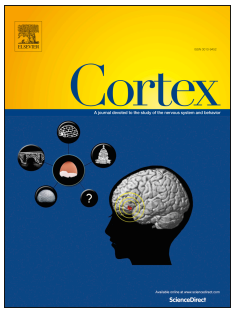
Accepted Manuscript



Expectations impact short-term memory through changes in connectivity between attention- and task-related brain regions

Christopher Sinke, Katarina Forkmann, Katharina Schmidt, Katja Wiech, Dr. med. Ulrike Bingel, Prof.

PII: S0010-9452(16)30010-7

DOI: 10.1016/j.cortex.2016.02.008

Reference: CORTEX 1686

To appear in: *Cortex*

Received Date: 6 October 2015

Revised Date: 8 December 2015

Accepted Date: 6 February 2016

Please cite this article as: Sinke C, Forkmann K, Schmidt K, Wiech K, Bingel U, Expectations impact short-term memory through changes in connectivity between attention- and task-related brain regions, *CORTEX* (2016), doi: 10.1016/j.cortex.2016.02.008.

Expectations impact short-term memory through changes in connectivity between attention- and task-related brain regions

Christopher Sinke[1,5], Katarina Forkmann[2], Katharina Schmidt[1,2], Katja Wiech [3,4], Ulrike Bingel [1,2]

[1] Department of Neurology, University Medical Center Hamburg-Eppendorf, Germany

[2] Department of Neurology, Essen University Hospital, Germany

[3] Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK

[4] Nuffield Department of Clinical Neurosciences, Nuffield Division Anaesthetics, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK

[5] Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Germany

Please address correspondence to:

Prof. Dr. med. Ulrike Bingel

Hufeland 55, 45149 Essen, Germany

Email: Ulrike.Bingel@uk-essen.de

Abstract

Over the recent years, neuroimaging studies have investigated the neural mechanisms underlying the influence of expectations on perception. However, it seems equally reasonable to assume that expectations impact cognitive functions. Here we used fMRI to explore the role of expectations on task performance and its underlying neural mechanisms. 43 healthy participants were randomly assigned to two groups. Using verbal instructions, group 1 was led to believe that pain enhances task performance while group 2 was instructed that pain hampers their performance. All participants performed a Rapid-Serial-Visual-Presentation Task (target detection and short-term memory component) with or without concomitant painful heat stimulation during 3T fMRI scanning. As hypothesized, short-term memory performance showed an interaction between painful stimulation and expectation. Positive expectations induced stronger neural activation in the right inferior parietal cortex during painful stimulation than negative expectation. Moreover, inferior parietal cortex displayed differential functional coupling with the left inferior occipital cortex under pain as a function of expectancy. Our data show that an individual's expectation can influence cognitive performance in a visual short-term memory task which is associated with activity and connectivity changes in brain areas implicated in attentional processing and task performance.

Keywords: expectation, fMRI, short-term memory, inferior parietal cortex, functional connectivity

Introduction

Expectations play a fundamental role during information processing in the brain. They guide the selection of information based on prior experience, allow for fast interpretation of input by reducing computational load and help resolve input ambiguity (Summerfield & Egner, 2009). The recent years have seen a steady increase in publications exploring the influence of expectations on perception in basic science (Summerfield & de Lange, 2014), pain perception (Benedetti, Lanotte, Lopiano, & Colloca, 2007) but also on its clinical implications (Benedetti, 2014). The literature on stereotype threat (Kit, Tuokko, & Mateer, 2008) supports the notion that (implicit) expectations can directly influence cognitive performance. Stereotype threat refers to the phenomenon that awareness of the membership to a certain group leads to performance differences in line with "stereotypes" held about the group. For example, women perform worse in math when being reminded that a test aims at mathematical abilities, tapping into the stereotype of women having poorer math abilities (Johns, Schmader, & Martens, 2005; Quinn & Spencer, 2001; Spencer, Steele, & Quinn, 1999). It has also been shown in elderly people (Barber & Mather, 2014) that activating a certain stereotype leads to a decrease in cognitive performance. Even cognitive deficits in neurological conditions can at least in part be triggered by stereotype threat (Suhr & Gunstad, 2002). Further evidence regarding the role of expectation on cognitive performance stems from randomized-controlled trials (RCTs) of treatments to restore or increase cognitive function in neurological or psychiatric disease. Cognitive performance and associated capabilities have been reported to also improve in the placebo arm of RCTs, supporting the effects of positive treatment expectations on cognitive performance e.g. in Alzheimer's disease (Ito et al., 2013).

Although these lines of evidence lend support to the notion that expectations can modulate cognitive function, little is known regarding neurobiological mechanisms underlying this effect. Colton et al (2013) explored brain regions underlying stereotype threat responses (related to age) and observed activity in posterior midline regions such as the precuneus, which has been associated with self-reflective thought and parahippocampal gyrus

implicated in autobiographical memory in older compared to younger subjects (Colton, Leshikar, & Gutchess, 2013).

Here we used fMRI to explore the neural mechanisms underlying the effects of expectation on task performance in a well-established Rapid-Serial-Visual-Presentation (RSVP) task allows for the investigation of target detection and short-term memory (Coull, Frith, Frackowiak, & Grasby, 1996).

To manipulate expectations participants were informed that concomitantly applied noxious heat stimulation would either enhance (positive expectancy group) or hamper (negative expectancy group) task performance. We hypothesized that differences in expectation regarding the effect of pain on task performance modulate task performance and that these differences are associated with changes in the activity within and between brain areas involved in attention direction and visual task processing.

Materials and Methods

Subjects

Behavioral and fMRI data were acquired in 48 healthy, right-handed subjects. Five subjects had to be excluded from the analyses for the following reasons: 3 due to technical problems with the presentation computer and 2 subjects were aware of the expectancy manipulation. Data of the remaining 43 subjects (20 males; mean age 25.25 years; range, 19-39 years) were included in the final analyses. All subjects had normal pain thresholds at the site of stimulation (Rolke et al., 2006), reported normal hearing, and normal or corrected-to-normal eyesight and had not taken any analgesic medication on the day of the experiment. Subjects further reported no known history of neurological or psychiatric diseases, including recurrent or chronic pain. The study was conducted in accordance with the Declaration of Helsinki and had been approved by the local ethics committee. All participants gave written consent to participate, were free to withdraw from the study at any time and received reimbursement for their participation.

Experimental paradigm

This study is part of a series of experiments investigating the influence of expectation on cognitive task performance. In these experiments pain was used as a tool to manipulate expectation. The experimental design comprised two factors, i.e. EXPECTANCY as a between-subject factor and STIMULATION as a within-subject factor. The study was performed on two days within the same week. On the first day, subjects were randomized into two groups in which either a positive or a negative expectation regarding the effect of pain on cognitive processes was induced by verbal and written instructions (see expectancy manipulation and Fig. 1). We chose to use a positive and a negative manipulation instead of a positive and a neutral condition for two reasons. First, we wanted to ensure that both groups are subjected to a *directed* manipulation of their expectations during the experiment (and particularly during the preparatory procedure). Second, the use of a positive and negative manipulation allowed us to explore the extremes of expectancy manipulation in this proof-of-principle study. Subjects completed preparatory procedures, including the assessment of pain-related personality traits, pain thresholds, calibration of painful thermal stimuli (visual analogue scale (VAS) level of 70, anchors: 0-100), and calibration of the presentation speed of the letters in the RSVP task (see below, Experimental procedures). Furthermore, participants completed a short training session in which they performed the main experimental task. This consisted of a rapid serial processing task (RSVP) in which subjects had to detect (detection task) and count (counting task) a target letter within a stream of rapidly presented letters either with or without concomitant painful thermal stimulation. Subjects were instructed to focus on the task. The actual fMRI experiment was conducted on day 2. Following a check of calibration parameters to ensure that the perceived pain intensity was at VAS 70 and task detection performance at 70% correct detected target letters, the main experiment was conducted. After the experiment subjects were debriefed about the manipulation.

