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Abstract

Developmental dyslexia is a specific disorder of reading acquisition characterized by a phonological core deficit. Sentence reading is also impaired in dyslexic readers, but whether semantic processing deficits contribute is unclear. Combining spatially and temporally sensitive neuroimaging techniques to focus on semantic processing can provide a more comprehensive characterization of sentence reading in dyslexia. We recorded brain activity from 52 children (16 with dyslexia, 31 controls) with functional magnetic resonance imaging (fMRI) and event-related potentials (ERP) in two separate counterbalanced sessions. The children silently read and occasionally judged simple sentences with semantically congruous or incongruous endings. fMRI and ERP activation during sentence reading and semantic processing was analyzed across all children and also by comparing children with dyslexia to controls. For sentence reading, we analyzed the response to all words in a sentence; for semantic processing, we contrasted responses to incongruous and congruous endings. Sentence reading was characterized by activation in a left-lateralized language network. Semantic processing was characterized by activation in left-hemispheric regions of the inferior frontal and superior temporal cortex and by an electrophysiological N400 effect after 240 ms with consistent left anterior source localization. Children with dyslexia showed decreased activation for sentence reading in inferior parietal and frontal regions, and for semantic processing in inferior parietal regions, and during the N400 effect. Together, this suggests that semantic impairment during sentence reading reduces dyslexic children's response in left anterior brain regions underlying the more phasic N400 effect and subsequently modulates the more sustained BOLD response in left inferior parietal regions.
Impaired semantic processing during sentence reading in children with dyslexia: combined fMRI and ERP evidence

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Abstract

Developmental dyslexia is a specific disorder of reading acquisition characterised by a phonological core deficit. Sentence reading is also impaired in dyslexic readers, but whether semantic processing deficits contribute is unclear. Combining spatially and temporally sensitive neuroimaging techniques to focus on semantic processing can provide a more comprehensive characterization of sentence reading in dyslexia.

We recorded brain activity from 52 children (16 with dyslexia, 31 controls) with functional magnetic resonance imaging (fMRI) and event-related potentials (ERP) in two separate counterbalanced sessions. The children silently read and occasionally judged simple sentences with semantically congruous or incongruous endings.

fMRI and ERP activation during sentence reading and semantic processing was analyzed across all children, and also by comparing children with dyslexia to controls. For sentence reading we analyzed the response to all words in a sentence, for semantic processing we contrasted responses to incongruous and congruous endings.

Sentence reading was characterized by activation in a left-lateralised language network. Semantic processing was characterized by activation in left-hemispheric regions of the inferior frontal and superior temporal cortex, and by an electrophysiological N400 effect after 240ms with consistent left anterior source localization.

Children with dyslexia showed decreased activation for sentence reading in inferior parietal and frontal regions, and for semantic processing in inferior parietal regions, and during the N400 effect.

Together, this suggests that semantic impairment during sentence reading reduces dyslexic children’s response in left anterior brain regions underlying the more phasic N400 effect and subsequently modulates the more sustained BOLD response in left inferior parietal regions.
Introduction

Developmental dyslexia is a specific disorder of reading acquisition with a high prevalence and a marked familial risk. There is a general approval that dyslexia is characterised by a phonological core deficit (Ramus, 2001, 2004).

Neuroimaging studies on the neural basis of dyslexia consistently reveal reduced activation in response to words or word-like stimuli within posterior parts of the reading network in the brain of adults and older children with reading disability (Brambati et al., 2006; Brunswick et al., 1999; Rumsey et al., 1997; Shaywitz et al., 2002; Shaywitz et al., 1998; Temple et al., 2001). Reduced activation in superior temporal and inferior parietal regions has been linked to the phonological core deficit in dyslexia, while reduced activation in inferior occipitotemporal regions suggests deficits in specialised visual word processing (McCandliss et al., 2003). In addition, increased frontal activation in older dyslexic readers suggests the development of compensatory neural mechanisms (Georgiewa et al., 2002; Shaywitz et al., 1998).

Most of these neuroimaging results have focused on deviant processing of isolated word-like stimuli. While this approach has successfully identified regions associated with the phonological deficit, it may not represent a sufficiently natural reading situation, in which semantic expectations based on context can facilitate word processing (DeLong et al., 2005). It remains unclear, whether such lower-level deficits also dominate during sentence reading, and how they affect higher order language processing.

Recent studies have thus started to investigate how brain processes during sentence reading are affected by dyslexia in children (Meyler et al., 2007) and adolescents (Kronbichler et al., 2006). Increased activation in left middle temporal regions was associated with better reading in 3rd and 5th grade children (Meyler et al., 2007), and also in adolescents (Kronbichler et al., 2006). In contrast to this age-independent effect activation in the left inferior parietal cortex was associated with better reading ability, but more in 5th graders than in 3rd graders, suggesting a developmental influence (Meyler et al., 2007). Consistent with this result a similar inferior parietal region was more strongly activated in adolescent fluent readers than in dyslexics (Kronbichler et al., 2006). Moreover, whereas in the children there was no region showing more activation with lower reading ability, in adolescents left inferior frontal regions were more strongly activated in dyslexics than in controls, suggesting that...
frontal compensatory mechanisms in dyslexia may develop over time (Georgiewa et al., 2002; Shaywitz et al., 1998). In addition, a region of interest analysis for the inferior occipito-temporal cortex revealed reduced activation in the visual word form area in adolescent dyslexics (Kronbichler et al., 2006).

While these studies show that neural processing in more natural reading situation is also impaired in dyslexia, they do not inform us whether this neural impairment specifically reflects semantic processing, as sentence reading encompasses not only semantic processing, but also additional, more basic word recognition processes typically preceding semantic elaboration, such as visual word recognition and phonological processing.

To isolate semantic effects during sentence reading with ERPs (Brandeis et al., 1995; Kutas and Hillyard, 1980), one typically contrasts sentence endings that are incongruous (unprimed) and congruous (primed) in the sentence context. The time-sensitivity of the ERP method reveals that incongruous sentence endings are processed differently from congruous endings and elicit a response which is more negative at parietal sites and more positive at anterior temporal sites while peaking at around 400 ms (Brandeis et al., 1995; Kutas and Hillyard, 1980). This ERP difference (i.e. incongruous minus congruous) around 400 ms is called the N400-effect (Brandeis et al., 1995).

A few ERP and MEG studies also investigated how dyslexic participants differ from controls during sentence reading. Brandeis et al. (1994) reported that 12-year-old children with dyslexia differed from controls during sentence reading especially for sentences with incongruous endings. An early segment of the N400 component differed in topography between dyslexics and controls, and was parietocentrally less negative for incorrect endings in dyslexics. Additionally, a late segment of the N400 was delayed in dyslexic children. Delayed and attenuated N400 incongruency effects were also reported in dyslexic adults in an MEG study (Helenius et al., 1999), whereas in another study with ERPs, the N400 incongruency effects were similar in adult dyslexics and controls, although the N400 itself was larger in dyslexics with slow presentation (Robichon et al., 2002). The semantic processing impairment seems to change with both development and modality, as younger children with dyslexia and language impairment tended to show even increased N400 incongruency effect during sentence reading (Neville et al., 1993).
Taken together the results of these ERP studies suggest that semantic processing during sentence reading may differ between disabled readers and controls from an early age on at around 400 ms, but they leave open which brain regions are involved. To address these questions, children with dyslexia were asked to read sentences with congruous and incongruous endings while we recorded their brain responses with fMRI and ERP techniques and compared them to a matched control group. This allowed us to characterise spatio-temporal aspects of their neural processing deficits during sentence reading, and especially during semantic processing.

We hypothesised that semantic effects during sentence processing would affect dyslexic children differently from controls indicated by reduced differences between incongruous and congruous sentence endings in posterior brain regions and around 400 ms. Semantic processes were defined as differential processing of incongruous and congruous endings, as opposed to basic word processing common to all words.

