniques with extremely high spatial resolution have started to dissociate specific roles of the MTL substructures during declarative memory formation (Otten et al., 2001; Strange et al., 2002).

In conclusion, our data suggest a modular MTL memory system (Mishkin et al., 1997; Eichenbaum, 2000; Brown and Aggleton, 2001; Fernández and Tendolkar, 2001), which forms declarative memories by behaviorally distinct but closely interacting operations (Fell et al., 2001). Within this system, the hippocampus performs a specific operation of declarative memory formation, which might initiate the biochemical cascade underlying synaptic plasticity - the presumed correlate of memory at the cellular level (Beck et al., 2000). In contrast, the subordinate parahippocampal region feeds the hippocampus with useful representations of the environment and performs a support operation during declarative memory formation, which might be in the semantic domain. This operation appears to make semantic representations of each study item available in the service of comprehension, semantic-associative processing, and memory formation (Craik and Lockhart, 1972; Nobre and McCarthy, 1995).

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Rhinal–hippocampal coupling during declarative memory formation: Dependence on item characteristics

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Abstract

Lesion and imaging studies have demonstrated that encoding and retrieval of declarative memories, i.e. consciously accessible events and facts, depend on operations within the rhinal cortex and the hippocampus, two substructures of the medial temporal lobe. Analysis of intracranially recorded EEG in presurgical epilepsy patients revealed that successful memory formation is accompanied within one second by a transient enhancement and later decrease of Rhinal–hippocampal phase synchronization in the gamma range, as well as enhanced connectivity in the low-frequency range. In these studies, words with a high frequency of occurrence were used as stimulus material. Here, we re-examined these effects in another group of 10 presurgical epilepsy patients, this time not only for high-frequency, but also for low-frequency words. For successfully memorized compared to later forgotten high-frequency words we again observed an early phase coupling and later decoupling within the gamma range, as well as enhanced coupling within the sub-gamma range. However, for remembered as compared to forgotten low-frequency words clear synchronization increases were only observed for the delta band, but not for the gamma band. Our data suggest, that broadband Rhinal–hippocampal coupling including the gamma range only occurs, when significant semantic associations are processed within rhinal cortex, as is the case for high-frequency words.

Keywords: Declarative memory; Depth EEG; Gamma activity; Phase synchronization; Medial temporal lobe; Hippocampus

Declarative memory enables us to remember past events and facts [33]. Lesion and neuroimaging data suggest that the medial temporal lobe (MTL) plays a crucial role in declarative memory, especially during the initial steps of memory formation [4,14,15,29,32]. Besides an activity increase of MTL structures, the connectivity between sub-regions appears to be a central factor supporting successful memory encoding. A recent fMRI study, for instance, has revealed an enhanced functional connectivity between the hippocampus and the perirhinal cortex (among other regions) after presentation of line drawings of complex objects, which were later remembered, compared to those, which were forgotten [25].

An important complementary approach to the investigation of declarative memory is the analysis of EEG data that are intracranially recorded from patients with MTL epilepsies during presurgical evaluation. In a word memorization paradigm with subsequent free recall, memory formation was found to be associated with the sequential activation of the rhinal cortex and the hippocampus [14]. Analysis of oscillatory processes within the gamma range indicated that successful memory formation is accompanied by an initial stimulus-related increase of phase synchronization between rhinal cortex and hippocampus (time range between 100 and 600 ms) and a later decrease (between 1000 and 1100 ms) [12]. The transient increase and decrease of Rhinal–hippocampal synchronization was interpreted to initiate and later terminate information transfer between both structures [6]. Phase coupling within the gamma range appeared to be escorted by increased low-frequency EEG coherence between rhinal and hippocampal recordings [11]. In these studies only common words, i.e. words with a high frequency of occurrence were used. Thus, it remained an open question, whether Rhinal–hippocampal coupling during memory formation may depend on item characteristics, such as word frequency.
High-frequency (common) words, as opposed to low-frequency (uncommon) words, have richer semantic contexts [19] and are more meaningful [23], hence give rise to more associative responses with shorter response times [7,23]. This relationship between word frequency and semantic associative processing probably causes the often-observed free recall advantage of high-frequency words [19]. In a prior study high-frequency words led to memory-related ERP effects in both, rhinal cortex and hippocampus, whereas low-frequency words were only associated with a memory-related difference within the hippocampus [17]. This outcome was interpreted to validate the hypothesis that the rhinal cortex participates in semantic operations which indirectly support memory formation, while the hippocampus is directly responsible for the initial steps of memory formation, which are insensitive to item characteristics [5,8,16,22]. Since in case of memorization of low-frequency words fewer associations are processed by the rhinal cortex compared to high-frequency words, one may argue, that much less information has to be transferred from rhinal cortex to the hippocampus. Thus, we wondered whether memory-related Rhinal–hippocampal phase coupling might depend on word frequency and thereby the amount of associative information transferred.

To answer this question, EEG was recorded (sampling rate: 173 Hz; bandpass-filter: 0.03–85 Hz, 6 db/octave; reference: linked mastoids) from 10 patients (four women, mean age 32.9 ± 12.6 years) with pharmacoresistant temporal lobe epilepsy while they performed a single-trial word list-learning paradigm with a free recall test. Multicontact depth electrodes had been implanted stereotactically along the longitudinal axis of each MTL during presurgical evaluation [30], because the zone of seizure onset could not be determined unequivocally by noninvasive investigations. The placement of electrode contacts within the hippocampus and the anterior parahippocampal gyrus, which is covered by rhinal cortex [1], were ascertained by magnetic resonance images in each patient [20]. All patients had a unilateral seizure origin within one MTL based on the analysis of seizure activity in the depth recordings (six patients–right; four patients–left). Only EEG recordings from the MTL contralateral to the zone of seizure origin were analyzed to reduce poorly controllable effects introduced by the epileptic process [9,24]. Experiments were conducted with adequate understanding and written consent of the subjects and in accordance with the Declaration of Helsinki.

Each patient participated in 20 study test blocks each containing nine semantically unrelated German nouns. Of the 180 nouns, 90 had a high frequency of occurrence (mean frequency: 415.2 ± 80.1/million [3], mean word length 5.98 ± 1.16 letters) and 90 had a low-frequency (mean frequency: 4.1 ± 1.0/million, mean word length: 6.13 ± 1.19 letters). The order of words was pseudorandomized across subjects under the constraints that each list of nine words contained four or five high-frequency words intermixed with four or five low-frequency words. Word length was balanced between lists, and neither semantic nor phonological similarities occurred within lists. During study, patients were instructed to memorize each word presented sequentially on a computer monitor. To prevent ongoing rehearsal, a distraction task was conducted after each study list (counting backwards in threes starting from a given number between 81 and 99). Thereafter, patients were asked to recall freely the previously displayed words in any order. There was a trend for high-frequency words to be better recalled than low-frequency words (mean recall rates 39.67 ± 12.74% versus 29.89 ± 10.12%; paired two-tailed T-test: ν = 2.23; p = 0.053).

Two training blocks were conducted immediately before the experiment to ensure that each patient had understood the task.

To compare successful and unsuccessful memory encoding, EEG was separated offline into segments for subsequently recalled and unrecalled study items. EEG was then subjected to a continuous complex wavelet transform (Morlet wavelets with 5 cycles length) in the frequency range from 2 to 48 Hz (2 Hz steps). Phases and phase differences between rhinal cortex and hippocampus were extracted for each trial and time point [12,21,27]. Then, Rhinal–hippocampal phase synchronization was quantified by an entropy measure [13]. The higher the synchronization value for a certain time point, the more stable are the phase differences between the two electrodes over all trials of the respective class (remembered/forgotten, low-frequency/high-frequency words). Finally, synchronization values were averaged for consecutive 100 ms time windows from −200 to 1500 ms relative to stimulus onset. Values were divided through the baseline values for the interval [−200:0 ms] and were transformed into percentage change relative to baseline.

For statistical analysis synchronization values were averaged for each subject within the following frequency bands: delta (2 Hz), theta (4–6 Hz), alpha (8–12 Hz), lower beta (14–20 Hz), upper beta (22–30 Hz) and gamma (32–48 Hz). The group average showed that the synchronization difference between remembered and forgotten words in the delta/theta/alpha range is similar for high- and low-frequency words, but differs markedly in the beta and gamma range (see Figs. 1 and 2).

Therefore, we performed four-way ANOVAs with word frequency (HF/LF), subsequent recall outcome (MEMORY), time window (TIME) and frequency BAND as repeated measures for both frequency ranges. For the lower bands, we found a main effect of MEMORY (p < 0.05; F_{1,9} = 7.38) expressing increased synchronization for remembered compared to forgotten words, as well as a BAND×MEMORY interaction (p < 0.01; F_{2,18} = 9.02; Huynh–Feldt ε = 0.88). This interaction was traced back to a main effect of MEMORY in the delta band (p < 0.01; F_{1,9} = 13.25), together with a lack of significant effects in the theta or alpha band. No significant HF/LF×MEMORY (p = 0.94; F_{1,9} = 0.01) or BAND×HF/LF×MEMORY interactions (p = 0.54; F_{2,18} = 0.57; ε = 0.80) were observed indicating that the subsequent memory effect was independent of word frequency in the delta/theta/alpha range.

In contrast, we found a significant HF/LF×MEMORY interaction (p < 0.05; F_{1,9} = 9.02) for the beta and gamma range showing that the subsequent memory effect depends on word frequency for the faster oscillations. This effect was not accompanied by a significant BAND×HF/LF×MEMORY interaction (p = 0.16; F_{2,18} = 2.00; ε = 1.20). The HF/LF×MEMORY interaction results from a trend for an increased synchronization for remembered vs. forgotten high-frequency words (p = 0.051; F_{1,9} = 5.06),...
Fig. 1. Rhinal–hippocampal phase synchronization in the upper beta and gamma range (22–48 Hz) for high-frequency words (left) and low-frequency words (right) (grand average). Above: differences of Rhinal–hippocampal synchronization [%] relative to the prestimulus time window [-200;0 ms] for subsequently remembered minus forgotten words. The different EEG frequencies are represented on the y-axis and time is depicted on the x-axis. Synchronization/desynchronization is coded on a color scale: red areas show an enhancement, blue areas a reduction of synchronization for subsequently recalled versus unrecalled words. Below: changes of Rhinal–hippocampal synchronization [%] relative to prestimulus baseline for subsequently recalled versus unrecalled words. Synchronization values were averaged across the upper beta and gamma range (22–48 Hz).

together with a trend for a decreased synchronization for remembered versus forgotten low-frequency words (p = 0.087; $F_{1,9} = 3.70$). When focusing on the gamma range between 32 and 48 Hz as done in a prior study [12], we observed a significant synchronization increase between 300 and 500 ms (paired one-tailed $T$-tests; each $p < 0.05$) for remembered vs. forgotten high-frequency words, but no significant synchronization enhancement for low-frequency words. The later desynchronization, which occurs between 1000 and 1300 ms for high-frequency words, emerges already between 600 and 900 ms for low-frequency words (600–700 ms: $p = 0.055$; 700–800 ms: $p = 0.064$). Compared to the gamma range, the synchronization enhancement in the sub-gamma range is less defined in time and rather seems to be broadly distributed across the trial.

In general, our findings for high-frequency words replicate the data of a prior study [12] indicating that successfully memorized compared to later forgotten items are accompanied by an early Rhinal–hippocampal phase coupling and later decoupling within the gamma range. In the previous investigation, the gamma synchronization increase showed an even earlier onset already in the [100;200] time window. This discrepancy may in part result from the fact that we used broader wavelets for time-frequency analysis in the prior study compared to the present investigation (7 cycle versus 5 cycle wavelets), which was adapted to concomitant evaluation of the sub-gamma range. Another difference between both studies is that we previously presented 240 word stimuli, whereas in the current study only 90 words were used for each category (high-frequency, low-frequency). Because considerably more trials entered the individual averages, the prior findings [12] have to be regarded as more reliable.

The phase coupling and decoupling in the gamma range for later remembered high-frequency words is associated with broadly distributed synchronization enhancements in
the sub-gamma range, which again are in accordance with previous data [11]. In other studies synchronization effects in the sub-gamma range have, for instance, been attributed to working memory processes [26,28,31], which could accompany long-term memory formation also in the present experiment, at least during the encoding phase. The synchronization increase in the delta range probably corresponds to the slow positive event-related component, which is observed within the hippocampus during declarative memory formation [14]. In the frequency range above delta even an early memory-related desynchronization seemed to occur for low-frequency words. The functional significance of this early Rhinal–hippocampal desynchronization is an open question.

The most important finding is that the memory-related increase of beta and gamma synchronization is absent for low-frequency words. This outcome is in line with models suggesting that different MTL substructures contribute to behaviorally different operations [5,8,16,22]. One hypothesis regarding the formation of new memories is that the hippocampus carries out an exclusively mnemonic operation in a serially organized declarative memory system, which is insensitive to item characteristics and modality. According to this hypothesis, the subordinate parahippocampal region feeds the hippocampus with information and supports memory formation by semantic processes, thus indirectly facilitating the transformation of experiences into long-term memory [16].

Our data suggest that a broadband Rhinal–hippocampal coupling including the gamma band only occurs, when significant semantic associations are processed within rhinal cortex, as is the case for high-frequency words. These data do not exclude that for low-frequency words still some isolated memory-related coupling occurs within the gamma-band – but this effect is not evident with regard to macroscopically recorded EEG. In the context of the present study, phase synchronization of gamma oscillations and the accompanying correlated neural firing have been suggested to subserve two basal functions. One is establishing temporal windows for neural communication, which are optimal for the transmission of information [10,18]. The other

Fig. 2. Rhinal–hippocampal phase synchronization in the 2–20 Hz range for high-frequency words (left) and low-frequency words (right) (grand average). Above: differences of Rhinal–hippocampal synchronization [%] relative to the prestimulus time window [−200;0 ms] for subsequently remembered minus forgotten words. Below: changes of Rhinal–hippocampal synchronization [%] relative to prestimulus baseline for subsequently recalled versus unrecalled words. Synchronization values were averaged across the 2–20 Hz range.
one is the formation of Hebbian assemblies due to the precise timing of action potentials [2]. According to this framework, broadband Rhinal–hippocampal synchronization including the gamma range may on the one hand support the memory related transfer of semantic information from rhinal cortex to hippocampus. On the other hand, Rhinal–hippocampal synchronization may enable the formation of associative Hebbian links between rhinal cortex and hippocampus.

Acknowledgements

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References

Temporal and Cerebellar Brain Regions that Support both Declarative Memory Formation and Retrieval

Using event-related fMRI, we scanned young healthy subjects while they memorized real-world photographs and subsequently tried to recognize them within a series of new photographs. We confirmed that activity in the medial temporal lobe (MTL) and inferior prefrontal cortex correlates with declarative memory formation as defined by the subsequent memory effect, stronger responses to subsequently remembered than forgotten items. Additionally, we confirmed that activity in specific regions within the parietal lobe, anterior prefrontal cortex, anterior cingulate and cerebellum correlate with recognition memory as measured by the conventional old/new effect, stronger responses for recognized old items (hits) than correctly identified new items (correct rejections). To obtain a purer measure of recognition success, we introduced two recognition effects by comparing brain responses to hits and old items misclassified as new (misses). The positive recognition effect (hits > misses) revealed prefrontal, parietal and cerebellar contributions to recognition, and in line with electrophysiological findings, the negative recognition effect (hits < misses) revealed an anterior medial temporal contribution. Finally, by inclusive masking, we identified temporal and cerebellar brain areas that support both declarative memory formation and retrieval. For matching operations during recognition, these areas may re-use representations formed and stored locally during encoding.

Keywords: declarative memory, event-related, fMRI, memory formation, recognition, retrieval

Introduction

The kind of memory one ordinarily means when using the term ‘memory’ is declarative memory, which enables us to consciously remember past events and facts (Cohen and Squire, 1980). Declarative memory is based on at least two fundamental mnemonic operations: memory formation and retrieval (Gabrieli, 1998). Since only a few years ago, event-related functional magnetic resonance imaging (ER-fMRI) has provided the unique opportunity to study the neural correlates of these mnemonic operations with great anatomical detail in healthy human subjects (Dale and Buckner, 1997; Josephs et al., 1997; Zarahn et al., 1997). Using ER-fMRI, encoding studies have shown that successful declarative memory formation, measured as the difference in brain activity between subsequently remembered and forgotten items, is accompanied by activity increases in medial temporal and inferior prefrontal areas (e.g. Brewer et al., 1998; Wagner et al., 1998; Kirchhoff et al., 2000; Davachi et al., 2001; Otten et al., 2001; Otten and Rugg, 2001a; Strange et al., 2002; Morcom et al., 2003; for a review, see Paller and Wagner, 2002) and activity decreases in posterior cingulate, parietal and dorsolateral prefrontal areas (Otten and Rugg, 2001b). ER-fMRI studies acquiring fMRI data during simple recognition memory tests and applying the so-called old/new effect, the difference in brain activity between correctly recognized old, previously studied items (hits) and correctly identified new, previously unstudied items (correct rejections), have shown activations in the anterior prefrontal cortex, parietal cortex, insula and medial-frontal areas including the anterior cingulate (e.g. Henson et al., 1999; Konishi et al., 2000; Donaldson et al., 2001a,b; for a review, see Rugg and Henson, 2002). The first aim of the present study is to replicate these subsequent memory and old/new effects, which were so far obtained in separate encoding and retrieval experiments, within a single study-test experiment.

Based on this empirical foundation, we aim to explore in the second step of this study whether recognition success can be associated with both regional brain activity increases and decreases. Brain activity increases for hits as compared to correct rejections (old/new effect) have been interpreted as related to the successful recovery of information from declarative memory (Donaldson and Buckner, 1999; Konishi et al., 2000; Donaldson et al., 2001a,b). A reversed old/new contrast, however, cannot delineate cleanly a brain activity decrease related to recognition success, because it would be heavily contaminated by neural correlates of repetition priming (Buckner and Koutstaal, 1998; Donaldson et al., 2001a). Repetition priming is an implicit memory phenomenon that improves processing efficacy of repeatedly processed items and that is regularly accompanied by weaker brain activity to old as compared to new items (Tulving and Schacter, 1990; but see Henson et al., 2000). However, repetition priming does not support conscious recognition (Donaldson et al., 2001a). Thus, the question that remains open is: can only repetition priming or also conscious recognition correlate with a decrease in neural activity? (Henson et al., 2003). Electrophysiological data in animals and humans suggest that recognition can also be accompanied by brain activity decreases (Smith et al., 1986; Brown et al., 1987; Miller and Desimone, 1994; Brown and Aggleton, 2001; Fernández et al., 2001). As outlined above, we cannot simply reverse the old/new effect. Rather, analogous to the subsequent memory effect, we compare brain activity to correctly recognized old items (hits) and old items misclassified as new (misses). In this contrast, henceforth called the recognition effect, all items are studied once before, but recognition success differs. Hence, a negative recognition effect (misses > hits) seems to be less contaminated by repetition priming than a reversed old/new effect, at least when primed and recognized items show stochastic independence in the sense that performance in the two tasks is uncorrelated at the level of individual items (Shimamura, 1985). And in addition, the recognition effect might generally be more closely related to recognition success than the old/new effect, because it does...
not include any difference related to the actual study status of the items. Thus, as our second goal, we aim to identify increases and decreases in brain activity associated with recognition success as indexed by a positive (hits > misses) and a negative recognition effect (misses > hits). A recent meta-analysis of four event-related fMRI studies employing different kinds of study material suggested that less anterior MTL activity is related to the amount of familiarity across a variety of stimulus materials (Henson et al., 2003). Another event-related fMRI study (Rom booths et al., 2001) found anterior parahippocampal gyrus activation in a comparison of new to often seen items, but this study did not control for performance. In line with these findings as well as with electrophysiological data (Smith et al., 1986; Miller and Desimone, 1994; Brown and Aggleton, 2001; Fernandez et al., 2001), we expect negative recognition effects in inferior temporal areas including the anterior MTL.

Given the encoding and recognition results of ER-fMRI studies reported above, there seems to be no or almost no overlap between brain areas involved in both memory formation and recognition (see also Gabrieli et al., 1997). If, however, a brain area would support these two operations, neural representations stored locally during encoding could be re-used during recognition. Such a module would not only be efficient and intuitive, its existence is supported by electrophysiological data. For instance, the so-called anterior MTL (N400), a negative component in event related potentials recorded invasively in epilepsy patients from the anterior MTL, probably from the perirhinal cortex (McCarthy et al., 1995) shows an amplitude difference between subsequently remembered and forgotten items during encoding (Fernandez et al., 1999, 2002) as well as between correctly identified old and new items during a recognition memory test (Smith et al., 1986). Therefore, this neural node within the anterior MTL seems to be critically involved in both memory formation and retrieval. However, most studies to date have examined either memory encoding or retrieval and have therefore not been able directly to compare encoding- and retrieval-related activations within subjects. The third aim of the present fMRI study is thus to characterize this node within a single study-test experiment by a functional imaging approach applying inclusively masking of the subsequent memory effect and either the positive or the negative recognition effect. Moreover, we aim to identify further brain areas whose activity is correlated with both successful memory formation and recognition by whole brain coverage.

Material and Methods

Subjects

Sixteen healthy volunteers (eight male, eight female) with normal or corrected-to-normal vision participated in the experiment. All subjects were consistent right-handers according to the Edinburgh Handedness Index (mean EHI = 88, range 73–100; Oldfield, 1971). Their mean age was 30 years with a range of 20–49 years. Following approval by the Medical Ethics Committee of the University of Bonn, all subjects gave their written informed consent according to the Declaration of Helsinki (1991). They were paid for their participation.

Stimuli and Task

Stimuli consisted of 480 color photographs of either buildings or natural landscapes without any buildings (240 for each category) that were selected to be similar in complexity, brightness and contrast.

In the study phase, 120 randomly selected pictures of buildings were randomly intermixed with 120 pictures of landscapes. Stimuli were presented sequentially for 800 ms each with a randomized inter-stimulus interval (ISI) of 2000–3000 ms (mean 2500 ms). Sixty null events, consisting of a black screen shown for 2500 ms, were randomly intermixed. Subjects were required to memorize each picture and to make a building-landscape decision by right hand key-press.

In the following recognition phase, all stimuli from the study phase plus 240 new, previously not presented photographs of buildings and landscapes were shown sequentially and again randomly intermixed. The presentation rate was self-paced by subjects’ responses, resulting in a mean ISI of 2065 ms (SD 229 ms). Subjects were required to press one of three keys according to the following response categories: picture seen before or not, picture seen before with high confidence, picture uncertain to be seen before or not, picture not seen before with high confidence.

Stimuli were presented using the Experimental Run-time System (http://www.erts.de) and back-projected onto a translucent screen positioned opposite the magnet bore using an LCD-projector. Subjects viewed the stimuli by way of a mirror mounted on the head coil while lying in a supine position with their head stabilized by an individually molded vacuum cushion.

fMRI Data Acquisition

All scans were performed on a 1.5 T scanner (Symphony; Siemens, Erlangen, Germany) using standard gradients and a circular polarized phase array head coil. For each subject, we acquired two series, one for the study phase and one for the recognition phase, of $T_2^*$-weighted axial EPI-scans including eight initial dummy scans parallel to the AC/PC line with the following parameters: number of slices (NS), 30; slice thickness (ST), 4 mm; interslice gap (IG), 0.4 mm; matrix size (MS), 64 x 64; field of view (FOV), 220 mm; echo time ($T_E$), 50 ms; repetition time ($T_R$), 2.95 s. The encoding run comprised 282 scans per subject. During recognition, we acquired 282–402 scans per subject (mean number of scans: 336), depending on the individual response times. $T_2^*$-weighted 3D-FLASH scans were acquired between the functional runs for anatomical localization (NS = 120; ST = 1.5 mm; IG = none; MS = 256 x 256; FOV = 230 mm; $T_E$ = 4 ms; $T_R$ = 11 ms).

fMRI Data Analysis

MR images were analyzed using Statistical Parametric Mapping (SPM99; www.fil.ion ucl.ac.uk) implemented in MATLAB (Mathworks Inc., Sherborn, MA). To correct for their different acquisition times, the signal measured in each slice was shifted relative to the acquisition time of the middle slice using a sinc interpolation in time. All images were realigned to the first image to correct for head movement and normalized into standard stereotaxic anatomical MNI-space by using the transformation matrix calculated from the first EPI-scan of each subject and the EPI-template. Afterwards, the normalized data with a reduced voxel size of $4 \times 4 \times 4$ mm were smoothed with a 8 mm FWHM isotropic Gaussian kernel to accommodate intersubject variation in brain anatomy. Proportional scaling with high pass filtering was used to eliminate confounding effects of differences in global activity within and between subjects. All analyses were restricted to trials on which encoding responses were correct. The expected hemodynamic response at stimulus onset for each event-type was modeled by two response functions, a canonical hemodynamic response function (HRF, Friston et al., 1998) and its temporal derivative. The temporal derivative was included in the model to account for the residual variance resulting from small temporal differences in the onset of the hemodynamic response, which is not explained by the canonical HRF alone. The functions were convolved with the event-train of stimulus onsets to create covariates in a general linear model. During recognition, the presentation rate was self-paced, hence reaction time to recognition trials was included in the model as a nuisance variable to discount the possibility of a confounding effect of differences in reaction times. Parameter estimates for the HRF regressor were calculated from the least mean squares fit of the model to the time series. Parameter estimates for the temporal derivative were not considered in any contrast. Subsequently, effects of interest were specified by appropriately weighted linear contrasts of the HRF parameter estimates and determined using planned comparisons on a
voxel-by-voxel basis; the corresponding linear combination of parameter estimates for each contrast were stored as separate images for each subject. For the sake of our study goals, trials related to ‘uncertain’ responses were modeled by a separate regressor, but not considered in any contrast.

An SPM99 group analysis was performed by entering contrast images into one-sample t-tests, in which subjects are treated as random variables. Voxels with a significance level of $P < 0.005$ uncorrected belonging to clusters with at least 10 voxels are reported. Since the subsequent memory effect and the recognition effect were computed bidirectionally, this effectively results in a two-sided threshold of $P < 0.01$. Activations are shown projected onto selected coronal slices of the mean high-resolution $T_1$-weighted volume, highlighting regions of interest. The reported voxel coordinates of activation peaks were transformed from MNI space to Talairach and Tournoux (1988) atlas space by non-linear transformations (http://www.mrc-cbu.cam.ac.uk/imaging/mnispace.html). To address further the question of overlap between areas involved in both encoding and recognition, we recomputed the subsequent memory effect and the recognition effects with a statistical threshold of $P < 0.05$. Then we inclusively masked the subsequent memory effect by the positive recognition effect and the negative recognition effect respectively. These analyses permit the identification, at a high level of sensitivity, of regions in which the subsequent memory effect overlaps with recognition effects, while maintaining an acceptable type I error rate. According to Fisher’s method of combining probabilities, the probability of two independent statistical tests conjointly attaining significance at $P < 0.05$ is $P < 0.017$.

**Results**

**Behavioral Results**

During encoding, the building–landscape decision task was made with a mean accuracy of 92% (range 85–98%). Incorrect responses were recorded for 5% (2–10%) and no responses for 3% (0–7%) of all encoding trials.

Recognition memory performance and reaction times are listed in Table 1. Accuracy of recognition was assessed by the difference in probabilities of a correct old judgment and an old judgment for a new item ($Pr = \text{probability hit} – \text{probability false alarm}$). While recognition performance did not differ between stimuli classes [mean $P_{\text{building}} = 0.40$ ($SD = 0.14$) versus $P_{\text{landscape}} = 0.43$ ($SD = 0.15$)], $t_{15} = 1.019$, n.s.), it was well above chance level [mean $Pr = 0.41$ ($SD = 0.13$), $t_{15} = 15.01$; $P < 0.0001$]. Collapsing across both stimuli classes (building and landscape), we obtained a sufficient number of trials for each response category to reach an adequate contrast-to-noise ratio for our ER-fMRI analyses (78–153 trials per subject for hits, 58–113 for misses, 93–170 for correct rejections and 52–97 for false alarms).

An ANOVA comparing reaction times (Table 1) for hits, misses, correct rejections, and false alarms revealed a reliable effect of response category [$F(3,45) = 8.42, P < 0.005$]. Post-hoc paired-sample $t$-tests showed that reactions to correctly identified old items were faster than incorrect reactions to old items ($t_{15} = 3.78$, $P < 0.005$), correct reactions to new items ($t_{15} = 3.21$, $P < 0.01$) and incorrect reactions to new items ($t_{15} = 5.99$, $P < 0.0001$). All other post-hoc tests did not reveal any reliable difference (max $t_{15} = 1.51$, n.s.).

**Imaging Data**

In an exploratory analysis, we directly compared encoding activity to photographs showing either buildings or landscapes. Processing of building stimuli compared to processing of landscape stimuli showed small bilateral, left lateralized activations in superior temporal areas [Talairach and Tournoux (1988) coordinates: $x = 52$, $y = 8$, $z = -16$ and $x = -44$, $y = -4$, $z = -16$], while processing of landscapes as compared to buildings showed more activity in a small area of the right middle frontal gyrus [Talairach and Tournoux (1988) coordinates: $x = 40$, $y = 20$, $z = 40$]. These findings may indicate a slightly higher degree of verbal coding for buildings and non-verbal visual-perceptual coding for landscapes (Kelley et al., 1998). Given, however that these small differential effects are not of primary interest for the purpose of our study and that there is no difference in recognition performance, both stimuli classes were pooled together to increase statistical power for all further analyses.

**Subsequent Memory Effect**

Initially, we sought to verify prior results regarding brain regions involved in successful formation of new declarative memories. Addressing this question requires a comparison between learning events that lead to the successful and unsuccessful formation of memories. As in previous studies, we acquired brain responses to each item during study and conducted contrasts to compare events that were remembered and those that were forgotten as measured by the subsequent recognition memory test during the second experimental run. Figure 1 and Table 2 show brain regions that exhibit significantly more activity to subsequently recognized than forgotten items. In line with previous findings, these encoding areas comprise bilateral fusiform and parahippocampal areas as well as areas in the left basal and lateral frontal cortex [Brodmann Area (BA) 45, 47]. Additionally, we found an activation in the left parietal lobe located in the angular gyrus (BA 39). All activations appear to be more pronounced in the left than the right hemisphere.

**Negative Subsequent Memory Effect**

In addition to areas predicting subsequent memory by an increase of activation, we intended to identify areas in which a decrease of activation is associated with subsequent memory. Table 2 shows areas that exhibit significantly more activity during learning for subsequently forgotten as opposed to subsequently remembered items. For this contrast we found activations in right medial parietal cortex (BA 7) and in left posterior cingulate cortex.

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Old</th>
<th></th>
<th>New</th>
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<td></td>
<td>Hits</td>
<td>Misses</td>
<td>Correct rejections</td>
<td>False alarms</td>
<td>Uncertain</td>
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<td>19</td>
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<td>1479</td>
<td>1462</td>
<td>1445</td>
<td>1727</td>
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<td>187</td>
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<td>103</td>
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</tbody>
</table>

Memory Formation and Retrieval • Weis et al.
Figure 1. Subsequent memory effect. Regions activated more in case of successful as opposed to unsuccessful memory formation during encoding. The activation map ($P < 0.005$, uncorrected; minimal cluster size 10 voxels) is shown overlaid onto a canonical brain rendered in three dimensions. Specific activations are additionally shown superimposed onto selected coronal slices of the mean high-resolution $T_1$-weighted volume. Slices are numbered according to coordinates of Talairach and Tournoux (1988). IFGa, anterior aspect of the inferior frontal gyrus; IFGp, posterior aspect of the inferior frontal gyrus; PHG, parahippocampal gyrus.

Table 2
Activation peaks with their localization, significance level and the size of the respective activation cluster (number of voxels)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Anatomical region</th>
<th>BA</th>
<th>Coordinates</th>
<th>t-value</th>
<th>No. of voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent memory effect</td>
<td>Left angular g.</td>
<td>39</td>
<td>–28 –72</td>
<td>40</td>
<td>5.27</td>
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<tr>
<td></td>
<td>Left fusiform g.</td>
<td>20</td>
<td>–44 –48</td>
<td>–28</td>
<td>6.15</td>
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<tr>
<td></td>
<td>Right fusiform g.</td>
<td>37</td>
<td>24 –56</td>
<td>–16</td>
<td>4.31</td>
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<tr>
<td></td>
<td>Left parahippocampal g.</td>
<td>PHG</td>
<td>35</td>
<td>–20 –8</td>
<td>–36</td>
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<tr>
<td></td>
<td>Right parahippocampal g.</td>
<td>PHG</td>
<td>35</td>
<td>36 –12</td>
<td>36</td>
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<tr>
<td></td>
<td>Left inferior frontal g.</td>
<td>IFGa</td>
<td>47</td>
<td>–44 44</td>
<td>–12</td>
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<tr>
<td></td>
<td>Left inferior frontal g.</td>
<td>IFGp</td>
<td>45</td>
<td>–40 12</td>
<td>28</td>
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<tr>
<td>Negative subsequent memory effect</td>
<td>Right precuneus</td>
<td>7</td>
<td>8 –48</td>
<td>52</td>
<td>3.94</td>
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<td></td>
<td>Left cingulate g.</td>
<td>24</td>
<td>–16 4</td>
<td>36</td>
<td>5.30</td>
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<td>Repetition priming effect</td>
<td>Left middle occipital g.</td>
<td>MOG</td>
<td>19</td>
<td>–36 –92</td>
<td>8</td>
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<tr>
<td></td>
<td>Left middle occipital g.</td>
<td>MOG</td>
<td>18</td>
<td>–20 –92</td>
<td>20</td>
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<td>Right middle occipital g.</td>
<td>MOG</td>
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<td>28 –84</td>
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<td>Left lingual g.</td>
<td>LG</td>
<td>–32 –64</td>
<td>–4</td>
<td>4.81</td>
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<tr>
<td>Old/new effect</td>
<td>Left superior parietal l.</td>
<td>SPL</td>
<td>7</td>
<td>–32 –64</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Left inferior parietal l.</td>
<td>SPL</td>
<td>40</td>
<td>–56 –32</td>
<td>40</td>
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<tr>
<td></td>
<td>Right inferior parietal l.</td>
<td>SPL</td>
<td>40</td>
<td>36 –40</td>
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<tr>
<td></td>
<td>Right fusiform g.</td>
<td>37</td>
<td>40 –48</td>
<td>–16</td>
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<td></td>
<td>Left superior temporal g.</td>
<td>LG</td>
<td>22</td>
<td>–60 –48</td>
<td>16</td>
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<td></td>
<td>Left cerebellum</td>
<td>CH</td>
<td>–20 –56</td>
<td>–36</td>
<td>6.32</td>
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<tr>
<td></td>
<td>Left cerebellum</td>
<td>CH</td>
<td>–44 –60</td>
<td>–48</td>
<td>4.68</td>
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</table>
Repetition Priming Effect

Repetition priming refers to an implicit memory phenomenon in which repeatedly presented items are processed more efficiently, most often accompanied by weaker brain responses to old as opposed to new items. Figure 2A and Table 2 show brain regions exhibiting a decrease of activation to previously seen stimuli as opposed to new ones. As expected, we found activations in bilateral middle occipital gyri (BA 18/19). Moreover, there is an activation in left lingual gyrus.

Old/New Effect

Figure 2B and Table 2 show five brain regions that exhibit more neural activity for correctly identified old items (hits) than for correctly identified new items (correct rejections): (i) a medial-superior frontal area including the superior frontal gyrus medially and laterally in the dorsal-lateral prefrontal cortex (DLPFC), the anterior cingulate and pre- as well as supplementary motor areas (BA 6, 32); (ii) an area in the right superior frontal gyrus (anterior prefrontal cortex: APFC, BA 10); (iii) bilateral, left lateralized areas in the parietal lobe within BA 7 and 40; (iv) an area in the left insula cortex (BA 13); (v) and, finally, bihemispheric activations in the cerebellum.

Positive Recognition Effect

To explore in more detail brain areas engaged in successful memory retrieval, we examined the difference in brain responses to correctly recognized old items (hits) and old new items (correct rejections). Table 2 shows these activations and their coordinates in Talairach and Tournoux (1988) atlas space.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Anatomical region</th>
<th>BA</th>
<th>Coordinates</th>
<th>t-value</th>
<th>No. of voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old/new effect</td>
<td>Right cerebellum</td>
<td>CH</td>
<td>20 -60 -36</td>
<td>4.18</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Right cerebellum</td>
<td>CH</td>
<td>48 -64 -40</td>
<td>4.08</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Left insula</td>
<td>13</td>
<td>-38 -4 16</td>
<td>4.09</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Left precentral g.</td>
<td>PCG</td>
<td>6 -40 0 36</td>
<td>5.18</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Left superior frontal g.</td>
<td>SFG</td>
<td>6 0 16 56</td>
<td>6.03</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Right cingulate g.</td>
<td>ACG</td>
<td>32 -4 36 28</td>
<td>7.08</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Right superior frontal g.</td>
<td>SFG</td>
<td>10 32 60 16</td>
<td>5.53</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Right inferior frontal g.</td>
<td></td>
<td>47 32 20 -16</td>
<td>4.15</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Right middle frontal g.</td>
<td>32</td>
<td>12 12 44</td>
<td>3.86</td>
<td>11</td>
</tr>
<tr>
<td></td>
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<td>23</td>
<td>-4 -12 24</td>
<td>4.79</td>
<td>27</td>
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<td>Positive recognition effect</td>
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<td>AG</td>
<td>39 40 -60</td>
<td>3.73</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Vermis, cerebellum</td>
<td>Ve</td>
<td>0 -60 -20</td>
<td>4.82</td>
<td>42</td>
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<tr>
<td></td>
<td>Left pons</td>
<td>Po</td>
<td>-16 -48 -24</td>
<td>5.63</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Right middle frontal g.</td>
<td>MFG</td>
<td>6 16 12 56</td>
<td>4.86</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Left cerebellum</td>
<td></td>
<td>-20 -72 -28</td>
<td>4.18</td>
<td>15</td>
</tr>
<tr>
<td>Negative recognition effect</td>
<td>Left parahippocampal g.</td>
<td>RC/Hi</td>
<td>-24 -20 -16</td>
<td>3.77</td>
<td>6</td>
</tr>
<tr>
<td>The subsequent memory masked</td>
<td>Vermis, cerebellum</td>
<td>Ve</td>
<td>0 -60 -20</td>
<td>3.21</td>
<td>23</td>
</tr>
<tr>
<td>The subsequent memory masked</td>
<td>Right angular g.</td>
<td>AG</td>
<td>39 40 -60</td>
<td>3.85</td>
<td>14</td>
</tr>
<tr>
<td>the positive recognition effect</td>
<td>Left pons</td>
<td>Po</td>
<td>-28 -32 -28</td>
<td>3.83</td>
<td>34</td>
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<tr>
<td></td>
<td>Left fusiform g.</td>
<td>FG</td>
<td>20 -36 -60</td>
<td>4.23</td>
<td>30</td>
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<tr>
<td></td>
<td>Left inferior temporal g.</td>
<td>ITG</td>
<td>20 -56 -16</td>
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<tr>
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<td>Left parahippocampal g.</td>
<td>RC</td>
<td>20 -36 -8</td>
<td>2.51</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Right parahippocampal g.</td>
<td>RC</td>
<td>20 40 0 -36</td>
<td>3.56</td>
<td>12</td>
</tr>
<tr>
<td>The subsequent memory masked</td>
<td>Left parahippocampal g.</td>
<td>RC/Hi</td>
<td>28 -24 -16</td>
<td>2.99</td>
<td>17</td>
</tr>
<tr>
<td>the negative recognition effect</td>
<td>Left cerebellum</td>
<td></td>
<td>-44 -48 -28</td>
<td>5.37</td>
<td>12</td>
</tr>
</tbody>
</table>

Coordinates are listed in Talairach and Tournoux (1988) atlas space. BA is the Brodmann area nearest to the coordinate and should be considered approximate (g., gyrus).
items misclassified as new (misses). This contrast (Fig. 3A and Table 2) shows some overlap with activations seen in the old/new contrast regarding gross anatomy, but with the following differences: (i) the right prefrontal activation is centered in the middle frontal gyrus (BA 6) instead of area BA 10; (ii) contrary to the cerebellar old/new effect, the cerebellar recognition effect appears to be stronger and more pronounced at midline structures like the vermis, the intermediate cerebellar hemispheres and the tonsils and it is extended to the relay station for cerebellar afferents, the pons; and (iii) there is an activation of the right angular gyrus, which is not seen in the old/new effect. Nevertheless, the overall location of activations in prefrontal, parietal and cerebellar areas is not entirely different from the old/new effect.