INSERT FIG 1 HERE

Experimental procedures

Day 1. On day 1, the experiment started with the **expectancy manipulation**. One group was informed that previous studies had shown that pain enhances cognitive processes like visual processing and memory (positive expectancy, N=22). The second group was provided with the opposite information, i.e., that previous studies had shown that pain disturbs cognitive processes like visual processing and memory (negative expectancy, N=21). Therefore standardized instructions were read out loud to the subjects by the experimenter. Both groups were informed that the purpose of the study was to use fMRI to investigate the neural processes underlying these known behavioral effects. In order to increase the credibility of the information provided, bar graphs showing the fictive behavioral effects of the mentioned studies were presented with a positive effect for the positively manipulated group and a negative effect for the negative manipulated group.

All subjects filled in a number of questionnaires (see below, Psychological questionnaires) assessing general anxiety and depression [ADS-K, State Trait Anxiety Inventory (STAI), state and trait scale], as well as pain-related psychological processing [Pain Vigilance and Awareness Questionnaire (PVAQ), Pain Anxiety Symptoms Scale (PASS-D), Pain Catastrophizing Scale (PCS)]. Following that, participants were familiarized with the heat pain stimuli. First, the individual **heat pain threshold** at the site of stimulus application (left inner forearm, 12 cm proximally from the wrist) was determined using the Method of Limits (Fruhstorfer, Lindblom, & Schmidt, 1976). Thresholds were obtained using ramped stimuli (1℃/s increase in temperature, starting at a basel ine of 35℃ and with an upper limit of 50℃ to avoid tissue damage, five repetitions, the first run is discarded). Participants had to indicate the first painful sensation by pressing a button. Subsequently, all subjects underwent a **temperature calibration** to determine the individual temperature level corresponding to an intensity level of 70 on a VAS (endpoints: 0, “not painful at all”; 100, “unbearably painful”). To

this end, subjects were presented with stimuli of varying temperature levels around their individual pain threshold (range: pain threshold -2℃ – pain threshold + 1.5℃, temperature difference of 0.5℃, each temperature was applied twice). After each stimulus, participants gave an intensity rating on the VAS that was presented on a computer screen. Using two buttons, subjects indicated the intensity of a stimulus by moving a red bar to a position on the VAS that corresponded to their perception. The temperature that corresponded to an intensity level of VAS 70 was calculated from the provided ratings using linear regression analysis. Subsequently, the presentation speed of the RSVP task was individually calibrated (**task calibration**). Subjects completed 70 RSVP trials while the presentation speed was decreased by 17ms (i.e., the refresh rate of the experimental computer) on every tenth trial. Participants were instructed to press a button with the index finger of the right hand as quickly as possible whenever they saw the letter 'A' ('detection task') and count the number of times the letter had been presented ('counting task'). The counting result was indicated by pressing the corresponding key on a number pad using the index finger (one target letter), middle finger (two targets) or ring finger (three targets) of the right hand. Responses, button presses, response time (RT), and intensity ratings were recorded as behavioral outcome measures. Calibration started with a presentation speed of 116 ms and ended with a presentation speed of 48 ms for each letter. The rate of correct detections was then calculated using Matlab® and the presentation speed corresponding to a correct detection rate of 70% was chosen as presentation speed for the main experiment. Upon completion of the calibration phase participants were familiarized with the actual experimental task. Using a VAS (endpoints in written form without numbers, scores were transformed by presentation), they first indicated their current mental state on a VAS assessing tiredness (endpoints: 0= "not tired at all"; 100= "extremely tired"), excitement (endpoints: 0= "relaxed" ; 100= "extremely excited"), fear of pain (endpoints: 0= "not fearful at all"; 100= "extremely fearful") and their expectation of how pain would influence their performance (endpoints: -5= "pain dramatically impairs performance", 5= "pain dramatically improves performance"; 0= "no influence"). For all ratings, the red indicator bar appeared at a random position on the VAS at

the beginning of the rating. To double-check the calibration of heat pain stimuli and the presentation speed of the letters, pain intensity of three heat pain stimuli (VAS 70) were rated by the subjects and 10 RSVP trials were presented at the calibrated speed. The first session ended with a short run of the RSVP task consisting of 30 RSVP trials (see below) of which 15 were presented with concomitant thermal painful stimulation. 5 consecutive RSVP trials were grouped into one block resulting in an overall block length of 18 seconds. Three blocks were presented with and three without concomitant painful stimulation in randomized order. Painful blocks and non-painful control blocks were cued by presenting a colored or white circle (control) for two seconds. A red circle was shown in the negative expectancy group and a green circle was presented in the positive expectancy group (see also Fig. 2). Pain was cued in order to allow expectation to specifically influence task performance during stimulus delivery.

Day 2. The fMRI session was conducted on the second day of the study. First, participants were reminded of the experimental instructions. Before the actual experiment, all subjects underwent a number of tests inside the MR scanner: To check whether the level of thermal stimulation determined on day 1 still yielded an intensity rating of VAS 70 when presented inside the scanner, 3 stimuli of the according VAS 70 temperature were presented. Participants had to indicate the perceived intensity for each stimulus using a VAS. In case the intensity ratings differed from the intensity obtained on day 1, the temperature was adjusted and the new temperature was again evaluated using 3 heat stimuli. Recalibrated temperatures did not differ significantly between groups (see Heat Pain Stimuli). The same procedure was conducted for the presentation speed of the RSVP task using 10 trials without heat pain stimulation. After completion of these tests, subjects had to rate their current mental state (see day 1) and performed the actual RSVP task (duration of ~20 min). As on day 1, letters were presented alone (“control”) or with concurrent painful thermal stimulation (“pain”). The experiment consisted of 15 painful and 15 control blocks presented in randomized order (corresponding to 75 RSVP trials in each condition, see Fig 1a). Each block was preceded by the presentation of a circle for 2s duration. A white circle indicated a

control block whereas a colored circle signalized a pain block. In the negative expectancy group a red circle was shown while the positive expectancy group saw a green circle introducing a pain block. The circle was followed by a white fixation cross with a variable duration of 3 - 7 s. Subsequently, 5 RSVP trials were presented. During each RSVP trial train of letters were presented for 2 s at an individually adjusted presentation speed for each letter (mean: 65 ms ± 18, ranging from 117 to 50 ms, no significant differences between groups). At the end of each trial, subjects were asked to indicate how often the target letter 'A' had been presented. When subjects had pressed the response button (max. response time 1.5 s) the next RSVP trial was started with an inter-trial interval (ITI) between 0.5 s and 1 s. Upon completion of the fifth trial (end of the block) subjects had to indicate their perceived pain intensity on a VAS scale (see Fig. 2 for details). The VAS rating was separated from the last RSVP trial of each block by the presentation of a fixation cross for 3-4 seconds. Pain and control blocks were separated by a variable ITI between 3 s and 7 s during which a white fixation cross was presented.

INSERT FIG 2 HERE

Stimuli

The presentation of the visual stimuli, the application of thermal stimuli, and the recording of behavioral data was performed using the software Presentation® (www.neurobs.com).

Visual stimuli

The visual stimuli comprised all letters of the alphabet presented in the font type 'Arial'. The letter A served as the target letter. The visual stimuli were presented on a back projection screen located behind the MR scanner. The screen could be seen via a mirror attached to the head coil. The letters had a visual angle of ~4° X 3° and were displayed for an individually adjusted duration between 50 and 117ms (M, SD: 65 ms ± 18 ms). The speed at

which letters were presented during the task was comparable between both groups (positive group: 63 ms ± 19 ms; negative group 68 ms ± 18 ms; t(41)=0.82, p=0.415).