**Materials and Methods**

**Subjects:**
The 52 children (mean age 11.5 years) who participated were grouped according to their reading scores (see Table 1): 16 children with dyslexia, 31 control children, and 5 children falling between the categories for dyslexic and normal reading. 44 children were part of a longitudinal study (Maurer et al., 2007; Maurer et al., 2003), 8 children participated only in 5th grade.
The children were screened for a history of neurological diseases or psychiatric disorders, and reported all normal or corrected-to-normal vision. Children from families with a foreign language background (i.e. both parents’ first language was not (Swiss-) German) were excluded from the study.

All children participated in two counterbalanced sessions with EEG and fMRI recordings, except for 14 children (4 with dyslexia, 9 controls, 1 from the between-category) who could not participate in the MR session because of dental braces. In addition, one control child was excluded from fMRI analysis, because of excessive movement artefacts (> ±1.8mm in each direction or > ±2° in each rotation axis). In 8 children (3 with dyslexia, 3 controls, 2 from the between-category) the movement artifacts were in the acceptable range, after the experiment was run in an additional fMRI session. For the ERP data 2 children from the control group had to repeat the experiment because of technical problems. The main analyses run without these
children replicated the results for the full group and are thus not reported. Children and their parents gave informed consent, and were compensated with a book voucher of 60 CHF for their participation.

Reading skills in 5th grade were assessed with a reading fluency measure, which is the core criterion to diagnose dyslexia in readers of the regular German orthography (Wimmer et al., 2000). To this end we used the “Ein-Minuten Leseflüssigkeitstest” (Landerl, personal communication), which requires the children to read from a list as many words as possible within 1 minute without making mistakes. The resulting “correct words per minute” score was compared to the distribution in a normative group of 56 children. These additional children were recruited from 5 different school classes reflecting the origin of the children in the ERP/fMRI study (2 from neighbourhoods in Zurich with higher socio-economic background, 2 from neighbourhoods in Zurich with lower socio-economic background, 1 from a rural area outside of Zurich), and were not further selected except for foreign language background (the same criterion as in the ERP/fMRI study), and for continuous schooling in German.

The reading scores in this normative group ranged from 42 to 138 correct words per minute with a mean value of 89, a median of 90, and a standard deviation of 18. The lack of prominent skewness (-0.38, SE = 0.32) and kurtosis (0.69; SE = 0.63), allowed for simple standardization.

Children from the ERP/fMRI study were classified as dyslexic if their “correct words per minute score” was below 10% of the norms (<61.6), and as controls if their score was equal or above 20% (≥75.0). The children with intermediate scores were excluded from the dyslexic-control group comparisons but included in the correlation analyses.

The result corresponded well with the classification based on a published reading test (Landerl et al., 1997) that most children from the longitudinal subsample had taken in 3rd grade. Accordingly, 13 (86.7%) of 15 dyslexic children in 5th grade, had been classified as dyslexic in 3rd grade, and the others as belonging to the intermediate category. No dyslexic 5th grader had been classified as a normal reader in 3rd grade. Similarly 22 (91.7%) of the 24 control children in 5th grade had been classified as normal readers, 2 as intermediate readers, but none as dyslexic in 3rd grade.
Nonverbal and verbal intelligence was assessed in 5th grade using the block design and the similarities subtest of the HAWIK-III intelligence test (Tewes et al., 2000).

As can be seen in Table 1, the children with dyslexia were not only slower in word reading (the criterion for grouping), but also in pseudoword reading. In contrast the groups did not differ in their estimated IQ (neither nonverbal nor verbal), and the small age difference (<2.5 months) also missed significance.

**Task**

Identical sentence reading tasks with semantically congruous and incongruous endings were used with EEG and fMRI. Some adaptation of the original (Brandeis et al., 1994) was necessary to allow also presentation in fMRI. From the original pool of sentences we chose 112 simple sentences with semantically congruous (50%) or incongruous (50%) endings (“The sky is blue / fat”) and added 20% null events for event-related fMRI modelling. The congruous sentences contained 48 colour word endings and 8 non colour word endings. The incongruous sentences ended with 48 non colour words and with 8 colour words. The children were asked to read the sentences silently, and to press a mouse button with the index or the middle finger of the right hand only occasionally, i.e. if the question ‘Yes – No?’ appeared after a sentence prompting their judgement on whether the previous sentence had been meaningful or not. While 32 sentences required an explicit judgement (28.6%; 8 from each category), 40 sentences with congruous colour endings and 40 sentences with incongruous non colour endings were not followed by a motor response and were used for the ERP and fMRI analyses.

In contrast to two earlier fMRI studies on sentence reading in dyslexia (Kronbichler et al., 2006; Meyler et al., 2007), we presented the words sequentially to allow for better modelling of the semantic priming effect to sentence endings with both event-related fMRI and ERPs. Each word in a sentence was presented in the centre of the screen for 280 ms with an SOA of 570 ms. For the sentences requiring a (delayed) response, an additional ‘Yes – No?’ screen was presented following the offset of the final word after 1080 ms. The sentence SOA (for all sentences) and the duration of the null events were 4700 ms. Congruous sentences, incongruous sentences and null events occurred in a pseudo randomised order for 14 min. The assignment of the
response buttons to the semantic judgment was counterbalanced across subjects. Both the fMRI and the ERP session included further tasks presented in a pseudorandomised order.

**fMRI recording and analysis**

Whole brain functional imaging data were acquired in the Children's Hospital Zurich on a 3T (GE medical systems) scanner using T2*-sensitive ultrafast multi-slice echo planar imaging (EPI) sequences sensitive to blood oxygenation level dependent (BOLD) contrast. The task was projected using MR compatible video goggles. The entire scanning session included 3 additional tasks and lasted about 2 hours. Children took a break (or more than one if necessary) during the scanning session between the tasks. In an event-related design we recorded 566 volumes (25 axial slices of 4.6 mm with 0.4 mm gap between slices, TR = 1499 ms, TE = 40 ms, slice resolution = 3.75 mm x 3.75 mm, 64 x 64 pixel matrix, flip angle 50°). The first 5 volumes were rejected to exclude T1 saturation effects. T1-weighted structural images were acquired using a standard 3-dimensional (3D) T1-weighted gradient echo sequence (172 slices, TR = 9.34 ms, TE = 2.1 ms, flip angle = 20°, voxel size = 1 x 1 x 1) to obtain a structural 3D volume. Particular care was taken to stabilise the children using a vacuum cushion, custom made padding and fixations. As a result, the head movements were below 2° in all rotation axes and below 50% of the voxel size in each direction for all children except for one child who was excluded. To reduce noise subjects were also provided with earplugs. Image processing and statistical analyses were carried out using SPM5 (Wellcome Department of Cognitive Neurology, London, http://www.fil.ion.ucl.ac.uk/spm). We were using the standard preprocessing steps including slice-scan-time correction, movement correction, normalisation to the Montreal Neurological Institute (MNI) template, and smoothing with a Gaussian kernel of 9 mm. For statistical analysis the data were high pass filtered with a cut-off of 128 s. In one event-related first level analysis we computed the sentence reading activations of any child. To model the design we used the onset of the first word of every sentence with the duration of 2.25s (1.5 scans) in fMRI statistics. The sentences which required a response were modelled separately but excluded from further statistical analysis.
In a second event-related first level analysis we focussed on the semantic incongruency effect comparing incongruous and congruous sentence endings. The first 3 words of each sentence, the null events and the response screens were all not modelled and served as an extended baseline to detect the percentage of signal change for the sentence ending. The onset of the final word in each sentence served as a single event and was convolved with the SPM5-implemented hemodynamic response function. Incongruous (n=40) and congruous (n=40) sentence endings which did not require a response were modelled separately as regressors of interest. Sentence endings which required a response were modelled separately but excluded from further statistical analysis.

For both group analysis designs we conducted the SPM5 implemented standard whole brain second level random effects analysis. We computed one-sample t-tests to reveal the entire group activations for sentence reading, the group’s additional activations while processing incongruous sentence endings compared to congruous sentence endings (incongruency effect) as well as the opposite contrast between congruous and incongruous sentence endings (congruency effect).

To detect the effect of dyslexia we computed group comparisons with two sample t-tests between dyslexic and control children for sentence reading versus fixation baseline as well as for the incongruency effect.

