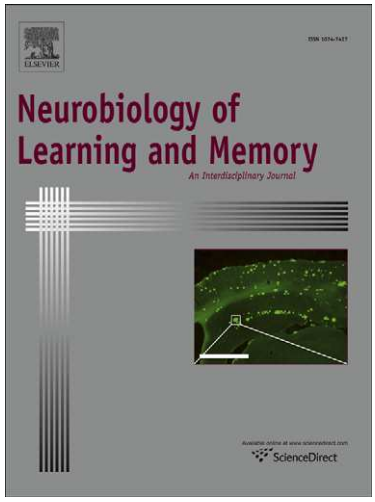
Placebo-mediated, Naloxone-sensitive suggestibility of short-term memory performance

Stern, J ; Candia, V ; Porchet, R I ; Krummenacher, P ; Folkers, G ; Schedlowski, M ; Ettlin, Dominik A ; Schönbächler, G

DOI: https://doi.org/10.1016/j.nlm.2011.01.005

Originally published at:
Stern, J; Candia, V; Porchet, R I; Krummenacher, P; Folkers, G; Schedlowski, M; Ettlin, Dominik A; Schönbächler, G (2011). Placebo-mediated, Naloxone-sensitive suggestibility of short-term memory performance. Neurobiology of Learning and Memory, 95(3):326-334.
DOI: https://doi.org/10.1016/j.nlm.2011.01.005



Placebo-mediated, Naloxone-sensitive suggestibility of short-term memory performance

Jair Stern, Victor Candia, Roseline I. Porchet, Peter Krummenacher, Gerd Folkers, Manfred Schedlowski, Dominik A. Ettlin, Georg Schönbächler

PII: S1074-7427(11)00006-2
DOI: 10.1016/j.nlm.2011.01.005
Reference: YNLME 5656

To appear in: *Neurobiology of Learning and Memory*

Received Date: 17 March 2010
Revised Date: 2 December 2010
Accepted Date: 12 January 2011

Please cite this article as: Stern, J., Candia, V., Porchet, R.I., Krummenacher, P., Folkers, G., Schedlowski, M., Ettlin, D.A., Schönbächler, G., Placebo-mediated, Naloxone-sensitive suggestibility of short-term memory performance, *Neurobiology of Learning and Memory* (2011), doi: 10.1016/j.nlm.2011.01.005

Placebo-mediated, Naloxone-sensitive suggestibility of short-term memory performance

Jair Stern,[1] Victor Candia,[1] Roseline I. Porchet,[1,2,] Peter Krummenacher,[1] Gerd Folkers,[1] Manfred Schedlowski,[3] Dominik A. Ettlin,[4] Georg Schönbächler[1,5*]

1 Collegium Helveticum, ETH and University of Zurich, Schmelzbergstr. 25 8092 CH-Zurich

2 Department of Experimental Psychology, University of Cambridge, Cambridge, CB2 3EB, UK

3 Medical Psychology and Behavioral Immunobiology, University of Duisburg-Essen, Hufelandstr. 55, 45122 D- Essen, Germany

4 Center for Oral Medicine, Dental and Maxillo-Facial Surgery, University of Zurich, Plattenstrasse 11, 8032 CH-Zurich

5 Department of Psychology, University of Cape Town, Rondebosch 7701, South Africa

*Corresponding author

Dr. Georg Schönbächler, Collegium Helveticum, ETH and University of Zurich, Schmelzbergstr. 25, 8092 CH-Zurich.
Phone: +41(0) 44 632 08 68, Fax: +41(0) 44 632 12 04

Abstract

Physiological studies of placebo-mediated suggestion have been recently performed beyond their traditional clinical context of pain and analgesia. Various neurotransmitter systems and immunological modulators have been used in successful placebo suggestions, including Dopamine, Cholecystokinin and, most extensively, opioids. We adhered to an established conceptual framework of placebo research and used the μ-opioid antagonist Naloxone to test the applicability of this framework within a cognitive domain (e.g. memory) in healthy volunteers. Healthy men (n = 62, age 29, SD = 9) were required to perform a task-battery, including standardized and custom-designed memory tasks, to test short-term recall and delayed recognition. Tasks were performed twice, before and after intravenous injection of either NaCl (0.9%) or Naloxone (both 0.15mg/kg), in a double-blind setting. While one group was given neutral information (S-), the other was told that it might receive a drug with suspected memory-boosting properties (S+). Objective and subjective indexes of memory performance and salivary cortisol (as a stress marker) were recorded during both runs and differences between groups were assessed. Short-term memory recall, but not delayed recognition, was objectively increased after placebo-mediated suggestion in the NaCl-group. Naloxone specifically blocked the suggestion effect without interfering with memory performance. These results were not affected when changes in salivary cortisol levels were considered. No reaction time changes, recorded to uncover unspecific attentional impairment, were seen. Placebo-mediated suggestion produced a training-independent, objective and Naloxone-sensitive increase in memory performance. These results indicate an

opioid-mediated placebo effect within a circumscribed cognitive domain in healthy volunteers.

Keywords: Placebo, Suggestion, Working Memory, Short-term recall, Naloxone, Opioids

Introduction

An ongoing challenge facing research on the placebo effect is how to properly disentangle its subjective and objective components (Harrington, 2008; Harrington, 1999; Moerman, 2002). Within clinical contexts in particular, conceptual ambiguities related to this problem often persist, hindering proper evaluation of standard biomedical therapeutic interventions, and presenting difficulties for the assessment, appreciation and harnessing of the power of placebo effects (Benedetti, 2009b; Frank, 1993; Kradin, 2008). (For a perspective on how objectivity and subjectivity have come have become interrelated in modern science see Daston (2007). For a review of the issues relating to objectivity within contemporary biomedical academia (Greene 2007; Lakoff 2006; Marks 1997; Relman 2007). Within the field of placebo research, endogenous opioids were the first neurobiological substrates consistently enlisted as a physiological mediator of the placebo effect – when the administration of the opioid-antagonist Naloxone was shown to reduce placebo-mediated analgesia (Levine, Gordon, and Fields, 1978). Since then, placebo research has expanded enormously and opioids continue to play a prominent role (Price, Finniss, and Benedetti, 2008; Zubieta and Stohler, 2009). For example, brain-imaging studies have begun to specify the role of opioids in placebo processes by localizing placebo-induced functional changes in opioid-signalling in the brain (Zubieta, Bueller, Jackson, Scott, Xu, Koeppe, Nichols, and Stohler, 2005). Such studies have begun to model the functional anatomy of multiple involved areas in the cerebral cortex, the midbrain and the basal ganglia involved during placebo-

mediated interactions (Faria, Fredrikson, and Furmark, 2008; Mayberg, Silva, Brannan, Tekell, Mahurin, McGinnis, and Jerabek, 2002; Wager, Scott, and Zubieta, 2007). They have also been able to account for endophenotypical functional traits that differentiate individuals showing stronger placebo responses from those who display weaker responses (Petrovic, Kalso, Petersson, and Ingvar, 2002; Scott, Stohler, Egnatuk, Wang, Koeppe, and Zubieta, 2008; Zubieta, Yau, Scott, and Stohler, 2006). In addition to opioids, other neurotransmitter systems such as Cholecystokinin, Dopamine and Serotonin have been implicated in placebo effects and, in some contexts, shown to interact with opioid-signalling (Benedetti and Amanzio, 1997; Furmark, Appel, Henningsson, Ahs, Faria, Linnman, Pissiota, Frans, Bani, Bettica, Pich, Jacobsson, Wahlstedt, Oreland, Langstrom, Eriksson, and Fredrikson, 2008; Scott, Stohler, Egnatuk, Wang, Koeppe, and Zubieta, 2007).

Changes in opioid-signalling were shown to be relevant beyond pain modulation in clinical conditions such as Parkinson's Disease, major depression and Post-traumatic Stress Disorder (PTSD) (Kennedy, Koeppe, Young, and Zubieta, 2006; Liberzon, Taylor, Phan, Britton, Fig, Bueller, Koeppe, and Zubieta, 2007; Oken, 2008). Placebo-mediated changes in opioid-signalling were also shown in relation to muscular endurance (Benedetti, Pollo, and Colloca, 2007) and the regulation of emotions (Eippert, Bingel, Schoell, Yacubian, and Buchel, 2008; Petrovic, Dietrich, Fransson, Andersson, Carlsson, and Ingvar, 2005).