Heat pain stimuli

To apply painful contact heat stimuli (plateau duration 18 s; mean temperature: 46.3℃ ± 1.1 (range 43.7℃ – 48.0 ℃) corresponding to a VAS rat ing of 73.2 ± 8.2; group comparison: temperature t(41)=0.18, VAS t(41)=0.41, no significant differences between groups) we used an MR-compatible thermal device (PATHWAY model CHEPS; Medoc). The heating and cooling rates were set to maximum (70 and 40℃/s, r espectively). The CHEPS thermode (27 mm diameter) was attached to the center of the left inner forearm using a bandage. The baseline temperature was set to 35℃ which served a s stimulation temperature during control blocks.

Psychological questionnaires

The interruptive function of pain has been suggested to be moderated by pain-related personality traits, such as pain-related fear (Eccleston & Crombez, 1999; Peters, Vlaeyen, & Kunnen, 2002) and pain catastrophizing (Grisart & Plaghki, 1999; Vancleef & Peters, 2006; Van Damme, Crombez, & Eccleston, 2004). To investigate the association of pain-related interference with distinct personality traits that may moderate the interruptive function of pain, participants completed the German version of a number of questionnaires assessing these traits, including the (1) PVAQ (Lautenbacher et al., 2009; McCracken, 1997); (2) PASS (McCracken, Zayfert, & Gross, 1992); German version: (Walter, D. Hampe, Wild, & Vaitl, 2002)) (3) PCS (Lautenbacher et al., 2009; Sullivan, Bishop, & Pivik, 1995); (4) Center for Epidemiological Studies–Depression Scale ((Radloff, 1977); German version: ADS-K (Hautzinger & Bailer, 1993)); and (5) STAI (Spielberger, Gorssuch, Lushene, Vagg, & Jacobs, 1983); German version: (Laux, Glanzmann, Schaffner, & Spielberger, 1992)). All questionnaires were analyzed following the respective manuals.

Analysis of behavioral data

Behavioral data were automatically recorded and logged by the stimulation program Presentation®. All behavioral data analyses were conducted using SPSS version 18.0. Results with a p<=0.05 are considered as statistically significant. All statistical analyses were performed using two-tailed testing. Reported numbers indicate mean value ± standard deviation (SD) unless otherwise stated. As all dependent variables were normally distributed (tested using Kolmogorov-Smirnow test), parametric tests were used throughout.

RSVP task

The individual mean detection performance was defined as the percentage of correctly detected target letters separately in each of the two conditions. Mean reaction times (RTs) were computed for correctly identified letters separately for each experimental condition. Trials with RTs shorter than 100ms or longer than 3 SDs above the individual mean RT were excluded from further analyses. The number of discarded trials did not differ between conditions or groups as revealed by an ANOVA with the within-subject factor STIMULATION and the between-subject factor EXPECTANCY (stimulation: $F(1,41)= 2.149$, $p=0.15$; expectancy: $F(1,41)= 0.003$, $p=0.955$; interaction: $F(1,41)=0.245$, $p=0.62$; positive expectancy, pain: 6.0 ± 3.8, positive expectancy, control: 6.6 ± 4.6, negative expectancy, pain: 5.6 ± 2.7, negative expectancy, control: 6.9 ± 4.2). The individual counting performance was defined as the percentage of correct responses. Task performance was compared using a 2X2 repeated measures ANOVA with the within-subject factor STIMULATION (pain/control) and the between-subject factor EXPECTANCY (positive/negative) and corresponding post-hoc t-test.

Pain-related psychological processing

All questionnaires were analyzed according to their respective manual. Questionnaire scores and expectancy ratings were correlated with performance measures (i.e., accuracy and RT) using Spearman's rank correlation separately for the detection and counting task.

fMRI data acquisition

MR scanning was performed on a 3T MRI system (Siemens Trio) with a standard 32-channel head coil. A total of 42 axial slices (voxel resolution 3X3X2 mm) per volume were acquired in descending order using a gradient EPI T2*-sensitive sequence with the following parameters: repetition time (TR), 2.15 s; echo time (TE), 25 ms; flip angle, 90°; field of view, 222 X 222 mm. Prior to the functional scans, an individual high-resolution anatomical image was obtained for each participant using a T1-weighted magnetization-prepared rapid acquisition gradient echo sequence (voxel resolution: 1X1X1 mm; TR, 2.30 s; TE, 2.98 ms; flip angle, 9°; field of view, 256 X 256 mm).

Image processing and statistical analyses

Image processing and statistical analysis of fMRI data was performed using SPM8 (www.fil.ion.ucl.ac.uk/spm). After removing the first six volumes to compensate for T1 saturation effects, preprocessing included slice timing and realignment to the first volume. The realignment parameters were then checked for excessive head movement. As pain stimuli often evoke involuntary movements that are correlated with stimulus onset, we corrected for the interaction of head motion and the inhomogeneities of the magnetic field (susceptibility movement interaction) using the unwarping procedure of SPM8. The maximum amount of head motion did not exceed 4 mm in any of the participants. The anatomical volume was coregistered with the mean echo-planar image. Both structural and functional volumes were normalized to standard Montreal Neurological Institute space. Functional images were resampled to a voxel size of 2 X 2 X 2 mm and finally smoothed with an 8 mm Gaussian kernel with FWHM.

fMRI analyses

Data analysis was performed using the General Linear Model (GLM). On the subject level, the model contained five regressors that coded for: (1) cueing of pain trials (modeled

duration: 5s), (2) cueing of control trials (modeled duration: 5s), (3) painful blocks (modeled duration: from beginning of the first RSVP trial until counting response of fifth trial), and (4) control blocks (modeled duration: from beginning of the first RSVP trial until counting response of fifth trial). An additional regressor-of-no-interest coded for the rating period following pain or control trials (modeled duration: from start of rating period until end of rating). Each boxcar stimulus function was convolved with a canonical hemodynamic response function, and data were high-pass filtered with a cutoff period of 128 s. The effects of interest were tested using linear contrasts of the parameter estimates for the regressors, resulting in a t-statistic for each voxel. In a next step, separate contrast images representing the conditions cueing pain, cueing control, pain block and control block were generated for each participant, which were subsequently included in a second GLM. At the group level, a random-effects approach was used (Friston et al., 1999), treating inter-subject variability as a random factor and including non-sphericity. At group level we tested for the main effects of EXPECTANCY and STIMULATION and their interaction.

The threshold for all analyses was set to $p <= 0.05$, family-wise error (FWE) corrected for multiple comparisons. Activations related to the very robust main effect of stimulation were corrected at a whole brain level. For all other analyses a region-of-interest (ROI) approach using small volume correction (Poldrack, 2007; Worsley et al., 1996) was used based on our a-priori hypotheses. As we expected attentional mechanisms to influence task-relevant and pain-processing areas, the following brain areas ware included as ROIs: inferior parietal cortex/superior parietal cortex (IPC/SPC), inferior occipital cortex and anterior cingulate cortex (ACC). The IPC/SPC was chosen as it is known to be involved in top-down attentional control (Shomstein, 2012), and the ACC as it is involved in pain processing (Apkarian, Bushnell, Treede, & Zubieta, 2005) and cognitive control (Bush, Luu, & Posner, 2000). The inferior occipital cortex was included as this area is relevant for object processing (Ishai, Ungerleider, Martin, & Haxby, 2000) and the sensory recruitment model (D'Esposito, 2007; Pasternak & Greenlee, 2005; Serences, Ester, Vogel, & Awh, 2009) posits that brain regions involved in the perceptual processing are also active during the maintenance (short-term

memory) of these stimuli. Furthermore it has previously been shown that this area is susceptible to the interruptive function of pain (Bingel, Rose, Gläscher, & Büchel, 2007). All regions were defined anatomically using the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), which also served to localize activation peaks. To further explore the functional relevance of the fMRI findings correlation analyses with behavioral data, e.g. task performance, were performed.