**Negative Recognition Effect**

Negative recognition effects were obtained by comparing brain responses to misses with responses to hits. As described in the introduction, repetition priming contaminates this effect to a lesser degree. Applying the same minimal cluster size as used for all other contrasts did not lead to a reliable negative recognition effect. However, considering clusters consisting of five voxels or more reveals a left anterior MTL activation (Fig. 3B, Table 2), which is exactly in line with our hypothesis based on electrophysiological findings in humans (Smith et al., 1986) and animals (Brown and Aggleton, 2001). The activation is centered in the anterior parahippocampal gyrus, but, as can be seen in Figure 3B, the activation might extend into the hippocampus.

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**Figure 2.** Repetition priming effect (A) and old/new effect (B). Regions activated more for new as opposed to old stimuli during recognition (A). Regions activated more for hits as compared to correct rejections during recognition (B). Activation maps (P < 0.005, uncorrected; minimal cluster size 10 voxels) are shown overlaid onto a canonical brain rendered in three dimensions. Specific activations are additionally shown superimposed onto selected coronal slices of the mean high-resolution T1-weighted volume. Slices are numbered according to coordinates of Talairach and Tournoux (1988). ACG, anterior aspect of the cingulate gyrus; CH, cerebellar hemisphere; LG, lingual gyrus; MOG, middle occipital gyrus; PCG, precentral gyrus; SFG, superior frontal gyrus; SPL, superior parietal lobule.
The Subsequent Memory Effect Inclusively Masked by the Positive Recognition Effect

To identify brain areas showing increased activity for both successful declarative memory formation and retrieval, we masked the subsequent memory effect by the positive recognition effect. Figure 4A and Table 2 show regions that are activated by these two contrasts. In line with our hypotheses regarding the critical role of the inferior and medial temporal lobe we identified bilateral activations in the anterior half of the inferior temporal cortex. In both hemispheres, this area reaches the depth of the collateral sulcus, which is covered by perirhinal cortex (Amaral and Insausti, 1990). Additionally, we identified a major activation in the cerebellar vermis and its afferent relay station, the pons. Further activations are located in left fusiform gyrus, right angular gyrus and in bilateral cerebellar hemispheres.

The Subsequent Memory Effect Inclusively Masked by the Negative Recognition Effect

Inclusively masking the subsequent memory effect by the negative recognition effect allows the identification of brain areas associated with activity increases during successful memory formation and activity decreases during successful memory retrieval. Figure 4B and Table 2 show brain areas exhibiting such a pattern of reactivity. Again, in line with our hypotheses we revealed an anterior MTL activation including the left hippocampus, but centered in the left parahippocampal gyrus.

Discussion

Memory Formation

Replicating almost all earlier findings, we revealed subsequent memory effects in a fusiform/parahippocampal and two left
inferior frontal areas, one in the posterior and one in the anterior aspect of the inferior frontal gyrus (Brewer et al., 1998; Wagner et al., 1998; Kirchhoff et al., 2000; Davachi et al., 2001; Otten et al., 2001; Otten and Rugg, 2001a; Strange et al., 2002). The additional subsequent memory effects in the parietal lobe and the cerebellar hemisphere were previously less often reported (Davachi et al., 2001; Otten and Rugg, 2001a). However, the left lateralization of the subsequent memory effects found here is not exactly in line with other studies also using picture stimuli (Brewer et al., 1998; Kirchhoff et al., 2000). It might be explained by the additional use of verbal codes for picture details (Kelley et al., 1998; Opitz et al., 2000). Regardless, our results confirm that prefrontal and medial temporal areas are involved in declarative memory formation, where prefrontal cortex may execute working memory operations associated with maintenance, selection and organization of incoming information (Wagner, 1999; Fletcher and Henson, 2001) and the MTL may execute a rather specific operation of declarative memory formation in the hippocampus and a subordinate support operation in the parahippocampal region. This support operation may make semantic representations of each study item available in the service of comprehension, semantic-associative processing, and memory formation (Nobre and McCarthy, 1995; Fernández et al., 2002).

The negative subsequent memory contrast, more activity for subsequently forgotten than subsequently remembered items, revealed only two small clusters of voxels in the precuneus and the cingulate gyrus. The location of these activations is roughly

![Image of brain scans showing activity in various regions](image-url)
congruent with activations described in the initial reports of this effect (Otten and Rugg, 2001b; Wagner and Davachi, 2001). These positive correlates of forgetting have been interpreted as related to task-appropriate and task-inappropriate allocation of neurocognitive resources away from the process leading to effective memory formation (Otten and Rugg, 2001b; Wagner and Davachi, 2001).

**Recognition**

The old/new contrast revealed major activations in the parietal lobe, in frontal midline structures (anterior cingulate and the superior frontal gyrus), the left insula, the right anterior aspect of the superior frontal gyrus and in both cerebellar hemispheres with a left hemispheric dominance. As intended, these findings replicate earlier ER-fMRI findings that suggest distributed cerebral and cerebellar brain regions participating in recognition memory (Henson et al., 1999; Konishi et al., 2000; McDermott et al., 2000; Cabeza et al., 2001; Donaldson et al., 2001a,b). Among these regions, the midline structures activated (anterior cingulate and the superior frontal gyrus) might control subject responses by evaluating stimulus representations restored in the parietal lobe (Buckner et al., 1996; Fletcher et al., 1996). Especially with the large number of stimuli used here, a high degree of interference or response competition makes an effective control of response selection and inhibition necessary (Carter et al., 1998; Braver et al., 2001; Potts and Tucker, 2001; Stern et al., 2001; Levy and Anderson, 2002). Together with the left prefrontal subsequent memory effect described above, the right anterior prefrontal activation is fully in accord with the hemispheric encoding/retrieval asymmetry (HERA) model of a prefrontal encoding and retrieval asymmetry as proposed initially by Tulving et al. (1994). The right anterior prefrontal activation might correlate with postretrieval monitoring processes and not with the actual process of memory retrieval (Rugg et al., 1996; Schacter et al., 1997; Buckner et al., 1998). The old/new effects in cerebellar hemispheres indicate that the cerebellum plays a role in memory retrieval (Bäckman et al., 1997; Cabeza et al., 1997; Andreasen et al., 1999). The implication of this finding will be discussed below, interpreted in the context of the areas involved in both memory formation and retrieval.

The newly introduced positive recognition contrast (i.e. more activity for hits than misses) revealed activations in the frontal and parietal lobe that are close to activations revealed by the old/new contrast, but without direct overlap. The cerebellar activation is compared to the old/new effect more centered at midline structures (i.e. vermis, intermediate cerebellar hemispheres and tonsils) and extended to pontine areas where input from prefrontal, parietal and temporal cortices is relayed to the cerebellum (Schmahmann, 1996). The failure to find exact overlap between the positive recognition- and the old/new effect must, like all null results, be treated with caution. This is especially so, given that the power to detect a recognition effect was lower than the power to detect an old/new effect, a consequence of fewer old misses than new correct rejections. Nevertheless, our findings seem to support the view that frontal, parietal and cerebellar regions are involved in the successful recovery of declarative memories during a recognition memory task.

The small negative recognition effect may indicate that less activity in the anterior MTL is related to recognition success. This finding is in line with our hypothesis and electrophysiological studies (Smith et al., 1986; Riches et al., 1991; Miller and Desimone, 1994; Brown and Aggleton, 2001). It is unlikely that this effect is solely based on repetition priming, because both classes of items have been encountered once before. However, since our study design does not provide a behavioral measure of repetition priming, we are unable to test stochastic independence between primed and recognized items. Though, the location of priming effects in occipital areas only (Fig. 2B) makes a repetition priming account for the negative recognition effect in the anterior MTL highly unlikely. Nevertheless, there seem to be alternative interpretations for the negative recognition effect: old items misclassified as new could be re-encoded during the test phase leading to an encoding related activity increase (Buckner et al., 2001), or the subjects’ new-decision could be accompanied by an activity increase related to novelty detection (Tulving and Kroll, 1995; Tulving et al., 1996). The first alternative interpretation is not mutually exclusive with the recognition account (see below) and the latter interpretation seems to be less plausible, because a reversed old/new contrast with more statistical power (more items) did not show any activation in the anterior MTL (data not shown).

Given our study design, we cannot dissociate between subprocesses within recognition - whether an activation is related to recollection or familiarity (Mandler, 1980). This issue could be further evaluated by a study design including for instance a source memory judgment (Cansino et al., 2002). However, following Brown and Aggleton (2001) or Brown and Bashir (2002), the negative recognition effect in the anterior MTL might rather support a familiarity-based decision than an actual recollective experience (Henson et al., 2003). It may reflect a process enabling recognition by more efficient processing of recognized stimuli with reduced neural activity during an active memory search (Jiang et al., 2000), or by a neural activity increase in the presence of novel stimuli or old stimuli incorrectly classified as new (Brown and Bashir, 2002).

**Memory Formation and Recognition**

The largest activation clusters of the subsequent memory effect masked by the positive recognition effect are located in the inferior and anterior medial temporal lobe as well as cerebellar and pontine regions. When masking the subsequent memory effect by the negative recognition effect, activations are located in the MTL.

Thus, the anterior inferior temporal cortex including the anterior parahippocampal region seems to be conjointly involved in both successful encoding and recognition. This finding confirms suggestions based on across-study comparisons of electrophysiological findings in epilepsy patients (Smith et al., 1986; Fernández et al., 1999, 2001, 2002). Such a module has originally been described on the basis of electrical recordings in non-human primates showing that this brain area is sensitive to both object encoding and object recognition (Desimone et al., 1984; Riches et al., 1991; Miller and Desimone, 1994). During recognition, the neural representation of each test stimulus, i.e. a unique pattern of activation that is evoked by a visually perceived item during recognition, may be matched with stored representations previously formed locally during encoding. Moreover, the inferior and medial temporal cortex is ideally located for this efficient pattern matching, because it is the final route of the ventral visual pathway, providing integrated visual and semantic information (Ungerleider and Mishkin, 1985; Haxby et al., 1991;
Nobre and McCarthy, 1995; Büchel et al., 1998; Lerner et al., 2001).

Our findings suggest an important role of the cerebellum and its afferent relay station, the pons, in declarative memory. Functional imaging studies provide mounting evidence that the cerebellum coordinates diverse aspects of cognitive processes (for a review, see Desmond and Fiez, 1998). Up to now, however, it is unclear whether the cerebellum provides domain-general computations supporting diverse cognitive operations or different operations with specific roles in particular cognitive domains. Several proposals have been made for a general operation, including a central timing processor (Keele and Ivry, 1990) for sequential parsing of temporally complex material (Llinás, 1974; De Zeeuw et al., 1998). Thach (1998) proposed that cerebellar processing entails stimulus–response linkage by grouping single-response elements into larger task adequate combinations. The cerebellum also seems to be involved in processes contributing specifically to learning and memory. It is not only critically involved in basic delay conditioning, where it is the locus of memory formation, consolidation, and storage (Thompson and Kim, 1996; Attwell et al., 2002), it is also involved in spatial learning and memory (Pellegrino and Altmann, 1979; Lalonde and Botez, 1990; Goodlett et al., 1992). Humans with acquired cerebellar lesions have, however, only minor deficits in declarative memory (Schmahmann, 1998). In imaging studies of declarative memory, cerebellar activations were rather obtained during retrieval than encoding tasks (Desmond and Fiez, 1998), suggesting that a cortical-cerebellar network self-initiates and monitors conscious retrieval (Bäckman et al., 1997; Andreasen et al., 1999) or that the cerebellum generates candidate responses during a search and selection process (Cabeza et al., 1997; Desmond et al., 1998). Our data show that the cerebellum participates in both memory formation and retrieval. However, the fact that cerebellar lesions cause only minor deficits in declarative memory suggests that the cerebellum is not directly involved in storage and retrieval operations. It might rather support mnemonic operations by providing a temporal structure for a coherent episode.

In conclusion, by replicating ER-fMRI studies investigating either memory formation or recognition we have provided within-study confirmation for brain areas involved in two fundamental mnemonic operations: either the formation or the retrieval of declarative memories. Based on this empirical foundation, we have described for the first time brain regions involved in two domain-general computations supporting diverse cognitive domains. Several proposals have been made for a general operation, including a central timing processor (Keele and Ivry, 1990) for sequential parsing of temporally complex material (Llinás, 1974; De Zeeuw et al., 1998). Thach (1998) proposed that cerebellar processing entails stimulus–response linkage by grouping single-response elements into larger task adequate combinations. The cerebellum also seems to be involved in processes contributing specifically to learning and memory. It is not only critically involved in basic delay conditioning, where it is the locus of memory formation, consolidation, and storage (Thompson and Kim, 1996; Attwell et al., 2002), it is also involved in spatial learning and memory (Pellegrino and Altmann, 1979; Lalonde and Botez, 1990; Goodlett et al., 1992). Humans with acquired cerebellar lesions have, however, only minor deficits in declarative memory (Schmahmann, 1998). In imaging studies of declarative memory, cerebellar activations were rather obtained during retrieval than encoding tasks (Desmond and Fiez, 1998), suggesting that a cortical-cerebellar network self-initiates and monitors conscious retrieval (Bäckman et al., 1997; Andreasen et al., 1999) or that the cerebellum generates candidate responses during a search and selection process (Cabeza et al., 1997; Desmond et al., 1998). Our data show that the cerebellum participates in both memory formation and retrieval. However, the fact that cerebellar lesions cause only minor deficits in declarative memory suggests that the cerebellum is not directly involved in storage and retrieval operations. It might rather support mnemonic operations by providing a temporal structure for a coherent episode.

In conclusion, by replicating ER-fMRI studies investigating either memory formation or recognition we have provided within-study confirmation for brain areas involved in two fundamental mnemonic operations: either the formation or the retrieval of declarative memories. Based on this empirical foundation, we have described for the first time brain regions supporting successful memory retrieval by both activity increases (frontal, parietal, cerebellar areas) and decreases (anterior MTL). Finally, we have initially identified within subjects and within one experiment inferior- and medial-temporal as well as cerebellar areas supporting both memory formation and retrieval. Such integrated modules may re-use stored representations formed locally during encoding for efficient matching operations during recognition.

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Process dissociation between contextual retrieval and item recognition

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INTRODUCTION

Dual-process models of recognition memory propose qualitative distinct forms of memory supporting recognition of an item [1,2]. While recollection, i.e. recognition of an item that is accompanied by contextual information, is truly episodic memory, recognition unaccompanied by contextual information can rely upon a sense of familiarity [1,3].

Lesion studies identified the medial temporal lobe (MTL) to be crucial for recognition memory [4], but the specific role of MTL subregions in contextual retrieval and item recognition is highly disputed [5,6]. Several event-related fMRI studies of memory formation have examined the difference in activity during encoding in different MTL subregions that leads to subsequent familiarity-based recognition as opposed to subsequent recollection [7,8]. These studies showed that encoding activity in the rhinal cortex selectively predicted familiarity-based recognition, whereas encoding activity in the hippocampus and posterior parahippocampal cortex selectively predicted recollection.

Event-related fMRI studies of recognition memory investigating contextual retrieval showed that hippocampal activity increased with recollection success [9,10] (but see [11]). However, several studies investigating item recognition using of the old/new effect, the difference in brain activity between correctly recognized old, previously studied items (hits), and correctly identified new, previously unstudied items (correct rejections), did not reveal any MTL activity increase [11,12] (but see [6]).

Electrophysiological studies have shown that anterior parahippocampal activity decreases during item recognition [13]. Also a recent meta-analysis of four event-related fMRI studies suggested that less anterior MTL activity is related to the amount of familiarity [14]. Thus, different functional processes, being either based on an activity increase or an activity decrease, might be involved with contextual retrieval and item memory in neighboring or overlapping MTL subregions.

To study an activity decrease associated with successful item recognition, a reversed old/new contrast is not suited, since simple repetition effects would confound it. On the other hand, a negative recognition effect (hits misses; old previously studied items misclassified as new) is less contaminated by repetition effects, because both items have been studied. This contrast revealed an anterior MTL effect, indicating that less activity in this brain region is related to item recognition success [12]. However, in that study no formal dissociation between recollection and item recognition was implemented. Therefore, in the present study, we investigated whether an MTL activity decrease is associated with simple, a-contextual item recognition and an MTL activity increase with associative, contextual retrieval.

MATERIALS AND METHODS

Subjects: Twelve healthy volunteers (six male; mean age 28 year, range 20–34) with normal or corrected-to-normal vision participated in the experiment. Written informed consent was obtained from each subject. Subjects were trained to press one of two keys as fast as possible if the stimulus was presented during study, whereas green was transformed into one of four single-color-scales: red, blue, yellow, or green. In the subsequent old/new recognition memory test, all stimuli were presented as gray scale photographs, and old responses were followed by a four-alternative source judgment referring to the color in which the stimulus was presented during study. Our results suggest a clear-cut process dissociation within the human MTL. While an activity increase accompanies successful retrieval of contextual information, an activity decrease provides a familiarity signal that is sufficient for successful item recognition. NeuroReport 15:2729–2733 © 2004 Lippincott Williams & Wilkins.

We employed a source memory task in an event related fMRI study to dissociate MTL processes associated with either contextual retrieval or item recognition. To introduce context during study, stimuli (photographs of buildings and natural landscapes) were transformed into one of four single-color-scales: red, blue, yellow, or green. In the subsequent old/new recognition memory test, all stimuli were presented as gray scale photographs, and old-responses
consent was obtained in a manner approved by the Medical Ethics Committee of the University of Bonn and according to the Declaration of Helsinki (1991). Subjects were paid for their participation.

Stimuli and task: Stimuli consisted of 360 gray-scale photographs of either buildings or natural landscapes (180 for each category) that were selected to be similar in complexity, brightness, and contrast.

The experiment was divided into four study–test cycles. Between the study and test phases, there were short breaks of a few minutes. During each of the four study phases, subjects saw 60 pictures, which were transformed into red-, blue-, yellow- and green-scale (15 pictures for each color). Subjects were required to memorize each picture together with its color and to make a building-landscape decision. During each of the four recognition phases 90 pictures (60 previously studied and 30 new) were presented as plain gray-scale photographs. Subjects were required to make an old/new decision for each picture and further to indicate the color in which the picture had been presented during study.

To counterbalance stimuli across subjects, all pictures where randomly divided into three sets of 60 buildings and 60 landscapes each. For the study phases, two of the three sets of pictures were selected for each subject, resulting in four subjects seeing the same 240 pictures during the study phases. For each of these four subjects, different subsets of 60 pictures each were transformed into red-, blue-, yellow- and green-scale, so that no two subjects saw the pictures in the same color.

During the study phases, stimuli were presented sequentially for 800 ms with a randomized interstimulus interval (ISI) of 3600–5600 ms (mean 4600 ms). Additionally, 120 phases of baseline stimulation (i.e. black screen), each lasting 2000 ms, were randomly intermingled as so-called null events. Both the ISI variation and the inclusion of null events have been shown to increase the statistical efficiency of event-related designs [15]. Subjects made the building-landscape decision by one of two alternative key-presses using the right hand.

During the recognition phases, stimuli were shown randomly intermixed with 180 null events at the same presentation rate as during study. Subjects were required to make the old-new decision by one of two alternative key-presses using the right hand. For those stimuli judged as old, four colored squares were subsequently displayed on the screen for 800 ms. The interval between the offset of stimulus presentation and the onset of the color display presentation was varied between 1200 and 2400 ms (mean 1600 ms). Subjects were required to indicate the color in which the item had been presented during the study phase by one of four alternative key-presses using the right hand.

fMRI data acquisition: Scans were performed on a 1.5 T scanner (Symphony, Siemens, Erlangen, Germany) using standard gradients and a circular polarized phase array head coil. We acquired T2-weighted axial EPI-scans parallel to the AC/PC line with the following parameters: number of slices (NS) 30; slice thickness (ST) 4 mm; interslice gap (IG) 0.4 mm; matrix size (MS) 64 × 64; field of view (FOV) 220 mm; echo time (TE) 50 ms; repetition time (TR) 2.95 s. T1-weighted 3D-FLASH scans were acquired for anatomical localization (NS 120; ST 1.5 mm; IG none; MS 256 × 256; FOV 230 mm; TE 4 ms; TR 11 ms).

fMRI data analysis: Statistical parametric mapping (SPM2, www.fil.ion.ucl.ac.uk) was used for data analysis. Preprocessing using standard procedures included realignment, unwarping, slice-time correction, normalization into the stereotaxic Montreal Neurological Institute space, and spatial smoothing with an 8-mm FWHM isotropic Gaussian kernel. The time series data were band-pass filtered to remove artifacts occurring over time. The expected hemodynamic response at stimulus onset for each event-type was modeled by a canonical hemodynamic response function (HRF) and its temporal derivative. The temporal derivative was included to account for residual variance. The functions were convolved with the event-train of stimulus onsets to create covariates in a general linear model. Subsequently, parameter estimates of the HRF regressor for each of the different conditions were calculated from the least mean squares fit of the model to the time series. A random-effects group analysis was performed by entering parameter estimates for all conditions into a within-subject one-way ANOVA.

RESULTS

Behavioral results: During study, the building/landscape decision task was performed with a mean accuracy of 94% (range 90–98%). All trials with missing or incorrect building/landscape decisions were excluded from further analyses.

Recognition memory performance and reaction times for the old-new decision are listed in Table 1. Accuracy of item recognition was assessed by the difference in probabilities of a correct old judgment and an old judgment for a new item (Pr−hit−probability hit−probability false alarm). While recognition performance did not differ between stimulus classes (mean (± s.d.) Pbuilding=0.41±0.14) vs mean Plandscape=0.40±0.17, t11=1.07, n.s.), it was well above the chance level of Pr=0 (mean Pr=0.41±0.15, t11=8.40, p<0.00001). The accuracy of source judgments was also well above the chance level of 25% (mean correct 50.8±11%, t11=7.98, p<0.001). Since recognition performance did not differ between stimulus classes (building/landscape) we collapsed their trials together.

Imaging data: Initially, we directly investigated the neural correlates of successful contextual retrieval by the positive source memory effect, more brain activity for hits with correct source judgment (i.e. correctly identified new items with correct color assignment) as opposed to hits with incorrect source judgment (incorrect color assignment). We found an increase in activity in bilateral MTL, centered in the anterior hippocampus (Fig. 1a) and extending into the parahippocampal gyrus and the amygdala (BA 28/34). The peak of the activity increase was located at Talairach and Tournoux [16] coordinates −16,−5,−17 (significant at T=4.47) on the left and at 24,−1,−17 (significant at T=4.01) on the right. The negative source memory effect, a decrease of activity for hits with correct source judgment as opposed to those with incorrect source judgment revealed no reliable difference, even after lowering the statistical threshold to p<0.05 uncorrected. Fitted hemodynamic
responses (Fig. 2) show that only hits with correct contextual retrieval exhibit a significant increase in activity as compared to all other conditions (main effect of condition: \( F(4,44) = 8.410, p < 0.005 \), minimum \( t_{1f} = 3.813, p < 0.005 \)). Thus, retrieval of contextual information is accompanied by a bilateral MTL activity increase.

In the next step, we tackled the neural correlates of successful item recognition without contextual retrieval. We initially assessed the negative item recognition effect, less activity for hits with incorrect source judgment as opposed to misses. This contrast revealed a decrease of activity in the right anterior MTL (Fig. 1b), peaking at 28,\(-17,\)−19 (significant at \( T = 3.79 \)). Hits without contextual retrieval and false alarms show an activity decrease below baseline, which is significantly different from all other conditions (Fig. 2; main effect of condition, \( F(4,44) = 8.410, p < 0.005 \), minimum \( t_{1f} = 3.813, p < 0.005 \)). Thus, correct item recognition and incorrect old judgments to new items is accompanied by an activity decrease in the anterior MTL.

It may seem that the positive source memory effect is more pronounced in the left and the negative item recognition effect in the right MTL. Therefore, we directly compared brain activity of the left and right MTL using a paired-sample \( t \)-test. However, we did not reveal a significant lateralization effect neither for the positive source memory effect nor the negative item recognition effect.

**DISCUSSION**

Our goal was to dissociate human MTL processes associated with either contextual retrieval or item recognition. In contrast to mere item recognition, a correct source judgment requires the retrieval of contextual information, in this case the color in which the picture was studied. Thus, we first examined the difference in brain activity between hits with and without correct source judgment, looking for an increase of activity associated with contextual retrieval. As predicted, this contrast led to an activity increase in bilateral MTL, centered in the anterior hippocampus. In line with prior studies [9,10] this finding indicates that an increase of activity of the hippocampus, which is reciprocally connected to numerous parts of associative cortex, is essential for the process of linking an item to contextual information during retrieval. Thus, the MTL seems to support truly episodic memory by an activity increase during the successful retrieval of contextual information.

To identify brain areas whose activity is related to simple item recognition success, we used the negative item recognition effect, a decrease of activity for hits with incorrect source judgment as opposed to misses [12]. In line with our hypothesis and our prior, yet unspecific finding [12], we revealed an anterior MTL deactivation, centered in the anterior parahippocampal gyrus. As shown in Fig. 2, also false alarms showed a significant activity decrease below baseline. These errors might be based on a feature overlap between items actually studied and un-studied, inducing a feeling of familiarity and leading to a false alarm. Hits with correct source judgment are supposed to be familiar as well. Hence, the smaller familiarity signal for hits with correct source judgments is difficult to interpret. Taking into account considerable spatial errors

**Table 1.** Mean item recognition performance/source recognition performance and reaction times (RT) with their s.d.

<table>
<thead>
<tr>
<th></th>
<th>Old</th>
<th>Misses</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Item + Source</td>
<td>Item only</td>
</tr>
<tr>
<td>Number % s.d.</td>
<td>146</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>RT (ms) s.d.</td>
<td>1491</td>
<td>288</td>
<td>1455</td>
</tr>
</tbody>
</table>

Note: Hits = correctly identified old, previously studied items; Misses = old, previously studied items, misclassified as new; Correct rejections = correctly identified new, previously unstudied, items; False alarms = new, previously unstudied, items misclassified as old; Item + Source = hit with correct assignment of the color; Item only = hit without correct color assignment. Percentage of all old items, all hits, and all new items.

**Fig. 1.** Positive source memory effect and negative item recognition effect. (a) Regions activated more for hits with correct source judgments as opposed to hits with incorrect source judgments (positive source memory effect). (b) Regions activated less for hits with incorrect source judgments as opposed to misses (negative item recognition effect). The activation maps are shown superimposed onto selected coronal slices of the mean high-resolution TI-weighted volume \((p < 0.001 \) uncorrected, minimal cluster size 10). Slices are numbered according to coordinates of Talairach and Tournoux [16].
due to signal distortion (susceptibility artifacts) and spatial filtering one cannot exclude partial spatial overlap between the negative item recognition effect and the positive source memory effect partially canceling each other out.

The anterior parahippocampal region is part of the final route of the ventral visual pathway, where higher order visual processing takes place and visual and semantic features of incoming information are integrated [17]. Evidence from studies in experimental animals suggests that this area plays a key role in visual recognition memory [18,19]. Specifically, a decrease in object-selective responses with repeated exposure has been shown [3]. Thus, it has been suggested that this region contributes to recognition memory by assessing relative familiarity, which is based on neuronal response decrements [3]. Our data suggest a similar mechanism in humans, in which more neural resources may be needed for items that are processed for the first time than for those that have been encountered before and are therefore already familiar. Thus, this operation might support item recognition by a familiarity signal, which essentially is based on a reduced processing demand for more familiar items.

However, more activity in the same parahippocampal region is associated with a higher probability of successful memory formation [12,20–22]. Thus, another way of looking at the negative item recognition effect concerns the amount of encoding activity elicited during recognition by new items and old items misclassified as new [23]. This idea is in line with electrophysiological data recorded from within this region in epilepsy patients, where the very same event related potential is correlated negatively with item recognition and positively with encoding success [13,24]. However, the two explanations are not mutually exclusive, they might rather represent the two sides of the same coin, where familiar items have less processing demands and deeply processed items are subsequently better remembered.

CONCLUSION

Our data provide first within-study evidence for a process-dissociation between contextual retrieval and item recognition within the human MTL. While an activity increase may play a key role in the reassociation of complex episodes, which is essential for successful contextual retrieval, a reduction of processing activity is sufficient for item recognition, which might be the basis for a feeling of familiarity.

REFERENCES


Word Imageability Affects the Hippocampus in Recognition Memory

Peter Klaver,1,2 Jürgen Fell,1 Thomas Dietl,4 Simone Schür,1 Carlo Schaller,3 Christian E. Elger,1 and Guillén Fernández1,5

ABSTRACT: Concrete words, whose meanings are readily imagined, are better remembered than abstract words. However, the neural correlates of this effect are poorly understood. Here, we investigated the effect of imageability on brain activity in the medial temporal lobe (MTL) processes underlying recognition memory. We recorded event-related potentials (ERPs) via depth electrodes from within the MTL in 14 patients with drug-resistant epilepsy. Patients performed a continuous word recognition task with words of high and low imageability (controlled for word frequency). Behaviorally, recognition performance was better for high, compared to low, imageable words. Two ERP components associated with recognition memory, the AMTL-N400 and the hippocampal late negative component, showed an old/new effect, but only the hippocampal P600 showed a main effect of imageability. We suggest that the hippocampal effect of imageability in recognition memory may be associated with conceptual or pictorial information processing of concrete words. © 2005 Wiley-Liss, Inc.

KEY WORDS: MTL; ERPs; imageability; recognition memory

INTRODUCTION

An important feature that affects memory for single words is concreteness or imageability: Words that have a concrete representation in the outside world can be easily imagined (Richardson, 1975) and are better remembered, compared with words that are verbally learned, such as abstract words (Paivio, 1971). The general theoretical view is that the benefit of concrete words in memory performance is due to the stronger semantic association with other concepts or perceptual representations. For example, Paivio proposed that this effect relies on dual or multiple representations in both the verbal and the pictorial or visuo-perceptual domain (Paivio, 1986). Schwanenflügel et al. (1998) made a more general proposition by suggesting that concrete words generate a richer semantic context than abstract words, such that they can more easily be associated with other concepts (Gregg, 1976; Walker and Hulme, 1999), whereas abstract words often require a sentential context to attribute meaning to the words (Kieras, 1975). Both researchers who claim that concreteness depends on multiple sensory representations and those who claim that concrete words are easily associated with other concepts agree on the hypothesis that concrete words engage rich semantic associations with other representations.

In the present study, we focus on the neural mechanisms underlying the memory benefit of concrete words in the MTL. Functional brain imaging and neuropsychological studies provided some insight in the neural mechanisms of this benefit and suggest that the MTL may contribute to the concreteness effect. Functional imaging studies showed that imageable words activate brain areas that are related to the pictorial or visual-perceptual representations, such as the left posterior fusiform gyrus (Fiebach and Friederici, 2004), which is covered by parahippocampal cortex (Amaral and Insausti, 1990). Several other studies found that concrete words activate brain areas in various tasks (D’Esposito et al., 1995; Mellet et al., 1998), although not all studies reported such activity (Friederici et al., 2000; Kiehl et al., 1999; Noppeney and Price, 2004). Two imaging studies that used a memory task reported no concreteness effect in the MTL (Jessen et al., 2000; Wagner et al., 1999). However, the absence of MTL activations might be due to susceptibility artifacts, which are common in this area (Ojemann et al., 1997) and remained an obstacle in measuring the MTL until a few years ago. A positron emission tomography (PET) study, which did not suffer from susceptibility artifacts, showed that processing concrete nouns activated bilateral perirhinal cortex (Wise et al., 2000), a brain region anterior to the fusiform gyrus, part of the MTL, and thought to support conceptual object processing (Buckley and Gaffan, 1998; McCarthy et al., 1995; Murray and Bussey, 1999). On the basis of this result, it was argued that the perirhinal cortex contributes to the activation of conceptual knowledge in concrete nouns (Scott, 2004).

Neuropsychological studies provided additional evidence that memory-related areas anterior to the fusiform gyrus might be associated with concreteness. For example, several neuropsychological single case studies investigated patients with left inferior anterior-temporal lobe lesions, and reported an advantage of abstract concepts in a variety of tasks, including memory and imagery tasks (Breedin et al., 1994; Cipolotti and Warrington, 1995; Warrington and Shallice, 1984).

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All these patients suffered from semantic memory deficits, which may have arisen from the disturbed mapping between input modality and semantic memory (Bozeat et al., 2000). Another study suggested hemispheric lateralization of imageability processing within the MTL (Jones-Gotman and Milner, 1978). These investigators found that patients with righttemporal lobectomy were impaired on learning concrete word pairs, whereas they performed normally on learning abstract word pairs. The authors suggested that the right MTL contributes to the memory for concrete words. Taken together, there is evidence that the MTL plays a specific role in the processing of concrete words. However, both functional imaging and neuropsychological studies have not been conclusive about whether the hippocampus or the surrounding cortex is involved in processing concrete words. In addition, these studies have provided no temporal information about the concreteness effect in the MTL.

### METHODS AND MATERIALS

One method that has both the spatial and temporal resolution to investigate neural mechanisms of the MTL are recordings from intracranial depth electrodes in patients with pharmacoresistant unilateral epilepsy who undergo presurgical diagnostics. The intracerebral depth electrodes are implanted in the MTL bilaterally, penetrating the hippocampus and the anterior parahippocampal gyrus, which is covered by ento- and perirhinal cortex. If seizures are proved to originate unilaterally, contralateral electrodes provide a rare chance to directly investigate memory processes within the MTL unrelated to epilepsy (Fernández and Tendolkar, 2001). Three depth event-related potentials (ERPs) are relevant in the study of verbal mnemonic MTL operations. First, recordings from the rhinal cortex showed a negative waveform that peaks around 400 ms after the presentation of words (McCarthy et al., 1995). This was termed AMTL-N400, and was thought to be indirectly related to memory and semantic processes (Fernández and Tendolkar, 2001). Several studies supported this idea. For example, the AMTL-N400 was reduced with stimulus repetition (Halgren et al., 1994; Nobre and McCarthy, 1995; Smith et al., 1986), independent of whether recognition was successful (Fernández et al., 2001; Grunwald et al., 2003). During memory formation, this component was found to be larger in amplitude if words were subsequently recalled, as opposed to later forgotten words (Fernández et al., 1999). This effect was found to be larger for high-frequency words, as opposed to low-frequency words (Fernández et al., 2002). Moreover, an effect of semantic processing on the AMTL-N400 was reported. Semantic priming of words reduced the amplitude of the AMTL-N400, and words with rich semantic content showed a larger AMTL-N400 than words that served only grammatical functions (Nobre and McCarthy, 1995). These studies demonstrate an effect of lexical-semantic processing on the AMTL-N400 and its indirect effect on memory performance.

The second depth ERP was recorded from within the hippocampus. These recordings showed a positive wave peaking between 400 and 800 ms (the P600). This wave was found to increase with successful memory formation (Fernández et al., 1999), independent of word frequency. In a continuous recognition task, the P600 increased for repeated words when subjects were required to attend to the repetitions of words, but not when the task was to attend to other types of targets (Grunwald et al., 2003). Also, in that study, correctly recognized words induced a larger P600, compared with unrecognized words. In addition to this role in memory processing, the P600 may also reflect more general semantic processing. This was suggested by findings of a larger P600 for real objects than for nonsense objects (Vannucci et al., 2003), and a larger P600 for famous faces than nonfamous faces (Trautner et al., 2004). Thus, the P600 might reflect associative processing of items in both memory encoding and continuous recognition tasks. Finally, a late negative component (LNC) was also recorded from within the hippocampus. The LNC was found to be larger for old than new words (Grunwald et al., 1995, 1998). This wave occurred when words were repeated, independent of whether recognition memory was tested. But the LNC did not occur in recognition memory tests in which repeated words were not recognized as old (Grunwald et al., 2003), or in explicit encoding tasks (Fernández et al., 1999). Thus, the LNC might reflect successful retrieval of information from declarative memory. Taken together, whereas the hippocampal P600 appears to reflect a semantic associative process, the LNC reflects more a successful retrieval process.

We recorded intracranial EEG, while patients performed a continuous word recognition memory task with imageable and nonimageable words (Rugg and Nagy, 1989). We controlled lexical processes by varying word frequency. High imageable words often have a low occurrence in language, but behavioral studies have shown that the memory benefit of concrete words did not depend on the distinctiveness of the words. Rather, the memory benefit of concreteness and frequency depended on different mechanisms. For example, high-frequency words are thought to be more interconnected with other words in long-term memory (Gregg, 1976). This facilitates the access to long-term memory and improves short-term memory performance by the efficient reintegration of partially decayed information (Hulme et al., 1997). Low-frequency words are thought to attract attention and are therefore more easily recognized than high-frequency words (Malmberg and Nelson, 2003; Mandler et al., 1982). Thus, whereas in some conditions high, and in other conditions low, frequency words have a memory benefit, behavioral studies on concreteness did not show a memory benefit for abstract words. But concreteness and word frequency both have been shown to affect the scalp recorded N400 waves (Fernández et al., 1998; Holcomb et al., 1999). Therefore, we controlled the memory benefit of concreteness for word frequency in the present study.