The cognitive and emotional implications of suggestion processes have been investigated in social psychology and psychotherapy research in various ways, involving concepts like self-efficacy beliefs and the Pygmalion effect, amongst others (Bandura, 2001; Frank, 1993; Zimbardo and Leippe, 1991). In an educational context, brief, well-targeted interventions have been shown to boost the scholarly performance of youth at risk with remarkably long-lasting effects and to significantly reduce the chance of being caught in a downward spiral of negative stereotyping and disappointment. (Ambady, Shih, Kim and Pittinsky, 2001; Cohen, Garcia, Purdie-Vaughns, Apfel, Brzustoski, 2009) This established body of work on social learning and cognition, together with more recent insights into placebo mechanisms from neuroscience and pharmacology (Benedetti, 2009a; Krummenacher, Candia, Folkers, Schedlowski, and Schönbächler, 2010), including work on the functioning of 'cognitive enhancers' (see e.g. Volkow, Wang, Ma, Fowler, Wong, Jayne, Telang & Swanson, 2006), indicate the possibility of addressing the placebo effect within cognitive domains beyond those encountered in clinical environments and emotional reaction experiments.“

Recently, several studies have provided evidence that following targeted interventions, and with the appropriate training, at least some cognitive functions, including fluid intelligence (Feuerstein, 1980; Jaeggi, Buschkuehl, Jonides, and Perrig, 2008), attentional states (Slagter, Lutz, Greischar, Francis, Nieuwenhuis, Davis, and Davidson, 2007; Tang and Posner, 2009) and working memory capacity (Klingberg, Fernell, Olesen, Johnson, Gustafsson, Dahlstrom, Gillberg,

Forssberg, and Westerberg, 2005).

Opioid receptors are widely represented in the brain (Henriksen and Willoch, 2008), being present in areas involved in learning, addiction and memory (Bruins Slot and Colpaert, 1999; McGaugh, 1989; Nestler, 2002). However, evidence for the direct involvement of endogenous opioid-signalling and of Naloxone in human memory has remained equivocal, or limited to specific contexts (Saddler, James, and Harington, 1985; Volavka, Dornbush, Mallya, and Cho, 1979). For instance, Naloxone-blockage of opioids was shown to increase memory performance in states of heightened emotional arousal (Katzen-Perez, Jacobs, Lincoln, and Ellis, 2001). Conversely, very high doses of Naloxone (2.0 mg/kg) were shown to produce memory impairments (Tariot, Sunderland, Weingartner, Murphy, Cohen, and Cohen, 1986). (For a review of opioid pharmacology (Gutstein and Akil 2001)

The present study sought to investigate placebo effect outside clinical and emotional contexts, within a cognitive domain that is easily accessible to objective measurements. To do so, memory functions were tested in healthy volunteers in relation to their susceptibility to placebo-mediated suggestion. Objective memory performance was assessed together with concurrent subjective self-estimations of performance success.

A double-blind experimental design was used and NaCl or Naloxone was

administered to two groups of participants between two series of memory tasks. While a 'suggestion group' (**S+**) was told that it might receive a drug with suspected memory-boosting properties, a second control group (**S-**) did not receive such information (see Methods). Intra-individual changes in memory performance and subjective self-estimations of participants were recorded. To account for potential test-related changes in stress level, salivary cortisol was measured.

We hypothesized that this setting would enable us to tease out objective from subjective effects following placebo intervention.

Methods

Subjects

Sixty-two healthy men (29 years, SD 9 years) were recruited using notice-board announcements. Prior to inclusion in the study, subjects were screened for normal memory capacity, using a digit span subtest from the revised Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler, 1981), as well as for general health problems using an extensive health questionnaire. Exclusion criteria included the presence of acute or chronic illness, in particular neurological and psychiatric, gastrointestinal, hepatic, renal or cardiac diseases. Further exclusion criteria included use of medication at the time of the study, a history of drug or alcohol abuse, smoking >5 cigarettes per day, simultaneous participation in other research studies and, finally, being under 18 or over 60 years of age. Females were excluded from the study to avoid potential confounding factors related to menstrual cycle-dependent variation in endogenous opioid-activation (Craft, Mogil, and Aloisi, 2004) and memory performance (Farage, Osborn, and MacLean, 2008; Mordecai, Rubin, and Maki, 2008). All subjects had normal vision, or vision that had been successfully corrected. The study was approved by the local ethics committee and was conducted according to the Helsinki guidelines for the treatment of experimental subjects. All volunteers gave their written informed consent and were paid to participate.

Study design

Participants underwent memory testing that was carried out with a memory

battery comprising 7 tasks specified below. For each memory task, participants gave a subjective success estimation rating regarding their perceived memory performance and also provided a saliva probe at the end of the experiments. Thereafter, with the exception of an injection-free control group consisting of 12 participants, participants received an intravenous (I.V.) injection of NaCl or Naloxone in a double-blind setting according to a randomization list. To ensure blinding of examiner and subjects, a study nurse not otherwise involved in the study applied the injection, which was labelled with numbers corresponding to a list containing the kind of substance being used; this was made accessible to the experimenter only after full completion of the study. After 5 minutes, the procedure was repeated with another memory task-battery, self-assessments and a saliva probe (Figure. 1).

- Insert Figure. 1 at about here -

Stimuli

With the task-batteries, 2 sets of stimuli were presented in counterbalanced order before and after the I.V. injection. For each subject and task, the sequence of the task versions was randomly assigned to either the pre- or post-injection task-battery block. All tasks used were selected or constructed to be, as far as possible, emotionally neutral, i.e. highly arousing stimuli were deliberately avoided in order to minimize the probability of eliciting strong emotions and stress among participants.

The participants started all tasks by pressing a computer keyboard button. In each session, subjects performed a short practice run immediately before testing. The distance from the screen was arbitrarily set at about 80 cm. All subjects confirmed verbally that this distance was appropriate and did not impede normal vision.

Multiple tasks

For both the short-term and delayed-recall memory domains, multiple tasks were used in order to adjust for random lapses in concentration, unrelated to the task, which might arise when using a single task. For an overview of the advantages of multiple testing (Shackman, Sarinopoulos, Maxwell, Pizzagalli, Lavric, and Davidson 2006).

Short-term recall tasks

Five sets of stimuli with negligible emotional load, including words, numbers, symbol-strings, geometric figures and images of objects, were visually presented. These different sets of stimuli were prepared in order to encompass a wider range of elements pertaining to different memory domains (e.g. verbal, numerical, visual).

Words (W): The two 15-word batteries of the Rey Recognition Test were used (Lezak, 1995). The words were reproduced verbally.

Numbers (N): Two sets of 12 two-digit numbers, randomly selected from a pool of integers from 0 – 99, were used.

Strings (S): Two sets of 12 two-digit strings, consisting of one random number and one additional random symbol (e.g. “4 #”, “9 !”, etc.), were used.

Images of objects (I): Twenty easily recognizable objects (e.g. a garden fence, sun glasses, a car, etc.) were custom-selected. These were standardized according to size and background to be intuitively visually distinctive.

Geometric Figures (G): Two sets of 12 stimuli were presented, with each stimulus consisting of two 2-dimensional geometrical figures (e.g. a circle and a triangle, a line and a dot, a square and a line, etc.) from an adapted version of the Benton Test according to Kramer (Benton, 1973; Kramer, 1974).

As we were not interested in the single tasks but in their average scores, task order in each session was as follows: W, N, S, I, G. The stimuli presented on a computer screen were shown in black (font size 72 for all symbols) against a white background. The presentation time was 2000 ms and the inter-stimulus intervals 1500 ms.

Delayed recognition tasks:

Two recognition tasks, one involving numbers and one comprising geometric figures, were presented 20 minutes after each of the respective recall tasks. Both recognition tasks contained a list of 20 items, where 10 were items from the list previously presented in the short-term condition and 10 were new. The participants were asked to press one of two buttons, depending on whether or not they thought the items presented had already been shown during the recall task 20 minutes before. No feedback was

given as to whether the subjects had performed correctly or incorrectly. The items for the delayed recognition task were first presented in the two short-term tasks (numbers and geometric figures). The second presentation, for the delayed-recall tasks, occurred 20 minutes later. The procedure was similar in both cases: the first one (the short-term tasks and the recognition tasks) took place before, the second one (again short-term and recognition tasks) after drug injection.