Psychophysiological interaction analysis

To further explore the mechanisms how the IPS/SPC region modulates visual short-term memory a psychophysiological interaction (PPI) analysis (Friston et al., 1997) was performed. A PPI analysis reveals differences in functional connectivity between a particular seed region and all other voxels across the entire brain as a function of a psychological factor. Here, we conducted a PPI analysis to identify brain regions that showed differential connectivity between the two groups using the right parietal cortex during painful stimulation as the seed because it showed a STIMULATION X EXPECTANCY interaction of neuronal activity [seed region (x, y, z) (52, -48, 52), as identified by the interaction contrast (negative expectancy $_{[control > pain]}$ > positive expectancy $_{[control > pain]}$); see Fig.5]. The blood oxygenation level-dependent time series was extracted from a sphere located in the parietal cortex (5 mm diameter, centered around the peak voxel) for every subject individually using the first eigen-time series (principal component analysis). The PPI regressor was calculated for each subject as the element-by-element product of the mean-corrected activation of the seed region (extracted time series) and the vector coding for the psychological variable (-1 on regressor painful blocks, 1 on regressor control blocks coding for areas disrupted by painful stimulation). Thus, our PPI tested for a pain-specific modulation of the functional connectivity between the right parietal cortex and any other brain region. Finally, the individual contrasts reflecting the interaction between the psychological and physiological variables (PPI regressor) were entered into a two-sample t-test. Looking for connectivity differences between both groups we hypothesized that connectivity between the attentional system (i.e.

parietal cortex) and task-relevant areas (visual areas like inferior occipital cortex processing and inferior frontal cortex for short-term memory) and pain-related networks (ACC) would differ between groups. Corrections for multiple comparisons in these regions were again based on the same anatomical masks as outlined above using the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) using small volume corrections (Poldrack, 2007; Worsley et al., 1996).

Results

Behavioral data

First stimulation-induced head movement was assessed by comparing movement parameters for the different conditions. An 2X3X2 ANOVA (STIMULATION [pain/control] X DIMENSION [x/y/z] X EXPECTANCY [positive/negative]) of the mean movement parameters during different conditions revealed no significant effect of stimulation $F(1,41)=0.001$, $p=0.98$), or expectancy ($F(1,41)=1.583$, $p=0.215$). Thus neither painful stimulation nor the manipulation induced significant head movement.

Groups did not differ in their ratings of excitement (VAS, positive expectancy: 23 ± 22; negative expectancy 28 ± 20; $t(41)=0.743$, $p=0.46$), fear of the painful stimulation (VAS, positive expectancy: 18 ± 20; negative expectancy 18 ± 18; $t(41)=0.023$, $p=0.98$) and tiredness (VAS, positive expectancy: 31 ± 22; negative expectancy 35 ± 23; $t(41)=0.67$, $p=0.54$).

All participants had normal thresholds to heat pain at the site of stimulus application (mean: 44.7℃ ± 2.5; positive expectancy: 44.2℃ ± 3.0; ne gative expectancy: 45.2℃ ± 1.8, $t(41)=1.27$, $p=0.21$). The mean temperature level for the painful stimuli that corresponded to a pain sensation of 70 on the VAS as determined in the calibration session was 46.2°C ± 1.0 (positive expectancy: 46.2℃ ± 1.1; negative expect ancy: 46.2℃ ± 1.0; $t(41)=0.18$, $p=0.85$). Pain ratings dropped from the calibrated intensity of 70 to 50.4 ± 19.4 (VAS; positive

expectancy: 48.8 ± 19.0; negative expectancy: 52.3 ± 20.2; t(41)=0.59, p=0.55) during task performance in painful blocks. Although no pain stimuli were applied during control blocks, subjects provided pain intensity ratings which did not differ between groups (3.2 ± 10.3 (VAS; positive expectancy: 3.6℃ ± 9.0; negative expectan cy: 2.7℃ ± 11.8; t(41)=0.285, p=0.777) neither in the pain, nor in the control condition.

Expectations regarding the influence of pain on task performance differed significantly between groups (t(41)=6.4, p=0.001), indicating that the experimental manipulation had been successful. Subjects with positive expectancy believed that pain slightly improved their performance (1.1 ± 1.5; significantly different from 0: t(21)=3.446, p=0.002) whereas subjects with negative expectancy believed that pain impaired their performance (-2.0 ± 1.7; significantly different from 0: t(20)=5.555; p=0.001). Comparing the absolute values of both groups showed that the manipulation induced greater effects on expectancy in the negative group as compared to the positive group (t(41)=2.1; p=0.039). Also expectancy ratings from day 1 and day 2 did not differ significantly (day 1: -0.59 ± 2.3, day 2: -0.41 ± 2.2, t(42)=0.6; p=0.51).

In the detection task, RTs (positive expectancy, pain: 381 ± 40ms, control: 378 ± 28ms; negative expectancy, pain: 379 ± 39ms, control: 378 ± 39ms) and accuracy (positive expectancy, pain: 82 ± 9.7%, control: 82 ± 9%; negative expectancy, pain: 83.4 ± 7.9%, control: 82.8 ± 9%) showed no main effect of STIMULATION (RT: F(1,41)=0.39, p=0.54; accuracy: F(1,41)=0.14, p=0.71) or EXPECTANCY (RT: F(1,41)=0.02, p=0.9; accuracy: F(1,41)=0.2, p=0.66) and no significant interaction (RT: F(1,41)=0.13, p=0.73; accuracy: F(1,41)=0.06, p=0.81). However, for the counting task, the 2X2 repeated measures ANOVA revealed an interaction between STIMULATION and EXPECTANCY (F(1,41)=4.4; p=0.043; see Fig. 3a) but no main effects (STIMULATION: F(1,41)=0.12, p=0.73; EXPECTANCY: F(1,41)=0.22, p=0.64).

We observed a negative correlation between the individuals' expectations and their difference in counting task performance between painful and control stimulation (control –

pain, r=-0.302, p=0.049), indicating that the more subjects expected pain to decrease their performance the poorer they actually performed during painful stimulation (see Fig 3b).

There was no significant correlation between counting accuracy, detection accuracy or RT and scores on the psychological questionnaires (see table 1 for the questionnaire scores).

INSERT TABLE 1 HERE

INSERT FIG 3 HERE

FMRI

We first identified brain areas, which responded to the painful thermal stimulation, pooled across both groups. The results show that the painful stimuli significantly activated the well-known cerebral pain network (Apkarian et al., 2005), including the insula and the anterior cingulate cortex (ACC; Table 2). Next, we were interested in brain areas in which activation during task performance was compromised during painful stimulation. Our analysis shows that - across groups - areas in the left parietal lobe and in the inferior occipital cortex showed less activation when participants performed the RSVP task during simultaneous painful stimulation (Fig. 4; Table 2).

INSERT FIG 4 HERE

Turning to the effect of our experimental manipulation of expectations, our analyses showed that activations did not differ significantly between both groups when analyzed across trials with and without concomitant painful stimulation.

The interaction analysis [negative expectancy $_{[control > pain]}$ > positive expectancy $_{[control > pain]}$] tested for brain regions that are associated with the observed behavioral effect of expectancy manipulation and stimulation. This analysis revealed that the increase in short-term memory performance in the positive expectancy group compared to the decrease in short-term

memory performance in the negative expectancy group during pain was associated with activity in the right SPC/IPC (Table 2 and Fig. 5).

INSERT FIG 5 HERE

The difference in activation between the control and the pain blocks was negatively correlated with the expectation subjects had concerning the interruptive function of pain (r=-0.427, p=0.005). The more subjects expected to benefit from pain during task performance, the more they activated the SPL/IPC in the pain condition relative to the control condition. To explore the modulatory mechanisms underlying these differential effects of the expectancy manipulation, we investigated changes in functional connectivity of the SPC/IPC depending on pain and manipulation using a PPI analysis. The PPI analysis tested for expectation related modulation during painful stimulation of the functional connectivity between the right SPC/IPC [(52, -48, 52); see Fig. 5A] and any other brain region depending on the expectancy modulation.