Given the manipulations and the theoretical background described above, we expected that a memory benefit of concreteness would be observable in processing in the hippocampus. Particularly, the P600 may be affected by the concreteness of words, since this wave seems to reflect semantic associative
processing. Word frequency was not expected to affect the P600. The LNC was not expected to increase with concreteness or word frequency, because this ERP has not been shown to be modulated by semantic processes (Vannucci et al., 2003). Concreteness may also affect the AMTL-N400, because surface ERP studies showed an effect of concreteness on the scalp recorded N400 when concrete words were presented in sentences (Kounios and Holcomb, 1994). However, no effect of concreteness on the N400 has yet been reported when lists of single words were presented. Word frequency may affect the AMTL-N400, because this wave is sensitive to lexical processes and was affected by word frequency during memory encoding (Fernández et al., 2002). We further tested the differential contribution of the left and right hemispheres on the memory benefit of concreteness. Several studies showed that particularly the right hemisphere contributes to the processing benefit of concrete words (Jones-Gotman and Milner, 1978; Kounios and Holcomb, 1994; Paivio, 1986), whereas others suggested a bilateral (Scott, 2004) or even left hemisphere (Fiebach and Friederici, 2004) contribution to concreteness benefit (Kounios and Holcomb, 1994). While the initially cited studies would predict that concreteness exhibit a larger difference on right hemisphere recording sites, the latter would predict no hemispheric differences or an increased activation to concrete words in the left hemisphere.

Fourteen patients with pharmacoresistant, localization related epilepsy submitted for presurgical evaluation participated in the study (6 female, mean age 38 ± 9 years). Noninvasive work-up had failed to localize the seizure onset zone. Therefore, bilateral MTL depth electrodes (n = 14), and additional subdural electrodes in nine patients, were implanted for seizure recording. All patients had a seizure onset zone restricted to one hemisphere, and all data used for the study were obtained from the contralateral hemisphere. We investigated eight patients with a left-sided epileptogenic focus and six with a right-sided focus. From the left-sided group, five patients had a hippocampal sclerosis, two had left temporal cortical malformations, and one patient had a unilateral left temporal, but multifocal seizure onset and was not recommended for surgical treatment. From the right-sided group, three had a right sided hippocampal sclerosis, two patients had cortical malformations in the right temporal lobe, and one patient had a right occipital epileptogenic lesion. Six months after epilepsy surgery, 11 patients remained seizure free and two patients had a >50% reduction in seizure frequency. The ERP investigation, employing a continuous visual word recognition paradigm (Rugg and Nagy, 1989), 300 German nouns were presented sequentially in uppercase letters (white against black background), in central vision (horizontal visual angle 3.0°), and for a duration of 200 ms (randomized inter-stimulus interval: mean: 1,800 ms, range: 1,400–2,200 ms). One-half of these words were repeated after 3 ± 1 (early) or 14 ± 4 (late) intervening stimuli. Patients were asked to indicate whether an item was new or old by pressing one of two buttons of a computer mouse in their dominant hand. Because earlier studies have revealed no reliable differences between ERPs to early and late repetitions in MTL recordings (Grunwald et al., 1998; Guillem et al., 1999), averages were collapsed across both lags for the present analysis.

The words were rated by 18 healthy volunteers (age 21–35, 11 female) for their imageability on a scale of 1–5. Six rated both lists of 150 words and 12 rated one-half of the list. Thus, each word was rated 12 times. We selected words with high and low imageability (HI and LI). HI had a mean score of >4.5, and LI had a mean score of <3.5. All words were further selected in a group of high- and low-frequent words (HF and LF). We used the Mannheimer word frequency, which consisted of word counts from a database of 6 million words [CELEX database (Baayen et al., 1995)]. HF had a mean frequency of >200 per 6 million words, whereas LF had a mean frequency of <150 per 6 million words. The words in each of the four categories (HI-HF, HI-LF, LI-HF, LI-LF) had a similar word length (2–8 letters), and number of syllables (range 1–4). Word categories did not differ in either average word length or number of syllables (Wilcoxon test Zmax < 1.9, n.s.). Word features are listed in detail in Table 1.

**RESULTS**

Recognition memory performance data are shown in Table 1. Accuracy of recognition was assessed by the difference in probabilities of a correct old judgment and an old judgment for a new item (Pr = probability hit – probability false alarm). Recognition data were submitted to two-way analysis of variance (ANOVA) with the factors word imageability and frequency. While recognition performance did not differ between high- and low-frequency words (F1,13 = 0.1, n.s.), high imageable words were better recognized than low imageable
words ($F_{1,13} = 9.4, P < 0.01$). There was no significant interaction between word imageability and frequency ($F_{1,13} = 0.1$, n.s.). Recognition performance for all word categories was well above chance level (all $t_{13} > 10, P < 0.001$).

We tested depth ERP potentials recorded from within the rhinal cortex and the hippocampus. Because of the limited number of items per word category and the high-performance rate it was not possible to test the ERP effect on concreteness as a function of accuracy (correct versus incorrect hits). We tested the ERP effects of repetition on concreteness (correct hits versus correct rejections). Figure 2A shows the grand averages of recordings from the rhinal cortex. The ERPs show an AMTL-N400 that occurred in a time window between 300 and 600 ms and peaked around 400 ms after word presentation. The AMTL-N400 appears to be modulated by an old/new effect but not by word imageability or frequency. To test this effect statistically, we submitted the mean ERP amplitudes of the 300- to 600-ms time window to a three-way ANOVA, in which the within-subjects factors were memory (hit versus correct rejection), word imageability (high versus low imageability), and word frequency (high versus low frequency). We found a main effect for the factor memory ($F_{1,13} = 6.4, P < 0.03$). This was reflected in a reduced AMTL-N400 for old words. There was no significant effect for word imageability and frequency (max $F_{1,13} < 2$, n.s). Interactions between factors were not significant (max $F_{1,13} < 2$, n.s). To test whether concreteness affected the AMTL-N400 differentially in the left and right hemisphere, we ran an ANOVA in which memory and concreteness were within subjects-factors, and hemisphere was a between-subjects factor. However, we found no evidence for a lateralization of the AMTL-N400. Neither the factor hemisphere was significant ($F_{1,12} = 0.1$, n.s), nor were there any interactions with the factor hemisphere (max $F_{1,12} < 3.2, P > 0.1$). Taken together, the data suggest that word imageability and word frequency did not affect the AMTL-N400. The recognition of old words is associated with a reduction of the AMTL-N400 amplitude relative to new words.

Figure 2B,C shows grand averages recorded from within the hippocampus. We found a positive wave in the time window between 300 and 600 ms, which peaked around 450 ms. This wave was followed by a late negative component between 600...

FIGURE 1. Localization of medial temporal lobe (MTL) depth electrodes. Left: Coronal magnetic resonance image (MRI) of a patient with bilateral depth electrodes in situ (Hi, hippocampus; R, right; L, left). As a result of MRI artifacts, the electrodes appear much larger than their actual size of 1-mm diameter. Filled ellipsoids in coronal and sagittal standardized drawings indicate the approximate location of MTL electrode contacts used to record EEG tracings analyzed in this study (Am, amygdala; Hi, hippocampus; Rc, rhinal cortex; Cs, collateral sulcus; Pg, parahippocampal gyrus). Upper and lower: Approximate locations of electrode contacts used to record EEG from the rhinal cortex and the hippocampus, respectively.
and 900 ms. The early positive peak represents the hippocampal P600, the latter negative wave the LNC. We tested the hippocampal P600 in a time window between 300 and 600 ms and the LNC between 600 and 900 ms. Again, we submitted mean amplitude values to a three-way ANOVA in which the within-subjects factors were memory (hits versus correct rejections), word imageability (high versus low imageability), and word frequency (high versus low frequency). We found a main effect for the factor imageability at the P600 ($F_{1,13} = 5.1$, $P < 0.05$). This was reflected by a larger positive wave for high than low imageable words. To test whether concreteness affected the P600 differentially in the left and right hemisphere, we applied an ANOVA with the factors memory and concreteness as a within-subjects factor, and hemisphere as a between-subject factor. We found no evidence for a lateralization of the P600. The factor hemisphere was not significant ($F_{1,12} = 0.1$, $P > 0.7$), and there were no interactions with the factor hemisphere (max $F_{1,12} < 0.5$, n.s). Thus, the P600 was only affected by concreteness of words, and not by recognition memory.

In a time window of the LNC (600–900 ms), we found a significant main effect for the factor memory ($F_{1,13} = 10.7$, $P < 0.01$). This was reflected by a larger LNC for old than new words. No other effects or interactions between the factors memory and word type were found either during the P600 or LNC time window (max $F_{1,13} < 1.5$, n.s). To test whether concreteness affected the LNC differentially in the left and right hemisphere, we applied an ANOVA with the factors memory and concreteness as a within-subjects factor, and hemisphere as a between-subjects factor. We found no evidence for a lateralization of the LNC. The factor hemisphere was not significant ($F_{1,12} = 0.1$, $P = 0.9$), and there were no interactions with the factor hemisphere (max $F_{1,12} < 0.1$, n.s). Thus, the P600 was affected by concreteness, and the LNC was affected by recognition memory.

## DISCUSSION

The present study investigates the effects of word imageability on neural activity in the human MTL. We found that concrete words induced distinct effects on neural activity in the hippocampus. In particular, word imageability affected both recognition memory performance and the P600. The P600 was recorded from within the hippocampus and may be related to the integration of words within semantic knowledge including both conceptual and pictorial information. Consistent with this interpretation, a recent study reported that real object induced a large P600, whereas nonsense objects induced no P600 (Vannucci et al., 2003). In another study, this wave was found to be larger for famous as compared with nonfamous faces (Trautner et al., 2004). Both studies suggested that objects with rich semantic associations activated the hippocampus. The fact that real objects and famous faces are semantically meaningful, whereas nonsense objects and nonfamous faces are not, draws a close parallel to the concreteness of words. Concrete words activate associations in a rich semantic context, including other conceptual information and a pictorial representation. Thus, we suggest that hippocampal activation induced by concrete words may relate to the processing of conceptual and pictorial information associated with concrete words.

It is unclear whether the memory benefit for concrete words relates to the effect of concreteness on the P600. One might argue that the P600 found in the continuous recognition test is the same effect as the slow positive wave that was found during encoding for subsequent free recall memory tests. Successful free recall of words induced larger positive wave around the 600 ms during encoding as compared with subsequently forgotten words. The magnitude of this effect has also been shown to correlate with the encoding success (Fernández et al., 1999). Furthermore, in a continuous recognition test others reported that correctly recognized words induced a larger P600 than repeated words that were not correctly recognized (Grunwald et al., 2003). These studies support the relation of the P600 to memory. An argument against this hypothesis is the lack of an interaction between the repetition effect and concreteness. If the repetition effect would differ between concrete and abstract words, the claim for a role of the P600 concreteness effect in memory would be stronger. Further evidence for either claim would be given if we were able to relate the concreteness effect to memory success (i.e. the difference between correctly recognized and

### Table 1

Word Characteristics and Recognition Memory Performance

<table>
<thead>
<tr>
<th></th>
<th>High imageable</th>
<th>High imageable</th>
<th>Low imageable</th>
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<tbody>
<tr>
<td></td>
<td>High frequency</td>
<td>Low frequency</td>
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<td>Low frequency</td>
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<tr>
<td>No. of words</td>
<td>31</td>
<td>57</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Word frequency (per 6 million)</td>
<td>782 (203–4152)</td>
<td>47 (2–140)</td>
<td>727 (214–3533)</td>
<td>43 (2–148)</td>
</tr>
<tr>
<td>Imageability</td>
<td>4.8 (4.1–5)</td>
<td>4.7 (4.1–5)</td>
<td>2.5 (1.6–3.3)</td>
<td>2.7 (1.5–3.4)</td>
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<td>No. of letters</td>
<td>4.9 (±0.2)</td>
<td>5.1 (±0.1)</td>
<td>5.3 (±0.2)</td>
<td>5.5 (±0.2)</td>
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<tr>
<td>No. of syllables</td>
<td>1.6 (±0.1)</td>
<td>1.8 (±0.1)</td>
<td>1.6 (±0.1)</td>
<td>1.9 (±0.1)</td>
</tr>
<tr>
<td>Hits–false alarms (%)</td>
<td>63 (±5)</td>
<td>65 (±4)</td>
<td>53 (±4)</td>
<td>53 (±5)</td>
</tr>
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</table>

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missed items). However, the limited amount of trials for each patient prevented such an analysis. Therefore, it is too preliminary to claim a direct relation between the P600 and the memory benefit of concrete words.

The effect of concreteness on the P600 might reflect either a greater projection of activity on the hippocampus from neocortical brain regions or originate from the hippocampus itself. Although we cannot completely exclude either hypothesis, we consider the latter hypothesis more likely. We found no effect of concreteness on the AMTL-N400, which is generated in the rhinal cortex. The rhinal cortex provides the major input and has the strongest anatomical connectivity to the hippocampus (Amaral and Insausti, 1990). In addition, the rhinal cortex has been shown to have extensive functional communication with the hippocampus (Fell et al., 2001). This suggests that the P600 is actually generated by a neural activity within the hippocampus. However, we cannot exclude that neural activity within the rhinal cortex, which are not reflected by the AMTL-N400, or activity from other cortical brain regions, which we did not record, would be responsible for the generation of the concreteness effect in at the P600.

FIGURE 2. Event-related potentials from within the medial temporal lobe (MTL). A: Depth ERPs recorded from the rhinal cortex for old (hits) and new words (correct rejections). The right part shows mean amplitudes (with standard error) of the AMTL-N400 in a 300- to 600-ms time window for each stimulus category (HI, high imageability; LI, low imageability; HF, high word frequency, LF, low word frequency). B: Depth ERPs recorded from within the hippocampus for high and low imageable words. The right part shows mean amplitudes (with standard error) in a 300- to 600-ms time window for each stimulus category. C: Depth ERPs recorded from the same contact within the hippocampus for old (hits) and new words (correct rejections). The right part shows mean amplitudes (with standard error) in a 600- to 900-ms time window for each stimulus category. For all ERP graphics, the time ticks on the x-axis reflect 200 ms and amplitude on the y-axis reflect 20 μV.
Two other ERP waves that reported in the present study, the hippocampal LNC and the AMTL-N400, were not significantly affected by concreteness. Previous studies on the LNC suggested that this ERP relates to the recognition of words (Grunwald et al., 2003), whereas it did not occur in encoding tasks (Fernández et al., 1999), and did not differ between meaningful and nonsense objects in a recognition task (Van pussi et al., 2003). The absence of an effect of concreteness on the LNC suggests that hippocampal brain activity associated with recognition was not affected by concreteness. It was rather surprising that the AMTL-N400 was not affected by concreteness given that scalp recorded ERP studies reported an effect of imageability on the N400 (Kounios and Holcomb, 1994). Previous studies about the role of the AMTL-N400 and the scalp recorded N400 suggested that the AMTL-N400 contributes to the neural generator of the N400 (Nobre and McCarthy, 1995). However, these were not the only neural generators contributing to the N400 (Halgren et al., 2002). Another reason may be that the task we used was different from those studies that reported a concreteness effect on the N400. Whereas we used a continuous recognition memory task, most investigators used variations of semantic judgment tasks in which concrete words were presented within sentences (Holcomb et al., 1999; West and Holcomb, 2000).

We found no evidence for hemispheric lateralization of concreteness. Although this finding is in line with imaging studies, which showed a bilateral hemispheric contribution to the processing of concrete words (Scott, 2004; Wise et al., 2000) we prefer to take caution on the interpretation of this result. First of all, no general inferences about hemispheric asymmetries of the effect should be drawn off our data, because recordings were taken from patients with an epileptic zone in the MTL contralateral to the one investigated here. Moreover, the statistical power was probably too small to find a possible distinction between the left and right hemisphere, since there were only six patients with right temporal lobe recordings, and eight patients with left temporal lobe recordings.

We found no effect of word frequency on activity in the rincipal cortex and hippocampus. The absence of word frequency effects on the AMTL-N400 amplitudes and recognition performance might be related to each other, and explained by stimulus selection and experimental design. In contrast to other studies on word frequency in memory, we did not use very low-frequency words because we were bound to the standard list of words in the clinical setting. Very low-frequency words can be distinct and improve memory performance, because they attract attention (Fernández et al., 1998; Glanzer and Adams, 1990; Gregg, 1976). In a memory encoding task, we found that better memory performance for high-frequency words correlated with a larger AMTL-N400 (Fernández et al., 2002), but showed no difference in hippocampal activation. A recent functional MRI study reported that brain activity in the left fusiform gyrus was more activated by low-frequency words that were better remembered than high-frequency words (Chee et al., 2003). These investigators also used a larger difference between high- and low-frequency words than in the present study. Hence, although word frequency has been shown to affect both memory performance and the AMTL-N400, our data suggest that the word frequency effect on the AMTL-N400 may not be observed for relatively high-frequency words, such as those we used in the present study. With respect to the hippocampal activity, we replicated the finding from Fernández and colleagues (2002) that word frequency did not affect the P600. They found no interaction between word frequency and the subsequent memory effect at the P600, and thus our data supports the idea that the P600 does not involve lexical processing.

The present study shows that the hippocampus plays a role in word concreteness. Previous fMRI studies reported that concrete words activate areas within the MTL, including the parahippocampal region (Scott, 2004). Neuropsychological studies also suggested a role of the MTL in the processing of concrete words (Jones-Gotman and Milner, 1978; Warrington and Shallice, 1984). However, neither neuropsychological lesion studies nor functional imaging studies could specify the role of the hippocampus in the processing of concreteness. Those methods do not have the capability to address hippocampal function as well as intracranial recordings, which directly monitor neural activity from within the hippocampus. Lesions in the MTL may include the hippocampus or disconnect structures that transmit activity into the hippocampus. These anatomical inter-actions are often not well controlled. On the other hand, functional imaging studies suffer from the problem that the signal is often abolished in the hippocampus. Yet, even though modern imaging techniques improved the signal in these regions (Strange et al., 2002), the problem remains that temporally and functionally distinct processes may extinct each other. In contrast, the present study showed that intracranial recordings were able to distinguish such processes.

Taken together, the significance of the present study relies on the role of concrete words on neural activity in the hippocam-pus. Even though the role of this activity is not yet clear, this new evidence may contribute to the discussion on concreteness in cognitive functions of the MTL.

**REFERENCES**


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The effect of word concreteness on recognition memory

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Concrete words that are readily imagined are better remembered than abstract words. Theoretical explanations for this effect either claim a dual coding of concrete words in the form of both a verbal and a sensory code (dual-coding theory), or a more accessible semantic network for concrete words than for abstract words (context-availability theory). However, the neural mechanisms of improved memory for concrete versus abstract words are poorly understood. Here, we investigated the processing of concrete and abstract words during encoding and retrieval in a recognition memory task using event-related functional magnetic resonance imaging (fMRI). As predicted, memory performance was significantly better for concrete words than for abstract words. Abstract words elicited stronger activations of the left inferior frontal cortex both during encoding and recognition than did concrete words. Stronger activation of this area was also associated with successful encoding for both abstract and concrete words. Concrete words elicited stronger activations bilaterally in the posterior inferior parietal lobe during recognition. The left parietal activation was associated with correct identification of old stimuli. The anterior precuneus, left cerebellar hemisphere and the posterior and anterior cingulate cortex showed activations both for successful recognition of concrete words and for online processing of concrete words during encoding. Additionally, we observed a correlation across subjects between brain activity in the left anterior fusiform gyrus and hippocampus during recognition of learned words and the strength of the concreteness effect. These findings support the idea of specific brain processes for concrete words, which are reactivated during successful recognition.

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Introduction

There is strong evidence from behavioral studies that the cognitive processing of concrete and highly imageable words is superior to that of abstract words. A positive effect of word concreteness has been shown for a variety of tasks including episodic long-term memory (Jessen et al., 2000), continuous recognition (Klaver et al., 2005), lexical decision (Bleasdale, 1987) and working memory (Van Schie et al., 2005).

Two competing sets of theories try to explain the differences in processing of concrete and abstract words. Multiple-coding approaches, like the dual-coding theory, claim that concrete words are not only encoded verbally, but that they are also represented non-verbally in an image based system (for a comprehensive overview, see Paivio, 1986). On the other hand, single-mode models, like the context-availability theory, try to explain the superiority of concrete word processing based only on differences in verbal processing claiming that concrete words can be more easily put into a semantic context (Schwanenflugel et al., 1991).

Obviously, the hypotheses derived from these theories are well suited for being addressed by neuroimaging techniques because they make specific predictions about activation pattern differences between the two groups of words. If there was any “dual coding” of concrete words, an activation of image-processing brain areas would be expected, when comparing concrete to abstract word processing. On the other hand, single-mode models predict activation differences between concrete and abstract words restricted to language processing brain areas.

Presently, there is converging evidence that when compared to concrete word processing, abstract word processing is associated with higher activation in left hemispherical areas that are known to be involved in semantic processing, i.e., the left inferior frontal gyrus (LIFG) (Perani et al., 1999; Jessen et al., 2000; Fiebach and

1 A common definition of the word concreteness encompasses the extent to which a word refers to features of objects or persons that can be sensualy experienced. Imageability, on the other hand, can be defined (and was defined as such in our study instruction) as the ability of a word to elicit internal images. Thus, imageability is an important subfeature of concreteness and ratings of word concreteness and imageability are highly correlated (Baschek et al., 1994). For convenience, the two labels are used synonymously throughout this article.
and the superior temporo-lateral cortex (Mellet et al., 1998; Kiehl et al., 1999; Wise et al., 2000; Binder et al., 2005). These findings support the so-called reinstatement hypothesis, which states that recollection of memory contents is associated with a reactivation of brain areas which were active during encoding. Thus, if there is brain activity specific for processing concrete words that underlies the concreteness effect in memory, as dual-coding theory predicts, one would expect to find a similar pattern of activation during both encoding and recollection.

Therefore, we investigated the neural mechanisms underlying the word concreteness effect during encoding and retrieval in a recognition memory paradigm. Specifically, we wanted to test: (1) whether the same pattern of left hemispherical activation described for abstract vs. concrete words is also present during memory encoding and retrieval; (2) which pattern emerges for the concrete vs. abstract comparison during encoding and retrieval and most importantly; (3) how these activations relate to successful memory formation and retrieval.

Methods

Subjects

Twenty-one subjects without any history of neurological or psychiatric disease were enrolled (12 female; mean age 27.4 years (±6.2); range 19–43 years). All subjects were right-handed according to the Edinburgh Handedness Scale. All subjects gave written informed consent and the study was approved by the local ethics committee.

Materials

We selected all simple (non-composite) nouns with a word length between 2 and 10 characters and a word frequency between 6 and 150 per million from a comprehensive database of German words (CELEX). These 1006 words were rated for their imageability by ten healthy subjects who did not participate in the fMRI experiment. The rating was on a 7-point Likert scale ranging from 1 to 7 using a standardized instruction. Out of the third with the highest and with the lowest imageability rating, 180 concrete and 180 abstract words were chosen, excluding synonyms and parallelizing the two word groups for word length and word frequency. The mean word length was 5.1 (±1.2) for concrete and 5.2 (±1.3) for abstract words (t=0.75, n.s.); the mean word frequency was 28.9 (±29.6) for concrete and 33.2 (±32.1) for abstract words (t=1.32, n.s.); and the mean imageability rating was 6.3 (±0.4) for concrete and 2.5 (±0.5) for abstract words (t=78.0, P<0.0001).

Task

During the encoding period, the subjects viewed 90 concrete and 90 abstract words randomly selected from the full list of words. The stimulus duration was 1 second (s), the interstimulus interval (ISI) was jittered between 4.5 s and 7.5 s with a fixation cross displayed. The subjects were informed that a recognition task would follow and they were asked to remember the words as well as possible. The duration of the encoding period was approximately 23 min. Between the encoding period and the recognition period, there was a break of approximately ten min during which the subjects could either leave the scanner or were subjected to a structural scan.

During the recognition period, the subjects saw the 180 words of the encoding period randomly intermixed with the other 180 words of the full list which were used as distractors. They made an old/new decision by pressing one of the four response buttons found on the hand grips (Nordic NeuroLab, Bergen, Norway) indicating whether they thought that a word was definitely old, probably old, definitely new or probably new. Again, the stimulus duration was 1 s with an ISI of 4.5–7.5 s during which the response could be given. The duration of the recognition period was 45 min.

For behavioral analysis, hits were defined as studied words that were confidently recognized; misses as studied words that were confidently judged to be new; correct rejections as new words which were confidently judged to be new; and false alarms as new words that were confidently judged to be old. As the main behavioral outcome measure, the corrected recognition rate (hits—false alarms) for concrete and for abstract words were compared across subjects with a dependent measures t-test. Only confidently given judgments were used. Reaction times for the old/new decision during recognition were compared by independent samples t-test.

fMRI data acquisition

The scanning was performed on a 1.5 T Avanto Scanner (Siemens, Erlangen, Germany) using a standard 8-channel head coil. During encoding and recognition, axial echo planar imaging (EPI) scans were acquired (426 and 842 scans, respectively) each including eight dummy scans. Scan parameters were: number of slices: 35; slice thickness: 3 mm; interslice gap 0.3 mm; matrix size: 64×64; field of view: 192 mm; echo time (TE): 50 ms; repetition time (TR): 3 s. The task was presented via video goggles (Nordic NeuroLab, Bergen, Norway) using E-prime presentation software (Psychology Software Tools; www.pstnet.com).

fMRI data analysis

The fMRI data analysis was done using Statistical Parametric Mapping 2 (SPM2, www.fil.ion.ucl.ac.uk/spm/). The preprocessing included realignment with unwarping, slice timing, normalisation to a standard EPI template and smoothing with a 12 mm Gaussian kernel. Re-sampled voxel size (after normalisation) was 3 × 3 × 3 mm. The hemodynamic response was modelled by a canonical hemodynamic response function and the temporal
derivative. For fMRI analysis, correct answers were defined as previously stated (i.e. confidently given old judgements for old words=hits; confidently given new judgements for new words=correct rejections), whereas for mistakes unconfidently given wrong answers were also counted (i.e. all old judgements for new words=false alarms; all new judgements for old words=misses). This was necessary because otherwise the number of events in each category would have been too small in many subjects. Correct responses which were not given confidently were modelled separately and were not included in the statistical analysis.

For modelling the encoding period, six vectors of stimulus onsets were used (abstract/concrete words that were either hits, misses or correct responses not given confidently). When modelling the recognition period, ten different vectors were constructed (abstract/concrete words that were hits, misses, correct rejections, false alarms or correct responses not given confidently). Parameter images for the respective contrasts of interest were generated for each subject and were then subjected to a second-level random effects analysis using a one-way analysis of variance (within-subject ANOVA) as a model. The predefined linear combinations of the group contrast images were then tested with a one sample t-test against a null hypothesis of no effect. The main contrasts were defined as follows (in brackets given the experimental part):

**Word type effects**
- Concreteness effect: concrete > abstract words
- Abstractness effect: abstract > concrete words

**Memory effects**
- Subsequent memory effect (learning): hits > misses
- Negative subsequent memory effect (learning): misses > hits
- Old/New-effect (recognition): hits > correct rejections
- New/Old-effect (recognition) correct rejections > hits

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<th>Table 1</th>
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<td>Uncertain “old” responses</td>
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Fig. 1. Statistical parametric t-map for abstract>concrete words (a) and hits>misses (subsequent memory effect) (b) during encoding (threshold P<0.001), projected onto a 3D-reconstruction of a canonical single subject brain.
Positive memory effect (recognition): hits>misses
Negative memory effect (recognition): misses>hits

Interactions between the word type effects and the different memory effects were calculated accordingly. The statistical threshold was set at a P-value of 0.001 voxelwise (uncorrected) with a cluster extent of >9 contiguous voxels and only clusters at \( P<0.05 \) at the cluster level (corrected for multiple comparisons) were considered significant. To test for regional overlaps between word type and memory effects, word type effects (threshold \( P<0.001 \)) were inclusively masked with the memory effects with a mask P-value<0.05. To more specifically test for differences in memory effects for the two word types the separate old/new-effect for abstract and concrete nouns during the recognition period (threshold \( P<0.001 \)) were inclusively masked with word type effects from the encoding period (mask threshold \( P<0.05 \)).

To test for brain areas associated with inter-individual differences in the memory concreteness effect, a second-level correlation analysis was performed. The t-maps for the subsequent memory effect during learning and the old–new effect during recognition were correlated with the extent of the concreteness effect over subjects. The extent of the concreteness effect was defined as the corrected recognition rate for concrete words minus corrected recognition rate for abstract words. For this analysis, activations of at least ten adjacent voxels at a significance level of \( P<0.001 \) without any further correction were interpreted.

Anatomical cluster labelling was done using the Anatomical Automated Labeling Tool for SPM (Tzourio-Mazoyer et al., 2002). For the transformation of MNI-coordinates in Talairach (TAL) Coordinates we used non-linear transformation according to: http://www.cbu.cam.ac.uk/imaging/common/mnispace.shtml.

Results

Memory performance

The corrected recognition rate (hits–false alarms) was significantly higher for concrete words than for abstract words (50.6±21.9% vs. 42.1±22.2%, \( t=3.0 \), \( P=0.007 \)). This difference was mainly based on a significantly smaller rate of false alarms for concrete words than for abstract words (9.1±7.5% vs. 13.4±9.0%, \( t=−2.7 \), \( P=0.015 \)), whereas the rate of hits did not differ significantly (59.7±19.4 vs. 55.6±18.9, \( t=1.6 \), n.s.). The percentage of correct rejections and misses did not differ significantly either. The reaction times for the old/new-judgement were significantly shorter for concrete words than for abstract words (1600±714 ms vs. 1642±713 ms, \( t=2.5 \), \( P=0.013 \)). Detailed results are shown in Table 1.

fMRI-data

Encoding

The contrast abstract vs. concrete words yielded a significant activation of the left inferior frontal gyrus (Brodmann Area (BA) 45) (Fig. 1, Table 2). There were no areas displaying significant activation for the opposite contrast. The comparison of subsequently remembered (hits) versus forgotten words (misses) (subsequent memory effect) showed four clusters of activation bilaterally in the inferior and middle frontal gyri (Fig. 1, Table 2). There was no significant activation for the opposite contrast (negative subsequent memory contrast). The area activated by the abstract vs. concrete contrast was overlapping with the left inferior frontal area seen with the subsequent memory contrast so that after inclusively masking the first contrast with the latter, this area still showed significant activation (Fig. 2). Left inferior frontal activation was also found when the subsequent memory contrast for abstract words alone was masked with the contrast abstract vs. concrete words, although this comparison was not significant at a cluster level. There were no significant interactions between word type and memory effects.

Recognition

During recognition, the activation pattern for the abstract vs. concrete words was similar to that during encoding with a significant activation of the triangular part of the left inferior frontal gyrus (BA45) (not shown). The concrete vs. abstract contrast showed a bilateral posterior activation involving the angular gyrus on both sides, together with parts of the inferior parietal lobe on the left side. Besides hand-motor activity for the button presses on one side, the old/new-effect yielded a

<table>
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<tr>
<th>Brain region</th>
<th>TAL-coordinates</th>
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</table>

Brain regions and TAL-coordinates of activation maxima. Note that only clusters that were significant on a cluster level of \( P<0.05 \) (corrected for multiple comparisons) are listed. Local maxima of subclusters are listed when they are more than 8 mm apart from the main peak activation. \( n \) = number of suprathreshold voxels, \( z \) = z-score at peak activation, \( P= \) P-value for the cluster (corrected for multiple comparisons).
widespread activation in the left precuneus/cuneus, left cerebellar hemisphere, right rolandic operculum, left angular gyrus, left supramarginal gyrus, right anterior cingulum, left and right ventral caudate and the frontal inferior triangular gyrus (for details, see Table 2). The positive memory contrast was characterised by a very similar pattern of activation as the latter. Hence, exclusively masking either of the two effects with the other at a mask level of $P<0.05$ left no significant activations exclusively present in either contrast. The converse contrasts (new/old and negative memory effect) did not show any significant activation besides that for hand motor activity. Again, no significant interactions between word type effects and memory effects were found.

When inclusively masking the concrete vs. abstract contrast with the memory contrasts, the left inferior parietal and angular activation was consistently significant at a cluster level (Fig. 3). This was regardless of whether masking was done with the memory contrasts for all words or for each word category separately. The right-sided posterior activation also persisted when masked with the memory contrasts, but lost significance at the corrected $P<0.05$ level after the masking procedures.

When inclusively masking the old/new-effect for concrete words with the contrast between concrete and abstract words from the encoding period, four regions displayed significant activation: Bilateral precuneus, left cerebellar hemisphere, bilateral posterior cingulate cortex and bilateral anterior cingulate cortex (Fig. 4, Table 3). For abstract words no significant activation was observed after the respective masking procedure.

The correlation analysis of the behavioral concreteness effect with the different memory contrasts yielded a positive correlation with the activation for the old/new-contrast during recognition in the left medial temporal lobe (left fusiform gyrus/
That is, subjects activating this region stronger during the correct recognition of studied words had a larger memory benefit from word concreteness (Fig. 5).

Discussion

In this study we investigated the positive effect of word concreteness on recognition memory by using fMRI. We found that intentional encoding of abstract vs. concrete words was associated with a stronger activation of the left inferior frontal gyrus (LIFG). The same region was associated with a positive subsequent memory effect. During encoding we found no areas that were activated more strongly by concrete words on our predefined significance level. During recognition there was a stronger bilateral activation of inferior parietal regions for concrete vs. abstract words. The left-sided parietal activation was associated with the correct identification of studied words. Additionally we observed precuneal, cerebellar and cingulate activations associated with correct identification of studied concrete words that also distinguished concrete from abstract word processing during encoding. Furthermore we found a correlation between brain activation in the left fusiform gyrus and hippocampus with the strength of the behavioral concreteness effect across subjects.

A stronger activation of the LIFG has been found in a number of studies for a variety of different tasks (Perani et al., 1999; Fiebach and Friederici, 2004; Noppeney and Price, 2004; Binder et al., 2005) including memory encoding (Jessen et al., 2000). The same region is also more strongly activated during the processing of low vs. high frequency words and words learned late in life compared to words learned earlier (Fiebach et al., 2003). This area furthermore shows task-dependent activation in semantic vs. syntactic processing (Friederici et al., 2003). Thus, there is converging evidence in literature that this region is critical for the effortless retrieval of information from a semantic knowledge system.

The fact that the LIFG is more strongly activated by abstract words is somewhat ambiguous with regard to its meaning for the behavioral effects of word concreteness and the theories trying to explain them. It could either signify that for concrete words, access to semantic knowledge is easier than for abstract words, as context availability theory would predict. In this case, the stronger activation of semantic processing areas would be the result of a more effortful semantic processing for abstract words. An alternative explanation in line with the dual-coding theory would be that processing of concrete words does not only rely on a semantic code, but also on a hypothetical image-based code, and as a consequence semantic processing is less important when dealing with concrete words. A prediction of context-availability theory on the behavioral effect of word concreteness is the easier access to semantic knowledge for concrete words as the underlying mechanism for their facilitated cognitive processing. In this case, one would expect a brain activation which is based on the difficulty of semantic processing to be associated with a lower performance level. In our study, however, the opposite is true. A stronger activation of the LIFG is found in parallel for the abstract vs. concrete effect and the subsequent memory effect. A possible interpretation of the data is that abstract words require stronger...
semantic processing than concrete words as a premise for successful encoding. One possible explanation for this could be a supportive role of other brain areas for the encoding of concrete words. However, our encoding data offer no positive evidence for this assumption since there were no additional brain areas activated more strongly by concrete words.

During recognition we observed stronger bilateral activation of the inferior parietal cortex and the angular gyrus for concrete vs. abstract words. This finding is in line with a recent study on concrete word processing without memory retrieval (Binder et al., 2005). Our study design allowed us to show that the left parietal activation was also associated with successful recognition irrespective of word type. This finding is not unexpected since this region is often found to be associated with correct recognition in recognition memory paradigms (e.g. Weis et al., 2004; Henson et al., 2005). More precisely, the region found in our study roughly corresponds to a region proposed to be specific for the recollection of a memory as opposed to mere familiarity (Wheeler and Buckner, 2004). The interpretability of this activation is limited by the fact that it could have reflected differences in memory level for concrete and for abstract words. However, this activation is also present for correctly rejected concrete vs. abstract words during recognition. Thus, this activation seems to be driven not only by the correct identification of studied words, but also by the processing of concrete words per se under a recognition task. This could mean that concrete words might be better suited to evoke specific contextual information, which is supposed to be the basis of recollection.

More direct evidence for brain regions being differentially involved in encoding and retrieval of concrete and abstract words was found by another masking procedure using the word type effects from the encoding period as a mask for the word type specific old/new-effects during retrieval. For concrete words, this analysis yielded significant activations in the left and right anterior precuneus, the left cerebellar hemisphere, and bilateral posterior and anterior cingulate cortex. The finding of a precuneous activation is in line with findings from classic PET (Fletcher et al., 1996) and fMRI studies (Henson et al., 1999) that suggested a role for the precuneus in the retrieval of imageable material. Meanwhile, studies have suggested a functional dissociation within the precuneus, with a more posterior region being involved in retrieving more abstract contents, and a more anterior region being involved in the retrieval of more visual contents (Lundstrom et al., 2003, Woodruff et al., 2005). The bilateral region found to be more strongly involved in successful retrieval of concrete vs. abstract words in our study corresponds to the latter. Stronger activations in this region were also present during the intentional encoding of concrete as compared to abstract words, which is in line with previous studies on concrete word processing (Binder et al., 2005). This finding supports the idea of a (content specific) reinstatement of neuronal activity from the encoding period while successfully retrieving this information. It furthermore supports the notion of an additional, imagery-based system for the encoding of concrete words, as proposed by dual-coding theory, although the role of the precuneus in this context must be further clarified (for a recent review, see Cavanna and Trimble, 2006). It must also be stressed that our results do not show that the specific reinstated brain activities are necessary for successful recollection—they could also be interpreted as a consequence of retrieval success (for a more detailed discussion of this aspect see Woodruff et al., 2005).