We further used a correlation approach to investigate effects of reading skills on semantic processing (Meyler et al., 2007). The “correct word per minute” score was added as a covariate in the second level analysis using the single subject contrast images provided by the SPM5 first level analysis of individual data.

The effects of dyslexia were analysed in more details with a region of interest (ROI) analysis on unsmoothed data to explain the incongruency effects of the voxel based analysis. MarsBar software (version 0.41; Brett et al., 2002) was used to extract the regions mean signal change in percent. The ROIs were defined by local maxima of the voxel based between-group comparisons (p<0.001, uncorrected). If not reported otherwise, the ROIs had a radius of 9mm, and are reported in Talairach coordinates.
We computed further ROIs based on the literature: A spherical ROI was located in the left fusiform gyrus centred at $-43/-54/-12$ ($r=5\text{mm}$) corresponding to the VWFA (Cohen et al., 2000; McCandliss et al., 2003). Additional spherical ROIs were located in the left middle temporal gyrus centred at $-65/-52/6$ (Meyler et al., 2007) and at $-57/-60/3$ (Kronbichler et al., 2006). These regions are known to be less activated in dyslexics during sentence reading (Kronbichler et al., 2006; Meyler et al., 2007), and generally during visual word processing (McCandliss and Noble, 2003).

**ERP recording and analysis:**

The EEG was recorded at the Department of Child and Adolescent Psychiatry, University of Zurich, using Synamps-1 (Compumedics Neuroscan, Charlotte, USA) amplifiers and an electrode cap (FMS, Munich, Germany). The children were seated in an electrically shielded, sound proof and air-conditioned room in front of a computer screen 1.2m away. The entire ERP session lasted about 3 hours.

The electrode montage included 65 electrodes consisting of all 10-20 system electrodes and the additional electrodes Fpz, FCz, CPz, POz, Oz, Iz, AF1/2, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5, TP7/8/9/10, P5/6, PO1/2/9/10, O1/2 plus two electrodes below the outer canthus of each eye. The electrodes O1/2 and Fp1/2 were placed 5% more laterally for more even coverage indicated by an apostrophe in the label (e.g. O1').

The EEG was referenced to the Fz electrode, sampled at 500 Hz/channel, bandpass-filtered between 0.1 and 70 Hz and calibrated to technical zero baseline. The impedance was kept below 20 kΩ (Ferree et al., 2000).

The ERPs were processed in Vision Analyzer software (Brain Products GmbH) including downsampling to 256 Hz, digitally low pass filtering with a 30 Hz filter, correcting for horizontal and vertical eye movements using and independent component analysis (Jung et al., 2000) and transforming to the average reference (Lehmann et al., 1980). Trials with artefacts exceeding ±100 µV in any channel (2 children ±120 µV) were automatically rejected. Before averaging the remaining trials were epoched 125 ms prior and 1125 ms following the stimulus.

ERPs were computed for 3 conditions from sentences that did not require a response: all words irrespective of position in a sentence, congruous sentence endings, and incongruous sentence endings. Difference waves were computed by subtracting the congruous ERP from the incongruous ERP.
The mean number of averaged sweeps was 397 (SD: ±47, range: 276-448) for the ERP in response to all words, and 36 each for the ERPs in response to incongruous (SD: ±4, range: 26-40) and congruous endings (SD: ±4, range: 22-40). Six children (2 with dyslexia, 4 controls) had an average number of less than 30, but visual inspection of their corresponding ERPs revealed no anomalies.

Grand averages were computed from the condition including all words and from the incongruous minus congruous difference wave.

For further analyses, time windows reflecting basic visual word processing and time windows reflecting semantic processing were selected based on the data of all 52 children. Time windows reflecting basic visual word processing were selected using adaptive segmentation according to maxima and minima in Global Field Power of the grand mean of the ERP in response to all words (see Maurer et al., 2005a; Maurer et al., 2005b; Maurer et al., 2006).

Time windows reflecting semantic processing were selected using Topographic Analysis of Variance (TANOVA) on raw ERP data (Maurer et al., 2003; Strik et al., 1998) indicating when congruent and incongruent sentence endings were processed differently (p<0.01).

In addition a hierarchical clustering algorithm (using the Cartool software by Denis Brunet: http://brainmapping.unige.ch/Cartool.htm) was applied to these time windows in order to test whether they could be further subdivided in microstates with constant ERP map topographies. Map clusters that correlated highly (>92%) were treated as one microstate.

An ERP mapping approach was used to analyse group differences between dyslexic children and controls. Mean microstate maps were computed at the individual level for ERPs averaged over all words (sentence reading) and for the ERP difference between incongruous and congruous endings (semantic processing). For each of the microstates we analysed group differences in map strength (t-test on GFP), and in map topography (TANOVA bootstrapping statistics). We computed TANOVA for both raw maps and normalised maps. The 3 statistical tests are complementary: t-tests on GFP reveals differences in map strength independent of topography, TANOVA on normalised maps reveals differences in topography independent of map strength, and TANOVA on raw maps reveals amplitude differences with constant topographies. In addition we used statistical t-maps for the group comparisons in the figures to facilitate interpretation of the results.
In order to test for latency differences between dyslexic children and controls we applied a Topographic Component Recognition (TCR / Brandeis et al., 1992; Brem et al., 2005). TCR uses a template map to search for the topographically most similar map in each individual ERP. For each microstate the mean segment in the grand mean of the 52 children was taken as template. In order to avoid a topographical match with noise time points with high GFP (i.e. low noise) were favoured by adding 5% GFP to the correlation (Brem et al., 2005; Steger et al., 2000). The latencies of the time points with the highest correlations were chosen for the group comparisons (t-tests).

To reveal brain regions which contribute to the topographic maps we computed the sources with the distributed source solutions LORETA (low resolution electromagnetic tomography, Pascual-Marqui et al., 1994) and LAURA (local auto-regressive average model, Grave de Peralta Menendez et al., 2001) at the GFP peaks of the grand mean of the N400b (379ms) and the late positivity (973ms). This inverse solution is based on the SMAC transform (Spinelli et al., 2000) of a realistic head model which is made of an average brain of 152 MRIs (Montreal Neurological Institute, Montreal, Canada) as implemented in the CARTOOL software (http://brainmapping.unige.ch/Cartool.htm).

**Behavioural analysis**

As more children participated in the EEG than in the fMRI session, behavioural data were analysed separately for EEG and fMRI sessions, and also separately for accuracy and reaction time resulting in 4 multivariate ANOVAs for repeated measures with the within subject factor “incongruency” (incongruous vs. congruous) and the between subject factor “dyslexia” (dyslexic vs. control children). The incongruous condition was composed of responses to both incongruous colour and incongruous non-colour endings, the congruous condition of responses to both congruous colour and congruous non-colour endings.
Results

**Behavioural data**

The behavioural analyses revealed that control children responded faster and were more accurate than dyslexic children in both the EEG (accuracy: $F(1,45)= 10.8$, $p<0.01$; reaction time: $F(1,45)= 9.6$, $p<0.01$, Supplemental Material, Table 1) and the fMRI (accuracy: $F(1,32)= 18.6$, $p<0.001$; reaction time: $F(1,32)= 11.2$, $p<0.01$) sessions. In addition, the children responded faster to congruous than incongruous endings in both sessions (EEG: $F(1,45)= 4.3$, $p<0.05$; fMRI: $F(1,32)= 5.5$, $p<0.05$), and were more accurate for incongruous than for congruous endings, although this difference reached significance only in the fMRI session ($F(1,32)= 5.5$, $p<0.05$), but not in the EEG session ($F(1,45)= 2.2$, $p>0.1$). The dyslexia factor did not interact with the incongruency factor in any of the analyses (EEG: both $p>0.1$; fMRI: both $p>0.2$).

**fMRI results**

**Sentence reading**

*All children.* The whole group voxel-based fMRI analysis of sentence reading revealed a language network including large portions of the left frontal gyrus, the right inferior frontal gyrus, the left fusiform gyrus, the left middle occipital gyrus, the left superior parietal lobe, the left precuneus and the left middle temporal gyrus ($p < 0.05$, FWE corrected, Table 3, Figure 1A).