Using a 5mm sphere around the SPC/IPC peak voxel as the seed for a whole-brain PPI analysis to test for functional connectivity differences disrupted by pain (interaction term: positive expectancy $_{[control > pain]}$ > negative expectancy $_{[control > pain]}$) we found that this area showed a weaker functional connectivity under pain with regions implicated in object processing, namely the left inferior occipital cortex in the positive expectancy group. In contrast, the negative expectancy group showed stronger connectivity with this area under pain (see Fig 6, Table 2). To further explore whether this area in the inferior occipital cortex is indeed involved in task performance we correlated the difference of parameter estimates from the main analysis for this voxel (-52 -64 -14, control - pain) with performance differences in the detection accuracy (control - pain). Here we found a significant correlation of the parameter estimates with detection accuracy (r=0.335, p=0.028).

INSERT FIG 6 HERE

INSERT TABLE 2 HERE

Discussion

In this study we used fMRI to examine the effect of expectation on visual task performance in healthy volunteers. Individuals' expectations concerning the influence of pain on cognitive performance were experimentally manipulated by verbal instructions before performing an RSVP task with or without concomitant thermal heat pain stimulation.

In line with our hypothesis we found that expectations influenced the effect of pain on short-term memory performance, as indicated by a significant interaction between stimulation and expectancy. Differences in task performance scaled with the expectation of the individual: The more benefit participants expected from painful stimulation, the greater their increase in task performance was during pain. These behavioral differences in task performance were associated with activity changes in the right inferior parietal cortex. Participants with a positive expectation regarding the effect of pain on task performance showed increased task-related parietal activity during pain, whereas those expecting negative effects of pain showed reduced task-related parietal activity during pain compared to the control condition. Again, these activity differences in the right inferior parietal cortex between painful and non-painful stimulation correlated with individual expectations. The more improvement participants expected under pain, the greater was the activity change in the right inferior parietal cortex. Finally, these expectancy-induced differences were associated with differences in functional connectivity between right inferior parietal cortex and left inferior occipital cortex.

Expectancy modulates task performance

Expectancy ratings showed a successful manipulation of the expectations participants had regarding the effects of pain on task performance that was directly linked to the performance

in the short-term memory task. Participants who expected to benefit from simultaneous painful stimulation performed better under pain than those who believed that the noxious stimulation would interfere with task performance. This observation is in line with studies from social threat literature showing that (implicit) expectations can modulate an individual's performance in the direction of the stereotype associated with a particular group membership (e.g. gender, age, race; for review see (Kit et al., 2008)). Furthermore, recent experimental studies have provided first evidence for an influence of positive expectations on task performance. Colagiuiri and colleagues (Colagiuri, Livesey, & Harris, 2011) showed that a positive expectation regarding the effect of an odor led to shorter response times in a visual search task. Similarly, Colagiuri and Boakes (Colagiuri & Boakes, 2010) demonstrated that the belief of having consumed caffeine, which would improve task performance, indeed increased accuracies in an RSVP task although participants were only given placebos.

Interestingly, the interactive effect between pain and the manipulation of expectations was only found in the short-term memory component but not in the detection task. This is in line with our previous findings showing that pain affected the memory component of a recognition task but not the accuracy of a categorization task (Forkmann et al., 2013). Although this difference in effect is difficult to interpret based on our data only, it is conceivable that pain is more likely to interfere with more complex cognitive functions such as short-term memory, which requires sustained attention, but to a lesser degree with basic functions like detection (see also (Moore, Keogh, & Eccleston, 2012)).

As evident from Fig. 3, the significant interaction in the counting task was at least partly driven by a group difference in performance in the control condition with better performance in the negatively manipulated group. Although this result might seem puzzling at first, it has to be pointed out that our manipulation was likely to induce a *relative* effect between the pain and the control condition in both groups. More specifically, it seems reasonable to assume that the explicit information that pain impairs task performance, for instance, also provided implicit information about the control condition such as that the absence of pain would lead to better outcome relative to the pain condition. As a consequence of this relative rather than

absolute manipulation, performance in the control condition differs between in the two groups as found in the current study. Note that this effect on the control condition is inherent to the manipulation and does not jeopardize the interpretation of the data but underscores the impact of expectations, explicit or implicit, on task performance.

Expectancy modulates activity and functional connectivity of the parietal cortex

On the neural level we found decreased activation under pain irrespective of the direction of the expectancy manipulation in occipital and left parietal areas (main effect) – an observation that is in line with the known interruptive effect of pain on task-related areas, as previously shown for visual processing (Bingel et al., 2007).

The more specific interaction analysis testing for brain regions showing a stimulation-related influence depending on the direction of the expectancy manipulation revealed a significant finding in the inferior parietal cortex, which showed increased activity during pain in the positive compared to the negative expectancy group (Fig. 5). Besides its key role in attention (Corbetta & Shulman, 2002), the inferior parietal cortex has previously been associated with short-term memory (Xu & Chun, 2006) and the modulation of working memory content (Koenigs, Barbey, Postle, & Grafman, 2009). Furthermore, the right inferior parietal area is known to be involved in top-down attentional control, helping to shift attention between tasks and locations (Shomstein, 2012). This area is therefore well suited to down-propagate effects based on expectations into other brain areas involved in task processing.

To further explore the mechanisms by which expectation modulates task performance, we conducted a PPI analysis, taking the inferior parietal lobe as the seed and testing for expectancy dependent connectivity changes of this brain area during stimulation. This analysis revealed expectancy-dependent connectivity changes during pain between the inferior parietal cortex and the left inferior occipital cortex. The relevance of this area for visual detection performance as part of the ventral visual processing stream is well established (Flowers et al., 2004) and, in our data, evident in the positive correlation between pain induced activity changes in this area and pain-induced changes in detection

performance. Sufficient processing of the target letters is mandatory for successful performance of the subsequent short-term memory task, which we found primarily affected by our expectancy modulation. The relevance of this sensory visual area for the visual short-term memory task is in line with Serences et al (Serences et al., 2009) as also emphasized in the sensory recruitment theory (D'Esposito, 2007; Pasternak & Greenlee, 2005) which states that the content held in short-term memory is implemented through activity in stimuli processing sensory areas.

Interestingly, functional coupling between the inferior parietal cortex and inferior occipital cortex was reduced during pain with positive compared to negative expectancy. As shown in Fig. 6, the comparison of parameter estimates extracted for the different conditions revealed that the STIMULATION X EXPECTANCY interaction was driven by changes in both expectancy groups. While positive expectancy led to a decrease in connectivity between the inferior parietal and inferior occipital cortex under pain, negative expectancy was accompanied by an increase in connectivity. Given that subjects with positive expectation performed better on the short-term memory task under pain, it seems reasonable to assume that increased IPC connectivity with task-related visual areas under pain has a negative impact on short-term memory performance.

In sum, our data suggest that the effect of expectations on visual short-term memory performance are associated with activity changes in the inferior parietal cortex, an area known to be involved in attentional control. This area seems to down-propagate the effects of expectation by changing its functional connectivity with task-relevant brain areas such as the inferior occipital cortex which is known to be involved in visual task performance (Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002; Ress, Backus, & Heeger, 2000). Based on the PPI results it can be speculated that the "default assumption" that pain inhibits performance is implemented through functional connectivity between SPC and occipital lobe and that a positive expectation releases this negative influence. Intriguingly, a behavioural study by Stern and colleagues (Stern et al., 2011) found that expectation effects on short-term memory performance were modulated by the administration of naloxone, suggesting an

involvement of opioidergic neurotransmission in this mechanism. The combination of neuroimaging with pharmacological modulations would therefore be a promising approach for future investigations to unravel the underlying neurochemical processes.