Activations of the cerebellar hemispheres during episodic memory retrieval have been described before in a number of studies (e.g. Weis et al., 2004, Cabeza et al., 2002). However, the exact role of the cerebellum in recognition memory is poorly understood. Since cerebellar lesions do not have a major impact on memory performance, a rather unspecific supporting role is widely assumed. With respect to concrete word processing, cerebellar activity has not been reported, which could be partly due to the fact that the cerebellum is rarely fully covered in imaging studies. Because the cerebellum is known to be involved in motor imagery (Ross et al., 2003), we speculate that this activation is due to the induction of imagined manipulations by concrete words such as tools. This question could be further addressed by a more specific item selection that allows a distinction between different classes of concrete words.

Posterior and anterior cingulate activations have also been linked to retrieval success in previous studies. Posterior cingulate activations are regularly found in combination with precuneal and
left lateral parietal activations (Wagner et al., 2005) and might reflect similar processes as discussed previously. Anterior cingulate activations in a recognition memory context are generally assumed to reflect decision-making processes when translating the recognition evaluation into a response (Fleck et al., 2006). A stronger activation of this area by concrete than by abstract words has been described in one early study (D’Esposito et al., 1997). As is the case for the other activations described before, we cannot rule out the possibility that common activation in this area during retrieval of concrete words and during online processing of concrete words in the encoding period reflects different cognitive processes that are not functionally linked.

Another hint at a brain region involved in the memory concreteness effect comes from the correlation of brain activity with the behavioral data. Subjects displaying a larger concreteness effect showed a stronger activation in the left anterior fusiform gyrus and the left hippocampus when correctly identifying learned words. The left middle and anterior fusiform gyrus has been repeatedly reported to be associated with the retrieval of visual object information (Wheeler and Buckner, 2003; Price et al., 2003) rather than with immediate object perception. It is also more strongly activated during the recollection of studied pictures as compared to studied words, even when the test items are words (Woodruff et al., 2005; Wheeler and Buckner, 2004). Although the activation found in our study lies even more anterior within the fusiform gyrus than in most of these studies, we assume it to be a correlate of the retrieval of visual information. This finding can be interpreted in accordance with both context-availability theory and dual-coding theory. On the one hand, it shows that the retrieval of contextual information is important for the concreteness effect. On the other hand, the nature of this information seems to be primarily visual as predicted by dual-coding theory.

The finding of a concreteness effect in brain activation during recognition, but not during encoding, may result from different mechanisms. One explanation is simply that of statistical power: during recognition, twice as many events could be analysed than during encoding. Another reason could be the different task demands: the intentional learning instruction under the encoding condition may have led to high inter-individual variability due to individual encoding strategies. The same reasons might explain the lack of significant medio-temporal activations which is commonly described in one early study (D’Esposito et al., 1997). As is the case for the other activations described before, we cannot rule out the possibility that common activation in this area during retrieval of concrete words in the encoding period reflects different cognitive processes that are not functionally linked.

In conclusion, our findings suggest that the anterior bilateral precuneus together with left hemispheric regions including the left inferior parietal cortex, left anterior fusiform gyrus and the left hippocampus are involved in the memory concreteness effect. Studies focussing on the interaction of these areas might supply us with important insights in the mechanisms of memory retrieval.

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Brief Communications

Oxytocin Makes a Face in Memory Familiar

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Social recognition is the basis of all social interactions. Here, we show that, in humans, the evolutionarily highly conserved neuropeptide oxytocin, after intranasal administration, specifically improves recognition memory for faces, but not for nonsocial stimuli. With increased oxytocin levels, previously presented faces were more correctly assessed as “known,” whereas the ability of recollecting faces was unchanged. This pattern speaks for an immediate and selective effect of the peptide strengthening neuronal systems of social memory.

Key words: oxytocin; social; face; recognition; memory; neuropeptide

Introduction

Across species, social recognition is the foundation on which all social relationships are built and maintained. The nonapeptide oxytocin is centrally involved in the regulation of basic social and reproductive behaviors, such as cohabitation, gestation, and breastfeeding, and in nonhuman mammals is crucial for social recognition (Carter, 1998, 2003; Ferguson et al., 2002; Winslow and Insel, 2004). In rodents, oxytocin enhances social recognition as indicated by decreased investigatory behavior toward a conspecific rodent during a second encounter (Ferguson et al., 2002; Bielsky and Young, 2004). In oxytocin knock-out mice, social memory is impaired and can be fully restored by a single injection of oxytocin before an initial social encounter (Ferguson et al., 2002). Remarkably, oxytocin knock-out mice have no deficits in nonsocial memory (Ferguson et al., 2000), suggesting that oxytocin modulates only social but not nonsocial memory. The influence seems to be specific to encoding, because an injection of oxytocin before an initial social encounter restores social recognition in these mice (Ferguson et al., 2000).

In humans, the influence of oxytocin on social in comparison with nonsocial memory has not yet been investigated. However, there is emerging evidence that oxytocin facilitates social cognition and prosocial behavior also in humans (Heinrichs and Domes, 2008). Men treated with oxytocin performed better in inferring the affective state from the eye region of human faces (Domes et al., 2007a). Oxytocin also increases social behaviors like trust (Kosfeld et al., 2005; Baumgartner et al., 2008).

In a pilot study, a separate group of men (age, 22.59 + 0.57 years) had rated the faces on a 7 point scale on valence (1, very negative; 7, very positive) and arousal (1, not at all arousing; 7, very arousing). A total of 120 of the 780 faces was then chosen (40 negative; 40 positive; 40 neutral) for the main study. A total of 120 grayscale Caucasian face stimuli (60 men; 60 women) was chosen from a pool of 780 faces that were selected from mainly four established databases: NimStim Face Stimulus Set (www.nimstafrica.org), Pictures of Facial Affect (Ekman and Friesen, 1971), International Affective Picture Set (Lang, 1999), Karolinska Directed Faces database (KDEF) (www.ki.se/cns/news/AKDEF-e.html). All faces showed direct gaze and were presented in an elliptic mask on a black background. In a pilot study, a separate group of men (n = 50; 22.33 ± 0.63 years) had rated the faces on a 7 point scale on valence (1, very negative; 7, very positive) and arousal (1, not at all arousing; 7, very arousing). A total of 120 of the 780 faces was then chosen (40 negative; 40 neutral; 40 positive) for the main study. A total of 84 faces (28 negative; 28 neutral; 28 positive) served as encoding material and 36 faces as distractors (12 negative; 12 neutral; 12 positive).

Non-social stimuli. A total of 120 grayscale nonsocial stimuli (30 photographs of house fronts; 30 artificial objects that were photographs of art sculptures; 60 landscapes) served for assessment of nonsocial memory. Like the faces, they were presented in an elliptic mask on a black background. Twenty-one houses, 21 objects, and 42 landscapes were encoded, and 9 houses, 9 objects, and 18 landscapes served as distractors.

Design and procedure. A placebo-controlled, double-blind between-groups design was used, with 22 men included in the oxytocin group (age, 22.59 ± 0.57 years) and 19 men (22.53 ± 0.52 years) in the placebo group. This work was supported by University of Zurich Young Investigator Research grants (Forschungskredit 2005; Forschungskredit 2006) (U.R.), U.S. was supported by Swiss National Science Foundation Postdoctoral Grant PBZH1-118850 and by a grant from the Swiss Federal Institute of Sports. M.H. was supported by Swiss National Science Foundation Grant PP001-114788 and the Research Priority Program “Foundations of Human Social Behavior” at the University of Zurich. All subjects provided written informed consent and were paid for participation. Data from three subjects were excluded from analyses. One did not attend the second session, and two met criteria for a mental health disorder based on the Symptom-Checkliste SCL-90-R (Derogatis, 1983). Participants were instructed to abstain from beverages with caffeine or alcohol during experimental days and maintained a regular sleep–wake cycle the two nights before and during the study, with sleep between 10:00–11:30 P.M. and 7:00–8:30 A.M.
The right two columns indicate results from pairwise statistical comparisons. *p < 0.05, significant differences between oxytocin and placebo in memory measures for faces, but not for nonsocial stimuli.

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<thead>
<tr>
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<th>Oxytocin</th>
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<td>Mean</td>
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<td><strong>Faces</strong></td>
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<tr>
<td>Hit rate remember</td>
<td>0.46</td>
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<td>False alarm rate remember</td>
<td>0.09</td>
<td>0.02</td>
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<tr>
<td>Hit rate know</td>
<td>0.29</td>
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<tr>
<td>False alarm rate know</td>
<td>0.20</td>
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<td>Recollection</td>
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<td>Familiarity</td>
<td>0.33</td>
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<td>Overview recognition</td>
<td>0.46</td>
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<td><strong>Nonsocial</strong></td>
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<td>Hit rate remember</td>
<td>0.56</td>
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<td>False alarm rate remember</td>
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<td>Overview recognition</td>
<td>0.44</td>
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Overall recognition memory = (hit rate (remember + know) – false alarm rate (remember + know)). Recollection = hit rate (remember) – false alarm rate (remember). Familiarity = (hit rate (know/(1 – hit rate (remember)))) – (false alarm rate (know/(1 – false alarm rate (remember))))

The influence of oxytocin on attention, wakefulness, and mood was assessed using the d2 letter cancellation test (Brickenkamp and Zillmer, 1998), the wakefulness scale of the Multidimensional Mood Questionnaire (Steyer et al., 1997), and the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988). Measurements were taken before oxytocin or placebo administration, 1 min before encoding (wakefulness; mood) and 1–5 min after encoding (wakefulness; mood; attention). At recognition testing, the same questionnaires were given before recognition testing and after the rating of the stimuli. All questionnaires have been broadly used and shown satisfactory internal consistency and validity.

**Statistical analysis.** Statistical analyses relied on ANOVA, which included a group factor treatment (oxytocin vs placebo) and, for analysis of recognition performance, a repeated-measures factor stimulus category (faces vs nonsocial). Additionally, ANOVAs for repeated measures investigated whether gender or valence of the faces contributed to the influence of oxytocin on recognition memory. Significant ANOVA main effects or interactions were specified by sub-ANOVAs and independent sample \( t \) tests. To explore whether arousal (as rated after recognition testing) modulated the influence of oxytocin on recognition memory, the individual average arousal ratings were introduced as covariates. Where appropriate, degrees of freedom were adjusted according to the Greenhouse–Geisser procedure. Effects on measures of attention, wakefulness, and mood were likewise assessed by ANOVA. To investigate whether subjects were aware of their drug condition, a \( \chi^2 \) test was used. Data are presented as mean ± SEM. All tests were two-sided and the level of significance was set at \( p < 0.05 \). All statistical analyses were performed using SPSS 16 (SPSS).

**Results**

**Rating of approachability during stimulus encoding**

The oxytocin and placebo groups did not differ in their approachability ratings for faces (oxytocin, 3.56 ± 0.12; placebo, 3.64 ± 0.14) and nonsocial stimuli (oxytocin, 4.59 ± 0.12; placebo, 4.34 ± 0.12) during the encoding phase (values of \( p > 0.13 \)). In addition, no significant difference in rated approachability was observed between the treatment groups for faces subj-
divided into negative (oxytocin, 2.46 ± 0.17; placebo, 2.47 ± 0.14), neutral (oxytocin, 3.90 ± 0.12; placebo, 4.16 ± 0.16), and positive (oxytocin, 4.31 ± 0.17; placebo, 4.29 ± 0.22) valence categories (all values of p > 0.18).

**Recognition of faces versus nonsocial stimuli**

Oxytocin differentially influenced overall recognition accuracy (hit rate – false alarm rate collapsed across remember and know responses) of social versus nonsocial stimuli (treatment by category interaction; \( F_{(1,39)} = 4.90; p < 0.05 \) (Fig. 1b; Table 1). Recognition accuracy for faces was superior in the oxytocin (0.46 ± 0.03) compared with the placebo group (0.36 ± 0.027; \( t_{(39)} = 2.29; p < 0.05 \)), whereas recognition accuracy for the nonsocial stimuli was comparable in both groups (\( p > 0.97 \)).

Analyses of recollection and familiarity revealed a more fine-grained picture of the oxytocin effect. Whereas oxytocin did not affect recollection (all values of \( p > 0.42 \)) (Fig. 1c; Table 1), the peptide strikingly affected familiarity judgments, depending on whether the stimulus was a face or not (treatment by category interaction; \( F_{(1,39)} = 14.32; p < 0.001 \) (Fig. 1d; Table 1). Familiarity judgments of the faces were superior in the oxytocin (0.33 ± 0.03) than in the placebo group (0.22 ± 0.028; \( t_{(39)} = 2.50; p < 0.05 \)). Specifically, subjects in the oxytocin group were less likely to give a know response to a new face (0.198 ± 0.02) than subjects in the placebo group (0.26 ± 0.03; \( t_{(39)} = 2.03; p < 0.05 \)). For nonsocial stimuli, familiarity scores (\( p > 0.39 \)) as well as number of false know responses (\( p > 0.80 \)) were comparable between the treatment groups.

**Influence of gender and valence on face recognition**

To explore whether the improved memory for faces after oxytocin was dependent on the gender of the face or its rated valence, ANOVAs were run including either an additional gender factor (male; female) or a valence factor (negative; neutral; positive).

Valence rated at the time of recognition testing, as expected, confirmed the differences between faces grouped into the negative (2.21 ± 0.09), neutral (3.77 ± 0.09), and positive face categories in all subjects (4.19 ± 0.12; all values of \( p < 0.001 \)). The oxytocin and placebo groups did not differ in their valence ratings (all values of \( p > 0.49 \)). Analysis of overall recognition accuracy, apart from confirming the improved effect of oxytocin (\( t_{(39)} = 2.29; p < 0.05 \)), revealed a main effect of valence (\( F_{(2,78)} = 33.2; p < 0.001 \)), indicating that negative (0.17 ± 0.01) and positive faces (0.16 ± 0.01) were generally recognized better than neutral faces (0.09 ± 0.01; values of \( p < 0.001 \)). However, this effect was not modulated by oxytocin (\( p > 0.82 \) for respective treatment by valence interaction). Analysis of familiarity scores, which were found to be most sensitive to the influence of oxytocin on face memories in the main analyses, revealed a similar picture. Familiarity differed between faces of different valence (main effect of valence with higher scores for negative and positive than neutral faces; \( F_{(2,78)} = 6.56; p < 0.01 \)). However, this effect again did not depend on the type of treatment (\( p > 0.89 \) for treatment by valence). Overall, these analyses did not reveal valence as a factor of any importance for the improving influence of oxytocin on face recognition.

Gender of the face was likewise excluded as modulator of the effects of the peptide on face recognition. There was no significant effect of gender on overall recognition accuracy (all values of \( p > 0.78 \)). Regarding familiarity scores, male faces were more familiar than female faces (male, 0.16 ± 0.01; female, 0.12 ± 0.02; main effect of gender; \( F_{(1,39)} = 5.05; p < 0.05 \)). The false alarm rate for know responses was also lower for male (0.10 ± 0.01) than female faces (0.13 ± 0.01) (\( F_{(1,39)} = 4.93; p < 0.05 \)). However, these effects of gender on familiarity and false alarms were again comparable in the placebo and oxytocin groups (values of \( p > 0.28 \) for treatment by gender).

**Influence of arousal on recognition performance**

Because previous studies indicated strong influences of arousal ratings of pictures on encoding of memories (McGaugh and Roozendaal, 2002; LaBar and Cabeza, 2006), in supplementary analyses we controlled for this possible influence by entering arousal (as rated after recognition) as covariate into ANOVAs of memory performance. None of these analyses revealed any significance for the arousal covariate (all values of \( p > 0.21 \), but they all confirmed the main effects of oxytocin reported for the original analyses.

**Attention, wakefulness, mood, and substance awareness**

Attention, as assessed by letter cancellation performance, increased from before substance administration (oxytocin, 397.2 ± 29.0; placebo, 390.78 ± 33.1) to the time after the period of stimulus encoding (oxytocin, 459.5 ± 36.4; placebo, 424.1 ± 33.7) (\( F_{(1,39)} = 20.65; p < 0.001 \)), but did not differ between groups (all values of \( p > 0.17 \)). Wakefulness did not change throughout the encoding session and also was not influenced by
oxytocin (all values of $p > 0.19$). Negative affect, as assessed by the PANAS, decreased across the encoding session ($F(1,39) = 8.16$; $p < 0.01$), but the measure did not differ between oxytocin and placebo groups (all values of $p > 0.27$). At recognition testing, again no differences between treatment groups were observed in all psychological measures (all values of $p > 0.63$). When asked in the end of the second session, subjects were unable to correctly identify whether they had received an active agent or placebo ($\chi^2$ test; $p > 0.25$).

**Discussion**

This is the first study to show that oxytocin improves recognition for faces, but not for nonsocial stimuli in humans. Our data indicate that a single dose of intranasally administered oxytocin 40 min before encoding causes a substantial improvement in the ability to recognize faces a day later, while leaving entirely unaffected the recognition of nonsocial stimuli. Our finding is consistent with previous observations suggesting a globally enhancing effect of oxytocin on processing of face stimuli (Guastella et al., 2008a,b; Savaskan et al., 2008). Most importantly, this result concurs with rodent studies that show oxytocin to be selectively essential for the establishment of memory of a conspecific, but not for learning of nonsocial information (Ferguson et al., 2000, 2002).

More specifically, the enhancing effect of oxytocin on recognition of faces versus nonsocial stimuli emerged for familiarity judgments, whereas recollection remained unaffected. The peptide strikingly improved familiarity judgments for faces, but not for nonsocial stimuli. This pattern shows that the advantage in social recognition after oxytocin expresses itself in a greater familiarity of previously encountered faces. Specifically, oxytocin lowered the detection threshold for faces. Indeed, the raw measure mainly affected was the false alarm rate for know responses, which was decreased after oxytocin administration, thereby distinctly improving the signal-to-noise ratio for discriminating new faces from old ones. Remarkably, recollection measures of face memory remained unaffected by oxytocin. Recollection reflects the conscious effortful retrieval of qualitative information of a study event, whereas familiarity judgments are based on a direct sensing of the memory strength (Yonelinas, 2002). Hence, the specific effect of oxytocin on familiarity of faces likely reflects an immediate strengthening of neuronal circuitry selectively representing social memories.

Additional analyses did not reveal any considerable influence of gender and valence of the face, or arousal on memory performance (all values of $p > 0.21$). Thus, the enhancing effect of oxytocin on recognition and familiarity of faces is independent of whether the face is that of a man or a woman, and whether the face is experienced as negative, neutral, or positive, indicating that the social nature of the stimulus per se is relevant for the memory effect of the peptide regardless of its phenotypic appearance (Savaskan et al., 2008). Also, there was no difference between the oxytocin and placebo groups in any measure of attention, alertness, and mood at encoding or at recognition testing, which excludes that differences in recognition were confounded by effects of the peptide on these nonspecific functions.

Together, our data indicate that oxytocin in humans immediately strengthens the capability to correctly recognize and discriminate faces. The identification of an evolutionarily highly preserved hormone accounting for improved recognition of conspecifics not only in rodents, but also in humans, points to a similar mechanism of social recognition across species.

In rodents, oxytocin is essential in the medial amygdala for establishing a social memory (Ferguson et al., 2002). Olfactory cues of a conspecific are conveyed via the main and accessory olfactory pathways to the medial amygdala where oxytocin acts to modulate encoding of the memory for the initial social encounter (Ferguson et al., 2002). The medial amygdala projects to the bed nucleus of the stria terminalis and via the lateral septum to the hippocampus, which is most crucial for storage and retrieval of many types of memories. After a social exposure, oxytocin knock-out mice show hypoactivation of the medial amygdala and several downstream projections of this nucleus (Ferguson et al., 2001). Interestingly, these mice simultaneously show a massive hyperactivation of other brain areas including the hippocampus and somatosensory cortex, which possibly reflects the recruitment of alternative pathways for processing social cues. Oxytocin administered into the medial amygdala of knock-out mice before an initial social encounter fully restores social recognition (Ferguson et al., 2001). Conversely, an oxytocin receptor antagonist administered to the medial amygdala of wild-type mice impairs social recognition. These findings show that the activation of oxytocin receptors in the medial amygdala is both necessary and sufficient for the successful formation of a social memory in mice.

In humans, faces constitute the primary social cue. The processing of faces relative to other visual stimuli recruits a distributed neural system in the human brain (Haxby et al., 2000). In particular, among other regions, numerous neuroimaging studies identified the amygdala, the superior temporal sulcus (STS), and a region in the fusiform gyrus, the fusiform face area (FFA), to be critically involved in face processing (Sergent et al., 1992; Haxby et al., 1994; Kanwisher et al., 1997; McCarthy et al., 1997) (for review, see Haxby et al., 2000; Adolphs, 2002; Vuilleumier, 2007). It has been proposed that the fusiform face area processes invariant aspects of faces and thus contributes to face identity perception, whereas the STS and the amygdala are more important for the processing of variable aspects of faces, such as eye gaze and emotional expression. However, these regions do not act separately from each other, but rather interact with each other, in particular the amygdala and the FFA (Vuilleumier, 2007).

The neuronal mechanisms mediating the effects of oxytocin on human face memories cannot be inferred from the present data. Expression of oxytocin receptors has been revealed in various brain regions, particularly in the amygdala and hippocampus (Insel and Shapiro, 1992; Gimpl and Fahrenholz, 2001; Landgraf and Neumann, 2004; Huber et al., 2005), but also in different regions of the neocortex (Insel et al., 1991; Gimpl and Fahrenholz, 2001). Recent functional magnetic resonance imaging studies indicated a specific modulation of amygdalar activity during face processing after administration of oxytocin (Kirsch et al., 2005; Domes et al., 2007b; Petrovic et al., 2008). Of note, one of these studies revealed oxytocin induced blood oxygen level-dependent signal changes also in the fusiform gyrus (Petrovic et al., 2008). Both amygdala and fusiform gyrus are involved in the acquisition of familiarity for faces (Kosaka et al., 2003). In previous experiments using the same face presentation as well as dose and timing of oxytocin as in the present study, we found that oxytocin administered before face encoding reduces activity in the amygdala (Domes et al., 2007b). This effect, like the enhancing effect of oxytocin on face familiarity in the present study, was independent on the valence or arousal value of the faces. Given that the amygdala contributes to emotion perception in faces, whereas face identity is mediated via the FFA (Adolphs, 2002; Vuilleumier, 2007), the independence on valence and arousal so consistently observed for the effects of oxytocin suggests a primary role for the FFA (rather than amygdala) in mediating the
enhanced facial familiarity after oxytocin, revealed in here. The focus of the effect of the peptide on familiarity rather than recollection of faces likewise suggests that oxytocin predominantly acts at the neocortical level of the face encoding circuitry. In combination, our observations argue for the view that the enhanced familiarity judgments for faces encoded under the influence of oxytocin involve both an action on the amygdala as well as the fusiform face area, with perhaps a leading role for the influence on the fusiform gyrus.

In summary, the findings of our study show a crucial function of oxytocin in the early processing of the most basic class of social stimuli (i.e., faces). Similar to animal studies, we find that oxytocin strengthens the encoding of conspecifics and is essential for the identification and recognition of individual conspecifics. Social recognition is an essential prerequisite of more complex social behaviors. Many animal and a few human studies have shown that oxytocin is involved in the regulation of complex social behaviors, such as trust, pair bonding, or parental care. In the light of our basic findings, oxytocin appears to provide an effective approach for selectively influencing and ameliorating the foundation of basic social competences in humans, especially in disease conditions.

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Little is known about the neural mechanisms underlying top–down control of repetition priming. Here, we use functional brain imaging to investigate these mechanisms. Study and repetition tasks used a natural/man-made forced choice task. In the study phase subjects were required to respond to either pictures or words that were presented superimposed on each other. In the repetition phase only words were presented that were new, previously attended or ignored, or picture names that were derived from previously attended or ignored pictures. Relative to new words we found repetition priming for previously attended words. Previously ignored words showed a reduced priming effect, and there was no significant priming for pictures repeated as picture names. Brain imaging data showed that neural priming of words in the left prefrontal cortex (LIPFC) and left fusiform gyrus (LOTC) was affected by attention, semantic compatibility of superimposed stimuli during study and cross-modal priming. Neural priming reduced for words in the LIPFC and for words and pictures in the LOTC if stimuli were previously ignored. Previously ignored words that were semantically incompatible with a superimposed picture during study induce increased neural priming compared to semantically compatible ignored words (LIPFC) and decreased neural priming of previously attended pictures (LOTC). In summary, top–down control induces dissociable effects on neural priming by attention, cross-modal priming and semantic compatibility in a way that was not evident from behavioral results.

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word can be interpreted. A conceptual level associates lexical information with semantically associated concepts (Levelt, 1999).

Brain imaging studies identified several brain areas showing neural priming that were associated with this cascade of visual word processing during reading and semantic decision tasks (Henson, 2003; Indefrey and Levelt, 2001; Price, 2000). For example, posterior and medial areas in the occipital cortex have been associated with early stages of visual perceptual processing (Dehaene et al., 2001). At a later stage of perceptual identification, word compounds may be conjoined to a single word form representation and matched with lexical information. These processes have been associated with the left occipitotemporal (LOTC) and posterior middle temporal gyrus (pMTG). Reductions of brain activity in the LOTC, at the border of the posterior fusiform gyrus and inferior temporal gyrus, may reflect visual word form priming (Cohen et al., 2002) although a strict account of this claim has been strongly criticized (Price and Devlin, 2003). A higher order function of this area in reading has been suggested in amodal priming studies using auditory and visual stimuli. Priming studies using a stem-completion task showed within-modality but not between-modality neural priming in this area (Badgaiyan et al., 2001; Schacter et al., 1999). Similar within-modality neural priming effects were found in a study using magnetoencephalography during a repetition priming task, suggesting amodal processing of words in the LOTC (Marinkovic et al., 2003). Several studies showed larger neural activity for concrete than for abstract words in the adjacent left mid-fusiform gyrus (Fiebach and Friederici, 2004; Mellet et al., 1998). This area showed partial overlap with object processing (Price et al., 2001) and showed increased activity during mental imagery (D’Esposito et al., 1997). This suggests a common neural representation for pictures and concrete words although cross-modal repetition priming has not been demonstrated in the LOTC. Functional imaging studies identified the posterior middle temporal gyrus and angular gyrus (pMTG/AG), mainly in the left hemisphere to be associated with the recoding of the written word into a lexical representation. This has been classically associated with the Wernicke area. For example, these areas were active for words, but not for pseudo-words, and showed lexical priming effects (Hagoort et al., 1999; Kotz et al., 2002; Petersen et al., 1990).

Following lexical identification, the lexical information of the word is semantically associated with other concepts. Two brain regions have been associated with these processes, the anterior middle temporal gyrus (aMTG) and left inferior prefrontal cortex (LIPFC). The aMTG was found to show a common representation between pictures and words (Vandenberge et al., 1996). The aMTG was also involved in semantic priming under conditions that allowed automatic processing, but did not allow for strategic processing (Mummery et al., 1999). Mummery and colleagues argued that semantic priming may occur automatically in the aMTG, whereas non-automatic priming may be related to different brain areas. A good candidate for non-automatic semantic processing is the LIPFC. This area may be associated with attentional/strategic semantic and mnemonic processing (Fiez, 1997; Gabrieli et al., 1998; Paller and Wagner, 2002). This was supported by lesion studies showing impaired strategic semantic priming, whereas automatic priming was unimpaired (Hagoort, 1997). Imaging studies showed neural priming in the LIPFC after studying words in a semantic task (Poldrack et al., 1998), but not in a perceptual task (Demb et al., 1995), suggesting that neural priming in the LIPFC is sensitive to the depth of word processing. This hypothesis particularly accounts for the anterior part of the LIPFC. That area showed neural priming after word repetitions within a semantic task (Wagner et al., 2000) for both words and pictures (Wagner et al., 1997), whereas the posterior part of the LIPFC showed priming both when words were previously presented in a perceptual and a semantic task. Both anterior and posterior LIPFC have also been associated with attention and top-down processing (Petrides, 2000). For example, recent meta-analyses reported that these areas were associated with attentive behavior in tasks that require coordinated orientation, reorienting and tagging to relevant information while ignoring potentially conflicting information (Derrfuss et al., 2004, 2005). Together, both anterior and posterior LIPFC may play an important role in both attention and priming, whereas the aMTG may be related to automatic semantic processing.

The current study particularly focuses on the role of top-down control of word priming. A typical paradigm to investigate top-down control is the Stroop paradigm (Stroop, 1935). In this paradigm, conflicting information is presented simultaneously, at a similar location, while subjects direct attention to one aspect of information and ignore the other. Repetition of the attended information has been associated with priming, i.e. the facilitation of a primed stimulus. Repetition of the ignored information as a target has been associated with reduction of priming (Maxfield, 1997; Mulligan and Hornstein, 2000). Positive priming can be reduced if subjects divide attention between words (Kahneman and Treisman, 1984). The general assumption is that dividing attention results in less processing and less priming of an item. This effect may occur at the perceptual level (Maxfield, 1997; Mulligan and Hornstein, 2000) and at the semantic or conceptual level of processing (Stone et al., 2000; Stone et al., 1998). Brain imaging studies suggested that spatial selective attention may be associated with the modulation of the neural priming effect (Eger et al., 2004). Under specific task demands, however, no priming occurs after ignoring a word (Glaser and Düngelhoff, 1984; Smith andMagee, 1980). Such an effect occurs particularly when pictures are semantically processed while simultaneously presented words are ignored. Several hypotheses have been made to explain this effect. Semantic processing of words may be slower than that of pictures, and consequently the word’s semantic information is not yet available when a response to pictures is already given (Smith and Magee, 1980). Alternatively, semantic processing of pictures evokes a general inhibition process on words, which prevents words to induce priming (Glaser and Düngelhoff, 1984). Both hypotheses explain why words are effectively not processed while pictures are simultaneously processed semantically. It is however not clear which neural mechanisms support this behavioral effect. Ignored words may induce no neural priming at all, or words may be partially processed but suppressed at a certain stage of processing by attention to the picture, so that no behavioral effect is measured.

We used functional MRI to study neural mechanisms of priming. Subjects were presented with a series of conjunctions of a word and picture superimposed on each other. In two Stroop tasks, the subjects were instructed to make a natural/man-made decision for either the word or the picture. This design addresses the effect of response competition. The words and pictures were either semantically compatible (i.e. natural or man-made) or incompatible (one was natural, the other man-made). The level of interference of the ignored stimulus has sometimes been measured with the effect of compatibility, i.e. ignored response incompatible pictures may
delay the processing of the attended word (Glaser and Düngelhoff, 1984). The repetition priming task followed the Stroop tasks. Here, brain activity was measured by fMRI while subjects performed the same task on a series of old words intermixed with new words (NW). Old words were either previously responded to or ignored and were either semantically compatible or incompatible with the superimposed picture. We will name these words “old attended compatible words (OACW)”, “old attended incompatible words (OAICW)”, “old ignored compatible words (OICW)” and “old ignored incompatible words (OIIICP)”. We expected that previously attended words on a semantic task exhibit reduced responses in visual word form and semantic processing related areas. The question was whether areas showing neural priming for repeated words reduce priming when attention is directed to the picture. We also test to whether attention to pictures generally or selectively inhibits processing of words at a specific stage. In other words, does specific neural priming occur for previously ignored words despite the absence of behavioral priming? Furthermore, we test whether the semantic compatibility of superimposed words and pictures during study affects the priming of words. If ignored words are suppressed while attending pictures, one would expect that these words show reduced neural priming compared to old attended words, independently of whether the attended picture during study was semantically compatible or incompatible with the word. If, however, ignored words should be semantically or lexically processed, one would expect that processing of the ignored word increased by the conflict between semantically incongruent superimposed words and pictures and therefore might induce increased neural priming in areas related to semantic/lexical processing. In addition, one might hypothesize that the semantic compatibility of pictures during study affects priming of previously attended words. The third question concerned another top-down mechanism in priming, namely cross-modal priming. To investigate this issue we show picture names in the repetition task that were either initially responded to or ignored as pictures and were either semantically compatible or incompatible with superimposed words. They are called “old attended compatible picture names (OACP)”, “old attended incompatible picture names (OAIP)”, “old ignored compatible picture names (OICP)” and “old ignored incompatible picture names (OIIIP)”. Whereas word priming can be caused by both perceptual features and semantic properties, picture name priming can only be caused by the common conceptual properties of the word and the picture. The question was whether pictures show cross-modal priming effects in areas that were involved in the processing of words. We also test whether cross-modal priming is reduced when attention is directed to words. Finally, we test whether priming of picture names is affected by the semantic compatibility of the superimposed words presented during study. If ignored words are not processed during study, priming of previously attended picture names should not be affected by the semantic compatibility of superimposed words during study, whereas priming of ignored pictures may be affected by the compatibility of previously attended words.

Methods

Participants

Twenty-four healthy volunteers participated in the experiment (9 female, mean age 27, range 21–37). All participants were right handed (Edinburgh handedness inventory). All subjects had normal or corrected-to-normal vision, none had a history of significant neurological disorders, and all gave informed written consent.

Stimuli and procedure

Participants viewed a series of trials in three tasks (see Fig. 1 for an example). In two Stroop tasks, line-drawings of common objects (Snodgrass and Vanderwart, 1980) were presented superimposed on German nouns (250 ms) and were followed by a delay (2000–2800 ms). A central fixation cross was shown during the delays. The pictures and words were differently colored (red/blue) and were presented on a white background. Subjects responded to either the words or the pictures by instruction in the two successive Stroop tasks. The repetition priming task immediately followed the Stroop tasks with a mean delay between first and second presentation of about 2 min. Only words were presented (250 ms), which had the same color as in the Stroop tasks and which were followed by a delay (2000–2800 ms). The repetition priming experiment consisted of new words and words that were previously responded to or ignored. Pictures that were previously responded to or ignored were repeated as picture names. In total, 200 words were presented during the repetition priming task with equally sized groups of new, old attended words, old ignored words, old attended picture names and old ignored picture names. Half of the words were natural, half were man-made. Natural stimuli were animals (61), fruits or vegetables (23), plants (4) or body parts (12). Man-made stimuli were clothes (19), tools (38), musical instruments (10) or other non-living objects (33). To control for the validity of the German picture names, we instructed ten different healthy subjects to make a picture naming task to forty living and forty non-living pictures. Picture names were included in the study if they had consistent responses for at least 80% of the subjects.

Fig. 1. An example trial is shown. Pictures and words were differently colored in red or blue. In the first task, subjects made a forced choice natural/man-made decision to words that were superimposed onto pictures. In this example, the picture is associated with an incompatible response with the word. In the second task, subjects were instructed to make the same decision task for the pictures. In this example, the picture is associated with a compatible response with the word. In the third task, new words were presented as well as words that previously responded to or ignored as words or as pictures.
Each task started with an instruction followed by a countdown and two ‘warm-up’ trials that were not included in the behavioral and imaging analysis. In the Stroop tasks, subjects made a forced choice natural/man-made decision for either the words or the pictures. Half of the ignored stimuli (words or pictures) were response compatible with the attended stimuli, half were incompatible. Responses to natural and man-made stimuli were assigned to the index or little finger, which was counterbalanced across subjects. The color of the pictures and words was also counterbalanced across subjects. The order of the Stroop conditions was counterbalanced so that half of the subjects responded to words or pictures that were ignored by the other half of the subjects. We did not balance the words and pictures due to a lack of a sufficient number of natural and man-made pictures. To account for a possible bias in the priming task for words and picture names, we compared response times on a man-made/natural decision task for words (885 ms) and picture names (881 ms) in a pilot study (T < 1, ns). There were no significant differences between words and pictures for the word length (range Word: 3–9, Picture name: 3–13), number of syllables (range W: 1–3, P: 1–4) and word frequency (range W: 0–1091, P: 0–2830) (all p > 0.1).

Critical fMRI data were acquired during the priming task. The experiment employed an event-related design and lasted about 25 min. The 200 trials in five stimulus categories were pseudo-randomly distributed over the experiment, so that no more than four stimuli of the same category were presented in sequence. The experiment additionally included 300 null events (1100 ms of fixation), which were pseudo-randomly intermixed among the trials, so that no more than four null-events were presented during a single inter-stimulus interval. The reason for this design was that jittering null events increases statistical efficiency when comparing between event types (Dale, 1999), whereas increasing delays or repetitions of the same category may reduce subject’s attention. Prior to scanning, participants were informed about the task and practiced under the supervision of the experimenter. In the scanner, subjects were instructed to respond by pressing a button as quickly and accurately as possible on a fiber-optic response pad with the right hand. They viewed the stimuli on a backlit projection screen through a mirror mounted on the head coil. The task was practiced again inside the scanner during the anatomical scan. The Experimental Run-Time System (www.erts.de) was used as a stimulus presentation program.

Magnetic resonance imaging

An axial spin-echo planar imaging sequence on a 1.5 T scanner (Siemens Symphony, Erlangen, Germany) was used to measure BOLD contrast. We acquired a series of 381 T2*-weighted scans. The scans were aligned along the AC/PC line. Each whole brain volume consisted of 25 slices (5 mm with a 0.5 mm gap, 3.44 × 3.44 mm in-plane resolution, field of view = 220 mm, repetition time (TR) = 2.5 s, echo time (TE) = 50 ms). During the Stroop tasks, 48 scans were acquired with the same procedure as during the priming task, so the sound level was comparable during the three sessions. However, the design of the Stroop tasks was not optimized for fMRI data analysis (e.g., null events), and thus these data were not analyzed. Anatomical images were acquired using a sagittal T1-weighted 3D-FLASH sequence, which was used to identify the anatomical locations of activations individually (120 slices; slice thickness: 1.5 mm without gap; 256 × 256 matrix; TR = 4 ms; TE = 11 ms).