Substances

Either Naloxone (1.5 mg/ ml) or NaCl (0.9%), both supplied by the Pharmacy of the Kanton Zurich, were intravenously injected with a dosage of 0.1 ml / kg body weight.

Cortisol measurement

Cortisol saliva samples were processed and concentrations measured as described by Meyer et al. (Meyer, Hauffa, Schedlowski, Pawlak, Stadler, and Exton, 2000).

Procedure

Placebo induction

All subjects were informed about the experimental procedures. Participants were randomly distributed into 4 groups (group membership was totally unknown to the experimenter) according to a predefined list containing the ampoules of both substances labelled with numbers. Groups were as follows: NaCl **S+** (n = 15, 15

right-handed), Naloxone **S+** (n = 15, 12 right-handed, three ambidextrous), NaCl **S-** (n = 21, 17 right-handed, 4 ambidextrous; please note that this group includes an injection-free group, see below) and Naloxone **S-** (n = 11, 10 right-handed, 1 left-handed) (**S+** = suggestion, **S-** = suggestion-free). Participants in the **S+** group were told that the study was intended to investigate the memory-enhancing properties of Naloxone. They were told that while Naloxone was an established substance in the context of intoxication diagnosis and treatment, strong indications for potential memory-related properties have come to the fore in recent research. The statement used to recruit the **S-** group was similar to the one used for the **S+** group, except that it did not include any information regarding the potential cognitive effects of the tested drug (see supplementary material for this information in full). In addition to the written information, the experimenter orally expressed to the **S+** group that the expectation was that memory-boosting properties would be elicited by the injected drug. The control group did not receive this information. After the experimental session, the participants were given full experimental debriefing.

A control group (n = 12) received no injection at all. This was done in order to control for a potential placebo effect due to the injection procedure on its own. This data set was merged with the NaCl **S-** group data after it was found that these two groups did not statistically differ regarding their objective performances, subjective evaluations and stress-marker accounts (memory tasks, subjective assessments, cortisol changes: all $p > 0.05$).

Stimulus presentation

All memory items were presented via a Macintosh laptop computer running Cedrus Superlab© Pro Version 4.0 software.

Data recording

Short-term free recall: The participants reproduced the recalled items on a paper sheet (numbers, strings, geometric figures and image names) or enumerated verbally (words) respectively. Items perfectly recalled were given full points. In the string and geometric tasks, half points were given for minor errors according to pre-established criteria (e.g. “3 #” instead of 3 *”, “6 =” instead of “6 _”, “8 %” instead of “8 :”).

Delayed-recognition task: “Yes” and “No” button-responses were recorded, along with reaction times (RTs). All correct reaction time responses ranging from 400 to 2000 ms were counted (no responses with reaction times between 200 and 399 ms were found; shorter reaction times were deemed to be random responses).

Subjective performance assessment

All subjects gave a subjective performance-estimation rating on a visual analogue scale (0–100 mm, representing low to excellent performance) for each task in both sessions. At the end of the second run, an overall comparison of the performances in the two runs was also expressed on a VAS-scale.

Data handling

Results of the seven single tasks were grouped according to the two domains: short-term recall (5 tasks: words, numbers, symbol strings, geometric figures, images) and delayed recognition (2 tasks: numbers and geometric figures). Given that the number of items varied between tasks, the results were normalized as a percentage of each task's possible maximum score. Thereafter, the difference in performance between sessions (session 2 *minus* session 1) was computed. In order to avoid evaluating similar memory domains twice, and considering that task items were not standardized upon a large population of subjects, correlations among task scores were computed. Only two tasks correlated significantly with each other, namely numbers versus images (Spearman-Rho= 0.498, $p<0.05$). All other tasks showed correlations with Rho <0.25 and were statistically insignificant. Number and image scores were therefore averaged and further evaluated as a single task score. Thus, the average over the short-term tasks was therefore calculated as: Short-term-performance = (W+S+(N+I/2)+GF)/4).

Statistical Analyses

All statistical analyses were computed using SPSS software package version 16.0 (SPSS, Chicago, IL). Data were controlled for normal distribution and homogeneity of variance using a Levene's test and Kolmogorov-Smirnov test. For all analyses, the significance level was set at $\alpha = 5$ %. Unless indicated, all results shown are means and standard error of the mean (SE). ANOVAs were

calculated based on the score differences (second run *minus* first run) for the four groups NaCl **S+**, Naloxone **S-**, NaCl **S-** and Naloxone **S-**. *Post hoc* comparisons were calculated by means of single Student's *t*-tests. These results were corrected by using a simple Bonferroni correction.

Test for substance effect on subjective performance estimation

To test for a potential substance effect in relation to the accuracy of subjective estimations of success, correlations were computed between the average score differences of objective- and subjective performance estimation. For this analysis, each of the two groups, NaCl and Naloxone, included the **S-** and **S+** conditions**.**

Test for subjective drug effects

A one factorial ANOVA for the subjective drug effect was computed. To account for cortisol influences on subjective drug effect, an ANCOVA with cortisol as covariate was then computed.

Accuracy of subjective performance estimation

Objective results and subjective performance estimation were compared through the calculation of Spearman Rank correlations.

Tests for potential confounders

To test for potential effects of the *injection procedure alone*, an injection-free

control group was included. A separated one factorial ANOVA, comparing the group receiving an NaCl injection without accompanying drug-related suggestion with the injection-free group, was performed on the average scores of differences in any domain (objective and subjective evaluations: short-term recall; delayed recall). In addition, cortisol concentration changes were evaluated by means of a one factorial ANOVA assessing cortisol concentration changes ($Cortisol_{post}$ minus $Cortisol_{pre}$) for all groups receiving injection. In order to test the receptivity for suggestive cues during Naloxone conditions, reaction times (used as markers of attention shifts) were analyzed by means of ANOVAs for the average score of reaction time changes of NaCl and Naloxone groups (RTs_{post} minus RTs_{pre}) during the delayed-recognition tasks.

Correction of missing data

Missing data were found for some subjects and were replaced by the respective group mean for the given task following the statistical considerations given in the SPSS statistical package. It is important to note that this procedure did not affect the results. Due to an unintended printing error on one examination sheet, data from a single task, the subjective evaluation of the image task, were not always recorded. Thus, in the subjective evaluation domain, the N-task was directly introduced into the calculations rather than the weighted value from N and I-tasks (see data handling above).

RESULTS

1. Objective Memory Performance

Short-term recall domain

The one factorial ANOVA for the averages of the differences "second *minus* first run" (hereafter "score differences") was significant ($F(3,58) = 4.86$, $p = 0.004$). After Bonferroni correction, *post hoc* comparisons showed a significantly higher memory performance score for NaCl **S+** compared to the 3 other groups, Naloxone **S+** ($p = 0.047$), NaCl **S-** ($p = 0.029$), and Naloxone **S-** ($p = 0.006$). (See Figure 2, left panel.) All other comparisons were statistically insignificant. The effect remained significant when cortisol-level changes were included as a covariate (*Group* ($F(3, 54) = 5.086$, $p = 0.004$). The factor *Cortisol* and its interaction with the factor *Group* were not significant.

- Insert Figure. 2, 3 and 4 at about here -

Delayed-recognition domain

The one factorial ANOVA for the score differences in delayed-recognition tasks comprising the same 4 groups was not significant ($F(3,58) = 1.56$, $p = 0.21$) and remained insignificant when computing cortisol-level changes as covariate.

2. Subjective Self-evaluation of performance Success

Short-term domain

The one factorial ANOVA for the score differences in the short-term recall tasks for the same four groups was significant ($F(3,58) = 3.81$, $p = 0.015$). *Post hoc*

analyses with Bonferroni corrections for multiple single comparisons showed a higher memory score for NaCl **S+** compared to Naloxone **S+** ($p = 0.030$) and NaCl **S-** ($p = 0.045$), and a weak trend when compared to Naloxone **S-** ($p = 0.081$). All other comparisons were statistically insignificant (see Figure. 2, right panel). The effect remained significant when computing cortisol-level changes as a covariate using ANCOVA ($F (3, 57) = 3.99$, $p = 0.012$).

Delayed recognition

The one factorial ANOVA for the score differences in the delayed-recognition domain was not significant ($F (3,58) = 0.14$, $p = 0.93$). The ANCOVA with cortisol as covariate was also not significant ($F (3, 57) = 0.51$, $p = 0.68$).