**Group contrast.** Dyslexic children showed less activation than normal reading control children in left hemispheric regions: the medial frontal gyrus, the superior frontal gyrus, the inferior parietal gyrus, the angular gyrus and the precuneus (2-sample t-test, $p < 0.001$ uncorrected, Table 3, Figure 1B). We found no activated region for the opposite contrast (2-sample t-test, $p < 0.001$ uncorrected).

**Reading speed covariate.** We also computed a voxel-based analysis with reading speed as a covariate including all 38 children which corroborated the results from the group comparison. We found an increased activation with increasing reading speed in the superior frontal gyrus, the anterior cingulate gyrus and the inferior parietal gyrus (Supplemental Material, Fig. 1A; $p < 0.001$ uncorr.; Supplemental Material, Table 2). We did not find any region negatively correlated with reading skills.
**ROI analyses.** Additional group comparisons (t-tests) were computed for ROIs based on the previously published effects of dyslexia during sentence reading (Kronbichler et al., 2006; McCandliss et al., 2003; Meyler et al., 2007). Dyslexic children showed less activation than control children in the VWFA (t(1,32) = 2.8, p < 0.05) and in both ROIs of the middle temporal gyrus (more anterior/Meyler: t(1,32) = 3.0, p < 0.01; more posterior/Kronbichler: t(1,32) = 2.4, p < 0.05).

**Semantic processing during sentence reading**

*All children.* In the whole group voxel-based fMRI analysis of the incongruency effects, incongruous sentence endings lead to increased activation compared to congruous endings in inferior frontal and superior temporal areas of the left hemispheric language network (p<0.001, uncorrected; Table 4, Figure 2A).

More activation for congruous than for incongruous endings were mainly found bilaterally within large portions of the superior frontal and the parietal lobe: the precuneus, the inferior parietal lobe, the cingulate gyrus, the middle frontal gyrus and the superior frontal gyrus of both hemispheres; as well as the right supramarginal gyrus and the right medial frontal gyrus (p<0.001, uncorrected; Table 4, Figure 2A).

**Group contrasts.** Dyslexic children showed reduced incongruency effects in the left inferior parietal cortex and in the precuneus compared to controls (p < 0.001 uncorr., Table 4, Figure 2B), but they did not show an increased incongruency effect in any region.

**Reading speed covariate.** The voxel-based analysis with reading speed as a covariate including all 38 children revealed an increased incongruency effect with increasing reading speed that corroborated the main effects from the group comparison. We found activations in the inferior parietal gyrus and the precuneus, and additionally in the supramarginal gyrus, the inferior temporal gyrus, the cuneus and the transverse temporal gyrus (Supplemental Material, Fig. 1B; p < 0.001 uncorr., Supplemental Material, Table 3). We did not find any region negatively correlated with reading skills for the same analysis.
**ROI analyses.** We computed separate Analyses of Variance with the within subject factors “incongruency” (incongruous vs. congruous) and “dyslexia” (dyslexic vs. controls) for the literature-based ROIs and for the ROIs based on the local maxima from the incongruency group comparison (Table 4).

In the VWFA ROI (−43/−54/−12) and in the more anterior middle temporal ROI (Meyler et al., 2007), the dyslexic children showed generally reduced activation compared to the controls (VWFA: F(1,32) = 8.9, p<0.01; MT: F(1,32) = 7.5, p<0.05), but these group main effects were not modulated by “incongruency”, nor were there any “incongruency” main effects (all F’s < 1).

In the more posterior middle temporal ROI (Kronbichler et al., 2006), the dyslexia main effect was less robust (F(1,32) = 4.0, p<0.1), but there was a trend for a “incongruency” by “dyslexia” interaction (F(1,32) = 4.1, p<0.1). The incongruency main effect was not significant (F<1).

In the inferior parietal ROI from the voxel-based group comparison, there was a strong “incongruency” by “dyslexia” interaction (F(1,32) = 23.3, p<0.001), whereas both main effects were not significant (both F’s < 1). This interaction was due to a relative activation increase for incongruous compared to congruous endings in controls (t(1,21) = 3.9, p<0.001), but also due to a activation decrease for incongruous compared to congruous endings in dyslexic children (t(1,11) = -3.2, p<0.01). This effect was mainly due to a differential response to incongruous endings, as the two groups did not differ for congruous endings (t < 1), but tended to differ for incongruous endings (t(1,32) = 2.0, p<0.1) with control children showing relatively more activation than children with dyslexia.

In the precuneus ROI from the voxel-based group comparison, there was decreased activation for incongruous compared to congruous endings (F(1,32) = 13.0, p<0.01), especially in the dyslexic children (F(1,32) = 14.6, p<0.001). The dyslexia main effect was not significant (F < 1).

**ERP results**

**Sentence reading**

**Segmentation.** The grand mean of all words during sentence processing showed 3 pronounced GFP peaks (see Fig. 3A) between 86 and 422 ms. Topographic clustering revealed that the 3 GFP peaks corresponded to 3 microstates with distinct
topographies, the P1 (86-151 ms), the N1 (152-280 ms), and the P2 (281-422 ms) (Fig. 3B).

**Map analyses.** The P1 maps were topographically different between dyslexic and control children (TANOVA-norm, p<0.05; TANOVA-raw, p<0.1). They were not different regarding map strength (GFP: t(1,45)=0.7, p>0.2). The t-maps in Figure 3C illustrate that the topographic differences were due to the central negativity extending more laterally in controls than in dyslexic children as indicated by significant differences at left and right temporal electrodes.

No group differences were found for the N1 maps (GFP, TANOVA-raw, and TANOVA-norm, all p>0.2). Although the t-maps for the group comparison in the P2 segment showed focal differences at a few posterior electrodes suggesting a more right lateralised P2 in dyslexics, the spatial analysis could not confirm significant differences (GFP and TANOVA-raw, both p>0.2; TANOVA-norm, p>0.11).

**Map latencies.** The latency analyses based on map templates (TCR) revealed no significant latency differences between the two groups for the P1 and the P2 microstates. However, the N1 microstate tended to be delayed in dyslexic children compared to controls (t(1,44.5)=1.8, p<0.1). As the P1 microstates differed topographically between dyslexic children and controls, we ran the latency analysis also with a P1 template derived from the average of the normalised P1 maps from dyslexic children and controls. This analysis yielded no significant difference (p>0.2). Similar results were obtained with correlations between latency measures and reading skills (correct words per minute). No significant correlations were found for the P1 (r=-0.10) and the P2 (r=-0.06) segments. There was a weak trend towards delayed N1 latencies with slower reading (r=-0.23, p<0.11) similar to the result in the group comparison.

**Semantic processing during sentence reading**

**Segmentation.** Incongruous sentence endings were processed differently (p < 0.01) from congruous endings in two time windows between 246 and 543 ms (N400) and between 617 and 1125 ms (late positivity, LP), as revealed by the TANOVA analysis across the entire group (Fig. 4A). Topographic clustering of the difference maps (incongruous ERP minus congruous ERP) divided each of these time windows in two
parts (for the raw maps see supplementary Figure 3), resulting in 4 microstates subsequently used for analysis: N400a (246-319 ms), N400b (320-543 ms), LPa (617-831 ms), and LPb (832-1125 ms). The difference maps (incongruous ERP minus congruous ERP) for the 4 microstates are illustrated in Figure 4B.

**Map description.** The early N400 effect microstate (N400a) showed a strongly left-lateralised topography with posterior negativity and anterior positivity (Fig. 4B). In the late N400 effect microstate (N400b) the posterior negativity and the anterior positivity were less clearly lateralised. The two microstates with the late posterior positivity showed more distinct topographies. The positivity was bilaterally more inferior, but with a left-lateralised tendency in the earlier part, and was more superior and central, although still slightly left-lateralised, in the later part.