Analysis of imaging data was performed using SPM2 (www.fil.ion.ucl.ac.uk/spm). The fMRI data were realigned for movement correction and unwarped. To correct for their different acquisition times, the signal measured in each slice was shifted relative to the acquisition time of the middle slice using a sinc interpolation in time. The fMRI data were then normalized to an SPM template with a resampled voxel size of 4 × 4 × 4 mm and smoothed with a Gaussian kernel (full width at half maximum: 8 mm). The expected hemodynamic responses at stimulus onset for five stimulus categories (new words, old attended and ignored words, old attended and old ignored picture names) were modeled by two response functions, which were a canonical hemodynamic response function (HRF) and its temporal derivative (Friston et al., 1998). The functions were convolved with the event train of stimulus onsets to create covariates in a general linear model. The vector onsets started after two dummy trials in order to let the subjects accommodate to the task. The first three scans which corresponded with the time between the countdown before the task and the third trial of the experiment were excluded from the analysis. Only correct responses were modeled. Incorrect responses were modeled with a regressor of no interest. Parameter estimates for each covariate were obtained by maximum-likelihood estimation while using a temporal high-pass filter (cut-off 128 s) and modeling temporal autocorrelation as an AR(1) process. All SPM comparisons were performed as random effects analyses across 24 subjects employing a one-way within-subject ANOVA with four stimulus categories that were contrasted against new words. Regions of interest (ROIs) with a diameter of 10 mm were selected on the basis of the coordinates of the visual word form area (Dehaene et al., 2001), anterior and posterior inferior prefrontal cortex (Wagner et al., 2000). The ROIs provide a small number of a priori regional hypotheses. The signal changes of four contrasts (NW-OAW, NW-OIW, NW-OAP and NW-OIP) were extracted from these regions and submitted to a two-way ANOVA with the factors attention (priming attended and ignored) and stimulus type (word repetition priming and picture–picture name priming). In a second analysis we estimated nine contrasts with old stimulus categories that were separated for whether these were compatible or incompatible with the superimposed stimulus during study. Signal changes of eight contrasts entered a three-way ANOVA with the factors stimulus type (word, picture), attention (attended, ignored) and compatibility (compatible, incompatible). We also report clusters of brain activity showing significant main effects or interactions after correction for the whole brain.

Results

Behavioral results

Stroop

As can be seen in the left part of Fig. 2, we found an effect of response compatibility on words. A two-way ANOVA was performed which showed a main effect of stimulus type (F(1, 23) = 35.9, p < 0.001) indicating that natural/man-made decisions for pictures were faster than for words. We also found an interaction between response compatibility and stimulus type (F(1, 23) = 6.5, p < 0.05). This effect could be explained by a compatibility effect for words (t(23) = 2.3, p < 0.05), but not for pictures (t(23) = 1.2, ns). These results indicate that word processing was affected by picture information, but not vice versa.
Priming

As seen in the right part of Fig. 2, the priming effect was substantially influenced by a prior response to the stimulus and by the type of stimulus. We found only a significant priming effect for OAW (t(23) = 3.5, p < 0.05). All other categories were not significant (maximum: t(23) = 1.3, ns). We found an interaction between stimulus type and Stroop condition (F(1,23) = 6.0, p < 0.05). This interaction could be explained by a larger priming effect for OAW than for OIW (t(23) = 3.4, p < 0.01), whereas there was no difference between OAP and OIP (t(23) = 0.4, ns). To control for the delay between the first and second presentation, we tested whether subjects having the word task first differed in priming from those that had the picture task first. There was no significant behavioral priming effect of order or interaction between task order and priming or attention (all F < 1). A three-way ANOVA with the factors attention, stimulus type and semantic compatibility showed no further dissociation. There was no significant effect of semantic compatibility or interaction with semantic compatibility. Taken together, attending and responding to pictures seemed to reduce repetition priming for simultaneously presented words. No evidence was found for a reliable priming effect of picture names, neither when they were previously attended nor ignored.

fMRI effects of attention on repetition priming

Since we were particularly interested in areas related to priming, we defined ROIs on the basis of previous studies that show word repetition priming and semantic priming effect for words. We analyzed three ROIs: the left anterior and posterior inferior prefrontal gyrus (aLIPFC (x = −43, y = 32, z = 15), pLIPFC (−43, 8, 34)), left fusiform gyrus (left occipital temporal cortex, LOTC (−46, −57, −20)). In the LOTC we found a significant effect of attention (F(1,23) = 4.5, p = 0.045), but not of stimulus type or an interaction between stimulus type and attention. As can be seen in Fig. 3, this indicated that attended stimuli showed increased priming as compared to ignored stimuli. In the aLIPFC we found trends to significance for attention (F(1,23) = 3.1, p = 0.09), stimulus type (F(1,23) = 3.4, p = 0.08) and the interaction between stimulus type and attention (F(1,23) = 3.5, p = 0.07). Comparing priming for old attended with old ignored stimuli in the aLIPFC resulted in a significant difference between OAW and OIW (t(23) = 2.6, p = 0.017) but not between OAP with OIP (t(23) = 0.3, ns). There was also a significant difference between OAW and OAP (t(23) = 2.7, p = 0.013). There were no main effects or interactions for the pLIPFC (all F < 3, ns) (Fig. 3). Thus, attention during study affected priming of both words and picture names in the LOTC, whereas the aLIPFC showed only an effect of attention on word repetition priming. We also performed the same factorial analysis on the whole brain and found no significant clusters showing interactions between attention and stimulus type. Words induced increased activity compared to pictures in the parahippocampal gyrus (BA 30, local max Z = 3.7, p = 0.002, x/y/z = −4/−40/−4) and extrastriate cortex (BA 19, Z = 4.4, p = 0.001, x/y/z = 12/−88/24). A trend to significance was found in the anterior middle occipital gyrus for the comparison between priming of previously attended words and ignored words (OAW-OIW; BA 19 Z = 4.0, p = 0.065, x/y/z = −52/−60/−8). This area largely overlapped with the ROI of the LOTC.

fMRI effects of attention and semantic compatibility on neural priming

Next, we tested whether semantic compatibility of superimposed words and pictures during study affected subsequent priming. An ANOVA with the factors stimulus type, attention and semantic compatibility was submitted to the three ROIs. In the LOTC we found an interaction between attention and semantic compatibility (F(1,23) = 5.9, p = 0.024) as well as trends to significance for the effect of attention (F(1,23) = 4.2, p = 0.052) and compatibility (F(1,23) = 4.0, p = 0.056). As can be seen in the lower part of Fig. 3, priming seemed to be reduced when semantically incompatible stimuli were superimposed during study or when stimuli were previously ignored (attended compatible–incompatible: t(23) = 3.2, p = 0.004; ignored comp–incomp: ns). A significant three-way interaction indicated that this effect was different for words and pictures (F(1,23) = 5.3, p = 0.03). There was a trend to significance for the effect of attention on words (attention effects: F(1,23) = 3.7, p = 0.065). In contrast, picture to picture name priming was affected by both the semantic compatibility of the word and attention (interaction attention by compatibility: F(1,23) = 12.1, p = 0.002). Comparing compatible and incompatible stimuli we found only a significant effect between compatible and incompatible attended pictures (t(23) = 4.9, p < 0.001), but not for ignored pictures or attended or ignored words (all t < 2, ns). Hence, the neural priming effect of previously attended pictures on picture names was reduced in the LOTC if the superimposed word during study was semantically incompatible with the picture.

The two frontal regions aLIPFC and pLIPFC showed a similar pattern of results, but different from the LOTC. We found interactions between attention and semantic compatibility (aLIPFC:
These interactions can be explained by the stronger effect of compatibility on previously ignored stimuli as compared to previously attended stimuli. The priming effect was larger for previously ignored stimuli that were incompatible with the superimposed stimulus during study than for those that were compatible with superimposed stimuli.
(ignored comp vs. incomp: aLIPFC t(23)=-2.3, p=0.032, pLIPFC t (23)=-2.4, p=0.027). No such effect occurred when stimuli were previously attended (attended comp vs. incomp, ns). Together, priming in the LOTC reduced when the stimuli were previously ignored and incompatible with the superimposed stimulus during study. This was particularly the case for previously attended pictures. Both anterior and posterior LIPFC showed no effect of compatibility on previously attended stimuli but showed an increase in priming if stimuli were previously ignored and incompatible.

A whole brain analysis showed both main effects of semantic compatibility, interactions between attention and compatibility on priming and three-way interactions between attention, compatibility and stimulus type. Detailed results are listed in Table 1 and Fig. 3. Semantic compatibility affected neural priming in the posterior cortex, particularly in extrastriate regions of the middle occipital gyrus and lingual gyrus (BA 18/19). Here, we found larger priming effects for compatible stimuli as compared to incompatible stimuli during study. We found significant interactions between attention and semantic compatibility in the left posterior inferior temporal cortex (including LOTC), left anterior and posterior inferior/middle prefrontal cortex (including aLIPFC and pLIPFC) as well as the right anterior middle frontal gyrus (BA 9/46), medial prefrontal gyrus and anterior cingulate gyrus (BA 9/32), right cerebellum, and posterior cingulate gyrus and precuneus (BA 30/31). All these areas, except for the left inferior/middle prefrontal gyrus, showed decreased neural priming for previously attended stimuli with incompatible as compared with compatible superimposed stimuli during study. Three-way interactions were found in the occipital cortex including the middle occipital gyrus, lingual gyrus (BA 18 and 19) and primary visual cortex (BA 17). These areas showed no neural priming for words, or effects of attention or compatibility on word repetition priming. However, these areas showed an interaction between attention and compatibility on priming of picture names (Fig. 3). This interaction indicated that previously attended pictures induced reduced priming on picture names if they were presented with semantically incompatible words during study.

### Discussion

The present study investigated the neural mechanisms underlying top–down control of word priming. Behavioral data replicated studies showing that words shown at fixation during a semantic decision task on superimposed pictures significantly reduced the behavioral priming effect. We found no evidence for cross-modal priming and no effect of attentional modulation on cross-modal priming. Furthermore, semantic compatibility did not significantly affect priming of words or picture names. These behavioral priming data support the hypothesis that ignored words are not processed while making a semantic response to superimposed pictures (Glaser, 1992; Glaser and Düngelhoff, 1984). Brain activity showed more complex effects of top–down modulation of priming. First, neural priming for old ignored words was reduced compared to old attended words in the LOTC and aLIPFC. In addition, we found effects of cross-modal priming and interactions between cross-modal priming and attention. We also found evidence that semantic compatibility of superimposed words and pictures affected both priming of words and picture names. We will discuss these findings in the context of current literature.

The first question was whether neural repetition priming was affected by attention. Imaging data support the hypothesis that attention increased neural priming. We found priming effects in the LOTC that increased for previously attended as compared to ignored stimuli. These effects were independent of whether a word or a picture name was primed. These data extend previous findings on attention dependent neural priming (Eger et al., 2004). That study reported reduced neural priming effects in object processing

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### Table 1

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Functional MRI results show attention and semantic compatibility related effects on neural repetition priming. Significant clusters or areas showing a trend to significance (*) are shown (p<0.05). The local maxima of each cluster are listed as x/y/z coordinates in MNI space, as well as distant areas within the same cluster. Brodmann areas (BA) are depicted for each cluster. Abbreviations: L/R is left/right, prefix ant/post=anterior/posterior, FG=frontal gyrus, G=gyrus.
sensitive fusiform gyrus if spatial attention was directed away from objects. There were two main differences between both studies. In our study we used words and found effects of attention in a more lateral and word form processing sensitive area (LOTC or visual word form area). Secondly, in contrast to Eger and colleagues, we used superimposed words and pictures so that attention affected stimulus processing even though both words and pictures were in the center of fixation. Thus, our findings support and extend that neural priming is modulated by selective attention.

The second question was if priming of ignored words was generally inhibited by a semantic decision to pictures, as proposed by Glaser (1992), and whether this would result in a general absence of semantic interference. Together, there is ample evidence that ignored words induce neural priming at a semantic level despite the strong top–down modulation when subjects make a semantic decision task to pictures.

The current findings seem to contradict findings showing that words are not processed during processing of pictures (Rees et al., 1999). An explanation for differences in these results may be related to the working load conditions during encoding. Rees and colleagues suggested that words are not processed at all while picture processing was difficult in a visual matching task. In our case the perceptual or processing load in the picture task was lower, so that ignored words might have been processed up to a certain level.

The third issue was whether pictures may prime picture names semantically and whether these priming effects depend on attention. We found no significant behavioral priming effect of pictures to picture names, which is in line with studies showing that picture to picture name priming is smaller than word repetition priming also if words and pictures are presented separately (Durso and Johnson, 1979). However, we found a main effect of attention on neural priming in the LOTC, which may be equivalent to the visual word form area and an interaction between stimulus type and attention in the aLIPFC. This suggests that picture names were primed similarly as words, at least in the LOTC. As far as we know cross-modal picture to word effects have not been reported in the LOTC, but these results are in line with the top–down modulation hypothesis for the LOTC (Buckner et al., 2000). They are also in line with findings showing semantic priming effects for objects in the fusiform gyrus (Simons et al., 2003) and support the criticism that LOTC processes only visual word forms (Price and Devlin, 2003). In summary, these data support the hypothesis that the LOTC plays an important role in attention dependent priming for conceptual information.

Finally, we were interested if cross-modal priming effects were affected by top–down modulations of semantic compatibility during study. Several brain areas showed similar top–down modulations on neural priming of picture names as of words. Interactions between attention and compatibility in several areas including the left fusiform gyrus and frontal cortex showed reduced neural priming responses for previously attended picture names and words when superimposed stimuli during study were semantically incompatible. Only the aLIPFC showed an increased response for ignored words and pictures when superimposed stimuli during study were semantically incompatible. These results strongly supported that cross-modal priming effects were modulated by attention and compatibility in a similar way. As far as we know this is the first study to show such effects. Several studies have reported common representations of pictures and words (Price et al., 2003; Vandenberghe et al., 1996) or effects of concreteness in the fusiform gyrus (Fiebach and Friederici, 2004; Mellet et al., 1998). The finding that priming of both normal and mirrored objects are similarly affected by spatial attention in this area also suggests top–down modulations of a higher-order representation (Eger et al., 2004). Thus, the current data suggest that cross-modal priming, or common representations between words and pictures, at least partially underlie the same top–down control mechanisms.

The current study furthermore shows strong effects of semantic interference on neural priming. The effects of interference on priming occurred particularly in the posterior cortex. We found main effects of compatibility, as well as interactions between attention and compatibility and three-way interactions between stimulus type, attention and compatibility. These results strongly support the role of semantic interference in the top–down control of priming. Interestingly, semantic compatibility affected differences between old and new stimuli even in areas that are not particularly...
sensitive to word priming, including several striate and extrastriate cortex. The data particularly suggest that top–down mechanisms affect neural priming related to pictures. A possible explanation for these findings may be related to the fact that picture names are directly associated with previously presented pictures. This association may have activated a top–down process in a similar way as during a mental imagery task and by means of an increase in neural activity in perceptual processing areas during repetition (Kosslyn et al., 1995). We also found that neural priming in these areas was reduced for picture names when previously attended pictures were presented with semantically incompatible words, whereas neural priming of words was unaffected by the semantic compatibility of superimposed pictures. An explanation for this effect may be that semantic interference of words intervenes with semantic processing of pictures. Repetition of pictures may then have induced less priming in perceptual processing areas.

Several other reasons have been discussed that modulate neural priming. For example, a prominent top–down effect on priming is negative neural priming. Negative priming represents the increase of response latencies after repetition of an ignored stimulus or conceptually related stimulus (Damian, 2000; Tipper and Driver, 1988). It is usually observed when ignored stimuli are repeated in the presence of a distractor and reduces when no distracting information is present (Allport et al., 1985; Lowe, 1979), but may also occur when no distracting information is present (Fox, 1995; Moore, 1994; Neill et al., 1994; Yee, 1991). Negative priming may reflect the cost of retrieving previously ignored information after the active inhibition of stimulus information (Neill et al., 1992). This may be associated with increased activity in the right dorsolateral prefrontal cortex (Egner and Hirsch, 2005). Increased activity after repetition of ignored stimuli has also been reported in medial parts of the inferior temporal lobe (Gazzaley et al., 2005; Vuilleumier et al., 2005). In the current study, no evidence was found for negative neural priming of ignored words, neither in frontal areas, nor in perceptual processing areas. There was also no evidence that negative neural priming coexisted with (or neutralized) positive neural priming when words showed no behavioral priming effect. There was, however, a difference with other brain imaging studies showing negative priming (Egner and Hirsch, 2005; Steel et al., 2001; Vuilleumier et al., 2005). In the priming task, we presented only the ignored item without distracting picture. Several behavioral studies showed that negative priming depends on the presence of a distractor during probe stimulus presentation (Allport et al., 1985; Lowe, 1979; Tipper and Cranston, 1985). For example, if only color patches (without the word) were presented following a conventional color Stroop task, positive priming instead of negative priming was found (Lowe, 1979). This suggests that priming can be reversed depending on whether a distractor is present or not. At least, studies showing negative priming without a distractor created an expectation that distractors might occur (May et al., 1995; Neill et al., 1994). In the current study we showed no distractors at the probe stimulus and created no expectation that a distractor might occur. Thus, in the context of those studies, the current imaging data are in line with the hypothesis that no negative neural priming for ignored stimuli occurs when no distractor is presented or expected, although caution must be taken since increases and decreases in neural activity may occur in the same brain areas (Gazzaley et al., 2005). These modulations in neural activity may be related to positive and negative priming. In such a case, the simultaneous occurrence of positive and negative priming may be mistaken for a modulation of positive priming.

Another aspect may modulate priming, namely stimulus familiarity. Previous studies reported that unfamiliar stimuli show increased neural responses upon repetition, whereas familiar stimuli show decreased responses (Grill-Spector et al., 2006; Henson et al., 2000). In the current study, we use familiar stimuli of words and pictures. These stimuli did not differ between categories since these were counterbalanced across subjects. Thus, this factor may not have affected the modulation of priming in the current study.

Taken together, the present study reveals multiple mechanisms of top–down control on repetition priming. We report that neural priming is affected by attention, semantic compatibility and cross-modal priming. We also show interactions between these top–down mechanisms on neural priming. In particular, neural priming of pictures to picture name was similarly affected by attention and semantic compatibility as word repetition priming, and ignored words induced neural priming effects at a semantic level, despite the absence of significant behavioral priming. These data thus extend previous studies showing modulations of neural priming.

References


Research report

Using visual advance information: an event-related functional MRI study

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Abstract

Our event-related functional MRI (efMRI) study investigates whether visual advance information (AI) affects rather perceptual or central response-related processing areas. Twelve subjects were required to make a go/no-go decision to a conjunction of a specific color and motion direction. The stimuli were preceded by a cue, providing 100% valid advance information about motion direction. Partial and full advance information (PAI and FAI) predicted possible targets, respectively, certain nontargets, neutral cues (NAI) gave no prediction. The time between cue and stimulus (stimulus onset asynchrony, SOA) was varied. A response benefit was found after PAI as compared with NAI. The benefit was small with a short SOA (150 ms), increased with intermediate SOA (450 ms) and sustained with long SOA (750 ms). Perceptual and central processing areas were more active with increasing SOA, but only central response-related processing areas were selectively modulated by cue information. In particular, supplementary motor area and bilateral inferior parietal lobe were more active with PAI than with NAI. If comparing NAI with FAI, more errors were made and activity was larger in central processing areas. Our results suggest that, depending on the processing time, cues providing perceptual information modulate central response-related processes.

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Topic: Visual psychophysics and behavior

Keywords: Magnetic resonance imaging; Motion; Color; Cueing; Stimulus onset asynchrony

1. Introduction

Human planning and goal directed behavior is strongly influenced by ongoing information that is given continuously and the capability to process and integrate this information. Studies on the processing of advance information (AI) investigate this feature of planning. If AI is given, responses can be made faster and more accurate [19,34]. Behavioral studies showed that AI undergoes several stages of processing before it can be used [6,22]. One crucial factor in the use of AI may be the reduction of stimulus/response uncertainty [6,22]. It is, however, unclear whether AI specifically changes parameters in the domain that it provides [36] or more general preparation processes [13]. Support for the first hypothesis comes from motor studies. Advance motor information was reported to change selective motor processes [23,36]. There is, however, no evidence from brain imaging studies supporting the hypothesis that visual AI changes perceptual processes. In a different line of visual cueing studies, repetition priming facilitated stimulus identification [7,17]. In another line of visual cueing investigations, attentional cues enhanced perceptual processing, as supported by behavioral [33], event-related potential [24,27] and brain imaging studies [17,37]. These studies, however, differ in three aspects from typical AI.
paradigms. First, compared with priming studies, AI is predictive whereas primes do not explicitly provide predictive information. Second, as compared to studies on visual attention, AI leaves no competitive bias with respect to a given parameter, i.e. in contrast to attentional cues, AI is fully predictive. It determines the number of features that need to be analyzed to complete a decision. Third, prior cueing studies used long delays between cue and stimulus, so that they did not allow conclusions about dynamical processes accompanying the use of cues [31]. In fact, the delays in those studies may have been too long (>4 s [16]) to find processes related to cue processing, because it takes only a few hundred milliseconds to take full advantage of AI [19]. In order to investigate brain areas that actually use AI, it is necessary to compare brain activity between conditions in which AI can be used with conditions in which AI cannot be used. The duration of the preparation time is a good variable to distinguish these conditions.

It was the aim of the present study to identify neural networks that accompany the use of AI, i.e. to investigate whether we could specify brain areas that correlate with AI if it is efficiently used to facilitate performance. For this purpose, we adapted a procedure developed by Kantowitz and Sanders [19] to an event-related functional magnetic resonance imaging (efMRI) experiment. Responses based on blood oxygen level dependent (BOLD) contrast were measured with efMRI during a go/no-go task in which multidimensional visual stimuli (color/motion) were preceded by AI about one of the stimulus features (direction of motion). Processes related to the use of AI were expected to be measurable with efMRI, because manipulating stimulus onset asynchrony (SOA) alters the processing time of AI but does not change other processes of stimulus perception and task response [6]. We included preparation times that were expected to separate between conditions in which AI could be used and another in which AI could not be fully used [19]. Thus, such an experimental design was expected to provide a window to fast processes that are involved in the use of AI. In addition, the design profited from the main advantage of fMRI, namely high spatial resolution, i.e. brain regions involved in central, motor processing and perceptual processes could be easily dissociated. Hence, if the use of AI involves perceptual processing, this would yield brain activity in visual processing areas for an SOA at which AI is effective. If stimulus/response uncertainty is reduced by nonvisual processes, areas outside the visual processing areas would be related to AI processing.

The participants were scanned while responding to targets within a series of stimuli. Targets were a specific conjunction of movement direction and color. In half of the trials, stimuli were preceded by an arrow indicating (with 100% validity) the direction of the movement (up/down). Up and down-going cues differed in the response prediction. Up-going cues gave partial advance information (PAI) by predicting a possible target. Down-going cues provided full advance information (FAI) by predicting a certain nontarget. In the other half of trials, stimuli were preceded by a neutral cue (NAI), providing no useful information about the imperative stimulus. In three conditions, the time between cue and the imperative stimulus was varied. In the SOA 150 ms condition stimuli followed immediately after the cue, which was presented for 150 ms. In two other conditions, intermediate (450 ms) and longer (750 ms) delays were given between cue and stimulus onset. These three SOA conditions were chosen to determine the SOA at which AI was used most efficiently. With a short SOA, advance information was expected to be hardly useful [22]. AI was expected to be useful with the intermediate SOA and remain useful with the long SOA [39]. The facilitation of performance under the presentation of cues with increasing SOA should allow the identification of brain areas that are involved in the use of AI. Furthermore, more insight in the use of AI may be attained by parametrically analyzing information load that follows a cue. Two alternative hypotheses are conceivable. With cue information either the perceptual task demand or the response uncertainty is expected to change. With cues indicating an irrelevant motion direction no feature requires analysis in order to give an accurate response. With a relevant motion cue one feature, and with a neutral cue, two features are required for analysis. Thus, the perceptual processing load varies with the cue information. On the other hand, the response probability is lowest (0%) if irrelevant motion cues are given, higher (25%) if neutral cues and highest (50%) if relevant motion cues are given. Thus, response probability varies with cue information. By analyzing the three levels of advance information in dependence of SOA, we were able to directly investigate whether the use of cues modulates central response-related or perceptual processing areas.

2. Methods

2.1. Participants

Twelve volunteers participated in the experiment (five female, age 21–30). All participants were right handed (Edinburgh handedness inventory, mean = 75). One subject was replaced, because he was not able to benefit from advance information during the training session. All subjects had normal or corrected-to-normal vision, none had a history of significant neurological disorders, and all gave informed written consent.

2.2. Stimuli and procedure

Participants viewed a series of trials and had to discriminate between stimuli which comprised a conjunction of color and motion direction (see Fig. 1 for an example). A trial consisted of a cue (150 ms), followed by a delay (0, 300 or 600 ms), a stimulus (96 ms) and a variable delay, so that
each trial lasted 2.36 s. During the delays, a central fixation cross was shown. The cues were either a centrally presented arrow giving AI about the motion direction (up or down), or a neutral cue (a vertical line with two inverted arrowheads at the endings) providing NAI. The cue images were equally sized (0.4° of visual angle high). The imperative stimuli were red or green figures consisting of three horizontally connected squares, which moved either up or down (0.3 × 0.3° of visual angle per square and 0.9° width by 0.3–0.6° height for the whole image). To simulate movement, the central square changed its position at each new refresh frame (every 16 ms) in a direction opposite to the peripheral squares. These stimuli were chosen because they limit the requirement of eye movements. Moreover, color and motion detection processes were expected to activate different pathways of perceptual analysis.

One combination of color and motion direction was the response-requiring target: red stimuli in which the central square was going up (and the peripheral squares down). The response probability was 25% in general, but increased to 50% after an arrow pointing up and decreased to 0% after an arrow pointing down (see Table 1 for details). The cues and stimuli were generated in such a way that perceptual differences between relevant and irrelevant stimuli were minimized in terms of luminance, size and discriminability. This allowed us to compare between different stimulus categories. Target and advance information was not balanced across stimulus categories, because no imaging study has shown differences in brain activity related to feature specific processing of color and motion direction, i.e. green versus red or up versus down. There was no main effect of color or motion direction in the imaging data that would challenge this assumption.

The subjects were instructed to respond to the target described above by pressing a button as soon and accurately as possible on a fiber-optic response pad with the right index finger. Nontargets had to be ignored. Furthermore, they were required to use AI. The experiment employed an event-related design with a pseudorandom trial order and was separated into two sessions, each lasting 25 min. There were 24 stimulus categories: CUE (AI, NAI), SOA (150, 450, 750 ms), FEATURE (motion, color), and RELEVANCE (target, nontarget feature). For presentation of results, motion direction and colors were labeled “M” and “C”, whereas relevant and irrelevant features were “+” and “−”. With these acronyms, go stimuli were denoted as M+C+ and no-go stimuli as M+C−, M−C+, M−C−. Thirty trials were presented in each stimulus category, so that 720 trials were pseudorandomly distributed over the experiment. The experiment included 120 null-events (2320 ms of fixation) that were pseudorandomly intermixed among the trials. This way of jittering with null-events around a short ISI allows a high statistical efficiency if comparing between event types [5]. The subjects were not notified about changing SOA. Prior to scanning, participants were informed about the task and practiced under supervision of the experimenter. In the scanner, they viewed the stimuli on a backlit projection screen through a mirror mounted on the head coil. The Experimental Run-Time System (http://www.erts.de) was used as stimulus presentation program. During the anatomical scan, subjects again practiced the task, with an SOA of 450 ms.

| Table 1 |
| The table shows the probability of each stimulus to occur after the presentation of cues |

<table>
<thead>
<tr>
<th>STIMULUS</th>
<th>M+C+ (go)</th>
<th>M+C− (no-go)</th>
<th>M−C+ (no-go)</th>
<th>M−C− (no-go)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUE</td>
<td>Neutral (NAI)</td>
<td>p=0.125</td>
<td>p=0.125</td>
<td>p=0.125</td>
</tr>
<tr>
<td></td>
<td>Up (PAI)</td>
<td>p=0.125</td>
<td>p=0.125</td>
<td>p=0.125</td>
</tr>
<tr>
<td></td>
<td>Down (FAI)</td>
<td></td>
<td></td>
<td>p=0.125</td>
</tr>
</tbody>
</table>
2.3. MRI acquisition and analysis

An axial spin-echo planar imaging sequence on a 1.5 T scanner (Siemens Symphony, Erlangen, Germany) was used to measure BOLD contrast. We acquired two series of 703 T2*-weighted scans. Each included three initial dummy scans. The scans were aligned along the AC/PC line. The task instruction was presented before scanning. Each whole brain volume consisted of 20 slices (6 mm with a 0.6 mm gap, 3.44 x 3.44 mm in-plane resolution, field of view = 220 mm, repetition time ($T_R$) = 2 s, echo time ($T_E$) = 50 ms). Anatomical images were acquired using a sagittal T1-weighted 3D-FLASH sequence, which was used individually to identify the anatomical locations of activations revealed (120 slices; slice thickness: 1.5 mm without gap; 256 x 256 matrix; $T_E$ = 4 ms; $T_R$ = 11 ms).

To correct for their different acquisition times, the signal measured in each slice was shifted relative to the acquisition time of the middle slice using a sinc interpolation in time. The functional MRI data were then realigned for movement correction, normalized to an SPM template and smoothed with a Gaussian kernel (full width at half maximum 12 mm). The expected hemodynamic responses at stimulus onset for each event-type were modeled by two response functions, which were a canonical hemodynamic response function (HRF) [11] and its temporal derivative. The functions were convolved with the event-train of stimulus onsets to create covariates in a general linear model. Parameter estimates for each covariate were calculated from the least mean squares fit of the model to the time series. Ninety-six parameters were estimated for each subject (2 sessions, 24 event-types (CUE(2), SOA(3), FEATURE(2), RELEVANCE(2)), 2 response functions per event-type). The preprocessing and statistical analyses at the single subject level were performed in SPM99 (www.fil.ion.ucl.ac.uk/spm). Because performance data showed no difference in the use of AI between SOAs of 450 and 750 ms, and to increase statistical power, trials with SOA 450 and 750 were collapsed so that 16 levels (SOA (150, 450/750), CUE (AI, NAI), FEATURE (M, C), RELEVANCE (+, −)). An effect of cues on motion processing was reported if the difference between M + C − and M − C − trials was larger with than without AI. An effect of cues on color processing was reported if the difference between M − C+ and M − C − trials differed between CUE conditions. Data were reported if voxels were significant after correction for multiple comparisons based on the false discovery rate (FDR)[12]. If specific tests were performed after a global interaction, the results of the interaction were used as a volume of interest for which the specific test results were corrected.

3. Results

3.1. Behavioral results

The subject’s response latencies showed strong effects of PAI with an SOA of 450, which sustained with longer SOA (see Table 2 for details). Statistical analyses confirmed an interaction between CUE and SOA ($F_{2,22} = 18.42, p < 0.001$), which could be explained by a larger benefit for PAI trials at an SOA of 450 as compared with 150 ms (SOA (150,450) x CUE: $F_{1,11} = 17.13, p = 0.002$; PAI at SOA (150,450): $t_{11} = 7.26, p < 0.001$; NAI at SOA (150,450): n.s.). This benefit remained constant at an SOA of 750 ms

<table>
<thead>
<tr>
<th>Reaction time</th>
<th>Hits</th>
<th>Correct rejections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAI</td>
<td>NAI</td>
</tr>
<tr>
<td>SOA 150</td>
<td>671  (30)</td>
<td>702 (29)</td>
</tr>
<tr>
<td>SOA 450</td>
<td>615  (32)</td>
<td>694 (31)</td>
</tr>
<tr>
<td>SOA 750</td>
<td>601  (35)</td>
<td>706 (32)</td>
</tr>
</tbody>
</table>

Reaction time (ms) and accuracy data (%) with standard error in brackets are listed for trials with AI and NAI.
(SOA (450,750) × CUE: n.s.). The benefit was smaller with a short (31 ms, $t_{11} = 4.39$, $p = 0.001$) than with intermediate (79 ms, $t_{11} = 6.58$, $p < 0.001$) and long SOA (98 ms, $t_{11} = 7.63$, $p < 0.001$). Due to ceiling effects, no improvement of response accuracy was shown with longer SOA. The number of hits did not change in dependence of PAI (SOA $F_{2,22} = 0.13$, n.s., CUE $F_{1,11} = 0.27$, n.s.). For NAI × CUE $F_{2,22} = 0.48$, n.s.). The number of correct rejections decreased with NAI and with longer SOAs, but only for NAI trials with an irrelevant motion direction and relevant color. Statistically, we found a main effect of CUE and an interaction between CUE and SOA for M × C+ trials (CUE: $F_{2,22} = 9.5$, $p = 0.01$; SOA × CUE $F_{2,22} = 5.0$, $p = 0.018$). This interaction could be explained as an effect of SOA on NAI trials ($F_{2,22} = 5.9$, $p = 0.01$), but not for FAI trials ($F_{2,22} = 2.3$, n.s.). We also found a significant main effect of CUE on M × C− trials ($F_{2,22} = 9.5$, $p = 0.01$). This could be explained by an increased number of false alarms for trials with an irrelevant color if PAI was given. All other tests for other stimulus categories were not significant. Taken together, we found that, response speed was facilitated with PAI depending on SOA. With increasing SOA, we also found a decrease of response accuracy with NAI if stimuli with an uncued feature were presented. Independent of SOA, response accuracy decreased with PAI if stimuli with an irrelevant color were given.

### 3.2. fMRI effects of partial advance information

Fig. 2 shows brain activity to all stimulus categories in dependence of cue and SOA. Targets seem to differ from nontargets with a short SOA (150 ms) both with AI and NAI. For nontargets with PAI and FAI, only activity in the lateral occipital cortex (LOC) was found, whereas targets induced activity in the left inferior parietal lobule (L-IPL), the primary motor area of the responding hand (L-M1), and cerebellar hemispheres bilaterally. For nontargets with NAI, we also found lateral occipital activity, and for targets primarily left parietal, primary motor and supplementary motor area (SMA). There was also activity on the border of the left inferior frontal gyrus (IFG) and superior temporal gyrus (STG). Trials with a long SOA (450 and 750 ms) seemed to show stronger and more extended occipital activity than trials with a short SOA. This occipital increase of activity was found for both target and nontarget trials and in trials with and without advance information. Outside the occipital lobe, brain activity seemed to show differences depending on AI. In NAI trials, bilateral IPL activity could be observed as well as activity in the response preparation related areas (supplementary motor area (SMA), pre-SMA, and L-M1). This pattern was found for both targets and nontargets. Trials with AI showed a different pattern, depending on the cue information. As compared with NAI, target trials with PAI seemed to show more activity in motor processing related areas (SMA, pre-SMA) as well as in the thalamus, left IFG, and right STG. Nontarget trials with PAI seemed to show more activity in the SMA. Nontarget trials with FAI seemed to show less activity in parietal areas as well as SMA and bilateral motor areas. Summarizing, these findings suggest that with SOA sufficient to process cue information, several response preparation related areas showed more activity after PAI as compared to trials with NAI. Stimuli with an irrelevant motion direction following NAI seemed to activate bilateral response preparation areas as well as bilateral parietal areas.

### 3.3. PAI and FAI

To evaluate these observations statistically, we tested the main effect of SOA, CUE and interaction between SOA and CUE in each stimulus condition. As can be seen in Table 3 and Fig. 3, the effect of SOA was significant in several stimulus categories with AI. In particular, activity in bilateral occipital areas increased in all stimulus categories, with both target and nontarget stimuli and independent of cue information. More areas showed an effect of SOA if PAI was presented as compared with FAI. Brain activity increased with long SOAs if targets were presented together with PAI in several response-related areas (pre-SMA, thalamus, primary motor area M1, and cerebellum) as well as in the bilateral IPL and left IFG. Nontarget trials with PAI showed similar increase with SOA, except for the primary motor cortex and thalamus. Nontarget trials with FAI showed no additional activity outside the occipital lobe, except for the precuneus that showed more activity if no stimulus feature was relevant. Considering NAI trials, we found an increase of activity in the bilateral occipital lobe as well as in response-related areas (pre-SMA, cerebellum) and the bilateral IPL. There was almost no difference between stimulus categories if NAI was given. One difference was that nontargets with a relevant motion direction had no stronger activity in response-related areas (SMA and cerebellum). Another difference was that bilateral motor cortices were more active if no feature matched the target stimulus. The data suggested that (Fig. 3) brain activity varied among nontargets presented after NAI. This could be due to an increase in response-related activity for stimuli with an irrelevant motion direction if no informative cue was given about the motion direction. Taken together, the SOA data suggested that both visual and nonvisual areas showed more activity with longer SOAs, but that if FAI was given only visual areas revealed this pattern. In addition, if time between cue and stimuli increases and no cue information was given, it seemed that subjects suffered from the lack of an FAI. This might lead to more response-related activity after NAI.

There was no significant main effect of CUE in any stimulus category. There was a significant interaction between CUE and SOA over all categories. Table 4 shows that several areas outside the visual cortex had a significant interaction. In particular, we found several response-related
Fig. 2. Event-related fMRI activation ($n=12$) in each condition at a short (150 ms) and long (450 and 750 ms) SOA with AI and NAI. Significant voxels are shown ($p<0.05$, corrected), which are coded to Z-scores and overlaid onto an individual brain.

Twelfth article
areas (pre-SMA, right cerebellum, and thalamus) as well as frontal (bilateral IFG and right medial frontal gyrus) and parietal areas (bilateral IPL and precuneus). To explain these interactions subsequent t-tests were conducted. Fig. 3 shows the pattern of activity over different stimulus categories in some of the relevant areas. We found more activity with PAI than with NAI in the SMA ($z = 3.85, p = 0.047$) and thalamus ($z = 3.87, p = 0.008$) if targets were presented. For non-targets with PAI, the SMA was also more active ($z = 3.34, p = 0.049$), as well as the right IPL ($z = 4.19, p = 0.002$) and cerebellum ($z = 3.95, p = 0.006$). If FAI was presented and both features were irrelevant we found more activity in the precuneus ($z = 4.49, p = 0.001$). In some areas, we found more activity with NAI than with FAI at a long SOA. However, if stimuli had the relevant motion direction no area was significantly more active with NAI. If stimuli had an irrelevant motion direction and a relevant color, we found more activity in a broad range of areas, the pre-SMA ($z = 4.47, p = 0.001$), cerebellum ($z = 4.73, p < 0.001$), left and right IPL ($z = 3.67, p = 0.017$ and $z = 4.5, p = 0.001$), left and right IFG ($z = 4.9, p < 0.001$ and $z = 5.31, p < 0.001$) as well as the right medial frontal gyrus ($z = 4.6, p < 0.001$). If both features were irrelevant, we found only more activity in the SMA ($z = 4.36, p = 0.001$).

Summarizing, these data indicate that response-related areas (pre-SMA, left M1 and right cerebellum) were particularly sensitive to advance information. These response-related areas were more active with PAI as compared with NAI, and were more active with NAI as compared with FAI. The bilateral IFG and IPL also showed this pattern of sensitivity to cue information, i.e. there was a tendency that, as compared with FAI, these areas showed more activity with PAI and a relevant motion feature as well as with NAI and an irrelevant motion feature. This suggests that PAI was used as to prepare a response, whereas the FAI was used not to prepare a response. If NAI instead of FAI was presented, this could lead to insufficient processing of the irrelevant motion feature and thus to a higher chance to produce false alarms.