Accuracy of subjective performance estimation within the short-term recall domain

Correlations were significant for both groups: $NaCl_{(objective\ vs\ subjective)}$: $r = 0.60$, $p < 0.01$, ($n = 36$); and for $Naloxone_{(objectve\ vs\ subjective)}$: $r = 0.53$, $p < 0.01$, ($n = 26$). The difference between the two correlations was not significant ($Zdiff. = 0.26$, $p < 0.796$ two-tailed) (Bruning and Kintz, 1997).

Subjective drug effect

The one factorial ANOVA for the score differences in subjective drug effect was significant ($F (3,45) = 4.74$, $p = 0.006$), even when accounting for cortisol in an ANCOVA ($F (3, 44) = 3.92$, $p = 0.014$). *Post hoc* tests with Bonferroni correction

showed a significantly higher score for NaCl **S+** compared to the 2 suggestion-free groups NaCl **S-** ($p = 0.042$), and Naloxone **S-** ($p = 0.010$). All other comparisons were statistically insignificant.

- Insert Table 1 at about here –

3. Potential confounders

Injection-free control group

The separated one factorial ANOVA comparing the NaCl **S-** group with the injection-free group was not significant for score differences in any domain (objective evaluations: short-term recall ($F(1,19) = 0.25$, $p = 0.63$); delayed recall ($F(1,19) = 0.76$, $p = 0.40$); and for the score of subjective estimation of performance success over the short-term recall and delayed-recall domains ($F(1,19) = 0.06$, $p = 0.82$).

Control of baseline performance

The baseline performance of all groups was compared (i.e. the first trials, before the drug injections). No significant differences were found (individual task comparisons and score comparisons: all $p>0.1$).

Cortisol concentration changes

The univariate ANOVA assessing cortisol-concentration changes ($Cortisol_{post}$ *minus* $Cortisol_{pre}$) for all groups receiving injection was significant ($F(5,59) = 2.39$,

p = 0.048). However, *post hoc* comparisons did not survive Bonferroni corrections.

Reaction times

The ANOVAs for the score differences of reaction-time changes (RTs_{post} *minus* RTs_{pre}) during the delayed-recognition tasks was statistically insignificant ($F(5,72) = 0.46$, $p = 0.81$).

Discussion

In the first part of this study we tested for effects of placebo-mediated suggestion on (1) memory performance and (2) subjective self-estimations of that performance. Between the two runs of memory tasks we administered an intravenous injection of a placebo substance (0.9%, 0.15mg/kg). While one group of volunteers was told that the injected substance might produce a memory-boosting effect (**S+**), the other (**S-**) received only drug-related information unrelated to potential memory effects. When comparing memory performance scores between the runs, we found a significant increase in memory performance for short-term recall tasks in the **S+** group, but not so in the **S-** group. This effect was not seen in delayed-recognition tasks.

After completing the tasks, the participants' estimations of performance success were assessed using a separate VAS for every individual task. Subjective estimations agreed with objective performance scores; compared to those in the **S-** groups, the participants in the **S+** groups estimated their performance success as being higher in the short-term memory tasks, but similar in the delayed-recognition tasks.

All in all, these results show that short-term recall performance was susceptible to placebo-mediated suggestion: performance was objectively enhanced and not just subjectively considered to have increased. This increase in performance occurred instantaneously, within minutes of the injection.

Many studies have highlighted suggestion-related *qualitative* changes in memory content resulting in, for example, memory distortion and 'false' memories (Schacter and Slotnick, 2004; Wade, Sharman, Garry, Memon, Mazzoni, Merckelbach, and Loftus, 2007). In addition, other studies have shown that the cognitive capacities within some memory domains may be increased or preserved over time through specific training regimes (Jaeggi et al. 2008; Klingberg et al. 2005) or modulated through hypnosis (Mendelsohn, Chalamish, Solomonovich, and Dudai, 2008). The present study extends these findings and shows a training-independent, quantitative boosting effect of placebo-mediated suggestion in a circumscribed memory domain that was objectively observed.

In the second part of this study we tested the role of μ-opioid processing on placebo-mediated suggestion and this time administered the μ-opioid-antagonist Naloxone as a placebo substance. After injecting either Naloxone or NaCl in a double-blind setting, we found that in the **S-** groups, objective and subjective evaluations of memory performance were similar in all memory domains. In the **S+** group, however, we found that contrary to the NaCl-condition, neither objective short-term memory scores nor self-estimations of these scores increased under Naloxone. In the delayed-recognition domain, objective and subjective scores were similar in all four groups.

While Naloxone failed to produce an inherent effect in the absence of suggestion,

the suggestion-related increase in performance measured in the NaCl-group was specifically blocked when Naloxone was administered to the **S+** group. These results indicate that the placebo effect within the short-term recall domain was opioid mediated.

We can only speculate about the anatomical pathways through which opioid signalling may fascilitate suggestive effects on cognition. Obvious candidates include the ventral striatum, the amygdala, the insular and anterior cingular cortices and possibly other structures where the opioid system interacts with dopaminergic neurotransmission (e.g. Zubieta & Stohler, 2009). The interactions may operate via influences on valence processing and/ or more directly on (working-) memory-related pathways

Several potential confounders were considered in this study, including (1) stress, (2) drug-induced emotional blurring and (3) unspecific drug-related cognitive effects potentially affecting attention. In the following section, these factors will be discussed separately.

Stress

Different levels of emotional strain elicited during test situations may affect test performance. For instance, acute stress levels, as measured by means of salivary cortisol-concentration changes, have been shown in some studies to correlate with decreased performance in memory tasks in healthy volunteers

(Kuhlmann, Piel, and Wolf, 2005; Wolf, Schommer, Hellhammer, McEwen, and Kirschbaum, 2001). In other studies, 'inverted u-shaped' dose-response effects of stress hormones in some brain areas such as the CA1 area of the hippocampus have been reported (Joels, 2006). It therefore seems conceivable that a placebo-mediated increase in memory performance may result from a comforting effect of the suggestion used and as a result of reduced stress. However, salivary cortisol-concentration changes in the course of the experiment were similar across all groups, and the inclusion of pre-to-post differences in individual cortisol concentration as a covariate in the statistical models did not change these results. We conclude that the experimental situation *per se* did not elicit substantial stress reactions among volunteers. Consequently, we firmly believe that neither stress nor stress alleviation contributed to the present findings.

Drug-induced emotional blurring

Although studies investigating the impact of Naloxone on emotion have not found significant effects at the timescales and substance concentration levels investigated in the present study (0.15 mg/kg), some dysphoric effects have been described at higher doses (0.2 mg/kg). In addition, increased tension- and confusion-scores have been reported (although at later times, several hours after injection) (Grevert and Goldstein, 1978; Martin del Campo, Dowson, Herbert, and Paykel, 1994; Tariot et al., 1986). Therefore, the Naloxone effect may have been the result of drug-induced emotional blurring. If this were the case, such an effect

would reduce volunteers' susceptibility to the suggestive intervention. We used correlations to compare scores of subjective estimation of performance success with objective scores under the action of both substances. We could not find any substance effects. In particular, we did not see any changes in accuracy of self-estimation under Naloxone, which clearly goes against an emotional blurring-effect of Naloxone as an explanatory factor for our results.

Drug-related unspecific cognitive effects

It could be argued that a Naloxone-triggered effect on alertness may have compromised attention among participants. It is known that attention and short-term memory processing have partially overlapping neuroanatomical substrates (Awh, Vogel, and Oh, 2006; Collette and Van der Linden, 2002; LaBar, Gitelman, Parrish, and Mesulam, 1999). While no differences were found between the NaCl- and Naloxone groups in the **S-** condition, it is still possible that Naloxone may have reduced the receptivity for suggestive cues. However, reaction-time comparisons of correct responses in the delayed-recognition tasks (used as markers of attention shifts) were not significant in any of the investigated groups, something clearly arguing against a possible substance effect compromising attention.

Study limitations

Our task battery assessed a limited spectrum of memory functions, which clearly precludes statements regarding other subsets of potentially affected memory

functions. Secondly, we did not use questionnaires to assess emotional states and therefore had to rely on previous findings published in the literature which suggest that Naloxone does not induce substantial emotional effects at low doses within the first hour after injection (Grevert and Goldstein 1978; Martin del Campo et al. 1994).