**Map analyses.** The early N400 effect microstate (N400a) did not differ between dyslexic children and controls (GFP, TANOVA-raw, and TANOVA-norm, all p>0.2). The later N400 microstate (N400b), however, was reduced (TANOVA-raw, p<0.05) and topographically distinct (TANOVA-norm, p<0.05) in dyslexic children compared to controls. GFP did not differ between the groups in this segment (p>0.2). The t-maps in Figure 4C illustrate that these N400 differences were due to reduced posterior negativity and anterior positivity in the dyslexic children.

The ERP maps during the first segment of the late posterior positivity were not different between dyslexic children and controls (GFP, TANOVA-raw, and TANOVA-norm, all p>0.2). During the second segment of the late posterior positivity, the t-maps showed focal group differences, at parietal and right temporal electrodes, but these differences did not quite reach significance in the mapping analyses (GFP and TANOVA-raw: p>0.2; TANOVA-norm: p=0.10).

**Map latencies.** The latency analyses revealed no significant differences between dyslexic children and controls (N400a, N400b, and LPa: all p>0.2; LPb: p=0.12). As the N400b microstate differed topographically between dyslexic children and controls, we ran the same analysis with an N400b template derived from the average of the normalised N400b maps from the dyslexic children and the controls. The analysis yielded no significant difference (p>0.2). Similarly, no significant correlations between latency measures and reading score (correct words per minute) were obtained for the
N400a ($r=0.01$), N400b ($r=-0.06$), and LPa (-0.09) segments. Only the LPb topography tended to be delayed with slower reading (-0.25, $p<0.1$).

**Pz Analyses.** Analogous to the fMRI ROI analysis we computed one ANOVA per microstate with the within subject factors “incongruency” (incongruous vs. congruous) and the between subject factor “dyslexia” (dyslexic vs. control) for the amplitudes at Pz.

In the N400a segment incongruous endings elicited less Pz-positivity than congruous endings ($F(1,45)=20.4$, $p<0.001$). Neither the dyslexia main effect nor the dyslexia-by-incongruency interaction were significant (both $F$’s < 1). Planned comparisons also did not reveal any group differences, neither for congruous ($t=-0.5$) nor for incongruous ($t=-1.0$) endings.

In the N400b segment incongruous endings also elicited less positivity than congruous endings (incongruency, $F(1,45)=46.4$, $p<0.001$), but this effect was more pronounced in control children than in children with dyslexia (incongruency x dyslexia, $F(1,45)=10.6$, $p<0.01$). The dyslexia main effect was not significant ($F<1$), Planned comparisons revealed a group difference for incongruous endings with Pz-negativity in controls but positivity in those with dyslexia ($t(1,45) = -2.4$, $p<0.05$), but not for congruous endings ($t=0.8$). The waveforms (supplementary Figure 3) illustrate a negative-going peak during the N400b segment for congruous endings, and a negative peak for incongruous endings which was more negative in controls than in dyslexic children.

In the LPa segment there was a main effect of dyslexia ($F(1,45)=8.1$, $p<0.01$), indicating more positive values for control children compared to children with dyslexia. Neither the incongruency main effect ($F<1$) nor the incongruency-by-dyslexia interaction ($F<1.4$) were significant. Planned comparisons revealed group differences for both incongruous ($t(1,45)=2.8$, $p<0.01$) and congruous ($t(1,45)=2.2$, $p<0.05$) endings.

In the LPb segment incongruous endings elicited more positive values at Pz than congruous endings ($F(1,45)=43.2$, $p<0.001$), especially in controls (incongruency x dyslexia, $F(1,45)=9.3$, $p<0.01$). Planned comparisons revealed no group differences when testing the conditions separately (incongruous: $t(1,45)=1.5$, $p>0.13$; congruous: $t(1,45)=-1.0$).
Source localisation

Estimating the sources of the grand mean over all 52 subjects at GFP peaks of the N400b and the late positivity using LORETA and LAURA both suggested a source distribution in the left hemisphere that included inferior frontal and middle temporal regions corresponding to the fMRI activation (Fig. 5). While anterior middle temporal sources were stronger for the N400 component, inferior frontal and posterior middle temporal sources were relatively stronger in the late positivity component.

In order to examine the correspondence between statistical characterizations of the local EEG and fMRI incongruency effects, we computed EEG source statistics for selected voxels: those voxels showing local source maxima of the grand mean incongruency effect, plus the voxel corresponding to the inferior parietal fMRI activation. To this end, current source density at the N400b and the LP GFP peak was compared to baseline (at time 0, before systematic incongruency effects are expected, using t-tests). As indicated in Figure 5, the inferior frontal (t(1,51)=2.15, p<0.05) and posterior temporal activation (t(1,51)=3.11, p<0.01) was significant for the late positivity, and the anterior temporal activation approached significance (t(1,51)=1.65, p<0.11) for the N400b using the LORETA algorithm. The LAURA algorithm did not yield any significant results despite its similar grand mean source distribution, suggesting that the two methods mainly differ in susceptibility to individual variation. In those voxels showing such significant N400b or late positivity effects compared to baseline, we tested whether the groups would differ, but found no significant differences (all p >.02).

Correlations between dyslexia effects in fMRI and ERPs

The incongruency effect in the inferior parietal ROI (-59/ -39/ 32) was significantly correlated with the N400 effect at the Pz electrode (r=-0.40, p<0.05), but not with the amplitude in the P1 Segment at electrode O2' (r=-0.10, p=ns). In addition, the inferior parietal incongruency effect was also correlated with the group effects for generic sentence reading in the fMRI ROIs (medial frontal: r=0.58, p<0.001; superior frontal: r=0.42, p<0.01; inferior parietal: r=0.27, p<0.1).

The correlation between the amplitude of the N400 effect and the incongruency effect in inferior parietal region is also supported by an additional voxel-based analysis of the incongruency effect in which the Pz amplitude of the N400 effect was used as a
covariate of interest. The cluster with the most significant effect (p<0.001) was found in the inferior parietal region (Supplementary Material Figure 4).

**Discussion**

The present study investigated deviant brain processes in dyslexic children during sentence reading with a focus on semantic processing. By combining the advantages of fMRI and ERP techniques we sought to characterise distribution and dynamics of neural impairments.

*Sentence reading and semantic processing across all children*

The children activated a left-lateralised network while reading sentences. The activation in inferior frontal, middle temporal, and fusiform regions is in good agreement with an earlier study investigating sentence reading in adolescents (Kronbichler et al., 2006), and with a recent meta-analysis depicting the language network activated in various sentence or text processing tasks (Vigneau et al., 2006). Also, the P1-N1-P2 sequence in the ERP elicited by all words in the sentences is typical for early components in response to visual word stimuli in children (Brandeis et al., 1994; Maurer et al., 2006) as well as in adults (Brandeis et al., 1995; Brandeis et al., 1994; Brem et al., 2006; Maurer et al., 2005a; Maurer et al., 2005b). The absence of prominent GFP peaks after 400ms suggests that averaging over the different word positions and classes largely eliminated later components, which were analysed in more detail for incongruous and congruous sentence endings.

The children in the present study showed increased activation for incongruous compared to congruous sentence endings in inferior frontal and superior temporal areas (anterior and posterior part). Inferior frontal modulation by contextual expectation has been previously reported in fMRI studies of sentence processing in adults (Baumgaertner et al., 2002; Kiehl et al., 2002; Kuperberg et al., 2003). The weaker modulations in temporal regions also agree with adult work by Baumgaertner et al. (2002) for (posterior) middle temporal regions (slightly different from our superior temporal activation) and by Kiehl et al. (2002) for (superior) anterior temporal regions.
Since other developmental fMRI studies on sentence processing did not examine effects of semantic priming (Kronbichler et al., 2006; Meyler et al., 2007), the present study is the first to indicate that children activate similar regions as adults during semantic processing in sentence reading.