Clinical implications

Cognitive impairments are a key feature of a wide spectrum of diseases, ranging from cancer (Ahles et al., 2007) to cardio-vascular (Everson, Helkala, Kaplan, & Salonen, 2001), neurological (Chiaravalloti & DeLuca, 2008) and psychiatric disorders (Millan et al., 2012) as well as chronic pain. Oftentimes, those cognitive deficits substantially contribute to the overall suffering of the patient. Our findings suggest that those deficits might not only reflect actual decline of cognitive capacities but also negative expectations patients have regarding their cognitive abilities. Even without detailed medical knowledge, patients are often aware that certain diagnoses are associated with compromised cognitive functioning that might, moreover, also be progressive. Naturally, this knowledge can lead patients to worry about the future trajectory of their disease even if they are not experiencing difficulties yet. As a consequence, these worries (and the related negative expectations) might increase the cognitive difficulties, which in turn might fuel the patients' concern and drive them into a vicious circle of negative expectations and declining cognitive ability.

~~Critically, there is first evidence suggesting that worries and anxieties can increase the risk of patients with mild cognitive impairment (MCI) to develop Alzheimer's disease (Mah, Binns, & Steffens, 2015). The extent to which patients showed symptoms of anxiety was related to medial temporal atrophy and predicted the conversion to Alzheimer's disease. Although this link requires further investigation, it is conceivable that worries and negative expectations aggravate pathological processes and thereby contribute to the aggravation of symptoms and disease progression.~~

~~Related to this aspect is the iatrogenic influence of the diagnosis itself.~~

In a study by Suhr and Gunstad (Suhr & Gunstad, 2002), patients with mild head injury were informed that they had been included in a research study to investigate cognitive effects of mild head injury. These patients were compared to those who were unaware of any inclusion

criteria. Interestingly, the former group performed significantly worse in tests assessing memory and intellectual abilities, supporting the notion that cognitive impairment is influenced by the subjects expectation.

If negative information about a disease can induce negative expectations, which in turn can decrease cognitive performance, positive information should have the potential to counteract this effect. Our data seem to support this notion. A short verbal instruction stating that pain might increase cognitive performance led indeed to better outcome. This is particularly remarkable given that based on its biological function as a warning signal pain tends to disrupt cognitive processes (Eccleston & Crombez, 1999). The fact that a simple verbal positive instruction can reverse this effect highlights the potential clinical relevance of such an intervention. It should, however, be noted that some expectancy modulations might be more plausible than others. In our study, the negative instruction induced a stronger effect than the positive manipulation. This is likely to reflect genuine expectations (or stereotypes) we hold, which are negative in the case of pain (Sinke, Schmidt, Forkmann, & Bingel, 2015). However, a formal test of such an unguided expectation would have required a neutral condition with no expectancy manipulation, which we chose not to implement for reasons mentioned above. We can therefore only draw conclusions on the *relative* effect of positive as opposed to negative manipulations and speculate about *a priori* assumptions people may have regarding the influence of pain on cognitive performance (which may vary considerably between individuals). In order to understand the broader implications of our findings, it has to be pointed out that here we used pain as a tool to manipulate expectation. However, expectations can be tied to any stimulus or contextual information that is related to cognitive performance and pain should only be viewed as an example. Additional studies are therefore needed to explore whether similar effects can be induced by other stimuli or contextual information including those of lower salience to identify information that could be most beneficial in guiding expectations to help individuals improve cognitive task performance.

Acknowledgements

This work was supported by German Research Foundation (DFG, grant numbers: FOR 1328, SFB 936/A4) and KW is funded by Medical Research Council (MRC UK, New Investigator grant).

References

Ahles, T. A., Saykin, A. J., McDonald, B. C., Furstenberg, C. T., Cole, B. F., Hanscom, B. S., … Kaufman, P. A. (2007). Cognitive function in breast cancer patients prior to adjuvant treatment. *Breast Cancer Research and Treatment*, *110*(1), 143–152. http://doi.org/10.1007/s10549-007-9686-5

Apkarian, A. V., Bushnell, M. C., Treede, R.-D., & Zubieta, J.-K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain (London, England)*, *9*(4), 463–484. http://doi.org/10.1016/j.ejpain.2004.11.001

Barber, S. J., & Mather, M. (2014). Stereotype Threat in Older Adults: When and Why Does It Occur and Who Is Most Affected? In *The Oxford Handbook of Emotion, Social Cognition, and Problem Solving in Adulthood*. New York: Oxford University Press.

Benedetti, F. (2014). Placebo Effects: From the Neurobiological Paradigm to Translational Implications. *Neuron*, *84*(3), 623–637. http://doi.org/10.1016/j.neuron.2014.10.023

Benedetti, F., Lanotte, M., Lopiano, L., & Colloca, L. (2007). When words are painful: Unraveling the mechanisms of the nocebo effect. *Neuroscience*, *147*(2), 260–271. http://doi.org/10.1016/j.neuroscience.2007.02.020

Bingel, U., Rose, M., Gläscher, J., & Büchel, C. (2007). fMRI reveals how pain modulates visual object processing in the ventral visual stream. *Neuron*, *55*(1), 157–167. http://doi.org/10.1016/j.neuron.2007.05.032

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, *4*(6), 215–222. http://doi.org/10.1016/S1364-6613(00)01483-2

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7*(12), 1139–1151. http://doi.org/10.1016/S1474-4422(08)70259-X

Colagiuri, B., & Boakes, R. A. (2010). Perceived treatment, feedback, and placebo effects in double-blind RCTs: an experimental analysis. *Psychopharmacology*, *208*(3), 433–441. http://doi.org/10.1007/s00213-009-1743-9

Colagiuri, B., Livesey, E. J., & Harris, J. A. (2011). Can expectancies produce placebo effects for implicit learning? *Psychonomic Bulletin & Review*, *18*(2), 399–405. http://doi.org/10.3758/s13423-010-0041-1

Colton, G., Leshikar, E. D., & Gutchess, A. H. (2013). Age Differences in Neural Response to Stereotype Threat and Resiliency for Self-Referenced Information. *Frontiers in Human Neuroscience*, *7*. http://doi.org/10.3389/fnhum.2013.00537

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201–215. http://doi.org/10.1038/nrn755

Coull, J. T., Frith, C. D., Frackowiak, R. S. J., & Grasby, P. M. (1996). A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. *Neuropsychologia*, *34*(11), 1085–1095. http://doi.org/10.1016/0028-3932(96)00029-2

D'Esposito, M. (2007). From cognitive to neural models of working memory. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *362*(1481), 761–772. http://doi.org/10.1098/rstb.2007.2086

Eccleston, C., & Crombez, G. (1999). Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychological Bulletin*, *125*(3), 356–366.

Everson, S. A., Helkala, E.-L., Kaplan, G. A., & Salonen, J. T. (2001). Atherosclerosis and cognitive functioning. In S. R. Waldstein & M. F. Elias (Eds.), *Neuropsychology of*

cardiovascular disease (pp. 105–120). Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers.

Flowers, D. L., Jones, K., Noble, K., VanMeter, J., Zeffiro, T. A., Wood, F. B., & Eden, G. F. (2004). Attention to single letters activates left extrastriate cortex. *NeuroImage*, *21*(3), 829–839. http://doi.org/10.1016/j.neuroimage.2003.10.002

Forkmann, K., Wiech, K., Ritter, C., Sommer, T., Rose, M., & Bingel, U. (2013). Pain-Specific Modulation of Hippocampal Activity and Functional Connectivity during Visual Encoding. *The Journal of Neuroscience*, *33*(6), 2571–2581. http://doi.org/10.1523/JNEUROSCI.2994-12.2013

Fruhstorfer, H., Lindblom, U., & Schmidt, W. C. (1976). Method for quantitative estimation of thermal thresholds in patients. *Journal of Neurology, Neurosurgery, and Psychiatry*, *39*(11), 1071–1075.