Over the last three decades, the role of opioid-signalling for placebo-mediated suggestion has been firmly established in diverse contexts ranging from pain to motor and mental disorders and emotions (Benedetti, Pollo, and Colloca, 2007; Eippert et al., 2008; Kennedy et al., 2006; Liberzon et al., 2007; Oken, 2008; Petrovic et al., 2005).

Our data demonstrate the objective susceptibility of a cognitive domain to placebo-mediated suggestion. That susceptibility, manifesting as increase in memory performance, was specifically blocked by the μ-opioid-antagonist Naloxone. Naloxone did not provoke any other interference with cognitive function, be it objectively or subjectively. The present data indicate that μ-opioid signalling within an emotionally "neutral" context does not interfere with the processing of the cognitive tasks used *per se*. However, it does interact with placebo-mediated suggestion, possibly triggering auxiliary processes that lead to increased cognitive performance. We provide evidence that the reported results were independent of stress-related processes.

We conclude that the scope of μ-opioid-dependent, placebo-mediated suggestive processes appears to be broader than usually considered and can also play a role in the modulation of cognitive functions (such as short-term memory performance in healthy volunteers). Most importantly, our data provide objective evidence for placebo-mediated suggestion.

Acknowledgments

We thank Helma Ammann for her technical assistance.

References

Ambady, N., Shih, M., Kim, A. & Pittinsky, T. L. (2001), Stereotype Susceptibility in Children: Effects of Identity Activation on Quantitative Performance. *Psychological Science*, 12 (5) 385-390

Awh, E., Vogel, E. K., & Oh, S. H. (2006). Interactions between attention and working memory. *Neuroscience,* 139, 201-208.

Bandura, A. (2001). Social cognitive theory: an agentic perspective. *Annual Review of Psychology,* 52, 1-26.

Benedetti, F. (2009a). No prefrontal control, no placebo response. *Pain*.

Benedetti, F. (2009b). Placebo Effects: Understanding the mechanisms in health and disease. Oxford: Oxford University Press.

Benedetti, F., & Amanzio, M. (1997). The neurobiology of placebo analgesia:

from endogenous opioids to cholecystokinin. *Progress in Neurobiology,* 52, 109-125.

Benedetti, F., Pollo, A., & Colloca, L. (2007). Opioid-Mediated Placebo Responses Boost Pain Endurance and Physical Performance: Is It Doping in Sport Competitions? *Journal of Neuroscience,* 27, 11934-11939.

Benton, A. L. (1973). Der Benton-Test Teil 1. Bern: Hans Huber.

Bruins Slot, L. A., & Colpaert, F. C. (1999). Opiate states of memory: receptor mechanisms. *Journal of Neuroscience,* 19, 10520-10529.

Bruning, J. L., & Kintz, B. L. (1997). Computational handbook of statistics: Allyn & Bacon.

Cohen, G. L., Garcia, J., Purdie-Vaughns V., Apfel, N., Brzustoski,P. (2009), Recursive Processes in Self-Affirmation: Intervening to Close the Minority Achievement Gap. *Science*, 324(5925) 400-403.

Collette, F., & Van der Linden, M. (2002). Brain imaging of the central executive component of working memory. *Neuroscience and Biobehavioral Reviews,* 26, 105-125.

Craft, R. M., Mogil, J. S., & Aloisi, A. M. (2004). Sex differences in pain and analgesia: the role of gonadal hormones. *European Journal of Pain,* 8, 397-411.

Daston, L. & Galison, P. (2007). Objectivity. New York: Zone Books.

Eippert, F., Bingel, U., Schoell, E., Yacubian, J., & Buchel, C. (2008). Blockade of endogenous opioid neurotransmission enhances acquisition of conditioned fear in humans. *Journal of Neuroscience,* 28, 5465-5472.

Farage, M. A., Osborn, T. W., & MacLean, A. B. (2008). Cognitive, sensory, and emotional changes associated with the menstrual cycle: a review. *Archives of Gynecology and Obstetrics,* 278, 299-307.

Faria, V., Fredrikson, M., & Furmark, T. (2008). Imaging the placebo response: a neurofunctional review. *European Neuropsychopharmacology,* 18, 473-485.

Feuerstein, R. (1980). Instrumental Enrichment: An Intervention Program for Cognitive Modifiability. Baltimore: University Park Press.

Frank, J. D. (1993). Persuasion and Healing: A Comparative Study of Psychotherapy. Baltimore: Johns Hopkins University Press.

Furmark, T., Appel, L., Henningsson, S., Ahs, F., Faria, V., Linnman, C., Pissiota, A., Frans, O., Bani, M., Bettica, P., Pich, E. M., Jacobsson, E., Wahlstedt, K., Oreland, L., Langstrom, B., Eriksson, E., & Fredrikson, M. (2008). A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety. *Journal of Neuroscience,* 28, 13066-13074.

Greene, J. A. (2007). Prescribing By Numbers: Drugs And The Definition Of Disease. Baltimore: Johns Hopkins University Press.

Grevert, P., & Goldstein, A. (1978). Endorphins: naloxone fails to alter experimental pain or mood in humans. *Science,* 199, 1093-1095.

Gutstein, H. B., & Akil, H. (2001). Opioid analgesics. In J. Griffith Hardman, L. E. Limbird, & A. G. Gilman (Eds.), The Pharmacological Basis of Therapeutics (pp. 569-620). New York: McGraw-Hill.

Harrington, A. (2008). The Cure Within: A History of Mind-Body Medicine. New York: W.W.Norton.

Harrington, A. E. (1999). The Placebo Effect: An Interdisciplinary Exploration. Cambridge, MA: Harvard University Press.

Henriksen, G., & Willoch, F. (2008). Imaging of opioid receptors in the central nervous system. *Brain,* 131, 1171-1196.

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences of the United States of America,* 105, 6829-6833.

Joels, M. (2006). Corticosteroid effects in the brain: U-shape it. *Trends in Pharmacological Sciences,* 27, 244-250.

Katzen-Perez, K. R., Jacobs, D. W., Lincoln, A., & Ellis, R. J. (2001). Opioid blockade improves human recognition memory following physiological arousal. *Pharmacology, Biochemistry and Behavior,* 70, 77-84.

Kennedy, S. E., Koeppe, R. A., Young, E. A., & Zubieta, J. K. (2006). Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. *Archives of General Psychiatry,* 63, 1199-1208.

Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlstrom, K., Gillberg, C. G., Forssberg, H., & Westerberg, H. (2005). Computerized training of working memory in children with ADHD--a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry,* 44, 177-186.

Kradin, R. (2008). The Placebo Response and the Power of Unconscious

Healing. New York: Routledge.

Kramer, J. (1974). Intelligenztest. Solothurn: Antonius.

Krummenacher, P., Candia, V., Folkers, G., Schedlowski, M., & Schönbächler, G. (2010). Prefrontal cortex modulates placebo analgesia. *Pain,* 148(3), 368-374.

Kuhlmann, S., Piel, M., & Wolf, O. T. (2005). Impaired memory retrieval after psychosocial stress in healthy young men. *Journal Neuroscience,* 25, 2977-2982.

LaBar, K. S., Gitelman, D. R., Parrish, T. B., & Mesulam, M. (1999). Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *Neuroimage,* 10, 695-704.

Lakoff, A. (2006). Pharmaceutical Reason Knowledge and Value in Global Psychiatr. Cambridge: Cambridge University Press.

Levine, J. D., Gordon, N. C., & Fields, H. L. (1978). The mechanism of placebo analgesia. *Lancet,* 2, 654-657.

Lezak, M. D. (1995). Neuropsychological Assessment (third ed.). New York: Oxford University Press.

Liberzon, I., Taylor, S. F., Phan, K. L., Britton, J. C., Fig, L. M., Bueller, J. A., Koeppe, R. A., & Zubieta, J. K. (2007). Altered central micro-opioid receptor binding after psychological trauma. *Biological Psychiatry,* 61, 1030-1038.

Marks, H. M. (1997). The Progress of Experiment: Science and therapeutic reform in the United States, 1900–1990. New York: Cambridge University

Press.

Martin del Campo, A. F., Dowson, J. H., Herbert, J., & Paykel, E. S. (1994). Effects of naloxone on diurnal rhythms in mood and endocrine function: a dose-response study in man. *Psychopharmacology (Berl),* 114, 583-590.