### 3.4. Parametric analysis of advance information and SOA

Two alternative hypotheses might explain why both PAI trials with a relevant motion direction and NAI trials with an irrelevant motion direction showed widespread activation as compared to trials with down-going stimuli presented after FAI. One explanation could be that there was more response preparation as compared with trials with FAI (response preparation hypothesis). Alternatively, the strong activation related to the processing of NAI might reflect the processing of multiple features within a stimulus. Less information would be needed for analysis with a...
Fig. 3. For a set of areas, which show effects of advance information, a bar plot is given providing the size of effect (with standard error) of all 16 stimulus categories, where SOA 450 and 750 trials are collapsed together. These areas are the supplementary motor cortex (SMA/pre-SMA at $x = -8$, $y = 8$, $z = 48$), left primary motor cortex (M1 at $-32$, $-12$, $56$), thalamus ($-16$, $-20$, $-4$), right cerebellum ($28$, $-60$, $-24$), left lateral occipital cortex ($-44$, $-80$, $-8$) and left inferior frontal gyrus ($-36$, $20$, $-4$). The bar plot of the right lateral occipital cortex was not shown, since this area showed similar pattern of activity as the left lateral occipital cortex.
The results (Table 4, Fig. 4) showed advance information for nontarget stimuli in dependence of hypotheses, we parametrically analyzed the three levels of increasing likeliness of a response. To evaluate these preparation hypothesis would predict more activity with less advance information; whereas the response cue (perceptual load hypothesis). The subject needed to prepare for an uncorrected $F$-test interaction between CUE and SOA over all stimulus categories after FDR-correction for the whole brain. Here the SOA conditions 450 and 750 ms are collapsed. The second row shows areas in which the difference between advance information conditions parametrically increased over all nontarget conditions with the three levels of SOA. The $F$-test results were FDR-corrected for the whole brain and used as a mask for subsequent $T$-tests. The results of the $T$-tests that were significant after correction for this mask are reported in rows 3, 4 and 5. These rows show the areas in which the difference between PAI and NAI, NAI and FAI or PAI and FAI parametrically correlated with SOA. There was no significant difference between NAI and PAI that needed to be reported. FAI and NAI, FAI and PAI are reported in the text. The last row of the table shows voxels that relate to the use of PAI on motion processing. For motion processing, nontargets were analyzed that showed more activity with PAI than for FAI but not for NAI and FAI parametrically correlated with SOA. There was a trend to significant difference between the two interactions. The left IPL showed more activity for PAI than for FAI but not for NAI and FAI parametrically correlated with SOA. There was, however, one area that showed no overlap between the two interactions. The left IPL showed more activity for PAI than for FAI but not for NAI and FAI parametrically correlated with SOA. There was a significant finding that would support the perceptual load hypothesis.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>The use of PAI in eFMRI</th>
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<tr>
<td></td>
<td>CUE × SOA</td>
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<tr>
<td>(Pre-)SMA[4/16/52]</td>
<td>4.13</td>
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<td></td>
<td>0.016</td>
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<tr>
<td>R-CB[28/–56/–32]</td>
<td>3.85</td>
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<td></td>
<td>0.019</td>
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<tr>
<td>L-IFG[36/20/–4]</td>
<td>4.86</td>
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<tr>
<td></td>
<td>0.009</td>
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<tr>
<td>R-IFG[28/–24/–12]</td>
<td>4.27</td>
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<td></td>
<td>0.013</td>
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<tr>
<td>L-IPL[52/–36/36]</td>
<td>3.61</td>
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<tr>
<td>R-IPL[60/–40/28]</td>
<td>4.13</td>
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<td></td>
<td>0.016</td>
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<td></td>
<td>0.022</td>
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<tr>
<td>Precun[0/–56/32]</td>
<td>3.96</td>
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<td></td>
<td>0.016</td>
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<tr>
<td>MI[36/–8/56]</td>
<td>3.79</td>
</tr>
<tr>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Thal[16/–12/–8]</td>
<td>3.43</td>
</tr>
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</table>

Test results for eFMRI related to the use of AI. The left part of the table shows voxels that had showed a significant $F$-test interaction between CUE and SOA over all stimulus categories after FDR-correction for the whole brain. Here the SOA conditions 450 and 750 ms are collapsed. The second row shows areas in which the difference between advance information conditions parametrically increased over all nontarget conditions with the three levels of SOA. The $F$-test results were FDR-corrected for the whole brain and used as a mask for subsequent $T$-tests. The results of the $T$-tests that were significant after correction for this mask are reported in rows 3, 4 and 5. These rows show the areas in which the difference between PAI and NAI, NAI and FAI or PAI and FAI parametrically correlated with SOA. There was no significant difference between NAI and PAI that needed to be reported. FAI and NAI, FAI and PAI are reported in the text. The last row of the table shows voxels that relate to the use of PAI on motion processing. For motion processing, nontargets were analyzed that showed more activity with PAI than for FAI but not for NAI and FAI parametrically correlated with SOA. There was a trend to significant difference between the two interactions. The left IPL showed more activity for PAI than for FAI but not for NAI and FAI parametrically correlated with SOA. There was a significant finding that would support the perceptual load hypothesis.

To test the response preparation and perceptual load hypothesis, we compared PAI, NAI and FAI with each other for each nontarget stimulus category in interaction with SOA. Supporting the response preparation hypothesis, we found an increased difference between PAI and NAI in interaction with SOA in response-related areas (pre-SMA, motor areas M1, cerebellum) and the bilateral IPL. However, no area showed more activity for NAI than for PAI, a finding that would support the perceptual load hypothesis. This was true, even after lowering the statistical threshold to an uncorrected $p = 0.05$. There were differences between PAI and FAI as well as between NAI and FAI in the response-related areas (SMA and cerebellum) and right IPL. There was, however, one area that showed no overlap between the two interactions. The left IPL showed more activity for PAI than for FAI but not for NAI and FAI ($z = 3.89, p = 0.008$, tested with an exclusive mask). There was a trend to significance ($z = 3.21, p = 0.079$) in this area if comparing stimuli with PAI and stimuli with an irrelevant motion direction after NAI. There was a significant difference in this area if comparing PAI with NAI, irrelevant of the features that followed the neutral cue ($z = 3.69, p = 0.015$). The other areas which showed differences between PAI and FAI, PAI and NAI, and between
NAI and FAI also showed a difference between stimuli with relevant and irrelevant motion direction if NAI was given. This suggests that these areas (SMA, cerebellum, and right IPL) were particularly sensitive to the no-go information. Taken together, we found support for the response preparation hypothesis for the processing of advance information, i.e. there was a stepwise increase in activity in response-related areas as well as in right IPL that depended on advance information and SOA. These areas showed increasing activity if the response probability and time to process a cue was higher. The left IPL was sensitive to advance information as compared with neutral cues, irrelevant of the stimulus features that followed the neutral cue.

### 3.5. Feature processing

To evaluate whether motion or color processing were differentially influenced by advance information, we compared nontargets with motion and color features presented after PAI and FAI in interaction with their presentation after NAI. It could be shown (Table 4) that nontargets after PAI exhibited increased activity in several response-related areas (pre-SMA, left primary motor cortex, and right cerebellum), as well as areas that have been indirectly related to motor processing (left IFG and right IPL). These areas exhibited an interaction between advance information and motion direction with a long SOA. This interaction could be explained as a difference in activity if advance information was given rather than if NAI was given. This indicates that a frontoparietal network, as well as response preparation related areas were involved if PAI could be effectively utilized.

Accuracy data showed that more false positive reactions were given after the presentation of NAI. This was particularly true for stimuli with an irrelevant motion direction and relevant color; one might hypothesize that activity in areas related to color processing was influenced by NAI. However, we found no evidence in our fMRI data that color processing was stronger after the presentation of NAI. Thus, nontargets with relevant and irrelevant colors presented after NAI were not differently processed than after the presentation of PAI. Rather, Fig. 3 shows higher motor preparation activity with a long SOA as well as on stimuli with a relevant color. This suggests that the absence of FAI has caused a high preparatory state for such stimuli, which may have led to a few erroneous responses in these trials.

### 4. Discussion

We set out to identify brain regions whose operations improve performance by the use of advance information,
i.e. to specify brain areas that distinguish AI processes in conditions in which AI can be used from conditions in which AI cannot be used to facilitate performance. It was of particular interest whether visual or nonvisual processes were related to the use of visual AI. Brain activity mainly increased with longer preparation time and the presentation of PAI in response preparation related areas, including the pre-SMA and primary motor cortex, which are related to central response processes, as well as the inferior parietal lobule and inferior frontal gyrus. These areas have all been suggested to be activated in the context of phasic alertness, response preparation and selective attention [18,41]. The data suggest that the utilization of AI involved stronger response preparation and support the hypothesis that AI reduced stimulus/response uncertainty [22]. Shortened reaction times seemed not to be achieved by manipulating visual processes as would be predicted on the basis of the model by Rosenbaum [36]. Rather, the present study supports the hypothesis by Goodman and Kelso [13], which stated that AI affects general preparation processes.

Activity in the visual cortex increased with SOA, but was not affected by cue information or the subsequent stimulus. Studies on alertness and covert orientation revealed a network that included these visual areas [38]. They found this activation in the visual cortex by comparing both tasks with rest but not by comparing the two tasks with each other, suggesting that activity in these visual areas relates to active visual processing. The present results indicate that visual processing is initiated by the cue presentation, but is not dependent on the cue information. Even if the cue carries no-go information, intrinsic alertness was not stopped. It is, however, not clear why visual processes were more extended with longer SOA. Some authors support the hypothesis that even short intervals in which subjects wait for a stimulus require vigilance and suggest that this is a form of sustained attention [35]. Others observed an increased activity in conditions with motivated attention [3]. Alternatively, one could argue that stimulus pairs with a short interval evoke nonlinear responses of the BOLD signal, so that the visual BOLD response becomes smaller with a short interval. However, recent studies suggested that the adaptation of neural responses do not occur when stimulus pairs differ [2,30]. Rather, the data suggest that attention is directed toward the imperative stimulus at the occurrence of a cue.

There may be several reasons why there was no difference between cue and stimulus conditions. Many studies clearly showed attention and task dependent activity in the visual cortex. These tasks were far more difficult than the task used here. For example, studies on spatial attention [20,28], nonspatial visual attention [4,25] and visual working memory [40] showed that visual areas could be modulated by visual instructions. These instructions improved perceptual discriminability. In the present study, however, performance was almost at ceiling level, so that cues could not improve the discriminability of the target stimuli. Another reason may be that the SOA was too short for subjects to be able to redirect attention towards specific features after a cue. Previous studies that showed strategic adaptation of selective visual attention used much longer SOA [15,37]. This interpretation is supported by studies reporting that the efficiency of selective attention increases with adaptation time [10]. Strategic adaptation does not increase within milliseconds, but rather within seconds or minutes, or depends on the repetition of specific stimuli [26,45] or stimulus-response sequences [14]. Even if selective attention has to be directed to a specific feature of an object, irrelevant object features cannot be ignored [21]. The theoretical background for this explanation was given by studies on visual search, showing that the perceptual quality of an upcoming event was not influenced by cues facilitating the search for a conjunction of visual features within a set of distractors [29]. Instead, object features are initially processed in parallel. This suggested that nonspatial cues do not influence the fast processes of stimulus identification but rather the processes that follow perceptual identification, namely slow selective attention search processes [44]. These search processes are thought to be influenced by factors such as the repetition of stimulus-response sequences and cue-driven instructions [14].

Outside the visual cortex, we found differences in brain activity that depended on the cue information. More brain activity was found with the presentation of NAI and PAI as compared with the presentation of FAI. This finding suggests that the cue indicating the occurrence of a possible target initiates a broad range of neural responses. Central response preparation areas were activated such as the SMA, motor areas, as well as bilateral inferior parietal and frontal areas. Even areas related to the preparation of the left hand, which was not active during the whole task, were more active after NAI than after FAI. One explanation for this pattern of results is that NAI activates unspecific warning processes, whereas PAI specifically activate motor processes. Previous fMRI and PET studies showed that these areas, in particular the pre-SMA, thalamus and parietal cortex, are involved in phasic selective attention and spatial orientation tasks [38]. Several studies showed covert orientation responses of selective attention in the bilateral inferior parietal and frontal cortex [1], and in bilateral inferior parietal cortex only if no distractors were given [8,9,15]. This hypothesis is also well reflected within studies on visual search. In these studies, the search for a multidimensional target stimulus accompanies continuous reorientations toward possible targets [43]. The search for potential targets is also clearly facilitated by visually guiding and instructive cues. Thus, as compared to FAI, both NAI and PAI induced similar activity. This could be related to reorientation after a cue indicating the occurrence of a potential target.

There are two other aspects that may be discussed in relation to visual search. First, visual search requires reori-
orientation towards potential targets after the rejections of identified nontargets [32,43]. In the present study, there was no spatial component requiring reorientation, and the strong activity in the inferior parietal cortex was found for both targets and nontargets. This suggests that inferior parietal areas are not only involved in spatial reorientation, but also in reorientation to new potential targets without a spatial component. Second, visual search studies provided the basis for the idea that conjunctions of features were more difficult to detect than single features [42]. If advance information was given, one could hypothesize that one feature instead of two features was needed to be analyzed. Contrary to this hypothesis, we did not find more activity with NAI than with PAI. Rather we found more brain activity with PAI. As argued above, we suggest that advance information activate response preparation processes rather than reduced the perceptual load. This idea was supported by visual search studies which reported that nonspatial cues facilitate search without affecting the perceptual identification, but rather modulate attention demanding processes that follow identification [29]. This interpretation was also supported by other cueing studies, reporting that relevant cues redirect attention with the occurrence of a potential imperative stimulus [38]. Such a reorientation is accompanied by the activation of both inferior parietal and frontal areas. These areas are also identified to play a role in movement preparation and initiation [41].

To summarize, the present study rendered several new results. First, effects of AI are revealed in a functional imaging study for the first time. The data demonstrate the importance of SOA timing, and the effect of SOA timing on human brain activity. More detailed studies will be needed in the future to parametrically modulate the effects of SOA on cue processing, as well as to elaborate the capacity of fMRI studies to monitor fast processes. Secondly, the present study points out the importance of selection for action in planning. Rather than changing parameters in the perceptual domain, visual advance information changed central response preparation processes. This result contrasts with assertions that parameters are changed at the level of the information that is provided by AI [36]. The present study emphasizes that response preparation processes can also be changed by advance visual information and extends models which state that response-related cues activate central preparation processes [13]. Thirdly, only an effect of cues on motion processing was found, not on color processing. The hypothesis that colors were less processed after FAI could not be confirmed on the basis of our fMRI data, although stimuli with a relevant color and irrelevant motion direction were more often falsely classified as targets if neutral cues were given. Functional imaging data suggest that this behavioral effect was due to a stronger increase in central response-related processing areas if NAI rather than FAI was given. Fourthly, the data show differences in processing of nontargets after the presentation of a neutral cue. We found more activity for nontargets with an irrelevant motion direction as compared to nontargets with a relevant motion direction. An explanation for this unexpected result may be that specific expectations regarding the occurrence of advance information affects the processing of features if advance information does not occur. Empirical evidence, however, for this hypothesis has yet to be established. Finally, we found no common effect of advance information that would be related to the processing of informative cues. This suggests that cues were processed in dependence of the potential go/no-go information.

Several open questions emerging from the present study need to be mentioned. First, despite the effort made to independently modulate cues and stimulus information, it remains unclear whether brain activations occur before or after stimulus presentation. This issue has been exemplified above: cues indicating relevant as well as irrelevant motion direction could directly initiate preparation processes and have an indirect effect on subsequent stimulus processing. Generally speaking, stimulus processing might interact with cue information, cue processes might continue until after the presentation of the stimulus, or the differences between short and long lasting processes might influence the level of activation. Clearly, such questions should be tracked with methods providing a higher temporal resolution, such as event-related potentials. A second remark on the study is that we found no effects of AI in the fMRI data with a short SOA despite the effect of AI in performance. It is difficult to explain this null-effect without further studies. The transitions on the utilization of AI could be investigated in the future with more fine-grained steps in SOA. A third issue is that previous cueing studies used SOAs that were much longer than the ones used here, so that areas found in those studies may be related to the differences in SOA compared to the present study. For example, several studies reported that prefrontal processes play a role in cue processing [15]. One might hypothesize that working memory could maintain cue information with such long SOAs. In contrast to previous cueing studies, we found almost no prefrontal brain activity. This fact may also not only be related to differences between tasks, but also to differences between delay times. The same question may be raised for perceptual processes. As has been argued above, different factors play a role in the strategical adaptation of perceptual processes to cue information. Future studies will be needed to capture circumstances in which cueing becomes effective. The reasons for the cue effectivity may depend on the response-related processes as described here. If time lags or strategy change, other perceptual processes may become relevant. Fourth, we argued that similar cue related findings have been discussed in relation to visual search. While this form of cueing studies have not received attention in the last two decades, it seems that this type of study may become useful in the study of visual search, because it is a simplified form of visual search without a spatial component. Fifth, differences in stimulus probability may have an effect on the
extent of activation. This was not balanced for PAI and FAI in this study. PAI cues were less predictive than the FAI cues, since PAI increased response probability from 25% to 50%, whereas FAI were fully predictive. Less predictive FAI might have led to smaller decreases of activity as compared with the neutral counterpart. Further studies need to investigate the relevance of cue probability and the relevance of the type of information that is given by the cues. Finally, the task instruction in the present study was to detect conjunctions of moving colored stimuli. It remains to be resolved whether the effects attributed to cue processing on the direction of motion can be generalized to other stimulus types within or beyond the visual system.

Acknowledgements

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References


A New Approach in Clinical Neuropsychology to the Assessment of Spatial Working Memory: The Block Suppression Test

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ABSTRACT

The Block Suppression Paradigm developed by Beblo, Klaver, Grubich, Wachowius, and Herrmann (1999) is based on the Corsi Block tapping test and requires that a subject reproduces every 2nd block in a given sequence. Results from two studies of a standardized version, the Block Suppression Test (BST), are presented here. In Study 1 the BST was administered to 48 healthy subjects along with a battery of comprehensive neuropsychological tests. The reliability of the BST proved satisfactory under psychometric analysis, while Principal Component Analysis (PCA) confirmed its validity. In Study 2 the BST was administered to a clinical sample of 31 brain-damaged patients to demonstrate its clinical practicability.

Research on a memory system now termed “working memory” dates back to the 19th century (Jacobs, 1887), with different models of working memory emerging in the meantime. One influential model, introduced by Baddeley and Hitch (1974), maintains that working memory requires that information are stored and manipulated simultaneously. They divided working memory into a supramodal central executive with flexible limited processing capacities and two modality specific storage systems: one for phonological information, the other for visuospatial information. In recent years the model of working memory has been advanced in the context of functional imaging studies. Parietal brain areas have been found to be related to working memory load (Cohen et al., 1997) and to the type of information, that is, verbal, spatial, or nonspatial information (Courtney, Ungerleider, Keil, & Haxby, 1996; D’Esposito et al., 1998; Jonides et al., 1998; Mecklinger & Pfeifer, 1996; Ungerleider, Courtney, & Haxby, 1998), whereas frontal areas are sensitive not only to memory load, but also to delay (Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997), cognitive interference (D’Esposito, Postle, Jonides, & Smith, 1999), and the suppression of irrelevant information (Desimone, 1996; Goldman-Rakic, 1987).

In addition to the research done on working memory in cognitive psychology and cognitive neuroscience, it has also gained importance in clinical neuropsychology. Since problems of working memory are a facet of many neurological diseases, for example, Parkinson’s disease (Hodgson, Tiesman, Owen, & Kennard, 2002), and are also known in psychiatry, for example, in
schizophrenia (Okada, 2002), the diagnosis and therapy of deficits of working memory is a valuable goal in both fields.

In clinical neuropsychology verbal and spatial working memory have usually been assessed by means of the digit and visual (block) spans forward and backward (Corsi, 1972; Wechsler, 1981, 1987). Memory spans forward basically require that information be stored short-term. Since working memory requires both the storage and manipulation of information, the memory span forward is a less valid indicator of working memory. In contrast, the digit span backward seems to require additional processing and is thus a measure of verbal working memory. Normative data and clinical experience confirm this assumption: the digit span backward is clearly shorter than the digit span forward (Wechsler, 1987). Cooper, Sagar, Jordan, Harvey, and Sullivan (1991) introduced a modification to the digit spans, the Digit Ordering Test (DOT). Their approach mandates that digits be reproduced in ascending order. Hoppe, Mueller, Werheid, Thoene, and von Cramon (2000) concluded that “the DOT addresses the manipulatory component of verbal working memory and conveniently detects respective deficits in clinical testing” (p. 38).

The situation in the spatial domain is far less satisfactory: the spatial memory (block) span backward, assessed with the Wechsler Memory Scale (Wechsler, 1987) or the Corsi Block Tapping Test (Corsi, 1972), seems to represent primarily the storage component of spatial working memory since both empirical data and clinical experience indicate that performance of it is similar to that for the spatial memory span forward (Wechsler, 1987). In our lab we transferred the principle of the Digit Ordering Test into the spatial modality (Beblo et al., unpublished data). The task required subjects to reproduce block sequences (presented to them on the Corsi Block Tapping Board) from left to right. Here again, the performance by healthy subjects and neurological patients was similar to that for the block span forward, indicating that no substantial additional executive demands had to be met.

Based on studies with nonhuman primates Goldman-Rakic (1987) and others (e.g., Desimone, 1996) hypothesized that suppression of irrelevant information requires working memory. Their paradigms have been adapted to human neuropsychological tests (e.g., Cambridge Neuropsychological Test Automated Battery, CANTAB). However, in addition to the inhibition of irrelevant information, these tests require the use of complex strategies and self-initiated behavior. Recently, we developed a new procedure to assess spatial working memory, a preliminary version of the Block Suppression Test (BST; Beblo et al., 1999). Subjects were required to reproduce only every second block of a series of Corsi-blocks. In this paradigm healthy volunteers and brain-injured patients showed block spans that were significantly shorter than both the block span forward and backward. Hence, this task seems to address processes not addressed by the classical spatial memory span tasks. We attributed these encouraging initial results to the need to actively suppress irrelevant spatial information. Nonetheless, some questions remained open:

1. Reliable presentation (1 block per second) of long sequences of blocks (e.g., 11 or 12 blocks) proved very difficult for the experimenters.
2. We limited the presentation in this preliminary version to a single item with a given number of blocks. In clinical samples we observed a floor effect and a small range of test results.
3. Since only a few other neuropsychological tests were administered in this preliminary study, validation remained insufficient.

The present two exploratory studies aimed at an initial first evaluation of the Block Suppression Test (BST), which had been revised to overcome these shortcomings. The objective of the first study was to assess its psychometric properties in a sample of healthy volunteers. The objective of the second study was to assess its clinical practicability in a sample of neurological patients and to gather initial information on its clinical validity. In both studies we also applied a parallel verbal version of the BST, the Digit Suppression Test (DST). In accordance with the procedure for the BST, the DST required subjects to reproduce only every second digit in a series of digits.
STUDY 1

PARTICIPANTS

The first study included 48 healthy subjects: 35 women (72.9%) and 13 men, respectively, without any signs of any neurological or psychiatric disease. Their mean age was 25 years ($SD = 5.17$), ranging from 19 to 39 years. All subjects but 1 were student at the University of Bielefeld and all had had 13 years of basic school education. Fourty-six subjects were right-handed while 1 patient was left-handed and 1 ambidextrous. All subjects provided their informed written consent.

TESTS

Working Memory and Memory Span

Block Suppression Test (BST)

To carry out the Block Suppression Paradigm we developed an electronic board that basically corresponded to the Corsi-Board (Corsi, 1972; Schellig & Haettig, 1993; Smirni, Villardita, & Zappala, 1983). A button illuminated by a red light was located on the upper surface of each block. This allowed the PC-controlled presentation of the block sequence, as well as the PC-registration of the response. The start of each sequence was announced by a short high tone and the finish by a short low tone. The block sequence followed an even rhythm of one illuminated light per second (500 ms illumination, 500 ms interval). Subjects were required to reproduce only every second block in a series of illuminated blocks, beginning with the first block, followed by the third, fifth and so on. Two trials were presented for each series of blocks. In the first trial the block sequence was “uncrossed,” that is, the path between the blocks to be reproduced did not cross itself, while the block sequence in the second trial was “crossed,” that is, the path crossed itself. The block sequence in the easiest trials consisted of 3 blocks, 2 of which had to be reproduced, while in the hardest trial, a series of 16 digits was presented, 8 of which had to be reproduced. A presentation was finished when a subject failed to reproduce two trials of the same length. Three different scores reflected the outcome:

1. The BST-reproduction span represented the maximum number of blocks which were reproduced correctly in at least one of the two trials.
2. The BST-presentation span represented the maximum number of blocks presented.
3. The BST-score represented a cumulative rawscore, with one point given for each correctly reproduced sequence.

Corsi Block Tapping Test

On the electronic board we also presented the block spans forward and backward according to Corsi (1972). In order to avoid ceiling effects, we extended the Corsi Block Tapping Test to nine blocks for block span forward and to eight blocks for the block span backward.

Digit Suppression Test (DST)

For the verbal modality we developed the Digit Suppression Test (DST). In the DST the subjects had to reproduce every second digit in a series of orally presented digits. Two trials were presented for each series of digits. In the easiest trials, a series consisted of 3 digits, 2 of which had to be reproduced, while in the hardest trial, a series of 16 digits was presented, 8 of which had to be reproduced. The task was finished when a subject failed to reproduce two trials of the same length. Analogous to the BST, the DST-reproduction span, presentation span and score reflected the outcome.

Digit Span Forward and Backward

Wechsler Memory Scale – Revised (Wechsler, 1987): In order to avoid ceiling effects, we included series of nine digits (forward) and eight digits (backward).

Working memory [from the “Testbatterie zur Aufmerksamkeitsprüfung” (TAP); Zimmermann & Fimm, 1992]: This computer-test was administered as a 2-back paradigm. Subjects had to decide whether the currently presented digit was identical to the digit presented two positions before.

Verbal Fluency

Subjects were required to name as many animals as possible with 1 min.

Reasoning

LPS-3 (from the “Leistungsprüfsystem”; Horn, 1983): each item on the LPS-3 consisted of a series of abstract visual shapes arranged, with one exception, according to a basic rule. The task required the subject to identify the wrong element.

Attention

Attention was assessed by means of the following subtests of the computerized “Testbatterie zur Aufmerksamkeitsprüfung” (TAP; Zimmermann & Fimm, 1992):

(Tonic) Alertness: This subtest assessed simple reaction time. The subject had to press a button as fast as possible when a cross appeared on the screen.

Go-nogo: This task assessed response selection and response inhibition. Five different patterns (two targets
and three distractors) were presented in random order. The subject had to respond to the target as quickly as possible.

**Flexibility:** This task required the subject to respond as quickly as possible to alternating concepts, letters alternating with numbers.

**Learning and Memory**

Auditory Verbal Learning Test (Rey, 1964; German version “VLMT”; Helmstaedter, Lendt, & Lux, 2001): due to the subjects’ high level of education, we applied this 15-item memory task in only three learning trials.

“Diagnosticum fuer Cerebralschaedigung” (DCS; Weidlich & Lamberti, 2001); this 9-item memory task required the subject to reproduce abstract figures over three trials.

**STATISTICAL ANALYSIS**

As indices of reliability we calculated split half reliability and Cronbach’s alpha (as an index of internal consistency). *t* tests were performed to compare the outcomes of BST with those of “traditional” memory spans. To examine relationships between variables, we calculated Pearson coefficients of correlation. All levels of significance were alpha = .05 and two-tailed. When necessary, alpha was corrected due to multiple comparisons (Bonferroni). In addition, a principal component analysis (PCA) was performed. Extraction was done according to the Kaiser-Criterion (Eigenvalues > 1), the component-matrix was Varimax rotated. Since the number of subjects (*N* = 48) was small, the PCA was used basically for exploratory purposes. All statistical procedures were performed with the “Statistical Package for the Social Science 10.0” (SPSS 10.0).

**RESULTS**

**Block Suppression Test (BST): Mean, Range, Reliability**

The scores for the parameters of the BST and the other memory spans are presented in Table 1. The ranges for all BST-parameters clearly were sufficient with no sign of either a floor or ceiling effect. Crossed and uncrossed trials did not differ, showing that performance was not significantly influenced by overlaps with the path between the blocks to be reproduced.

Reliability was satisfactory, with Cronbach’s alpha = .81 and split half reliability = .82.

**BST and Traditional Block and Digit Spans**

Since scores for the different digit and block span paradigms were not comparable, only reproduction spans were used to compare the results on the BST and the Digit Suppression Test (DST) with those for the “traditional” memory spans. Figure 1 illustrates the differences between the block and digit spans forward and backward and the BST/DST-reproduction spans.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
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<td>1.7</td>
<td>4–14</td>
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<tr>
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<tr>
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<td>8.2</td>
<td>8</td>
<td>2.3</td>
<td>4–14</td>
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</table>
Due to multiple comparisons (nine), the level of significance was corrected to alpha = .006. Data indicated that

1. While the digit span forward was longer than digit span backward, \( t(47) = 9.31, p \leq .001 \), there were no differences between the block spans forward and backward, indicating that the demands of these tasks were similar.

2. By contrast, the BST-reproduction span was shorter than both the block span forward, \( t(47) = 7.35, p \leq .001 \), and the block span backward, \( t(47) = 6.27, p \leq .001 \).

3. The same was true for the DST-reproduction span compared to the digit spans forward, \( t(47) = 19.22, p \leq .001 \), and backward, \( t(47) = 7.45, p \leq .001 \).

4. While the digit span backward and the block span backward were of comparable lengths, the digit span forward was longer than the block span forward, \( t(47) = 4.55, p \leq .001 \). The outcomes of the BST and DST did not differ significantly.

**Validity: Correlations and Principal Component Analysis**

The correlations between the results of the neuropsychological tests in our sample were generally small. An exploratory analysis revealed significant correlations between the BST-reproduction span and the DST-reproduction span (\( r = .31, p = .035 \)), the block span backward (\( r = .42, p = .004 \)), the digit span backward (\( r = .29, p = .05 \)), reasoning (LPS-3, \( r = .29, p = .05 \)), simple reaction time TAP; \( r = -.32, p = .03 \), working memory (TAP, \( r = -.35, p = .017 \)), and

<table>
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<th>Factors</th>
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<tr>
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<td>Digit span forward</td>
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<tr>
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<tr>
<td>BST</td>
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<td>Block span backward</td>
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<tr>
<td>Block span forward</td>
<td>-</td>
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<tr>
<td>LPS 3</td>
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<td>Working memory (Mdn, TAP)</td>
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<tr>
<td>Go-nogo (Mdn, TAP)</td>
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<td>Flexibility (Mdn, TAP)</td>
<td>-</td>
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<td>DCS (learning)</td>
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<tr>
<td>AVLT (learning)</td>
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<tr>
<td>Alertness (Mdn, TAP)</td>
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<td>Eigenvalues</td>
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<td>Interpretation</td>
<td>Working memory I</td>
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</table>
flexibility (TAP; \( r = .31, p = .038 \)). BST-reproduction spans thus correlated with the parameters of other tests of working memory and tests of executive functions (aside from simple reaction time) but not with those of learning tests.

For a multivariate evaluation of the data, we carried out a PCA. In accordance with the Kaiser-Criterion, we extracted four factors that account for 60% of the total variance. Table 2 presents the rotated factors.

Factor 1 was composed of the DST, the digit spans, and fluency. Thus, it represented mainly the verbal component of working memory. Since both fluency and working memory could be regarded as executive functions, in the broader sense Factor 1 represented verbal executive functioning.

Factor 2: The BST, the block spans, working memory (TAP) and reasoning (LPS-3) loaded on Factor 2. The negative loading of the working memory task of the TAP did not stand for a negative relation since short reaction times in this task and high scores on the other tasks represented superior outcomes. In contrast to Factor 1, Factor 2 represented the nonverbal component of working memory. In addition to the working memory functions, the nonverbal LPS-3 also loaded on Factor 2. In the broader sense Factor 2 represented nonverbal executive functioning.

Factor 3 consisted of the go-nogo and flexibility task as well as the simple reactions. Fluency and the nonverbal learning task (DCS) also loaded here. On the whole, Factor 3 focused mainly on speed-tasks and nonverbal learning.

Factor 4: The reaction times on the working-memory and go-nogo task (TAP) and the auditory verbal learning task (AVLT) loaded on Factor 4. It represented psychomotor speed (comparable to Factor 3) and verbal learning.

STUDY 2

PARTICIPANTS

In the second study BST was administered to 31 patients from the Neurological Rehabilitation Center Bad Aibling in order to assess its clinical practicability. All patients provided their written informed consent and all fulfilled the following selection criteria:

- neurological disease involving brain,
- no acute impairment with an interval of less than 2 weeks between injury and participation in this study,
- sufficient vigilance to submit to a standardized neuropsychological examination for at least 1 hr,
- no severe aphasic disorder that would bar a structured clinical interview and a standardized neuropsychological examination.

Twenty-three men (74%) and 8 women ranging in age from 19 to 72 years, with a mean age of 46 years \((SD = 14.97)\) participated in the study. On average, patients had had 10.2 years of basic school education \((SD = 1.87)\). Twenty-nine patients were right-handed, while 1 patient was left-handed and 1 ambidextrous.

Clinical diagnoses included stroke (15 patients) and headtrauma (13 patients), while the 3 remaining patients had undergone a tumor-resection. Ten patients exhibited unilateral left hemisphere lesions, and 9 patients unilateral right hemisphere lesions, while 7 patients showed bilateral lesions. For the remaining 5 patients no data on the location of a lesion were available. Of those patients with right hemisphere or bilateral lesions, 6 suffered from visual neglect. Of those patients with left hemisphere or bilateral lesions, 4 suffered from residual aphasic symptoms that could not be classified by means of the Aachen Aphasia Test (Huber, Poeck, Weniger, & Willmes, 1983). Eleven patients suffered from a hemiparesis and 1 patient from a residual tetraparesis. The median interval between the injury and participation in the study was 7 weeks.

TESTS

The BST, DST, and block spans forward and backward were administered as described in Study 1. The digit spans forward and backward were derived from the Wechsler Adult Intelligence Scale – Revised (WAIS–R; Wechsler, 1981).

STATISTICAL ANALYSIS

As indices of reliability, we calculated Cronbach’s alpha, split-half and test-retest reliability. To obtain the test-retest reliability, we administered the BST at baseline and again 2 days later. Because all patients suffered from a recent brain disease that involved a rapid change in their mental abilities, a brief test-retest interval was necessary. Test-retest reliability was calculated as Pearson \(r \) between the test scores obtained
on the two occasions, \( t \) tests were performed to compare the results of the BST with those for “traditional” memory spans. Nonparametric statistics were used for the exploratory comparison of subgroups due to the small sample size (\( N < 10 \)). All levels of significance were alpha = .05 and two-tailed. When necessary, alpha was corrected due to multiple comparisons (Bonferroni).

RESULTS

BST: Mean, Range, Reliability

The scores for the BST-parameters and the other memory spans are presented in Table 3. Range and distribution of frequencies were both satisfactory, with no indication of a floor effect (only 1 patient had a BST-score of 1, while 2 patients had a score of 2).

Reliability was satisfactory, with a Cronbach’s \( \alpha = .87 \) (test) and .91 (retest), and a split half reliability = .84 for test and retest. Test-retest reliability was \( r = .81 \).

BST and Traditional Block and Digit Spans

Figure 2 illustrates the differences between the block and digit spans forward and backward and the BST/DST-reproduction spans.

Due to multiple comparisons (nine), the level of significance was corrected to alpha = .006. The relations between the spans were very similar as those for healthy subjects:

1. The digit span backward was shorter than the digit span forward, \( t(30) = 8.14, p \leq .001 \). The block spans forward and backward were of comparable lengths.
2. The BST-reproduction span was shorter than the block spans forward, \( t(30) = 9.61, p \leq .001 \), and backward, \( t(30) = 6.35, p \leq .001 \).
3. The DST-reproduction span was shorter than the digit span forward, \( t(30) = 9.68, p \leq .001 \), but not significantly shorter than the digit span backward (\( p \leq .001 \)).
4. The digit span backward and the block span backward were of comparable lengths, while the digit span forward was longer than the block span forward, \( t(30) = 4.22, p \leq .001 \).

The outcomes of the BST and DST did not differ significantly.

Clinical Practicability of the BST

All patients understood the instructions for the BST but 7 reported being unable to suppress blocks. Compared with the remaining 24 patients, these 7 exhibited a reduced performance on the BST (medians = 2/4; \( U = 20, p \leq .001 \)) and on the digit span backward (medians = 3/4; \( U = 32, p = .008 \)) but not on the other spans when alpha was corrected to .008, according to six comparisons. As had been expected, qualitative

<table>
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<tr>
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<th>( SD )</th>
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<tr>
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<td>2–6</td>
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<td>BST-presentation span (3–16)</td>
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<td>3–12</td>
</tr>
<tr>
<td>BST-score (1–28)</td>
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<td>1–16</td>
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<td>5.9</td>
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</table>
analysis of the data revealed that patients with visual neglect ($N = 6$) tended to neglect blocks which were presented in the contralateral visual field. Acceptance of the BST was as high as that for the other neuropsychological tests.

**EXPLORATORY ANALYSIS: PATIENTS VERSUS HEALTHY SUBJECTS**

An exploratory comparison of the patients in Study 2 with the healthy subjects in Study 1 revealed clearly significant differences between all block and digit parameters, including those of the BST and DST ($p < .001$). A comparison of Figures 1 and 2 show that all numerical differences between healthy subjects and patients on the memory-spans (digit and block spans forward and backward, BST) amounted to 1.3 (aside from the difference of 0.7 in the DST), indicating that the BST was not disproportionately difficult or easy for older brain-damaged patients.

**DISCUSSION**

Standard tests to assess spatial working memory are still rare in clinical neuropsychology, although the assessment of working memory is a major diagnostic topic. We developed the Block Suppression Test (BST), a new approach to assess spatial working memory for clinical purposes. Presented here are the results from two exploratory studies. Data indicated that reliability, validity and clinical practicability of the BST were clearly satisfactory.

Before discussing the results in detail, some methodological limitations to these studies have to be considered. First of all, the samples in both studies were small, $N = 48$ in Study 1 and $N = 31$ in Study 2. Therefore, especially the results on the PCA in Study 1 require cautious interpretation. In Study 1 we investigated only students at the University of Bielefeld, young, well-educated people. Thus, the variance among test results was small; calculated correlations therefore underestimate the relationships between the variables (Bortz, 1985). Given these limitations, the present results indicate the most robust correlations among variables. The sample in Study 2 was too small to permit analysis for relevant subgroups, for example, subdivided according to neurological disease or lesion location.