Grisart, J. M., & Plaghki, L. H. (1999). Impaired selective attention in chronic pain patients. *European Journal of Pain*, *3*(4), 325–333. http://doi.org/10.1016/S1090-3801(99)90014-9

Hautzinger, M., & Bailer, M. (1993). *Allgemeine Depressions Skala*. Weinheim: Belz.

Ishai, A., Ungerleider, L. G., Martin, A., & Haxby, J. V. (2000). The Representation of Objects in the Human Occipital and Temporal Cortex. *Journal of Cognitive Neuroscience*, *12*(supplement 2), 35–51. http://doi.org/10.1162/089892900564055

Ito, K., Corrigan, B., Romero, K., Anziano, R., Neville, J., Stephenson, D., & Lalonde, R. (2013). Understanding Placebo Responses in Alzheimer's Disease Clinical Trials from the Literature Meta-Data and CAMD Database. *Journal of Alzheimer's Disease*, *37*(1), 173–183. http://doi.org/10.3233/JAD-130575

Johns, M., Schmader, T., & Martens, A. (2005). Knowing is half the battle: teaching stereotype threat as a means of improving women's math performance. *Psychological Science*, *16*(3), 175–179. http://doi.org/10.1111/j.0956-7976.2005.00799.x

Kit, K. A., Tuokko, H. A., & Mateer, C. A. (2008). A Review of the Stereotype Threat Literature and Its Application in a Neurological Population. *Neuropsychology Review*, *18*(2), 132–148. http://doi.org/10.1007/s11065-008-9059-9

Koenigs, M., Barbey, A. K., Postle, B. R., & Grafman, J. (2009). Superior Parietal Cortex Is Critical for the Manipulation of Information in Working Memory. *The Journal of Neuroscience*, *29*(47), 14980–14986. http://doi.org/10.1523/JNEUROSCI.3706-09.2009

Lautenbacher, S., Huber, C. P., Kunz, M. P., Parthum, A. P., Weber, P. G., Griessinger, N., & Sittl, R. (2009). Hypervigilance as Predictor of Postoperative Acute Pain: Its Predictive Potency Compared With Experimental Pain Sensitivity, Cortisol Reactivity, and Affective State. *Journal of Pain February 2009*, *25*(2), 92–100. http://doi.org/10.1097/AJP.0b013e3181850dce

Laux, L., Glanzmann, P., Schaffner, P., & Spielberger, C. D. (1992). *Das State-Trait-Angstinventar (Testmappe mit Handanweisung, Fragebogen STAI-G Form X1 und Fragebogen STAI-G Form X2)*. Weinheim: Beltz.

Mah, L., Binns, M. A., & Steffens, D. C. (2015). Anxiety Symptoms in Amnestic Mild Cognitive Impairment Are Associated with Medial Temporal Atrophy and Predict Conversion to Alzheimer Disease. *The American Journal of Geriatric Psychiatry*, *23*(5), 466–476. http://doi.org/10.1016/j.jagp.2014.10.005

McCracken, L. M. (1997). “Attention” to pain in persons with chronic pain: A behavioral approach. *Behavior Therapy*, *28*(2), 271–284. http://doi.org/10.1016/S0005-7894(97)80047-0

McCracken, L. M., Zayfert, C., & Gross, R. T. (1992). The pain anxiety symptoms scale: development and validation of a scale to measure fear of pain. *Pain*, *50*(1), 67–73. http://doi.org/10.1016/0304-3959(92)90113-P

Millan, M. J., Agid, Y., Brüne, M., Bullmore, E. T., Carter, C. S., Clayton, N. S., … Young, L. J. (2012). Cognitive dysfunction in psychiatric disorders: characteristics, causes and

the quest for improved therapy. *Nature Reviews Drug Discovery*, *11*(2), 141–168. http://doi.org/10.1038/nrd3628

Moore, D. J., Keogh, E., & Eccleston, C. (2012). The interruptive effect of pain on attention. *Quarterly Journal of Experimental Psychology (2006)*, *65*(3), 565–586. http://doi.org/10.1080/17470218.2011.626865

Pasternak, T., & Greenlee, M. W. (2005). Working memory in primate sensory systems. *Nature Reviews Neuroscience*, *6*(2), 97–107. http://doi.org/10.1038/nrn1603

Pessoa, L., Gutierrez, E., Bandettini, P. A., & Ungerleider, L. G. (2002). Neural Correlates of Visual Working Memory: fMRI Amplitude Predicts Task Performance. *Neuron*, *35*(5), 975–987. http://doi.org/10.1016/S0896-6273(02)00817-6

Peters, M. L., Vlaeyen, J. W. S., & Kunnen, A. M. W. (2002). Is pain-related fear a predictor of somatosensory hypervigilance in chronic low back pain patients? *Behaviour Research and Therapy*, *40*(1), 85–103. http://doi.org/10.1016/S0005-7967(01)00005-5

Poldrack, R. A. (2007). Region of interest analysis for fMRI. *Social Cognitive and Affective Neuroscience*, *2*(1), 67–70. http://doi.org/10.1093/scan/nsm006

Quinn, D. M., & Spencer, S. J. (2001). The Interference of Stereotype Threat With Women's Generation of Mathematical Problem-Solving Strategies. *Journal of Social Issues*, *57*(1), 55–71. http://doi.org/10.1111/0022-4537.00201

Radloff, L. S. (1977). The CES-D Scale A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*, *1*(3), 385–401. http://doi.org/10.1177/014662167700100306

Ress, D., Backus, B. T., & Heeger, D. J. (2000). Activity in primary visual cortex predicts performance in a visual detection task. *Nature Neuroscience*, *3*(9), 940–945. http://doi.org/10.1038/78856

Rolke, R., Baron, R., Maier, C., Tölle, T. R., Treede, R.-D., Beyer, A., … Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic

Pain (DFNS): Standardized protocol and reference values. *PAINÂ®*, *123*(3), 231–243. http://doi.org/10.1016/j.pain.2006.01.041

Serences, J. T., Ester, E. F., Vogel, E. K., & Awh, E. (2009). Stimulus-Specific Delay Activity in Human Primary Visual Cortex. *Psychological Science*, *20*(2), 207–214. http://doi.org/10.1111/j.1467-9280.2009.02276.x

Shomstein, S. (2012). Cognitive functions of the posterior parietal cortex: top-down and bottom-up attentional control. *Frontiers in Integrative Neuroscience*, *6*. http://doi.org/10.3389/fnint.2012.00038

Sinke, C., Schmidt, K., Forkmann, K., & Bingel, U. (2015). Phasic and tonic pain differentially impact the interruptive function of pain. *PLoS ONE*, in press.

Spencer, S. J., Steele, C. M., & Quinn, D. M. (1999). Stereotype Threat and Women's Math Performance. *Journal of Experimental Social Psychology*, *35*(1), 4–28. http://doi.org/10.1006/jesp.1998.1373

Spielberger, C. D., Gorssuch, R. L., Lushene, P. R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press, Inc.