Mayberg, H. S., Silva, J. A., Brannan, S. K., Tekell, J. L., Mahurin, R. K., McGinnis, S., & Jerabek, P. A. (2002). The functional neuroanatomy of the placebo effect. *American Journal of Psychiatry,* 159, 728-737.

McGaugh, J. L. (1989). Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. *Annual Review of Neuroscience,* 12, 255-287.

Mendelsohn, A., Chalamish, Y., Solomonovich, A., & Dudai, Y. (2008). Mesmerizing Memories: Brain Substrates of Episodic Memory Suppression in Posthypnotic Amnesia. *Neuron,* 57, 159-170.

Meyer, G., Hauffa, B. P., Schedlowski, M., Pawlak, C., Stadler, M. A., & Exton, M. S. (2000). Casino gambling increases heart rate and salivary cortisol in regular gamblers. *Biological Psychiatry,* 48, 948-953.

Moerman, D. E. (2002). Meaning, Medicine, and the "Placebo Effect". Cambridge: Cambridge University Press.

Mordecai, K. L., Rubin, L. H., & Maki, P. M. (2008). Effects of menstrual cycle phase and oral contraceptive use on verbal memory. *Hormones and Behavior,* 54, 286-293.

Nestler, E. J. (2002). Common molecular and cellular substrates of addiction and memory. *Neurobiology of Learning and Memory,* 78, 637-647.

Oken, B. S. (2008). Placebo effects: clinical aspects and neurobiology. Brain, 131, 2812-2823.

Petrovic, P., Dietrich, T., Fransson, P., Andersson, J., Carlsson, K., & Ingvar, M. (2005). Placebo in emotional processing--induced expectations of anxiety relief activate a generalized modulatory network. *Neuron,* 46, 957-969.

Petrovic, P., Kalso, E., Petersson, K. M., & Ingvar, M. (2002). Placebo and opioid analgesia-- imaging a shared neuronal network. *Science,* 295, 1737-1740.

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: recent advances and current thought. *Annual Review of Psychology,* 59, 565-590.

Relman, A. S. (2007). Medical professionalism in a commercialized health care market. *Jama,* 298, 2668-2670.

Saddler, J. M., James, M. F., & Harington, A. P. (1985). Naloxone does not reverse ethanol analgesia in man. *Clinical and Experimental Pharmacology and Physiology,* 12, 359-364.

Schacter, D. L., & Slotnick, S. D. (2004). The cognitive neuroscience of memory distortion. *Neuron,* 44, 149-160.

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., & Zubieta, J. K. (2007). Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron,* 55, 325-336.

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., & Zubieta, J. K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Archives of General Psychiatry,* 65, 220-

231.

Shackman, A. J., Sarinopoulos, I., Maxwell, J. S., Pizzagalli, D. A., Lavric, A., & Davidson, R. J. (2006). Anxiety selectively disrupts visuospatial working memory. *Emotion,* 6, 40-61.

Slagter, H. A., Lutz, A., Greischar, L. L., Francis, A. D., Nieuwenhuis, S., Davis, J. M., & Davidson, R. J. (2007). Mental training affects distribution of limited brain resources. *PLoS Biology,* 5, e138.

Tang, Y. Y., & Posner, M. I. (2009). Attention training and attention state training. *Trends in Cognitive Sciences,* 13, 222-227.

Tariot, P. N., Sunderland, T., Weingartner, H., Murphy, D. L., Cohen, M. R., & Cohen, R. M. (1986). Naloxone and Alzheimer's disease. Cognitive and behavioral effects of a range of doses. *Archives of General Psychiatry,* 43, 727-732.

Valentijn, S. A., Hill, R. D., Van Hooren, S. A., Bosma, H., Van Boxtel, M. P., Jolles, J., & Ponds, R. W. (2006). Memory self-efficacy predicts memory performance: results from a 6-year follow-up study. *Psychology and Aging,* 21, 165-172.

Volavka, J., Dornbush, R., Mallya, A., & Cho, D. (1979). Naloxone fails to affect short-term memory in man. *Psychiatry Research,* 1, 89-92.

Volkow, N. D., Wang, G., Ma, Y. Fowler, J. S., Wong, C. Jayne, M., Telang, F. & Swanson, J. M. (2006), Effects of expectation on the brain metabolic responses to methylphenidate and to its placebo in non-drug abusing subjects. *Neuroimage*, 32 (4) 1782-1792.

Wade, K. A., Sharman, S. J., Garry, M., Memon, A., Mazzoni, G., Merckelbach, H., & Loftus, E. F. (2007). False claims about false memory research. *Consciousness and Cognition,* 16, 18-28; discussion 29-30.

Wager, T. D., Scott, D. J., & Zubieta, J. K. (2007). Placebo effects on human mu-opioid activity during pain. *Proceedings of the National Academy of Sciences of the United States of America,* 104, 11056-11061.

Wechsler, D. (1981). Manual for the Wechsler Adult Intelligence Scale—Revised. New York: Psychological Corporation.

Wolf, O. T., Schommer, N. C., Hellhammer, D. H., McEwen, B. S., & Kirschbaum, C. (2001). The relationship between stress induced cortisol levels and memory differs between men and women. *Psychoneuroendocrinology,* 26, 711-720.

Zimbardo, P. G., & Leippe, M. R. (1991). The Psychology of Attitude Change and Social Influence. Boston: McGraw-Hil.

Zubieta, J. K., Bueller, J. A., Jackson, L. R., Scott, D. J., Xu, Y., Koeppe, R. A., Nichols, T. E., & Stohler, C. S. (2005). Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *Journal of Neuroscience,* 25, 7754-7762.

Zubieta, J. K., & Stohler, C. S. (2009). Neurobiological mechanisms of placebo responses. Annals of the New York Academy of Sciences, 1156, 198-210.

Zubieta, J. K., Yau, W. Y., Scott, D. J., & Stohler, C. S. (2006). Belief or Need? Accounting for individual variations in the neurochemistry of the placebo effect. *Brain, Behavior, and Immunity,* 20, 15-26.

Legends to Figures and Tables

Figure 1: Study design:

M tasks = memory tasks; SEP = subjective estimation of performance; SEDE = subjective estimation of drug effect

Figure 2:

Objective performance (left panel) Higher gain in short-term memory span for the NaCl **S+** group as compared to the other groups (all $p < 0.05$). *Subjective estimation (right panel)* Higher increase in self-assessment scores in the short-term memory domain for the NaCl **S+** group as compared to the groups NaCl **S-** and Nalox **S+** ($p < 0.05$)

Figure 3:

Objective memory performance results are illustrated for the individual tasks, showing the suggestion effect (3a) and the substance effect (3b). (* = $p<0.05$)

Figure 4:

Subjective performance estimations are illustrated, showing suggestion effect (4a) and the substance effect (4b). (* = $p<0.05$). Please note that subjective 'Image'-task data is missing due to a technical error (see 'Correction of missing data', in the last part of the methods section).

Table 1:

Results for pre and post-injection trials. The objective performance is depicted in the upper panel. Depicted are the individual trials as mean % score with the corresponding SE. Subjective success, as estimated on a visual analogue scale (VAS), is depicted in the lower panel. Values are presented as means and SE of VAS improvement in %. Post = post injection, pre = pre injection. 'Medication-effect' corresponds to the subjective score for the overall effect of the drug.

Supplementary material

Group instructions

Suggestion group (S+)

Study goals

The goal of the present study is the assessment of the influence of Naloxone on memory function. Naloxone is a substance commonly used for diagnosis and treatment in cases of suspected overdose following the use of intoxicants (opioids). Some studies on the effects of Naloxone on memory function have been carried out. The results of these studies revealed a strong enhancement of memory in patients suffering from impaired brain function. Nevertheless, studies on healthy volunteers are still required. Consequently, we are interested in the further assessment of the positive memory effect of Naloxone when using a therapeutic dosage of (0.15 mg/kg) in healthy volunteers. In so doing, we aim to obtain new insights into the role of Naloxone within a cognitive setting free of pain.

Suggestion-free group (S-)

Study goals

The goal of the present study is the assessment of the influence of Naloxone on memory function. Naloxone is a substance commonly used for diagnosis and treatment in cases of suspected overdosage following the use of intoxicants (opioids). Some studies on the effects of Naloxone on memory function have been carried out. The results of these studies have been contradictory (positive,

negative or no effects were reported) and no further studies have been carried out. Consequently, we are interested in the further assessment of the effects of Naloxone when using a therapeutic dosage of (0.15 mg/kg). In this way, we aim to obtain new insights into the role of Naloxone within a cognitive setting free of pain.