Interestingly, there were also sizeable regions with more activation for congruous than incongruous sentence endings, including the bilateral parietal cortices, and the precuneus. These regions have been shown to be deactivated during sensory tasks, and it has been suggested that they belonged to a default network that is activated during rest (Halder et al., 2007; Raichle et al., 2001). The functional role of the default network is not entirely clear, but a role in memory processes has been proposed, as similar areas are activated during successful memory retrieval (Buckner et al., 2005). The congruency effects in the parietal and precuneus regions were due to reduced deactivation for congruous than incongruous endings (compare also Figure 1), and thus modulated overall deactivation in this region. Such modulation may occur because the same processes that are active during baseline are relatively more active during the congruous than during the incongruous condition. As default activation has been linked to successful memory integration (Buckner et al., 2005), a reduced level of deactivation during the congruous condition may reflect the same active process as during baseline, but not in the incongruous condition where successful memory integration is hardly possible.

Alternatively, a process that is different from the one responsible for relative activation during baseline may be involved, and reflect increased language-specific or attentional engagement for congruous endings (Kuperberg et al., 2003). Thus, the incongruency and the congruency fMRI effects may reflect different aspects of semantic processing, effects of semantic access in inferior frontal and temporal regions, and effects of semantic integration in bilateral parietal and precuneus regions. Alternatively, however, a different degree of deactivation in these parietal regions may result from the extent to which attentional resources are allocated in a sentence task, as suggested by Kuperberg et al. (2003).

Incongruency of the sentence ending strongly modulated the ERP to the last word starting at about 240 ms. A posterior positive and anterior negative topography was stronger for congruous than for incongruous endings, resulting in a centro-parietally negative N400 effect for the difference between incongruous and congruous endings.
This N400 effect could be topographically differentiated into an earlier more left-lateralised and inferior N400a negativity, and a later more central and superior N400b negativity centred around 400 ms (e.g. Brandeis et al., 1995; Brandeis et al., 1994; Kutas and Hillyard, 1980). The later N400b effect showed a consistent (difference-) topography even though the topographies of the incongruous and congruous ERPs changed from negative/negative-going to positive over centro-parietal channels (see waveforms in supplementary Fig. 3). Such an N400 effect with its typical centro-parietally negative distribution marks semantic integration processes during sentence reading (Friederici, 2004; Kutas and Federmeier, 2000).

A second phase of differential processing started after 600 ms with posterior positivity that was also located more inferior with a left-lateralised tendency in an earlier microstate and more superior in a later microstate. The late positive effect after 600 ms presumably corresponds to the P600 effect that has been associated with congruency judgement during sentence processing (Kolk et al., 2003; Sabisch et al., 2006). Processing related to congruency judgement can be expected to occur in the present experiment also for sentences to which children do not respond, because the rare response prompts occurred only some time after a sentence was presented.

The distributed sources of semantic components indicated by inverse solutions of GFP peaks are in excellent agreement with our fMRI results. While the anterior temporal N400 sources corroborate earlier EEG and MEG studies on sentence reading (see van Petten and Luka, 2006 for a review), the additional inferior frontal sources suggest that the corresponding activation in the fMRI data starts within 400 ms. A link between inferior frontal / anterior temporal fMRI activation and the N400 effect was also made in a previous multimodal sentence reading study on pragmatic anomalies using ERPs and fMRI (Kuperberg et al., 2003). Inferior frontal activation seems to continue and even increase during the later time segments, as indicated by the source localization of the late positivity. In addition to the increase in frontal activation there was also an increase of posterior temporal activation which was reflected in both source localization methods.

While the combined use of the EEG and fMRI methods provided complementary information regarding timing and localization of semantic effects in the present study, these effects may be somewhat underestimated because the repetition inherent in the sequential design leads to a reduced N400 (Besson and Kutas, 1993). Future studies using simultaneous EEG and fMRI recordings that do not require repetitions...
Effects of dyslexia during sentence reading and semantic processing

The inferior parietal reduction of activation during generic sentence reading in children with dyslexia compared to controls at -53 -45 41 (and extending into the angular gyrus -50 -60 33) is in good agreement with earlier studies (supramarginal gyrus at -60 -42 30 in Kronbichler et al., 2006; angular gyrus at Tal.: -36 -62 33 in Meyler et al., 2007). It has been suggested that underactivation in this temporoparietal region might reflect the phonological processing deficit (McCandliss et al., 2003; Temple et al., 2001), but other explanations have also been put forward, such as a deficit in orthographic-phonological translation (Shaywitz et al., 2002), or verbal working memory or semantic integration deficits (Booth et al., 2007). The involvement of other than phonological impairments (Meyler et al., 2007) for reduced inferior parietal activation (Kronbichler et al., 2006; Meyler et al., 2007) seems likely, as the German dyslexics were not impaired in phonological decoding, and showed rather a deficit in reading fluency (Kronbichler et al., 2006).

The design of the present study allowed us to investigate the role of semantic processes more directly by experimental contrasts. Dyslexic children showed a reduced difference between semantically incongruous minus congruous sentence endings in the inferior parietal region than controls. Although this area was slightly more anterior than the dyslexia effect in the analysis of generic sentence reading, it covered most of the supramarginal gyrus area reported by Kronbichler et al. (2006) thus suggesting that the reduced inferior parietal activation during sentence reading is due to a semantic impairment.

Such an interpretation in terms of semantic processing deficits is consistent with the N400 literature (Kutas and Federmeier, 2000; van Petten and Luka, 2006). The location of this impairment in inferior parietal cortex during sentence reading in dyslexia is also in agreement with the finding that the correlation between semantic association within word pairs, and activation in inferior parietal region was weaker in dyslexics than controls (Booth et al., 2007), thus supporting the interpretation of a semantic impairment.

However, the possibility can not be excluded that priming of sentence endings in the present experiment extends - in addition to semantics - also to phonology or...
orthography. Such an interpretation would still mean that dyslexic children are not only impaired in basic word recognition mechanisms, but that they are also impaired in integration at the sentence level, or in using sentence context for reading.

As the group difference in the incongruency contrast represents a double difference, the ROI analyses which consider the percent signal change relative to baseline are important for the interpretation of the effects.

The group incongruency effects in both the inferior parietal and precuneus regions reflect a modulation of an overall deactivation compared to baseline. As we have discussed for the congruency effects of the whole group analysis, such a pattern can still reflect differences in active brain processes, with less deactivation characterising the more active condition, and possibly involving processes which are also functional at “rest” during baseline.

An alternative explanation for the incongruency group effect of the inferior parietal difference is that it reflects a group difference of a congruency effect in nearby lateral parietal and precuneus regions, and might thus be related to the default mode or to memory retrieval effects (Buckner et al., 2005). Following this explanation dyslexic children would show a larger congruency effect than control children due to increased deactivation for incongruous endings. The ROI analysis for the inferior parietal effect lends credit to both possibilities as the significant interaction between group and incongruency was based on a significantly larger activation for incongruous than congruous endings in the control children and significantly larger activation for congruous than incongruous endings in the dyslexic children.

In the precuneus, however, the ROI analysis for the incongruency group effect seems to favour the second explanation, as the interaction between group and incongruency reflected a larger activation for congruous than incongruous endings in dyslexic children, whereas the two types of sentence endings were associated with a similar level of activation in the control children in this region.

Although in the present case the baseline included the first 3 words of the sentence, and signal decrease differs from typical deactivation, earlier studies have reported reduced activation in dyslexic children and adolescents compared to controls in this inferior parietal region, which was mainly due to a deactivation in relation to baseline in the dyslexic group (Hoeft et al., 2006; Hoeft et al., 2007). Interestingly, the same inferior parietal region showed also a reduction of gray matter in dyslexic adolescents compared to both age-matched and reading-level-matched controls (Hoeft et al., 2007).
2007), which points to a critical role of this region for the development of dyslexia. Our results suggest that dysfunction in this inferior parietal region, and possible gray matter anomalies, does not only affect phonological processing, but also semantic processing during sentence reading.