Psychometric analysis revealed the BST to be sufficiently reliable and internally consistent. As had been expected, there was no difference in the lengths of the block spans forward and backward in either the healthy subjects or the neurological patients. Thus, the block span backward requires no additional executive processing compared to the block span forward, which represents primarily the storage component of spatial working memory. By contrast the length of the BST-reproduction span was clearly shorter than that of the “traditional” block spans in both groups of subjects. This finding confirms the assumption that the suppression of irrelevant blocks is an active executive process that requires additional working memory capacity (Desimone, 1996; Goldman-Rakic, 1987) even if the outcomes may have been additionally influenced by other variables (e.g., the chronological conditions). Therefore, the BST confirms the definition of working memory as requiring both the storage and manipulation of information (Baddeley & Hitch, 1974).

To investigate validity, in Study 1 we first determined the correlations between the BST and other neuropsychological variables. Correlations were generally small, possibly due to the highly selected sample of healthy subjects with small variance among test results. However, the BST correlated primarily with the parameters of other
tests of working memory and of executive functions. In a further investigation we carried out a PCA. According to this multivariate approach, the BST shared one factor (Factor 2) with the “traditional” block spans, the tests “working memory” (TAP) and “reasoning” (LPS-3). The latter finding is in line with those of Kyllonen and Christal (1990) who showed working memory to be strongly related to reasoning skills. By contrast, the go-nogo task, which also has been regarded as a test of executive functioning, did not correlate with the BST. One possible explanation for this finding is the fact that the go-nogo task used in this study is based on psychomotor speed. Accordingly, the go-nogo paradigm was located on Factor 3 and Factor 4, both of which represented speed. With regard to modality, Factor 2 represented mainly the non-verbal tests aside from the test “working memory” (TAP), which used digits as stimuli. As a whole, these data are a preliminary indication of the convergent and discriminatory validity of the BST.

The BST was not disproportionally more difficult for neurological patients than the “traditional” memory spans. The range of scores on the BST for both the healthy subjects and the neurological patients was sufficient, indicating that the BST might discriminate within samples whose proficiency levels differed from one another. This outcome is not self-evident since other paradigms of working memory such as the 2-back paradigm show floor effects for cognitively impaired patients (Carter et al., 1998). Thus, although the BST represented a cognitively demanding task, it nevertheless showed a wide range of test-results, even among cognitively impaired patients.

The clinical practicability of the BST with regard to its instructions and its acceptance was sufficient. However, a few patients were unable to follow the instruction to pay attention to only every second block presented. We discovered that this problem was due not to the instruction itself, but to the mental inability to suppress the processing of visual input. In these patients the digit span backward was also reduced, a finding which indicates that they suffered from a more general problem of working memory rather than from a specific deficit with regard to the suppression of cognitive processing. Finally, as with other visual tests, we advice against administration of the BST to patients with visual neglect.

In the Digit Suppression Test (DST), we developed a verbal version of the BST. Our data showed that the DST provides an alternative measure of verbal working memory. Moreover, the data indicated that the BST and the DST spans were comparable in length and correlated significantly. Together, the BST and DST provide analogous tasks with comparable executive demands in order to analyze both the spatial and verbal modalities of working memory in clinical neuropsychology.

Further research is needed to confirm our results and to obtain (normative) data on the BST in different subgroups of healthy subjects according to age, sex, and level of education. Furthermore, the analysis of different subgroups with regard to the neurological disease, lesion location, and clinical features might deliver important information on the clinical validity of the BST.

ACKNOWLEDGMENTS

We thank Dr. Ingo Keller and Katrin Pahlke (Neurological Rehabilitation Center Bad Aibling) for supporting our study.

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Dysfunctional neural network of spatial working memory contributes to developmental dyscalculia

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**Abstract**


Using functional MRI the current study compares brain activity associated with spatial working memory processes in 8–10-year-old children with DD and normally achieving controls. Both groups showed significant spatial working memory related activity in a network including occipital and parietal regions. Children with DD showed weaker neural activation compared to the control group during a spatial working memory task in the right intraparietal sulcus (IPS), the right insula and the right inferior frontal lobe. Performance tests outside the scanner showed impaired working memory proficiency in children with DD. Bringing behavioral performance and neural activity together we found significant correlations of right IPS activity with performance on the verbal digit span forward and the spatial Corsi Block Tapping test.

Our findings demonstrate for the first time an involvement of spatial working memory processes in the neural underpinnings of DD. These poor spatial working memory processes may inhibit the formation of spatial number representations (mental numberline) as well as the storage and retrieval of arithmetical facts.

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1. Introduction

Developmental dyscalculia (DD) is characterized by difficulties representing and manipulating numerical information nonverbally and visuo-spatially, in learning and remembering arithmetic facts and in executing arithmetic procedures. DD in children has a prevalence of 3–6% in the school aged population, what is comparable to dyslexia, and high rates of comorbidities, such as ADHD (Koumola...
et al., 2004; Shalev, Auerbach, Manor, & Gross-Tsur, 2000). Yet little is known about the underlying deficits. The question of whether this difficulty in learning mathematics is due to a single impairment or a combination of impairments in a more general cognitive system is still open (Butterworth, 2005; Mix & Sandhofer, 2007). One impediment to research on DD is the complexity of the numerical domain that includes verbal, visuo-spatial, memory, and executive functions (Ardila, Galeano, & Rosselli, 1998; Geary, Hamson, & Hoard, 2000; von Aster, 2000). This wide array of cognitive factors that could contribute to DD poses a special challenge to investigate this disorder.

Deficits in working memory systems have been argued to substantially contribute to specific deficits in building cognitive representations of number, the formation of concepts and procedures as well as arithmetic fact retrieval in children with DD (Geary, 1993; von Aster & Shalev, 2007). Working memory refers to the mental capacity responsible for the temporary processing and storage of information (Rosselli, Matute, Pinto, & Ardila, 2006). It requires both the simultaneous processing of incoming and the retrieval or manipulation of retained information (Siegel & Ryan, 1989). This capacity for information processing is limited, since higher demands on the former will negatively influence the access to the latter, and vice versa. Therefore, variation in this capacity is reflected in performance in any cognitive activity (Camos, 2008), including arithmetic.

Several studies investigated the role of working memory in typically achieving children and children with DD (Bull, Espy, & Wiebe, 2008; D’Amico & Guarnera, 2005; Geary et al., 2000; Geary & Hoard, 2001; McLean & Hitch, 1999; Rosselli et al., 2006; Siegel & Ryan, 1989). Van der Sluis, van der Leij, and de Jong (2005) showed that children with arithmetic disabilities performed worse on a task requiring the memorization of dynamic visual information—these results are consistent with other findings (McLean & Hitch, 1999), reporting lower performance of children with arithmetic disabilities on the Corsi Block Tapping task. Concerning the different aspects of working memory, children with poor arithmetic performance generally appear to have normal phonological working memory (McLean & Hitch, 1999; Siegel & Ryan, 1989), although their capacity of spatial working memory is impaired.

Spatial working memory is modulated by a broad network of regions including predominantly frontal and parietal regions. Children performing visuo-spatial working memory tasks show the same, but decreased activation pattern compared to adults, especially the dorsolateral prefrontal cortex is less recruited (Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002; Nelson et al., 2000; Scherf, Sweeney, & Luna, 2006).

To date, only a few studies have investigated children with DD by means of anatomical or functional brain functions. Kuclian et al. (2006) showed that children with DD have weaker brain activation in the IPS and the middle and inferior frontal gyrus of both hemispheres for approximate calculation than typically achieving children. Evidence of parietal dysfunction in DD has also been reported by Price, Holloway, Rässänen, Vesterinen, and Ansari (2007). In a recent study investigating structural brain volume in children with and without DD Rotzer et al. (2008) found reduced grey matter volumes in frontal and parietal regions. Hence, the question arose whether these differences are related to specific number processes or whether they may be attributed to more domain general factors such as working memory and attention.

The current study aims, for the first time, to compare the functional neuroanatomy of children with and without DD while performing a spatial working memory task. We hypothesize that children with DD show weaker activation in brain areas related to spatial working memory, such as the frontal and parietal cortex, since children with DD seem to have impaired spatial working memory capacities that are modulated by frontal and parietal brain regions.

2. Methods

2.1. Participants

The study included 11 girls and 3 boys with the diagnosis of developmental dyscalculia and 12 age-matched controls with age appropriate calculation performance (ZAREK-R; von Aster, Weinhold Zulauf, & Horn, 2006). None of the participants had neurological or psychiatric disorders. They were not on medication and had no exclusion criteria for MRI. Five children were not included—two children with DD refused scanning, another two children with DD and one control child showed less than 60% accuracy rate within the scanner task. The remaining group included 10 children with DD (8 female, 2 male; mean age, 10.4; SD, 1.2) and eleven controls (9 female, 2 male; mean age, 10.2; SD, 1.0). Parents gave informed consent and children received a voucher for their participation. The study was approved by the local ethics committee based on the World Medical Association’s Declaration of Helsinki (WMA, 2002).

2.2. Behavioral testing

Behavioral evaluation was carried out during two sessions before scanning. Mental ability was measured with three verbal (Vocabulary, Arithmetic and Similarities) and non-verbal performance subtests (Picture Arrangement, Block Design) of the Wechsler Intelligence Scale for Children (HAWIK-III) (Tewes, Rossmann, & Schallberger, 2000). (population mean = 100, SD = 15). Handedness was examined through the Edinburgh Handedness Inventory (Oldfield, 1971). Numerical abilities were assessed using the Neuropsychological Test Battery for Number Processing and Calculation in Children (ZAREK-R). This neuropsychological battery examines the progress of basic skills in number calculation and arithmetic and identifies and characterizes the profile of mathematical abilities in children with dyscalculia. It is composed of 11 subtests, such as reverse counting, subtraction, number reading, dictating, visual estimation of quantities, digit span forward and backward. Criteria for developmental dyscalculia were met if a child’s performance in the ZAREK-R was 1.5 SD below average in three subtests or in the total score. Spatial working memory performance was measured with the Corsi Block Tapping test, a test assessing spatial working memory span. On a board with 9 cubes, the examiner taps the cubes in a given sequence. Subjects are required to repeat the cube sequences in the same order immediately after they have finished. While the sequences gradually increase in length, the number of cubes last tapped on in two consequently correct sequences is defined as maximum span. Children were also tested on the Block Suppression test—this test is based on the Corsi Block Tapping test and requires the subject reproducing every 2nd block in a given sequence (Behbo, Mack, Brinkers, Hartje, & Klaver, 2004). This task requires children to suppress irrelevant spatial information actively.

2.3. Paradigm design

The scanner paradigm is an adaptation of the Corsi Block Tapping test (Klingberg et al., 2002). Participants were asked to remember the location of three red dots, which were presented sequentially in a 4 × 4 grid, each dot for 2333 ms. After a delay period of 1500 ms, a red circle appeared for 1500 ms and they had to press a button with their right index finger when the circle was in the same location as any of previously presented dots. If not, they had to press another button with their right middle finger. The control condition used the same stimuli as the working memory task, but with green dots. Children just had to watch the dots and press a button when a green circle appeared. Three working memory trials (red dots) alternated with three control trials (green dots) for three times. The presentation order was counterbalanced across subjects. The time between conditions was jittered between 5000 and 15000 ms. Subjects were carefully instructed about the experimental procedure and had to practice trial tasks, before entering the scanner.

2.4. Image acquisition

Brain images were acquired on a 3.0 T whole-body scanner (GE Medical Systems, Milwaukee, WI, USA) using a standard 8-channel head coil. Scan parameters were number of slices (NS): 36 (parallel to the AC-PC line); slice thickness (ST): 3.4 mm; matrix size (MS): 64 × 64; field of view (FOV): 220 mm × 220 mm; flip angle (FA): 45°; echo time (TE): 31 ms; repetition time (TR): 2100 ms. The task was presented via video goggles (MRI Audio/Video System, Resonance Technology, Inc., USA) using E-Prime software (Psychology Software Tools Inc.). Three-dimensional anatomical images of the entire brain were obtained by using a T1-weighted gradient echo pulse sequence (NS = 172, ST = 2.0 mm, TR = 9.988 ms, TE = 2.916 ms, FOV = 240 mm × 240 mm, FA: 20°, MS = 256 × 192).

2.5. Data analysis

2.5.1. Behavioral data

Two sample t-tests and non-parametric Mann–Whitney tests were used as planned comparisons to evaluate behavioral tests outside the scanner. Non-
parametric Mann–Whitney tests were used to evaluate mean response times (red and green circles) and accuracy rate of the scanner task. All statistical procedures were performed with the "Statistical Package for the Social Science 14.0" (SPSS 14.0).

2.5.2. Imaging data

Functional images were analyzed with statistical parametric mapping software (SPM5; http://www.fil.ion.ucl.ac.uk/spm/software/spm5). Brain volumes for each individual were spatially realigned and unwarped. No child had to be removed from the study because of movement artefacts (maximum movement of less than one image-pixel size). A mean functional image volume was constructed for each participant for each session from the realigned image volumes. These mean images were then segmented using an age-matched grey matter brain template (Cincinnati (http://www.irc.cchmc.org/software/pedbrain.php)) and normalization parameters were estimated during the segmentation process. These normalization parameters were applied to the original functional brain images for spatial normalization on the children template. Normalized images were resliced to 3 mm3 and smoothed with a 9 mm full width at half maximum isotropic Gaussian kernel.

To generate statistical maps for each subject we modelled the expected hemodynamic response for the working memory and control task with a canonical hemodynamic response function, and its temporal and dispersion derivative. The functions were convolved by the event train of stimulus onsets of every dot to create covariates in a general linear model. Three scans were discarded to accommodate for normal physiological noise. Intraparietal sulcus (IPS) (33/63/6), right insula (45/-36/6) and right inferior frontal gyrus (33/42/0). ROI spheres of 8 mm radius were generated and averaged for the analysis. Analyses were performed using the MarsBar toolbox (http://marsbar.sourceforge.net/) in SPM5. For each participant percent BOLD signal change was extracted from unsmoothed voxels in each ROI, which was correlated with behavioral data of working memory tests and calculation tests. All data are reported in Montreal Neurological Institute (MNI) stereotactic space.

3. Results

3.1. Behavioral performance (outside the scanner)

Mean scores and standard deviations for tests are presented in Table 1. All subjects scored an intelligence quotient (IQ) of 97 or more on the HAWIK-III subtests. This means that all children were within the average range and there was no significant group difference in estimated total subtests IQ or performance IQ but there was a significant difference in verbal IQ. Analysis of the ZAREKI-R of children with DD showed significant different percentile ranges compared to normally achieving children at different subtests and the total score (see Table 1). Table 1 shows also lower performance of the children with DD compared to the control children in all working memory tasks (Corsi Block Tapping test, Block Suppression test and digit span forwards) except of digit span backwards.

3.2. Behavioral performance (inside the scanner)

Behavioral data during scan session demonstrated that both groups had equivalent performance on the working memory task regarding reaction time (p > 0.42) and accuracy rate (p > 0.49).

Table 1

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics.</th>
<th>Dyscalculic group (N=10)</th>
<th>Control group (N=11)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>10.4 (5/4/1)</td>
<td>10.2 (9/2/0)</td>
<td>p &gt; 0.5</td>
</tr>
<tr>
<td>SD</td>
<td>1.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Total IQ</td>
<td>103.7</td>
<td>109.4</td>
<td>p &gt; 0.06</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>103.2</td>
<td>110.7</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>104.8</td>
<td>107.5</td>
<td>p &gt; 0.4</td>
</tr>
<tr>
<td>ZAREKI-R, “addition” (percentile rank)</td>
<td>33.3</td>
<td>80.9</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ZAREKI-R, “number writing” (PR)</td>
<td>36.1</td>
<td>90.6</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ZAREKI-R, “subtraction” (PR)</td>
<td>9</td>
<td>70.0</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>ZAREKI-R, “number comparison words” (PR)</td>
<td>37.6</td>
<td>75.6</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ZAREKI-R, total (PR)</td>
<td>17.6</td>
<td>69.1</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Corsi Block Tapping test</td>
<td>4.5</td>
<td>5.3</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Block Suppression test</td>
<td>1.9</td>
<td>3.1</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Digit span forwards</td>
<td>4.4</td>
<td>5.3</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Digit span backwards</td>
<td>3.0</td>
<td>3.5</td>
<td>p &gt; 0.05</td>
</tr>
</tbody>
</table>

a Handedness (N: right/ambidexter/left)
b N = 8.

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Table 2
Regions of significant activation during spatial working memory task in control and dyscalculic children. Listed are peak voxels ($p_{	ext{uncorrected}} < 0.0001$). (L = left, R = right).

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>MNI coordinates</th>
<th>T score voxel level</th>
<th>Number of voxels in cluster ($k_E$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R middle occipital gyrus</td>
<td>48, −78, −15</td>
<td>9.07</td>
<td>87</td>
</tr>
<tr>
<td>L middle occipital gyrus</td>
<td>−36, −80, 9</td>
<td>6.85</td>
<td>36</td>
</tr>
<tr>
<td>L superior and intraparietal cortex</td>
<td>−27, −60, 57</td>
<td>10.19</td>
<td>125</td>
</tr>
<tr>
<td>L inferior frontal gyrus</td>
<td>−33, 36, 6</td>
<td>7.37</td>
<td>37</td>
</tr>
<tr>
<td>R middle frontal gyrus</td>
<td>24, −6, 66</td>
<td>8.36</td>
<td>22</td>
</tr>
<tr>
<td>L putamen</td>
<td>−27, 9, 0</td>
<td>6.39</td>
<td>59</td>
</tr>
<tr>
<td>L caudatus</td>
<td>−18, 18, 3</td>
<td>11.6</td>
<td>290</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>−24, −69, −33</td>
<td>8.92</td>
<td>110</td>
</tr>
<tr>
<td>L cerebellum</td>
<td>−18, −48, −27</td>
<td>10.28</td>
<td>172</td>
</tr>
<tr>
<td>L thalamus</td>
<td>−12, −24, 15</td>
<td>9.57</td>
<td>373</td>
</tr>
<tr>
<td><strong>Dyscalculic group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R cuneus</td>
<td>33, −75, 30</td>
<td>8.25</td>
<td>235</td>
</tr>
<tr>
<td>L cuneus</td>
<td>−24, −93, −6</td>
<td>12.84</td>
<td>439</td>
</tr>
<tr>
<td>R lingual gyrus</td>
<td>21, −102, −12</td>
<td>11.12</td>
<td>116</td>
</tr>
<tr>
<td>R inferior occipital gyrus</td>
<td>42, −90, −15</td>
<td>8.83</td>
<td>159</td>
</tr>
<tr>
<td>L middle occipital gyrus</td>
<td>−51, −72, 0</td>
<td>8.22</td>
<td>129</td>
</tr>
<tr>
<td>L superior and intraparietal cortex</td>
<td>−21, −63, 69</td>
<td>11.71</td>
<td>344</td>
</tr>
<tr>
<td>R precuneus</td>
<td>24, −57, 45</td>
<td>8.64</td>
<td>120</td>
</tr>
<tr>
<td>L inferior parietal lobe</td>
<td>−45, −45, 54</td>
<td>8.9</td>
<td>27</td>
</tr>
<tr>
<td>R thalamus</td>
<td>12, −24, 12</td>
<td>9.78</td>
<td>104</td>
</tr>
<tr>
<td>L putamen</td>
<td>42, −90, −15</td>
<td>8.83</td>
<td>159</td>
</tr>
</tbody>
</table>

Table 3
Regions showing significantly greater activation in control compared to dyscalculic children. Listed are peak voxels ($p_{	ext{uncorrected}} < 0.001$). (L = left, R = right).

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>MNI coordinates</th>
<th>T score voxel level</th>
<th>Number of voxels in cluster ($k_E$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R inferior frontal gyrus</td>
<td>33, 42, 0</td>
<td>4.19</td>
<td>22</td>
</tr>
<tr>
<td>R intraparietal sulcus</td>
<td>36, −42, 51</td>
<td>3.52</td>
<td>13</td>
</tr>
<tr>
<td>R insula</td>
<td>45, −3, 6</td>
<td>3.44</td>
<td>21</td>
</tr>
</tbody>
</table>

Fig. 2. Shows significant correlations between behavioral test results (Corsi Block Tapping test and the digit span forward) and mean percent BOLD signal change within regions of interest at the right IPS ($x = 36, y = −42, z = 51$) and the right insula ($x = 45, y = −3, z = 6$). (grey squares = dyscalculic children, dark triangles = control children).

3.3. fMRI results

In control children the working memory task elicited greater activation when compared with the control task in the following network: bilateral middle occipital, superior and intraparietal and cerebellar regions, but also the left inferior and the right middle frontal gyrus, the left thalamus and the basal ganglia (Table 2).

Children with DD, on the other hand, activated clusters in the right inferior occipital gyrus, the cuneus, the right precuneus and left superior, inferior and intraparietal cortex.

Three regions showed significantly greater activation for the working memory task in the control group compared with the dyscalculic group. Control children showed significantly enhanced activation in the right inferior frontal lobe, the right insula and in the right IPS. There were no regions that showed significantly greater activation in the dyscalculic group compared to the control group (Table 3, Fig. 1).

3.4. Whole brain level correlation analysis and non-independent ROI analyses

The whole brain level correlation with behavioral scores of spatial working memory provided no significant results at the statistical threshold that we used for all tests ($p < 0.001$ uncorrected). The non-independent correlation analyses revealed that the Corsi Block Tapping test ($p = 0.022$) and digit span forward ($p = 0.017$) significantly correlated with the ROI in the IPS. The latter test correlated also with the ROI of the right Insula ($p = 0.016$) (see Fig. 2). There were no other significant correlations with working memory tasks, calculation tests or the frontal ROI.

4. Discussion

Our study provides first evidence for significant changes in neural responses of underlying spatial working memory processes in dyscalculic children compared to normally achieving controls. Con-
trol children activated a broad network of bilateral middle occipital and bilateral superior and intraparietal areas during spatial working memory task. Moreover, they activated right middle and left inferior frontal areas, left thalamus and the cerebellum bilaterally. These findings are largely consistent with other studies (Smith & Jonides, 1999; Ungerleider & Haxby, 1994; Wager & Smith, 2003). In contrast to Klingberg et al. (2002), we found no activation in the superior frontal sulcus. This region has been found to exhibit sustained activity during the delay period when information is held in WM. An explanation for this discrepancy in results may lie in the difference between tasks. Klingberg and colleagues used both low and high load conditions, in which three, respectively five dots had to be held in WM. We discarded the high load condition, because we expected children with DD to exhibit problems with high working memory load and aimed to minimize inter-individual and group differences in behavioral performance during scanning.

Children with DD showed no activation clusters in frontal areas but additional clusters within the cuneus, bilaterally, and the right precuneus. Over all, activation clusters seem to be deviant from control children and may indicate a selective impairment of the dorsal stream. Nonetheless, the task was highly sensitive in terms of functional brain imaging. All children were performing above chance level (>60% correct answers) and showed comparable reaction times, indicating that differences in functional brain activation are related to task and not to task difficulty. Additionally, fMRI revealed significant activation patterns associated with cognitive performance outside the scanner.

Our results demonstrate reduced activation in working memory relevant brain areas, such as the right IPS, the right inferior frontal lobe and in the right insula in children with DD when compared to the control group. These activation differences are shown in relatively small clusters which might be caused by the small group size but they are in close relationship to spatial working memory processes (Bor, Duncan, & Owen, 2001; Klingberg, 2006; Smith, Jonides, & Koepe, 1996).

Like in our VBM study (Rotzer et al., 2008), the right IPS plays a crucial role in the neural network of children with DD. Decreased activation in the right IPS of children with DD during a non-numerical spatial working memory task strongly argues for a central role of the right IPS in both working memory capacity and the acquisition of spatial number representations and arithmetic concepts. There is a recent study revealing atypical activation in the right intraparietal sulcus (Talairach coordinates: 33, −50, 52) during a non-symbolic, numerical magnitude processing task in children with DD (Price et al., 2007). The authors strengthen the hypothesis that DD is caused by ontogenetic disruption of the neural circuitry that supports fundamental representation of numerical magnitude. Our results might indicate that deficient spatial working memory lies at the core of difficulties in non-symbolic numerical magnitude processing.

In a recent study by McNab et al. (2008) a region including the right inferior frontal gyrus and the insula was identified to be associated with inhibition and working memory manipulations. The authors argue that such inhibition processes may play a role in resistance to distraction, which is linked to working memory or, alternatively, an involvement of working memory processes in inhibition tasks (Aron & Poldrack, 2005; Roberts, Hager, & Heron, 1994). Therefore, our results may indicate that children with DD have specific impairments in inhibiting irrelevant information. This is in accordance the clinical observation of frequently associated symptoms of inattentiveness and distractibility in children with DD (von Aster & Shalev, 2007). Complementary to these differences in neural activation clusters children with DD show significant deficits in working memory tests. The performance in the Corsi Block Tapping test, the Block suppression test, the subtest ‘subtraction’ of the ZAREKI-R and the digit span forward was significantly lower in children with DD compared to normally achieving controls. These results are in line with findings from other studies (Schuchardt, Maelher, & Hasselhorn, 2008). Visuo-spatial short-term memory span was found to be a predictor specifically of math ability. Correlation and regression analyses revealed visual short-term and working memory to specifically predict math achievement at each time point (Bull et al., 2008; Schuchardt et al., 2008).

D’Amico and Guarnera (2005) examined children with a battery of working memory tests, and found that dyscalculic children showed a deficit in digit span forward, but only when the representation of numerical information was required, rather than the representation or rehearsal of verbal information. Our data are in line with these findings. Interestingly, in our study there are no differences between groups regarding the digit span backward, which is predominantly a measure of verbal working memory. Some studies have found impairments in this domain (D’Amico & Guarnera, 2005; Rosselli et al., 2006), whereas others suggest that children with DD do not appear to have a deficit in working memory for language-related tasks (McLean & Hitch, 1999; Schuchardt et al., 2008). Our results may be explained by the small group size of examined children and therefore additional research about the role of verbal working memory in children with DD is required.

In order to bring the findings from behavioral testing and functional MRI together we conducted correlation analyses on a whole brain level and based on functional ROIs. Whole brain analyses revealed no significant correlations, but significant results of our non-independent correlation analyses were found. These results have to be considered complementary to the results of the group contrast and interpreted carefully because of the small group size, which may contribute to the null result of the whole brain analysis, and significant ROI results, which were based a non-independent contrast between groups (Vul, Harris, Winkielman, & Pashler, 2009). Nevertheless, ROI analyses have the advantage compared to the whole brain analyses that they are based on independent voxel signals in unsmoothed data, which reduces the chance for a false positive result. Activation in the right IPS significantly correlated with the Corsi Block Tapping test and the digit span forward. Digit span forward is a measure of verbal short-term memory and the correlation between the performance on this test and the IPS is in good accordance with a recent study (Majerus et al., 2008) showing a relation between activation of the right IPS and short-term memory for order information. The correlation of the Corsi Block Tapping test performance and the IPS accentuates the close relationship between this region and the impaired spatial working memory capacity in children with DD. But as illustrated in Fig. 2 there are also children without DD with bad performance at the Corsi Block Tapping test showing decreased activation in the right IPS. The role of the IPS in calculation and in spatial working memory processes has been increasingly discussed in recent years and still remains a matter of debate (Ansari & Dhital, 2006; Cohen Kadosh et al., 2005; Dehaene, Bossini, & Giraux, 1993; Dehaene, Molkko, Cohen, & Wilson, 2004; Dehaene, Speike, Pinel, Stanescu, & Tsivkin, 1999; Fias & Fischer, 2005; Knops, Nuerk, Fimm, Vohn, & Willmes, 2006; Nieder, 2004, 2005; Shuman & Kanwisher, 2004; Zago et al., 2008). A study in adults investigated the contributions of spatial working memory manipulation during the addition of numbers (Zago et al., 2008). They found that calculation and spatial manipulation share a common network at the right fronto-parietal hemisphere and that the anterior IPS is involved in tasks requiring magnitude processing with symbolic (numbers) and non-symbolic (locations) stimuli.

In our study we evaluated the neural underpinnings of spatial working memory in children with DD with a task similar to the Corsi...
Block Tapping test. Given that this task has no obvious arithmetical or numerical content, the differences in cortical activity between children with DD and normally achieving children in the right IPS strongly supports the notion that a spatial working memory deficit significantly contributes to DD. Our data support the view, that poor spatial working memory capacity may hinder the acquisition of spatial number representations in children with DD (Geary, 1993; van Aster & Shalev, 2007).

Therefore, our results provide novel information about the influence of spatial working memory on the acquisition of arithmetic competencies and help to further improve the understanding of DD.

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References


Dorsal stream development in motion and structure-from-motion perception

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Little is known about the neural development underlying high order visual perception. For example, in detection of structures by coherently moving dots, motion information must interact with shape-based information to enable object recognition. Tasks involving these different motion-based discriminations are known to activate distinct specialized brain areas in adults. Here, we investigate neural development of normally developing children using functional magnetic resonance imaging (fMRI) during perception of randomly moving point-light dots (RM), coherently moving dots that formed a 3D rotating object (SFM) and static dots. Perception of RM enhanced neural activity as compared to static dots in motion processing-related visual areas, including visual area 3a (V3a), and middle temporal area (hMT+) in 10 adults (age 20–30 years). Children (age 5–6 years) showed less pronounced activity in area V3a than adults. Perception of SFM induced enhanced neural activity as compared to RM in adults in the left parietal shape area (PSA), whereas children increased neural activity within dorsal (V3a) and ventral brain areas (lingual gyrus) of the occipital cortex. These findings provide evidence of neural development within the dorsal pathway. First, maturation was associated with enhanced activity in specialized areas within the dorsal pathway during RM perception (V3a) and SFM perception (PSA). Secondly, high order visual perception-related neural development was associated with a shift in neural activity from low level shape and motion specialized areas in children, including partially immature area V3a, to high order areas in the parietal lobule (PSA) in adults.

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Introduction

Research on visual perception and cognition has led to the understanding that vision is not merely a matter of passive perception; but rather an intelligent process of construction (Zeki, 2001 and references therein). These constructive processes are age-dependent and reflect the integration of color, shape and motion information into the representation of the child's environment. A neurobiological theory of visual development postulates at least three visual systems: one early, rudimentary subcortical and two cortical systems (Atkinson, 1984; Atkinson, 2000). One cortical system comprises areas located in the ventral occipital and temporal lobes. It is commonly referred to as the "what" pathway because damage to these regions leads to deficits in the ability to discriminate between visual objects. The other cortical system includes areas located in the dorsal occipital and parietal lobes. It is commonly referred to as the "where" pathway because damage to these regions leads to deficits in the ability to identify the locations of visual objects in space (Haxby et al., 1991; Milner and Goodale, 1995; Ungerleider and Mishkin, 1982). Whereas the ventral pathway is prone to process, among others, visual identity and feature information (e.g. color, luminance, faces and object identities), the dorsal pathway is inclined to process spatial relations and motion direction information.

There is strong evidence that the dorsal stream is more vulnerable to neurodevelopmental disorders than the ventral stream, which has been described in children aged 4 years and older (Braddick et al., 2003). In normally developing children, the parsing of the visual array into globally organized forms appears to develop more securely than the equivalent parsing by relative motion. The integration of local motion into the perception of coherent translational global motion is a basic integrative process of the motion pathway, for which norms of behavioral performance in the 4–10 year age range are already established (Gunn et al., 2002; Parrish et al., 2005). Recent findings, however, animated the unresolved debate on the neural mechanisms underlying the development of motion processing,
particularly after 4 years of age. For example, a recent functional brain imaging study showed that full development of coherent motion in hMT+ is not reached until adolescence (Bucher et al., 2006). Tasks inducing dynamic visual adaptation (Schauf et al., 1999), configural object recognition (Rentschler et al., 2004) and haptic priming upon configural visual stimuli (Jüttner et al., 2006) require even stronger visual processing demands and possibly the involvement of dorsal stream processing in object recognition. It has been shown that these functions do not mature until adolescence.

The detection of structures-from-motion (SFM) at least partly depends on the detection of coherent motion. At some stage, however, shape processing needs to be activated by coherent motion. Braddick and colleagues (2003) suggested that the development of integrative processing in structure from motion is constrained by the development of global coherent motion processing. This idea was based on findings that perception of biological motion or structure from motion develops at about the same age as the detection of coherent motion. For example, 3–6-month-old infants can already detect SFM (Arterberry and Yonas, 1988; Arterberry and Yonas, 2000; Kaufmann-Hayoz et al., 1986; Yonas et al., 1987). Others, however, suggested that a third area, probably in the posterior, superior parietal cortex, needs to be activated that binds both motion and shape processing areas (Zeki, 2001). This (temporary) binding between shape and motion may be related to attention or spatial processing, and which may have a different developmental time course (Oakes et al., 2006; Rentschler et al., 2004; Ross-Sheehy et al., 2003). Thus, it remains unknown to what extent neural development of SFM processing depends on both the development of motion processing-related areas and areas that are not directly related to shape or motion processing.

Brain imaging studies in adults showed that random motion (RM) activates areas at different levels of the cortical motion pathways, including dorsal visual area 3a (V3a), area V5 (middle temporal area hMT+), the inferior/superior parietal lobule and ventral areas in the lingual and fusiform gyrus (Cornette et al., 1998; Sunaert et al., 1999). In contrast to RM, coherent motion activates areas in the parieto-occipital junction, but also enhances activity in extrastriate areas responding to RM (Braddick et al., 2001; Braddick et al., 2000). As compared to RM, 3D SFM activates areas within the parieto-occipital cortex and parietal cortex, but some studies also reported enhanced activity in extrastriate areas related to RM perception (Murray et al., 2003; Orban et al., 1999; Paradis et al., 2000). The question is whether young children up to the school age show differences in brain activity during RM perception, and whether these differences are limited to the certain parts of the dorsal stream. A further question is whether the limitations observed in high order visual capacities of 5–6 year old children are associated with high order visual areas and functions. In this case, one may hypothesize that age-related differences only occur in stimuli that require high order visual processing. Alternatively, age-related differences may be due to maturation in low order visual processing areas, in which case stimuli requiring either low or high order visual processing would induce age-related differences in neural activity. Here, we measured neural activity in adults and 5–6 year old children in an fMRI experiment while they perceived RM stimuli and SFM stimuli. Because of limitations in scanning time in young children, we did not include an intermediate coherent motion condition. We found that adults activated dorsal and ventral occipital areas during RM perception in contrast to perception of static dots and that children showed less pronounced activity in dorsal area V3a. High order perception of SFM stimuli enhanced neural activity in adult parietal cortex as compared with RM. Children showed less pronounced activity in this area, but more in lower visual areas related to shape and motion processing.

Methods

Subjects

Ten normally achieving pre-school children (mean age 6 years, range 5 years 6 months–6 years 9 months, 4 male) and 10 right handed adults (mean age 26 years, range 20–29, 4 male) were scanned. All subjects and parents of the children gave written informed consent prior to participation. All subjects had no history of neurological or psychiatric disorder. The children were slowly introduced to the scanner and its equipment. For all children, a teddy bear was positioned on the scanner table in order to explain the scanning procedure to the child in an attempt to ease reservations about the procedure and alleviate anxiety. Children were able to watch a cartoon video during anatomical acquisitions. In order to improve compliance and reduce head motion, children listened to a story presented on the headphone. Because of a limitation in head space within the MR head coils, we chose to not use a headphone in adults. Parents stayed outside the scanner room but were able to talk to the children between the scans. The study was approved by a local ethics committee. The families were given

Fig. 1. (A) Three types of stimuli were presented, static dots, randomly moving dots and moving dots that formed a 3D structure (cylinder, box or ‘house shaped’ figures). These stimuli were adapted from Murray et al. (2003). (B) An example of partial functional brain imaging perpendicular to the V1 coronal axis, thus covering the occipital cortex and parietal lobule.
a child’s story-CD as a token of our appreciation. Adult volunteers were given financial compensation for their participation.

**Stimuli**

Subjects viewed randomly moving dots (RM), moving dots that formed a 3-D rotating structure by coherent movement (SFM) and static dots (STAT) as control stimuli. The stimuli were downloaded from the reference provided by Murray and colleagues (http://redwood.uncdavis.edu/scott/research/sfm/; see Fig. 1A for a schematic illustration, adapted from Murray et al., 2003). All stimuli consisted of an array of 450 dots subtending 10° of visual angle. For RM stimuli, each dot moved in a random direction with constant speed (4°/s). The dots in the SFM condition were projections of rigid, transparent, geometric shapes including a cube, cylinder and ‘house shaped’ figures. Dots were randomly selected from a uniform distribution on the object surface and kept fixed relative to the rotating object surface and orthographically projected onto the image plane. Dots were rotated on a randomly chosen 3-D axis for 40° in 1.5° increments. Both motion stimuli had the same direction and speed, but direction and speed were randomly reassigned to different dots to create random motion. The motion stimuli were generated by creating moving sequences at a rate of 20 Hz with 28 frames stored as a bitmap. A sequence of 80
frames was played forward and backward so that motion was continually observed. The first frame was the same for every SFM and RM. The baseline (STAT) presented the 25th frame from the RM stimuli. The total presentation time of each stimulus was 4000 ms. Stimuli were presented through optical goggles during a 12 min scanning session. The three conditions were presented in a balanced order of 18 blocks of trials that were separated by a 2 s interval (54 trials per condition, 4 s per trial). All subjects were instructed to passively view the stimulation.

fMRI data acquisition and analysis

Brain images were acquired on a 3.0 T Scanner (General Electric, Milwaukee, USA) using a standard 8-channel head coil. To estimate blood oxygenation level-dependent (BOLD) contrast, 343 echo planar imaging (EPI) scans were acquired including 2 dummy scans. The scans were aligned perpendicular to the V1 coronal axis thus covering the occipital and parietal lobe (see Fig. 1B for an example). Scan parameters were numbers of slices (NS): 26; slice thickness (ST): 2.7 mm; matrix size (MS): 96 × 96 zero-filled to 128 × 128; field of view (FOV): 230 mm; flip angle (FA): 50°; echo time (TE): 32 ms; repetition time (TR): 2 s. The task was presented via video goggles (MRI Audio/Video System, Resonance Technology, Inc., USA) using Presentation software (www.neurobs.com). Additionally, a high-resolution anatomical reference T2-weighted scan was acquired (NS: 52; ST: 2.7 mm; MS: 256 × 256; FOV: 230 mm; FA: 90°; TE: 12.3 ms; TR: 10.6 s). Functional MRI data analysis was done using Statistical Parametric Mapping 2 (SPM2, www.fil.ion.ucl.ac.uk/spm/). Pre-processing included realignment with unwarping. No subject was excluded from the analysis because of excessive movement, since only one child had maximum movement of 3.5 mm in z-direction. All other subjects did not exceed 2.5 mm movement in z-direction and 1.5 mm in all other directions, which was less than 1 voxel size. We transferred functional and anatomical data from adults and children into a common stereotactic space. For this purpose, T2 images of all subjects were segmented, and normalization parameters were estimated for grey matter images on a standard grey matter template in Montreal Normalization Institute space. The EPI images data were coregistered upon the T2 image and normalization parameters were applied to both the T2 images (1 mm3) and EPI images (3 mm3). EPI data were then smoothed with a 6 mm full width at half maximum Gaussian kernel. The hemodynamic response was modeled by a stick function to each stimulus presentation in each category convolved with a canonical hemodynamic response was modeled by a stick function to each stimulus, ROI (7), hemisphere (left, right) and between-subject factor group (adult, child).