Research Highlights

- Short-term memory recall is objectively increased after placebo-mediated suggestion.

- Naloxone specifically blocks the suggestion effect without interfering with memory performance.

- These results indicate an opioid-mediated placebo effect within a circumscribed cognitive domain.

Figure 1

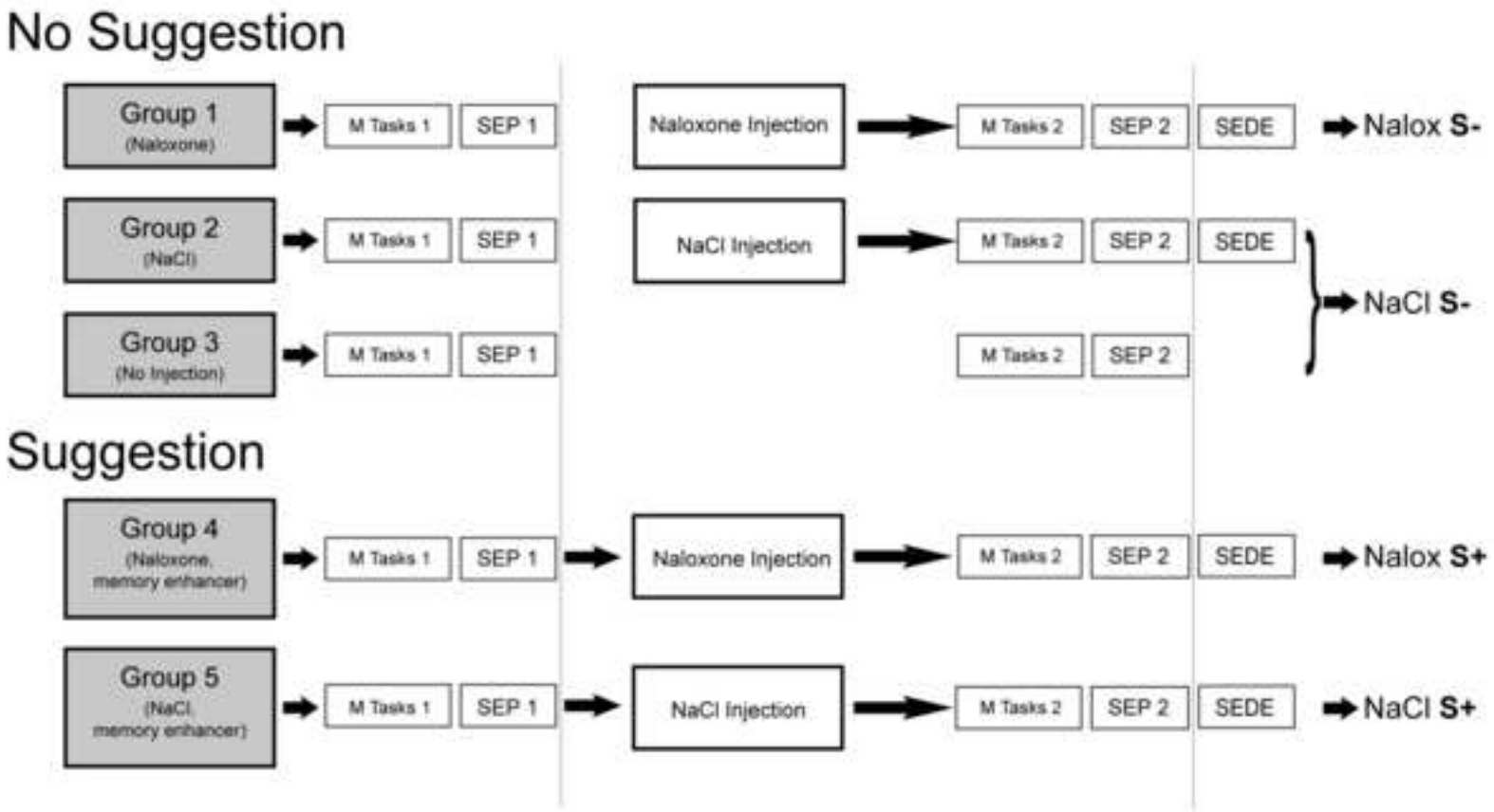
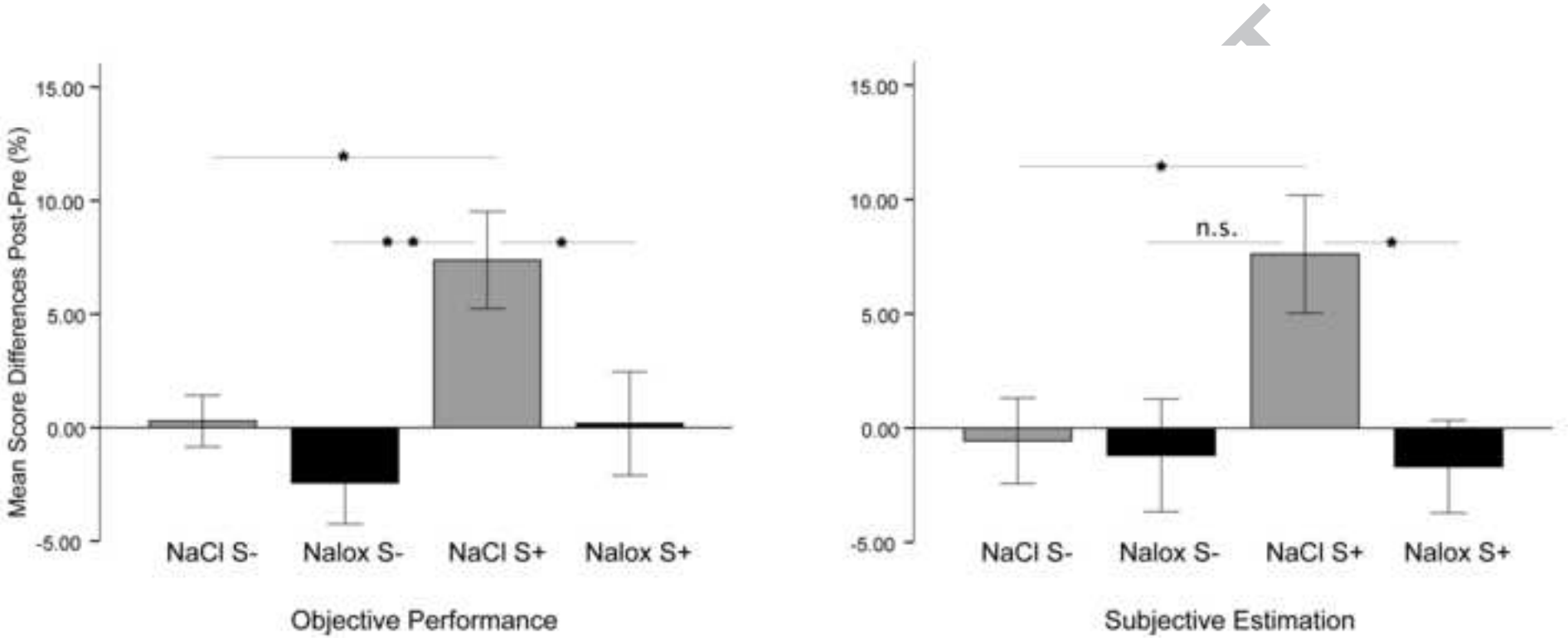
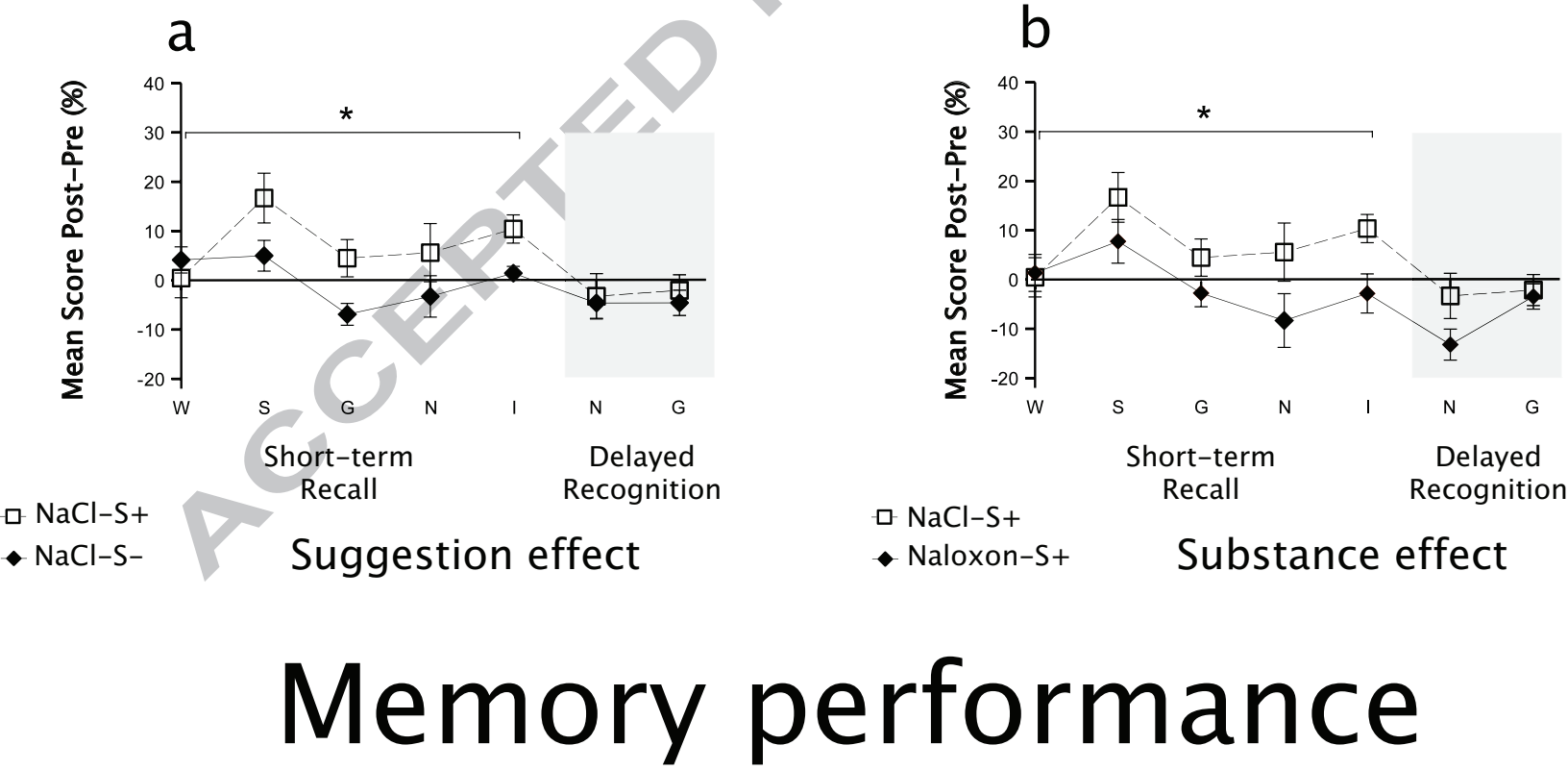