In addition to the inferior parietal effect of dyslexia during sentence reading, decreased activation in children with dyslexia compared to controls was found in superior frontal areas. Although no significant group differences were reported for this region in the two previous studies on sentence reading (Kronbichler et al., 2006; Meyler et al., 2007), control children in the Kronbichler study showed activation in a similar superior frontal region, which was absent in the dyslexic participants. The more robust effect in the present study may be related to the way the sentences were presented. In the two previous studies more complex sentences with all words of a sentence presented simultaneously were used, whereas in the present study the simple sentences were presented word by word requiring the first words of the sentence to be kept in mind. This may have led to higher demands on working memory in the present study increasing differences between dyslexics and controls. This is in agreement with a recent study showing that high demand on phonological working memory leads to activation differences between participants with and without dyslexia in a nearby superior frontal region (Vasic et al., in press).

However, as the children in the present study were younger than the participants in the Kronbichler study, more robust dyslexia effects in superior frontal regions may be found at a younger age during sentence reading tasks. While our dyslexia effects during sentence reading in inferior parietal areas agree with two previous studies (Kronbichler et al., 2006; Meyler et al., 2007), the voxel based analysis could not replicate group differences in the middle temporal gyrus found in both these studies. The less robust temporal effects in our study compared to the two other studies may again be related to the difference in stimulus material or presentation mode. However, we found a similarly reduced activation for dyslexics compared to controls in the ROI analyses of left middle temporal areas using the coordinates of the Meyler and the Kronbichler study. Whereas the group difference in the Meyler ROI was not modulated by semantic incongruency, the slightly more inferior and posterior middle
temporal ROI from the Kronbichler study showed a strong trend towards an interaction between dyslexia group and incongruency. Similar to the Kronbichler study, we also found decreased activation during sentence reading in dyslexic children compared to controls in the VWFA ROI in the left inferior occipito-temporal cortex. Unlike the dyslexia effects in the inferior parietal and posterior middle temporal regions, these inferior occipito-temporal group differences were not modulated by incongruency of the sentence endings. This suggests that reduced activation in inferior occipito-temporal regions is related to general deficits of word reading in dyslexia, in agreement with studies using isolated word form or letter stimuli and reporting inferior occipito-temporal deficits (Brambati et al., 2006; Brunswick et al., 1999; Cao et al., 2006; Paulesu et al., 2001).

While the fMRI results show which dyslexia effects during sentence reading are effects of generic word reading, and which effects are modulated by semantic priming, the ERP data provide critical information about the time course of these processing deficits. Dyslexia effects during generic sentence reading were already found in the early P1 component. A similar result of reduced P1 amplitudes was already reported in an earlier study with the same paradigm, but a different subject group (Brandeis et al., 1994), and with a different paradigm, but with partly overlapping subjects as in the present study at a different age (Maurer et al., 2007), lending support that relatively early visual processing is impaired in children with dyslexia. Such an early deficit may not be word-specific, as attenuated P1 components also occurred before learning to read (Maurer et al., 2007), or with non-language stimuli (Solan et al., 1990). The lack of N1 effects is also consistent with our previous work on sentence reading in dyslexia. The finding confirms that while single word N1 attenuations are present in younger children with dyslexia such as 2nd graders (Maurer et al., 2007), such an attenuation is no longer present in older children with dyslexia or while reading sentences for comprehension. Dyslexia effects at the N1 level for sentence reading at this age may instead manifest itself as a processing delay, as suggested by the statistical trend in the latency analysis.

Although several microstates were identified during which incongruous sentence endings were processed differently from congruous endings, only the microstate
around 400 ms was also reduced in dyslexic children compared to controls. This N400 incongruency effect is typically interpreted as an effect of semantic priming by sentence context (for reviews see Friederici et al., 2004; Kutas and Federmeier, 2000; Van Petten and Luka, 2006). This indicates that dyslexic children are impaired regarding semantic integration during sentence reading starting within the first 400 ms. The reduced N400 effect in the dyslexic children in the present study is in agreement with two earlier studies covering both dyslexic children (Brandeis et al., 1994) and dyslexic adults (Helenius et al., 1999). Younger children with dyslexia had shown an even larger N400-effect than controls in one previous study (Neville et al., 1993). This suggests that the reduction of the N400-effect in dyslexic participants also develops with age, thus paralleling the effect found in the inferior parietal area for sentence reading (Meyler et al., 2007). Reduced N400 effects during sentence processing in dyslexia seems to be limited to reading tasks, as no difference in the N400 effect between dyslexic and control children at a similar age were found with sentences presented in the auditory modality (Sabisch et al., 2006).

Moreover, the group differences in the N400-effect could be attributed mainly to the incongruous endings, as the two groups differed for incongruous but not for congruous endings in this time range (Supplemental Material, Fig. 3). This suggests that dyslexic children hardly differ from controls while reading simple sentences with highly primed endings, but that their brain response to semantically unexpected endings is reduced. Importantly, however, this did not lead to more pronounced behavioural deficits for incongruous than for congruous endings, as the dyslexic children exhibited a similar increase of error and reaction time compared to the controls for both ending types. The absence of semantic effects at the behavioural level in this group of dyslexic children is also in agreement with their normal performance in the similarities subtest of the WISC. Further research, using additional semantic processing measures such as priming or comprehension in visual, as well as in auditory tasks, should determine whether this pattern reflects a genuine dissociation between behavioural and neural markers of semantic deficits, or whether it results from the delayed response requirement allowing for additional compensation.

Results from earlier studies (Brandeis et al., 1994; Helenius et al., 1999) indicated not only a reduced, but also a delayed N400 effect in dyslexia. In the present study there was no significant latency difference of the N400 effect. The greatly reduced
size of the N400 effect in the dyslexic children resulted in a flat GFP curve and may have made the latency detection less reliable, even though a topographic correlation approach was used. This suggests that reduction and not latency delay are the most prominent characteristics of the N400 effects in this group of dyslexic children reading sentences. Alternatively, repeating the sentence reading test, as required for a sequential multimodal study, may have attenuated latency effects, consistent with effects of word frequency on component latencies in the N400 time range (King and Kutas, 1998).

While both neuroimaging modalities suggest that semantic processing during sentence reading is impaired in dyslexic children compared to controls, it takes their combination to clarify that this impairment is localised mainly to inferior parietal cortex of the left hemisphere according to the fMRI data and occurs mainly around 400 ms according to the ERP data. The correlation of the incongruency effects in inferior parietal cortex and around 400 ms, i.e. during a narrow time slot an in a small part of the active networks detected with each imaging modality, may indicate a direct relation between fMRI and ERP effects.

However, the N400 source localisation suggests that the fMRI and ERP effects are less directly related. The N400 was localised to a network including anterior temporal and inferior frontal regions, where we found no semantic group differences in the voxel-based fMRI analysis, and this network did not include the left inferior parietal cortex with the strongest semantic effects in the fMRI data. The current source density values within this fMRI-derived inferior parietal region showed no significant N400 source activation compared to baseline, but signal to noise ratio was generally low for localization of such a complex source pattern. This may also explain why the group differences in the incongruency effect significant at the scalp (Pz) could not be found at the corresponding source level. Although some left posterior activation was also evident in the N400 LORETA solution, this activation was minor and well posterior to the left inferior parietal fMRI activation. This discrepancy may be explained by different time resolutions of the two methods, and especially by the property of fMRI to integrate over distinct neural events with split-second timing differences. Thus the semantic impairment during sentence reading in dyslexia may exhibit a different behaviour over time depending on the brain region involved with more phasic activation in brain regions responsible for the N400 effect, and more
sustained activation in inferior parietal cortex. While we can not exclude that the
N400 source localisations are not entirely reliable, the convergence with intracranial
N400 localisations, and the consistency across the two methods argue for a correct
localisation.

In conclusion, the present study extends earlier results on word and sentence
processing in dyslexia by showing that impairments in inferior parietal regions - unlike
impairments in the inferior temporal VWFA - are modulated by semantic
expectations, and co-occur with a reduction of the N400 effect. The correlation
between N400 reduction and reduced inferior parietal incongruency effect in
combination with N400 source localisation suggests that semantic impairment results
in a N400 reduction in anterior brain regions which may be hard to detect in the
hemodynamic response, and in a subsequent sustained attenuation of an inferior
parietal response dominating the fMRI data.

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**Figure legends**

Figure 1. fMRI results of sentence reading.