It is not trivial to generalize ROIs from adult subjects to children because the location of specialized brain areas may be shifted within the developing brain. Previous studies have tested the possibility to generalize across age within a common space for 7 year old children (Burgund et al., 2002; Kang et al., 2002). The children were one (maximally 2) years younger than in the study by Kang and colleagues, which was considered to be a similar age group. In order to verify the normalization procedure and the choice of ROIs, the contrast between RM and STAT was calculated in two exemplary subjects at two significance levels ($p < 0.05$ corrected for the whole brain and $p < 0.001$ uncorrected). Percent signal changes were also calculated from two ROIs (areas V3a and hMT+). It could be shown (Fig. 2C) that similar clusters were activated by RM in adults and children, but that the level of activity was different, particularly in area V3a. This result justifies the choice of ROIs and do not suggests that brain areas are shifted with age in this sample.

Imaging results

Motion

Figs. 2A and B show fMRI results from adults and children. As compared with static stimuli RM yielded enhanced neural activity in adults in the lateral and dorsal part of the occipital cortex, as well as in the ventral occipital cortex and posterior middle temporal gyrus (Fig. 2A). These areas correspond to previously described bilateral lateral occipital sulcus (LOS), visual area 3a (V3a) and middle temporal area (hMT+) (Murray et al., 2003; Orban et al., 1999; Sunaert et al., 1999; Tootell et al., 1997). A similar pattern of brain activity was found in children (Fig. 2B), with few apparent differences in the distribution. Children showed enhanced activity in bilateral LOS, but less in medial occipital areas that extend into dorsal and ventral parts of the occipital cortex (see Table 1 for detailed results) and in hMT+. Whole head analysis showed no significant differences between groups except for a larger effect for RM in children than adults in the left precentral gyrus (Talairach coordinates $x = -36, y = -15, z = 45, \rho < 0.001$).

The ROI analysis (collapsed over left and right hemisphere, Fig. 3A, top part) showed differences in the neural response to RM in different regions (ROI: $F_{6,108} = 11.0, p < 0.001$). Significantly enhanced activity was found in adults and children in motion processing-related areas (LOS, V3a, hMT+, all $p < 0.01$) as well as in shape-related areas lateral occipital (LO), superior lateral occipital (SLO) and posterior fusiform (PF) (all $p < 0.01$), but not in SFM-related parietal shape area (PSA). A significant interaction between group and ROI ($F_{6,108} = 4.5, p = 0.004$) indicated that RM induced larger neural activity in adults than in children in motion sensitive area V3a (adult > child, $t_{18} = 2.9, p < 0.01$). A trend to significance was found in hMT+ ($t_{18} = 1.8, p = 0.09$). Furthermore, there was a significant hemispheric lateralization effect in LO that did not depend on maturation (right > left LO, $p < 0.01$).

In a more general analysis, we separated the ROIs into larger functional areas to investigate whether RM affected shape or motion areas differently in children than in adults. Fig. 3B shows neural responses to RM (dark grey) in motion (blue), shape (orange) and shape/motion-related areas (orange/blue). The data...
suggest a larger difference between motion- and shape-related areas in adults than in children during RM perception. This observation was confirmed in a significant interaction between age and visual feature specialized area ($F_{1,18}=21.4$, $p<0.001$). This result indicated that RM enhanced activity specifically in motion areas of adults, whereas children showed less neural specialization.

To further investigate whether RM-related activity depended on age, we calculated regression coefficients on age within ROIs (Fig. 3C). We found significant age-dependent increases in V3a activity (regression coefficient $R^2=0.3$, $p=0.01$). A slightly better fit was found for a logarithmic increase in activity within V3a than for a linear increase ($R^2=0.27$, $p=0.02$). No other area showed correlations between age and brain activity ($hMT^+$, $R^2=0.13$, $p=0.11$; all other, $R^2<0.05$, $p>0.5$). Thus, neural specialization could be shown by larger differences in response to RM between motion and shape areas in adults than in children, but particularly in dorsal area V3a.

### Structure-from-motion

Functional brain imaging data in adults replicated findings that SFM enhanced neural activity as compared with RM in several areas related to shape processing, and also in areas not involved in elementary shape or motion perception, particularly on the occipitotemporal and occipitoparietal junction and further upward into the dorsal stream of the parietal cortex (Fig. 2A). The former areas probably correspond with VIP/S/POIPS (Orban et al., 1999) or POJ (Paradis et al., 2000). The latter area corresponds with PSA (Murray et al., 2003), cIPS (James et al., 2002) or DIPSL/DIPSA (Orban et al., 1999). In children, however, SFM yielded enhanced activity in dorsal and ventral parts of the occipital cortex, but not in the parietal lobule (Fig. 2B).

Whole head analysis yielded group differences for SFM. Adults showed enhanced neural activity compared to RM in the inferior and superior parietal lobule (detailed results are listed in Table 1). The superior parietal activity was located medial and superior to area PSA in Brodmann area 7, whereas the left lateral area was located in the inferior parietal lobule on the border of the precentral gyrus in Brodmann area 40. In contrast, SFM yielded enhanced neural activity in children in the lingual gyrus on the border of the parahippocampal gyrus and fusiform gyrus. This area partially overlaps with area PF. Activity was primarily found in the right hemisphere, but at a lower statistical threshold ($p<0.005$), also left fusiform activity was found. The areas may be identical or adjacent to the posterior part of LO reported earlier ($x=-36$, $y=-71$, $z=-13$) (Grill-Spector et al., 1999) or with ventral surface areas involved in motion and shape processing (Braddick et al., 2000).

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### Table 1

<table>
<thead>
<tr>
<th>Effect</th>
<th>Area</th>
<th>Coordinates LH</th>
<th>Z</th>
<th>$p$-value</th>
<th>Coordinates RH</th>
<th>Z</th>
<th>$p$-value</th>
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<td>−70</td>
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<td>Precuneus</td>
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<td>−71</td>
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<td>0.014</td>
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<td>−15</td>
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</table>

Talairach coordinates ($x/y/z$) are listed from left (LH) and right hemisphere (RH) local maxima of significant clusters (FDR corrected $p<0.05$, * represents trends to significance). $Z$-values are listed for voxels at the local maxima. BA is the Brodmann area nearest to the coordinate and should be considered approximate (g. is gyrus, l. is lobe).
The ROI analysis (Fig. 3A) showed that adults and children exhibited different responses to SFM in some but not all areas (Interaction ROI × GROUP: $F_{6,108} = 4.2$, $p = 0.004$). SFM induced enhanced activity in adult PSA ($p < 0.003$), but not in children (n.s., adults > children $p = 0.057$). In contrast, SFM enhanced neural activity in children more than adults in areas hMT+ (children, $p = 0.051$; adults n.s.; children > adults $p = 0.042$) and PF (children, $p = 0.001$; adults n.s.; children > adults $p = 0.035$).

In a more general analysis, we separated the ROIs into larger functional areas to investigate whether SFM affected shape or motion areas differently in children than in adults. Fig. 3B suggests that SFM enhances neural activity in shape-related areas more strongly than in motion-related areas. This observation is supported by a significant interaction between shape- vs. motion-related ROIs (excluding PSA) and SFM-RM ($F_{1,18} = 5.2$, $p = 0.034$). We found no significant group effect or interaction between shape- vs. motion-related ROIs and group. This result indicates that both adults and children recruit neural activity in shape-related areas during SFM perception.

To further investigate whether SFM-related neural activity is dependent on age, we calculated regression coefficients on age within ROIs after averaging the percent signal change over the left and right hemisphere ROIs (Fig. 3C). We found significant results and trends to significance for an age-dependent logarithmic decrease in neural activity in motion processing-related areas hMT+ ($p = 0.04$) and V3a ($p = 0.07$) and shape-related area PF ($p = 0.03$). This decrease indicated that these areas exhibited enhanced activity for SFM as compared with RM in children, but that this activity attenuated in the maturing brain. On the other hand, PSA showed a trend to a logarithmic increase in activity.
(p<0.06), which indicated that SFM enhanced neural activity in PSA in more mature subjects. Except for area PF ($R^2=0.23$), all areas ($R^2$: hMT+ = 0.21, V3a = 0.17, PSA = 0.18) showed a better fit for a logarithmic age-dependent change in activity than for a linear change. Together, the results indicate that SFM enhanced neural activity as compared with RM in dorsal areas within the parietal lobule in adults. Children on the other hand showed enhanced activity under the same conditions within dorsal and ventral areas of the occipital lobe that are related to motion and shape processing, including areas that may not be fully mature such as areas hMT+ and V3a. Parietal areas showed no significant neural activity during perception of SFM in children.

Discussion

The aim of the current study was to investigate the neural basis of development in visual perception. As far as we know, this is the first study to show direct evidence that neural activity in the dorsal stream of the occipital cortex and parietal lobule was not mature by the age of 6 years. We also suggest that age-dependent neural activity depends on the complexity of the motion stimulus and that high order processes are substituted by low order processes in the immature brain. These claims are discussed in more detail.

In line with previous studies, we found that RM activated areas in the ventral and dorsal part of the occipital lobe (Cornette et al., 1998; Sunaert et al., 1999). Ventral activity was found in the lingual gyrus (predominantly in the right hemisphere), whereas dorsal stream activity was found in areas V3a, LOS and hMT+. There was clear evidence that differences in neural development of visual perception can be linked to the dorsal stream. Adults showed neural specialization within dorsal brain areas, particularly area V3a, whereas children activated both dorsal and ventral areas, with less apparent neural specialization. For SFM, a different pattern was found. SFM increased activity compared to RM in both adults and children in the left lateral part of the middle occipital gyrus (SLO) and a dorsal area at the parieto-occipital junction. Adults showed enhanced SFM-related neural activity only in dorsal areas, including several areas within the parietal lobule, whereas children enhanced neural activity during SFM perception in dorsal and ventral stream areas of the occipital cortex. These data provide evidence for maturation in the parietal lobule and are in line with general anatomical delayed development of the M-pathway in the dorsal stream including the parietal lobule, which showed that grey matter does not reach maturity by the age of 6 years (Braddick et al., 2003; Gogtay et al., 2004; Sowell et al., 2004). For the frontal cortex, it has been suggested that task unrelated activity decreases during maturation, whereas task-related activity increases (Booth et al., 2003; Bunge et al., 2002; Casey et al., 2005; Schlaggar et al., 2002). As far as we know, this is the first study to show that a similar developmental mechanism occurs within the parietal lobule and in area V3a within the dorsal part of the occipital cortex.

The second question was whether developmental differences were stimulus dependent and limited to high order visual processing. The present results support this hypothesis. First, RM and SFM showed developmental effects in different areas. Area V3a showed age-dependent differences in response to RM, whereas areas in the parietal lobule showed age-related differences in response to SFM. There was no area that showed common age-dependent difference related to RM and SFM. Second, the same area V3a that was not specifically activated in children during RM perception showed enhanced activity during SFM perception, which strongly suggests that neural activity in area V3a depends on both maturation and stimulus complexity. Third, age-dependent effects related to SFM perception were different in high order processing areas than in areas related to motion and shape processing. Areas in the parietal lobule were only activated by adults, whereas common neural activity was found in both age groups on the occipital parietal junction, suggesting that both groups similarly processed coherent motion (Paradis et al., 2000). Children, however, showed increased neural activity during SFM perception in shape- and motion-related areas. Thus, we assert that children and adults use different neural mechanisms in the perception of high order visual stimuli and that age-related differences in neural activity arise from the high order visual features of the SFM stimulus.

It remains an open question as to whether increased activity in children in the occipital lobe during SFM has a functional role in perception. Behavioral developmental studies show that SFM can be detected by infants (Arterberry and Yonas, 2000) and reach a mature level at the age of 7 (Parrish et al., 2005). Dependent on the perceptual features and the attentional demands during the task, however, developmental differences occur even until adolescence (Schauf et al., 1999). In our task, we used passive viewing instructions, so that the perceptual demands are low, but the relation to perceptual performance and attentional demands is unclear. Thus, given that perceptive capabilities are different between adults and children, and that children can principally perceive SFM stimuli, we tend to suggest that reduced maturation is substituted by increased neural activity in areas involved in feature specific analyses, whereas the engagement of adult dorsal areas in the parietal lobule during SFM perception relates to maturation. The relation between neural activity in these areas and perceptual capability remains to be answered in future studies.

The present results partially differed from previous studies. For example, in contrast to Murray and colleagues (2003), we found no reduced activity in V1 by SFM as compared with RM. They argued that SFM induced a top-down suppression of V1 activity. In contrast to that study, we did not use an attention demanding perceptive task. Studies that used a passive viewing task reported no stimulus-dependent V1 difference in activity (Paradis et al., 2000). Our results are in line with the latter findings. Furthermore, we found no direct evidence that SFM activated motion processing-related areas. SFM did not significantly enhance activity in areas related to RM in adults, though it enhanced activity in shape processing-related areas. This result contrasts with Murray and colleagues (2003) who showed increased activity in area hMT+ by SFM in adults. Again, these results may be related to the use of a passive viewing task, since they are in line with findings that SFM does not enhance neural activity in hMT+ when a passive viewing task is used (Paradis et al., 2000).

Another difference between the current and several other studies with adults on high order perception is that we used no coherent motion condition. We know from previous reports that such stimuli activate intermediate areas within the dorsal stream on the border of the occipital and parietal cortex (Braddick et al., 2001; Braddick et al., 2000; Orban et al., 1999; Paradis et al., 2000). Since we scanned young children, we were limited in scanning time (approximately 12 min). We thus chose to use a more complex condition of 3D SFM instead of a coherent motion condition to contrast with RM. Future studies are needed to provide a more fine-grained analysis of neural development.
Other aspects might cast doubt on our conclusions. First, it is not trivial to spatially normalize young children with an adult anatomical template. Yet, the present results seem to be anatomically valid. Structural imaging studies reported that particularly the parietal and frontal cortex differ in both grey and white matter (Sowell et al., 2002). The present results support a functional–anatomical development particularly in the parietal lobe, which cannot be entirely attributed to general differences in brain activity, since children show some activity in these areas in the contrast between RM and static control stimuli. Rather, these age-related differences are stimulus specific. Furthermore, the normalization procedures as applied here are in line with normalization comparison studies. Two studies reported that both timing and peak activations were comparable between 7- and 8-year-old children and adults after normalization into a common stereotactic space (Burgund et al., 2002; Kang et al., 2002). The children tested here were 1 to 2 years younger than in those studies. We further showed in an individual subject analysis that activity within ROIs was present in both adults and children, but that the level of neural activity differed. This suggests that functional brain areas in children were not spatially shifted as compared with adults. Nevertheless, the way in which maturation is expressed in neural activity in younger children is still under debate, and cannot be entirely solved here.

Secondly, children may have used different eye movement strategies during perception than adults, which might have biased imaging results based on the lack of eye tracking control and long stimulus presentation. The relation between eye movement and perception is an issue on its own. In the current study, we preferred to minimize control over eye movement in order to not bias potential perceptual control mechanisms, which may differ between adults and children. Thirdly, stronger head movement during the task in children may bias fMRI results. Clearly, children moved generally more than adults, but no child moved beyond acceptable ranges and we found stimulus-dependent neural activity that cannot be explained by movement alone. Fourth, children listened to a story while viewing whereas adults did not. This might be a potential confound inducing cross modal interference. However, the story barely exceeded scanner noise and could hardly be heard so that it is unlikely to interfere with neural activity during visual processing. Another reason is that the effect on visual processing is small. An interaction between highly demanding processing condition (mental imagery) and rest could only be verified in visual cortex in a PET study when scanner noise was compared with a no noise condition. Only after ROI analysis in the cuneus a task by condition effect could be shown (Mazard et al., 2002). Thus, there is little reason to believe that these factors biased the main results. Taken together, the current study provides evidence that dorsal brain areas are not fully developed in 6-year-old children, even during simple motion perception. Perception of SFM stimuli engages high order brain areas that show structural changes in neural development, whereas low order feature specific brain areas are used less with increasing maturation.

Acknowledgments

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References


Role of dorsal and ventral stream development in biological motion perception

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Little is known about the functional development of dorsal and ventral visual streams. The right posterior superior temporal sulcus (pSTS) represents a pivotal point of the two streams and is involved in the perception of biological motion. Here, we compared brain activity between children (aged 5–7 years) and adults (aged 20–32 years) while they were viewing point-light dot animations of biological motion. Biological motion-related activation was found in right pSTS of adults, and in right fusiform gyrus and left middle temporal lobe of children. Group comparisons revealed increased activity in pSTS for adults and in fusiform gyrus for children. Only poorly performing children showed fusiform gyrus activity. These findings indicate that pSTS functioning is not adult-like at the age of 6 years. NeuroReport 19:1763–1767 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: biological motion perception, children, development, functional MRI, ventral and dorsal stream

Introduction

Perception of other individuals’ movements and intentions is essential for successful interactions in a social environment. Adults are highly sensitive in identifying different actions even in displays that contain reduced information about biological motion. Beyond infancy there are only a few behavioural studies investigating sensitivity to biological motion in typically developing children and adults. Young children have generally served as a control group for comparison with a clinical population [1, 2]. The performance of typically developing children increases linearly up to the age of 5 years [3], and from this age on children perform in an adult-like manner [1]. Differences between adults and children over 5 years of age in sensitivity to biological motion have been observed only in more demanding biological motion recognition tasks, for example, when point-light animations were embedded within an array of dynamic noise dots [2, 4].

The extrastriate area most closely associated with the perception of biological motion is the posterior part of the superior temporal sulcus (pSTS) [5–7]. Neuroimaging data provide evidence that biological motion processing occurs at the confluence of dorsal and ventral visual stream areas [8] in which the pSTS represents a pivotal point [9]. The number of neuroimaging studies investigating biological motion perception in children is very limited and inconsistent. One study reported biological motion-related neural activity in the pSTS that correlated positively with age in 7 to 10-year-old children [10]. For the same age group, activity in the pSTS related to perception of eye gaze shifts was reported in another study [11]. No age-related effects within the pSTS were found. Child and adult data were not compared directly in either study. Studies on the functional development of the ventral pathway indicate that face perception elicits ventral stream activity in both preschool (5–8 years) and school-age (9–11 years) children but only school-age children showed activation in the fusiform face area [12]. Moreover, functional activity shifts from being bilateral and more widespread to a more localized profile [13]. These results also indicate that ventral stream functioning is not mature at preschool age. Studies on the development of visual motion processing report that both activation pattern [14, 15] and electrophysiological responses [15] develop up to adolescence, suggesting that functional dorsal stream development also undergoes substantial progression from infancy to adulthood.

In this study, we used event-related functional MRI to examine for the first time the functional development of extrastriate areas involved in biological motion processing by comparing the activation patterns of 5 to 7-year-old children and adults. On the basis of neuroimaging results [14] of dorsal and ventral stream development we hypothesize that for biological motion processing in children as young as those in our group functional activity within dorsal regions may be substituted for the engagement of networks within the ventral stream, which are known to mature earlier [16]. With accumulated experience and maturation, dorsal regions then become increasingly involved in biological motion processing.

Materials and methods

Participants

Twenty-one adults and 23 children were recruited from the local community. A local ethics committee approved the study and all participants were treated according to
the Declaration of Helsinki. Functional MRI data from 10 children and three adults were excluded because of excessive head motion (over 4 mm in either x-plane, y-plane or z-plane) or technical problems. The final data set included 18 healthy adult volunteers (10 females) (mean age: 27.54 ± 3.7 years) and 13 children (five girls) (mean age: 6.59 ± 1.2 years).

Experimental design
Point-light animations depicting a front view of three different human actions (walking, jumping and waving) (BM) and scrambled versions of the same animations (SM) were used as stimuli. Animations were also masked by noise dots representative of biological motion in snow (BM_s) and equivalent scrambled motion (SM_s). The interstimulus interval was randomized between 1 and 13 s and showed a fixation cross. The number of pictures varied between 36 and 76 depending on the depicted motion, but presentation time was, at 4 s, the same for all stimuli. Biological motion sequences were taken from standardized point-light pictures applying 15 white point-light dots presented on a black background [17]. Scrambled point-light images were created using a customized Matlab script (The MathWorks, Natick, Massachusetts, USA) by permuting and randomly shifting the starting position of the point lights. Trajectories were kept intact, except that each point-light trajectory was randomly rotated in 90° increments and/or mirrored. Rotation and reflectance of dots by scrambling additionally disrupts local form information that may remain after spatial scrambling. Starting positions were chosen within a region so that the total area encompassed by the figure was similar to that of the biological motion figures. Noise versions of biological and scrambled motion (BM_s, SM_s) were created by adding 33 randomly distributed dots of the same size as biological and scrambled motion (BM_s, SM_s) were created that of the biological motion figures. Noise versions of biological and scrambled motion (BM, SM, BM_s, SM_s) were obtained in each participant in a general linear model while in a general linear model using a temporal high-pass filter (cut-off 128 s) and modelling temporal autocorrelation as an AR(1) process. Incorrect and missed responses were modelled as a covariate of no interest. We applied planned t-tests in a second level random effect analysis for the contrast biological motion greater than scrambled motion (irrespective of noise): BM_all (BM + BM_s) greater than SM_all (SM + SM_s). For within-group and between-group comparison (adults > children, children > adults) a threshold level of P value of less than 0.001 (k ≥ 5, two-tailed, uncorrected) was applied to report significant voxels.

Results

Functional MRI acquisition and analysis
All participants underwent a short behavioural practice session before the brain imaging session to assure that task instructions were understood and biological motion could be discriminated from scrambled motion. To present the stimuli an MR-compatible video goggle (MRI Audio/Video System, Resonance Technology, Inc., Northridge, USA) was used. Participants indicated their decision on a response box (Lumina LP-400, Cedrus Cooperation, San Pedro, USA).

All scans were collected on a 3.0 T General Electric MR-scanner (General Electric, Milwaukee, Wisconsin, USA). To estimate blood oxygen level-dependent contrast gradient echo echo-planar imaging (EPI) scans were acquired. The scans were aligned to the anterior and posterior commissure (flip angle = 50°, field of view = 22 cm, matrix = 64 × 64, slice thickness = 2.7 mm, repetition time = 2500 ms, echo time = 32 ms, 246 repetitions, 32 slices). A three-dimensional T1-weighted anatomical scan (FOV = 230 × 198 × 158 mm, matrix = 224 × 192 × 132; TR = 8.6 ms; TE = 2.1 ms) of the whole brain was acquired. The two initial EPI scans were discarded to allow for T1 saturation effects. Using SPM2 (Wellcome Department of Cognitive Neurology, University College London Medical School, London, UK; www.fil.ion.ucl.ac.uk/spm/) functional images were realigned and unwarped to correct for motion artefacts. Following recent studies that have tested the possibility of generalizing results across age for adults and 6 and 7-year-old children we transferred the functional and anatomical data of adults and children into a common stereotactic space [14,18]. To this end, individual T1-weighted anatomical images were taken for coregistration with the functional images. T1-weighted anatomical images were segmented and the normalization parameters were estimated by warping grey matter images to a standard grey matter template based in Montreal Neurological Institute space. Both EPI (to 3 mm³ voxels) and T1-weighted (to 1 mm³) images were resampled after deformation with the normalization parameters. EPI images were then spatially smoothed using a 9-mm full-width-at-half maximum Gaussian kernel. Neural activity was modelled by a stick function to each stimulus presentation in each category convolved with a canonical haemodynamic response function and its temporal derivative. Parameter images for the four covariates of biological motion, scrambled motion and their noise versions (BM, SM, BM_s, SM_s) were obtained in each participant in a general linear model while in a general linear model using a temporal high-pass filter (cut-off 128 s) and modelling temporal autocorrelation as an AR(1) process. Incorrect and missed responses were modelled as a covariate of no interest. We applied planned t-tests in a second level random effect analysis for the contrast biological motion greater than scrambled motion (irrespective of noise): BM_all (BM + BM_s) greater than SM_all (SM + SM_s). For within- group and between-group comparison (adults > children, children > adults) a threshold level of P value of less than 0.001 (k ≥ 5, two-tailed, uncorrected) was applied to report significant voxels.

Behavioural data
A mixed effect repeated measures analysis of variance on reaction times and accuracy rates with within-subject factor condition biological motion and noise revealed no significant main effect or interaction of noise [accuracy: F(1,29) = 1.27; P = 0.27; reaction time: F(1,29) = 0.64; P = 0.43]. Therefore, noise conditions were collapsed in all subsequent analyses (BM_all / SM_all). Reaction time analyses revealed a significant effect of condition [F(1,29) = 50.96; P < 0.001] with shorter reaction times for BM_all than for SM_all in both groups and a trend towards interaction of condition and group [F(1,29) = 2.96; P < 0.1]. The difference between the reaction times in BM_all and SM_all tended to be larger in adults (mean BM_all = 808.07 ms; SD = 142.75; mean SM_all = 1036.68 ms; SD = 249.15) than in children (mean BM_all = 1364.02 ms; SD = 220; mean SM_all = 1503.87 ms; SD = 249.15). A significant main effect of the factor group [F(1,29) = 57.36; P = 0.001] was also observed, indicating faster reaction times across all conditions for adults than for children. A significant main effect of the factor condition on accuracy [F(1,29) = 7.38; P = 0.01] indicated that both groups
made more mistakes in SM_all than BM_all. In addition, children made significantly \( F(1,29) = 23.33; P < 0.001 \) more mistakes (mean=90.38%; SD=1.43) than adults (mean=86.45%; SD=0.50). No other main effect or interaction reached significance.

**Functional MRI results**

Brain regions showing significant responses to biological motion (BM_all > SM_all) are listed separately in Table 1 for within-group and between-group comparisons.

When biological and scrambled motion responses (BM_all > SM_all) were compared in adults, enhanced neural activity was found in the right anterior cingulate gyrus, pSTS, supramarginal gyrus and cuneus (Table 1; Fig. 1). In children, we found enhanced activation patterns in right fusiform gyrus and left middle temporal gyrus (hMT +) for the same comparison. Group comparison revealed increased activation in adults compared with children in right pSTS. Contrast (children > adults) revealed a significant difference in right nucleus caudatus and right fusiform gyrus.

To test whether task difficulty confounded group differences, we separated both groups into good (AD_g, CH_g) and bad performers (AD_b, CH_b), on the basis of the median in accuracy rate. A post-hoc one-way analysis of variance of the four groups was then performed for the contrast BM_all greater than SM_all. The main effects and interactions of performance and age were masked by group comparison (AD_g + AD_b > CH_g + CH_b). A liberal statistical threshold \( P < 0.05 \), uncorrected) was used to prove significance. This analysis revealed an interaction of age and performance in the right fusiform gyrus \( x = 39, y = -51, z = -12; Z = 2.21; P < 0.014 \). This interaction indicated that only in poorly performing children the right fusiform gyrus was activated \( Z = 4.64, P < 0.001 \), but not in well-performing children, or in any adult \( (P > 0.05) \). No main effect of performance or other significant interaction with performance was found in the right pSTS or any other area.

**Discussion**

The aim of this study was to investigate the neural development of biological motion perception in preschool and school-age children and to clarify the extent to which successful processing (i.e. perception) of biological motion depends on the development of dorsal stream functioning. In accordance with earlier studies we found that biological motion perception in adults [5–7] elicited task-specific activity in right pSTS – the area most closely associated with biological motion perception, and a pivotal point of the dorsal and ventral stream. Moreover, activation clusters

![Activation maps for the contrast biological motion (BM_all) greater than scrambled motion (SM_all) are thresholded at a voxelwise uncorrected \( P \) value of less than 0.001 (two-tailed) and a spatial extent of five contiguous voxels. The maps are shown superimposed onto selected coronal/sagittal/axial slices of a canonical T1 template provided by SPM2. The anterior-posterior level is based on Montreal Neurological Institute coordinates.](image)

**Table 1** Cerebral region with corresponding Brodman area (BA), Z values and MNI coordinates for peaks

<table>
<thead>
<tr>
<th>Region</th>
<th>k</th>
<th>Side</th>
<th>MNI coordinates (x, y, z)</th>
<th>SPM (Z)</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Biological motion &gt; scrambled motion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pSTS</td>
<td>156</td>
<td>R</td>
<td>3</td>
<td>39</td>
<td>3.82</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>19</td>
<td>R</td>
<td>63</td>
<td>18</td>
<td>3.44</td>
</tr>
<tr>
<td>Cuneus</td>
<td>21</td>
<td>R</td>
<td>45</td>
<td>30</td>
<td>3.42</td>
</tr>
<tr>
<td>children</td>
<td></td>
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</tr>
<tr>
<td>Biological motion &gt; scrambled motion</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Fusiform gyrus</td>
<td>14</td>
<td>R</td>
<td>24</td>
<td>3</td>
<td>3.39</td>
</tr>
<tr>
<td>hMT</td>
<td></td>
<td></td>
<td>3</td>
<td>37</td>
<td>3.78</td>
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<tr>
<td>Adults &gt; children</td>
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<td>pSTS</td>
<td>27</td>
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<td>Children</td>
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<tr>
<td>Biological motion &gt; scrambled motion</td>
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</tr>
<tr>
<td>Nucleus caudatus</td>
<td>15</td>
<td>R</td>
<td>12</td>
<td>-6</td>
<td>3.58</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>9</td>
<td>R</td>
<td>42</td>
<td>-12</td>
<td>3.34</td>
</tr>
</tbody>
</table>

All significant voxels are reported at a threshold of \( P \) value < 0.001 uncorrected. For the contrast biological motion greater than scrambled motion stimulus conditions with and without noise were collapsed.

hMT, human middle temporal lobe; k, cluster size; L, left; MNI, Montreal Neurological Institute; pSTS, posterior superior temporal sulcus; R, right.
were detected in right anterior cingulate gyrus, supramarginal gyrus, and cuneus. Compared with children, we found enhanced biological motion-related activity in right pSTS in adults. During biological motion perception children exhibited increased activity in right fusiform gyrus and left hMT+. In comparison with adults, however, children induced greater activation in right fusiform gyrus and Cuneus nucleus. These findings suggest that perception of biological motion may activate the dorsal stream and pSTS in adult participants, whereas in children ventral regions are recruited for processing biological motion. In addition, we found that effortful performance might contribute to activity in right fusiform gyrus because only poorly performing children showed increased activity in this area. In contrast, performance level seems not to affect activity within pSTS. The data, therefore, provide evidence for a more protracted development of task-specific functioning of the dorsal system.

A possible explanation might be that the dorsal pathway hosts more complex functions than the ventral pathway. Functions within the dorsal stream seem to rely on life-long learning (plasticity) whereas in the ventral stream they might be more constant. For instance, during biological motion perception, dorsal stream areas have to integrate information from sensory systems with proprioceptive feedback to generate ‘body-centred’ representations for action. As the child’s body is developing physically, important factors such as length and weight of limbs continue to change. Thus, it may be more important to retain plasticity in the dorsal than in the ventral stream ([19]).

These findings differ in part from earlier studies. For example, our results do not agree with the behavioural findings of Freire et al. [4], who reported differences in biological motion recognition when distractors of different numbers of dots were used. This study used a fixed and relatively small number of random noise dots. This might explain why no behavioural differences between biological motion with and without noise could be detected. Furthermore, it is difficult to compare our results with earlier imaging studies with children as no study made a direct comparison between children and adults [10,11]. Mosconi et al. [11] used a gaze perception task and found pSTS activity in children. Carter et al. [10] reported that age in 7 to 10-year-old children correlated with pSTS activity during biological motion perception. Our data are in line with the latter findings and show no significant activity in the pSTS related to biological motion perception in children that were about 2–3 years younger. Furthermore, both studies were ambiguous as to whether differences in performance level affected brain activity in this area. Here we could show that this result was independent of performance level. In addition, we were able to show that biological motion-related brain activity in the right fusiform gyrus was sensitive to performance, as, only poorly performing children showed activity in this area. Our results are in line with findings that maturation occurs well into childhood and even adolescence [14,15]. The former study showed that neural activity within dorsal regions of the occipital and parietal lobule was not mature at the age of 6 years [14]. We also agree with results indicating that ventral regions are engaged more in 6-year-old children during effortful high-order visual perception [14]. Our findings provide additional support for the hypothesis that functional development of the dorsal stream is not yet complete at the age of 6 years. They further agree with behavioural reports that children do not reach adult levels in tasks depending on dorsal stream functioning before the age of 7–8 years [20].

Conclusion
Taken together, these findings show that in preschool and school-age children biological motion perception engages ventral areas only when performance is poor, whereas the classical network for biological motion processing in the dorsal stream and pSTS is recruited later during development, independently of performance. Therefore, we conclude that the functional segregation into dorsal and ventral stream is still immature at the age of 6 years.

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Interactions between memory and visual system
Top-down modulation of memory and visual system
Vestibular modulation of memory
Neuroendocrine modulation of memory
Dorsal and ventral neural pathways
Visual semantics and language
Neural development of memory and visual system
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3 Peer-reviewed review articles
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More than 30 poster contributions on national or international conferences

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Cognitive Neuroscience Society

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Guest Lecture at the University of Lausanne „Seminar Cognitive Neuroscience“

March 2006
Invited talk at the University of Zurich „Brainfair“

October 2006
Invited talk at the Regional Teachers conference „Schools at the Mutschellen“, Mutschellen

June 2004
Invited talk at the Annual meeting of the Organization of Human Brain Mapping, Budapest

September 2007
Invited talk at the 10th Congress of the Swiss Society of Psychology, Zurich
“Neural mechanisms of memory: the role of sensory and conceptual information on memory”

February 2009
Guest Lecture at the University Children’s Hospital Zurich “Development of vision in preterm born adolescents“

February 2009
Guest Lecture at the Morning teaching course at the University Children’s Hospital Zurich “What do functional brain images mean?”
June 2009
Invited talk at the Swiss Joint Face Lab Meeting (Bern) “Oxytocin in face recognition”

September 2009
Invited talk at the European Science Foundation (ESF) Conference on “Gene expression to neurobiology and behavior: human brain development and developmental disorders”

September 2009
Invited talk at the 10th International Conference of the European Society of Magnetic Resonance in Neuropediatrics (ESMRN)

Grants
April 1996 – March 1999
German Science Foundation (DFG) scholarship for the Graduateschool “Biological foundations of neural diseases” at the Otto-von-Guericke University Magdeburg

October 2007 – September 2008
Hartmann-Müller Foundation (Project 1165) „Visual perception in very low birth weight children: relating fMRI to neurodevelopmental profiles“, acknowledged to Dr. rer. nat. Peter Klaver and Dr. med. Bea Latal (1.4.2007-31.3.2008: 46’230 SFrs).

October 2009 – September 2012
Research grant application for Swiss National Science Foundation (Project CR1311_127115) “Common neural mechanisms of working memory and episodic memory in typical and atypical development”, main applicant Dr. Peter Klaver, Co-applicants: PD Dr. Bea Latal, and Prof. Dr. Ernst Martin. (1.10.2009-31.9.2012: 318’296 SFrs.)

September 2009 (submitted)
Research grant application for the Zurich Neuroscience Center (ZNZ): “The effect of oxytocin on social memory of adolescents with post-traumatic stress disorder after sexual abuse”, main applicant Dr. Peter Klaver, Co-applicants: PD Dr. Markus Landolt, Prof. Dr. Ernst Martin
PUBLICATION LIST - Original articles


**PUBLICATION LIST- Review articles**


**PUBLICATION LIST- Submitted manuscripts for peer reviewed journals**


**PUBLICATION LIST- Book chapters and published abstracts**


Scholar activities and teaching

**Lecturer**

*Since September 2006, each semester*
Institute of Psychology, University of Zurich, PF 2478 T “Neuropsychologische Untersuchungsmethoden”

*Since January 2006, every week*
Children’s University Hospital Zurich, University of Zurich, MF 1036 “Research seminar on developmental neuropsychology and brain mapping”

*Since February 2007, each semester*
Department of Child and Adolescent Psychiatry, MF 779 “EEG-Fields and brain function”

*Since April 2008, each semester*
Zurich University of Applied Science, Department of Special Education, Certificate course „Neurosciences and Therapeutic Pedagogy”

**Regular workshops and seminars**

*April 2000 – December 2004, each semester*
Neuroimaging for medical students at the University of Bonn

*March 2005 – December 2005, every week*
Journal club for cognitive neuroscience at the University of Zurich

*Since January 2007, every year*
Neuroimaging for psychology students at the University of Zurich (Organization Prof. U. Ehlert)

*Since January 2006, three times per year*
Brain science for scholars from the canton of Zurich

**Other**

*January 2009*
Workshop and seminar “Active learning and memory” at the Institute of Applied Psychology, Zurich

*1994, one week*
Practical course experimental methods in psychology at the University of Groningen (Organization Prof. G. Mulder)

*Summer-Autumn 1993 every week*
Private teacher in polish language for advance conversation

**Supervisor of Master of Science, Ph.D. and M.D. theses**

Master students in Psychology (“Lizentiatssarbeit”): Ms. S. Poltéra, Ms. C. Zimmermann, Ms. E. Miramontes, Mr. S. Lang on HMS project 1165.

PhD student Dr. phil. S. van der Mark “Mapping functional connectivity in dyslexic and normal reading children” (cooperation with Prof. D. Brandeis, Prof. E. Martin)
PhD student Dr. des. S. Rotzer “Structural and functional brain anatomy in children with developmental dyscalculia: What counts?” (cooperation with Prof. M. von Aster, Prof. E. Martin)

PhD student Dr. des. M. Dosch “Neural development of social cognition” (cooperation with Prof. E. Martin)

PhD student Dr. phil. J. Lichtensteiger “Development of dorsal stream functioning in biological and structure-from-motion perception in 5-7 year old children” (cooperation with Prof. E. Martin)

MD student Dr. med. M Schnaidt „Top-down control of priming by visual attention: a functional magnetic resonance imaging study“ (cooperation with Prof. G. Fernández)