Figure 2



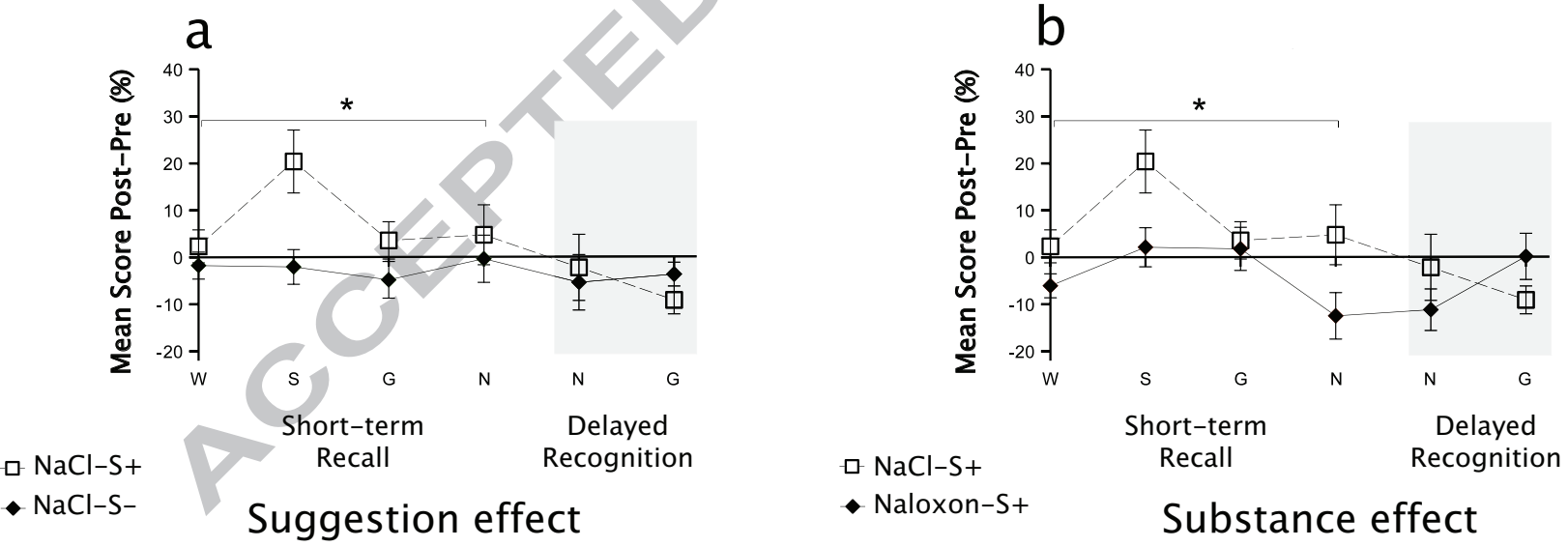
Short-term recall

Figure 3



Memory performance

Figure 4



Subjective success estimation

Memory Performance (split by pre & post)
(Score (%))

Group	NaCl-S+				Nalox.-S+				NaCl-S-				Nalox.-S-			
	pre	(SE)	post	(SE)	pre	(SE)	post	(SE)	pre	(SE)	post	(SE)	pre	(SE)	post	(SE)
W	63.1	4	63.5	4	66.7	4	68.0	4	69.5	3	73.6	4	67.3	5	67.3	4
S	47.5	5	64.2	5	53.3	3	61.0	5	53.8	4	58.7	3	47.7	7	56.4	6
G	59.4	4	63.9	3	69.2	4	66.4	3	67.5	2	60.6	2	66.1	2	57.3	3
N	60.6	5	66.1	5	77.8	4	69.4	5	72.9	3	69.6	5	73.5	6	61.4	8
I	63.0	3	73.3	3	73.7	3	76.3	3	67.7	2	69.1	2	70.6	2	66.3	2
N recognition	77.3	3	74.0	3	82.0	3	71.4	3	80.6	2	76.2	3	81.1	3	77.5	2
G recognition	85.0	3	82.1	2	83.0	3	78.5	3	83.2	2	78.1	2	87.9	2	73.6	3
Cortisol (Δ nmol/l)	5.0	1	5.3	1	10.3	2	10.8	1	5.6	1	4.8	1	9.7	2	14.0	2

Success Estimation
(Mean VAS (%))

Group	NaCl-S+				Nalox.-S+				NaCl-S-				Nalox.-S-			
	pre	(SE)	post	(SE)	pre	(SE)	post	(SE)	pre	(SE)	post	(SE)	pre	(SE)	post	(SE)
W	61.9	4	64.2	4	67.7	3	61.6	3	69.2	4	67.9	4	74.9	3	73.3	2
N	46.7	6	51.5	5	64.0	4	51.5	4	57.6	4	57.3	5	69.5	6	61.3	3
S	34.1	5	54.5	8	49.1	3	51.3	3	51.0	4	48.9	5	53.4	6	60.9	4
GF	57.5	5	61.1	5	53.5	5	55.3	5	59.5	4	54.5	5	67.3	4	61.1	3
N recognition	51.3	7	49.2	5	66.2	4	55.0	3	58.1	3	52.8	5	56.9	8	49.1	4
G recognition	69.6	6	60.5	6	58.2	5	58.4	5	70.4	3	66.8	4	67.1	5	57.8	4
Medication Effect			17.1	4			8.3	3			-1.1	6			-2.5	1