The whole group fMRI analysis (one-sample t-test, p < 0.05, FWE corrected) revealed that the children activated a predominantly left-hemispheric language network during sentence reading that included inferior frontal, middle temporal, and inferior occipito-temporal regions (A: red). The reverse contrast indicated “default” activation (i.e. larger activation during baseline than during sentence reading) mainly in posterior occipito-parietal regions (A: blue). The group contrast (2-sample t-test, p < 0.001 uncorrected) between dyslexic and normal reading children revealed decreased activation in frontal and inferior parietal regions of the left hemisphere for children with dyslexia (B).

Figure 2. fMRI results of the incongruency effect.

The whole group fMRI analysis for the incongruency contrast (incongruous vs. congruous sentence endings, p < 0.001, uncorrected) revealed increased activation for incongruous relative to congruous endings in inferior frontal and superior temporal areas within the left hemisphere (red). Increased activation for congruous compared to incongruous (blue) sentence endings was found bilaterally in inferior parietal and middle/superior frontal regions, as well as in precuneus and cingulate regions (A). Dyslexic children showed reduced incongruency effects (p < 0.001, uncorrected) compared to controls in the supramarginal gyrus of the left inferior parietal cortex and in the precuneus (B). This effect reflected a group-specific pattern of differential deactivation for incongruous (i) and congruous (c) endings mainly due to increased deactivation following incongruous endings for the dyslexic (Dys) compared to the control (Con) children.

Figure 3. ERP results of sentence reading.

The ERP response to all words in a sentence consisted of 3 clear GFP peaks (A), which corresponded to 3 microstates with stable topographies (B). The ERP maps of the children with dyslexia (dys) and of the controls (ctrl) differed in the P1 microstate (TANOVA, t-map), but not in the N1 and P2 microstate (TANOVA).

Figure 4. ERP results of the incongruency effect.
Incongruous and congruous sentence endings were processed differently during two time windows (A), each of which was further divided into 2 microstates with stable topographies (B). The difference maps (incongruous – congruous) differed between children with dyslexia (dys) and controls (ctrl) during the N400b microstate (TANOVA, t-map), but not during the other 3 microstates (TANOVA) (C).

Figure 5. LAURA and LORETA source localisations

The source distributions of the N400b GFP peak (at 379ms) and the LP GFP peak (at 973 ms) were estimated using the LAURA and LORETA algorithms. Across the whole group of children the inverse solutions revealed a network consisting of inferior frontal and temporal regions. The anterior middle temporal sources of the N400 were reduced in the late positivity, while inferior frontal and posterior temporal sources increased. Current source density at these time points were tested vs time zero in the voxels showing local maxima for the grand mean incongruency effect: LAURA: -53, -6, -10 (middle temporal gyrus); -45, 48, -4 (middle frontal gyrus); -49, -62, 7 (middle temporal gyrus). LORETA: -52, -6, -5 (superior temporal gyrus); -49, -62, 7 (middle temporal gyrus); -50, 14, 10 (precentral gyrus) and in inferior parietal cortex showing the fMRI group incongruency effect (-59, -39, 32). Significance of the effects is indicated in the figure (*: p<0.05, +: p<0.11; ns: not significant).

Tables

Table 1: subjects

<table>
<thead>
<tr>
<th></th>
<th>Whole group</th>
<th>Dyslexics</th>
<th>Controls</th>
</tr>
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<tbody>
<tr>
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<td>(10.9 – 12.2 years)</td>
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<td>(23 girls)</td>
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<td>Age (y)</td>
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<td>mean ±SD</td>
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*p<0.05, **p<0.01, ***p<0.001; SLT: Salzburger Lesetest.
Table 2. Behavioural data

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<td>1536 (±432)</td>
<td>1163 (±336)</td>
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Table 3. Sentence reading activation in fMRI (whole group and group differences)

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Sentence reading vs. baseline (whole group)

Sentence reading vs. baseline (controls vs. dyslexics)
Table 4. fMRI incongruency effect (whole group and group differences)

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<th>Location</th>
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| Incongruency effect (controls vs. dyslexics) |        |       |       |       |                           |     |
| 58           | 3.72   | 3     | -47   | 55    | Precuneus                 | 7   |


References:


Sentence reading (activation and deactivation): whole group

Sentence reading: controls - dyslexics
Incongruency/congruency effect: whole group

Incongruency effect: controls - dyslexics
A

B

C

dys

ctrl

t-map

TANOVA

raw       ns       p<0.05
norm      ns       p<0.05

246-319  N400a
320-543  N400b
617-831  LPa
832-1125 ms LPb

0.95 0.96 0.97 0.98 0.99 1 2 5 2 5 0 3 7 5 5 0 0 6 2 5 7 5 0 8 7 5 1 0 0 0

-1 2 5 0 3 7 5 5 0 0 6 2 5 7 5 0 8 7 5

246-543 ms
617-1125 ms

ns             p<0.05               ns                  ns
ns             p<0.05               ns                  ns

246-543 ms 617-1125 ms

p<0.01  p<0.05
Incongruency effect (whole group)

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Supplementary Material: Tables

SM Table 1. Behavioural results during sentence reading task.

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<th>EEG RT</th>
<th>fMRI ACC</th>
<th>fMRI RT</th>
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<td>D, F(1,45) = 10.1**</td>
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<td>D, F(1,32) = 10.8**</td>
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<td>I, F(1,32) = 4.4*</td>
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<td>I, F(1,32) = 4.4*</td>
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D: dyslexia, I: incongruency; *: p<0.05, **: p<0.01, ***: p<0.001.

SM Table 2. Correlation between reading speed and sentence reading activation in fMRI

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<th>correlation reading speed vs. sentence reading</th>
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<th>y</th>
<th>z</th>
<th>Location</th>
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SM Table 3. Correlation between reading speed and the incongruency effect in fMRI

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Supplementary Material: Figure legends

SM Figure 1. Correlation between reading speed and fMRI activation.

The correlation analyses (p < 0.001, uncorrected) between the reading score and fMRI activation revealed regions (A) in the superior frontal gyrus, the anterior cingulate gyrus, and the inferior parietal gyrus for sentence reading (see also SM
Table 2), and (B) for the incongruency effect in the inferior parietal gyrus, the supramarginal gyrus, the precuneus and the inferior temporal gyrus.

**SM Figure 2. Incongruency effects: one sample t-tests.**

Both the control children (A) and the children with dyslexia (B) showed increased activation for incongruous compared to congruous endings in inferior frontal regions. In addition, the control children also showed increased activation for incongruous than congruous endings in the inferior parietal, the superior temporal and middle occipital regions of the left hemisphere, although only the inferior parietal activation effect was larger than in dyslexic children when compared directly (see manuscript).

**SM Figure 3. ERP-maps with group differences and selected waveforms in response to incongruous and congruous sentences endings**

The ERP maps (A) in response to incongruous and congruous sentence endings show posterior positivities in all 4 microstates indicating that the posterior negativity of the N400 effect results from reduced posterior positivity for the incongruous endings (first 3 rows). Difference t-maps between children with and without dyslexia (4th row) indicate that the reduced N400 effect (N400b; see manuscript) resulted mainly from differences in response to incongruous endings. Prominent group differences were also found for microstate LPa, but similarly for incongruous and congruous endings.

Waveforms (B) in response to incongruous and congruous sentence endings are shown at 3 midline electrodes (occipital: Oz; parietal: Pz; central: Cz) for the dyslexic (red) and control (black) children. The segments showing incongruency effects based on the map comparison are indicated in grey.

**SM Figure 4. Correlation between the N400 at Pz and fMRI activation**

Adding the N400 amplitude at Pz electrode to the fMRI incongruency model in SPM revealed a significant correlation (p<0.001) in the inferior parietal lobule (Talairach coordinates: -50/ -44/ 44) indicating an increasing fMRI incongruency effect with an increasing N400 effect.
Correlation: reading speed vs. sentence reading

Correlation: reading speed vs. incongruency
Incongruency effect: controls

Incongruency effect: dyslexics
Correlation: N400 at Pz vs. incongruency