Stern, J., Candia, V., Porchet, R. I., Krummenacher, P., Folkers, G., Schedlowski, M., … Schönbächler, G. (2011). Placebo-mediated, Naloxone-sensitive suggestibility of short-term memory performance. *Neurobiology of Learning and Memory*, *95*(3), 326–334. http://doi.org/10.1016/j.nlm.2011.01.005

Suhr, J. A., & Gunstad, J. (2002). "Diagnosis Threat": The Effect of Negative Expectations on Cognitive Performance in Head Injury. *Journal of Clinical and Experimental Neuropsychology*, *24*(4), 448–457. http://doi.org/10.1076/jcen.24.4.448.1039

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*, *7*(4), 524–532. http://doi.org/10.1037/1040-3590.7.4.524

Summerfield, C., & de Lange, F. P. (2014). Expectation in perceptual decision making: neural and computational mechanisms. *Nature Reviews Neuroscience*, *15*(11), 745–756. http://doi.org/10.1038/nrn3838

Summerfield, C., & Egner, T. (2009). Expectation (and attention) in visual cognition. *Trends in Cognitive Sciences*, *13*(9), 403–409. http://doi.org/10.1016/j.tics.2009.06.003

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage*, *15*(1), 273–289. http://doi.org/10.1006/nimg.2001.0978

Vancleef, L. M. G., & Peters, M. L. (2006). The Interruptive Effect of Pain on Attention. *The Journal of Pain*, *7*(1), 21–22. http://doi.org/10.1016/j.jpain.2005.11.003

Van Damme, S., Crombez, G., & Eccleston, C. (2004). Disengagement from pain: the role of catastrophic thinking about pain. *Pain*, *107*(1–2), 70–76. http://doi.org/10.1016/j.pain.2003.09.023

Walter, B., D. Hampe, Wild, J., & Vaitl, D. (2002). Die Erfassung der Angst vor Schmerzen: Eine modifizierte deutsche Version der Pain Anxiety Symptoms Scale (PASS-D). *Der Schmerz*, *16*(Supplement 1), 83.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping*, *4*(1), 58–73. http://doi.org/10.1002/(SICI)1097-0193(1996)4:1<58::AID-HBM4>3.0.CO;2-O

Xu, Y., & Chun, M. M. (2006). Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature*, *440*(7080), 91–95. http://doi.org/10.1038/nature04262

Table Caption:

Table 1:

Table 1: **Psychological questionnaires:** Results of the questionnaires for each group. No statistical differences between groups could be detected.

Table 2:

Table 2: **BOLD activation peaks**. Coordinates are denoted by x, y, z in mm according to the MNI-space (Montreal Neurological Institute). Strength of activation is expressed in t-scores (df=82). T-values marked with (*) are corrected using small volume correction (SVC) in a-priori regions of interest (see Methods) at an FWE corrected level of $p<0.05$ while no mark indicates FWE correction with $p<0.05$ at whole-brain level.

Figure captions:

Figure 1:

Fig1: Expectancy manipulation. (A) Randomization of subjects into experimental groups. (B) Mean expected effect of pain on task performance for the positive expectancy group and negative expectancy group obtained on a VAS [-5 to 5]. Error bars indicate standard error of the mean (SEM). * = $p<0.05$.

Figure 2:

Fig. 2: Experimental design. The main experimental paradigm performed with fMRI consisted of 15 painful and 15 non-painful (control) blocks. Each block started with a visual cue presented for 2s, which indicated whether a painful or non-painful block would follow. After a short variable period (3 - 7 s) the individually calibrated thermal stimulation was applied for 18s concomitant to the task. At the end of each block, subjects had to rate the intensity of the stimulus on a VAS [0-100]. Each block comprised 5 Rapid Serial Visual Presentation (RSVP) trials in which subjects had to detect and count the occurrence of the target letter “A”.

Figure 3:

Fig. 3: Behavioral effects of expectancy manipulation. (A) Interaction between stimulation and expectancy manipulation for the counting accuracy [%] in the RSVP task. Error bars indicate standard error of the mean (SEM). * = $p<0.05$. (B) Correlation between differences in counting performance (control - pain blocks) and the expectation subjects have about the influence of pain on their performance.

Figure 4:

Fig 4: Brain activation disrupted by pain: (left) BOLD activations in the inferior occipital cortex (control stimulation > painful stimulation) overlaid on a T1 weighted image (for details see Table 2). The image is thresholded at $p=0.001$ uncorrected for visualization purposes. (right) Parameter estimates of pain-related BOLD responses for the activation peak in the left inferior occipital cortex plotted for visualization purposes (extracted from the peak voxels of activation – for details see Table 2). Error bars indicate standard error of the mean (SEM). * = $p<0.05$.

Figure 5:

Fig 5: Brain activation for the STIMULATION X EXPECTANCY interaction. (upper) BOLD activations in the inferior parietal cortex (control stimulation > painful stimulation) in the negative expectancy group compared to the positive expectancy group overlaid on a T1-weighted image (for details see Table 2). The image is thresholded at p=0.001 uncorrected for visualization purposes. (lower left) Parameter estimates of pain-related BOLD responses for the activation peak in the right inferior parietal cortex plotted for visualization purposes (extracted from the peak voxel of activation – for details see Table 2). Error bars indicate standard error of the mean (SEM). * = p<0.05. (lower right) Correlation between the expectation subjects had about the influence of pain on their performance and the difference of the parameter estimates for painful and control blocks plotted for visualization purposes (extracted from the peak voxels of activation in the right inferior parietal cortex – for details see Table 2).

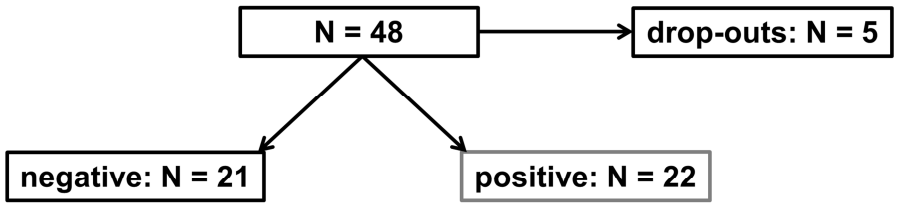
Figure 6:

Fig.6: Psychophysiological interaction. (upper) The right inferior parietal cortex ("seed") was defined as a sphere (5mm diameter) centered around the peak voxel (52, -48, 52). This particular region showed a STIMULATION X EXPECTANCY interaction (revealed by the contrast: negative expectancy $_{[control > pain]}$ > positive expectancy $_{[control > pain]}$); see Results). A PPI analysis revealed a reduction in functional connectivity between the right inferior parietal cortex and left inferior occipital cortex during painful stimulation for positive expectation compared to negative expectation. For visualization purposes results are overlaid on a T1-weighted image and thresholded at p=0.001 uncorrected. (lower left) Parameter estimates of the PPI analysis for the activation peak in the right inferior occipital cortex plotted for visualization purposes (extracted from the peak voxel of activation – for details see Table 2). Error bars indicate standard error of the mean (SEM). * = p<0.05.

	Positive expectancy	Negative expectancy
STAI – A	35,3 ± 7.8	33.7 ± 4.1
STAI – B	36.7 ± 7.4	33.3 ± 7.5
PASS – D1	18.3 ± 6.8	21.9 ± 9.9
PASS – D2	20.8 ±5.5	18.7 ± 5.6
PASS – D3	10.7 ± 6.0	12.5 ± 6.8
PASS – D4	11.9 ± 5.3	12.6 ± 6.2
ADS	7.9 ± 5.9	6.9 ± 4.1
PCS	16,0 ± 8.0	18.0 ± 10.0
PVAQ	37.3 ± 9.4	38 ± 7.9

	MNI Coordinates (mm)							
	Left			Right				
Region	x	y	z	x	y	z	Voxel level (T)	Cluster size
Pain-related neuronal activation (pain > control)								
Rolandic operculum/insula				40	-22	20	16.6	2873
	-58	-2	6				8.97	134
Insula	-36	-20	-18				9.7	168
	-40	-2	-6				7.73	98
	-34	2	14				6.3	53
Superior medial frontal	-18	50	-2				7.5	112
Anterior cingulate cortex				20	38	2	6.98	341
Middle cingulate cortex				2	6	40	5.5	19
Supplementary motor cortex (BA 6)				4	-18	48	5.5	8
Superior parietal cortex				24	-46	70	5.4	12
Task-related activity disrupted by pain (control > pain)								
Postcentral Gyrus	-38	-28	60				5.61	153
Posterior Cingulate cortex	-20	-40	24				5.4	19
Inferior occipital gyrus	-30	-92	-10				5.2	4
IPC\SPL				28	-72	58	4.33*	82
				42	-38	46	4.11*	50
				52	-30	50	4.04*	8
STIMULATION X EXPECTANCY [negative expectancy $_{(control > pain)}$ > positive expectancy $_{(control > pain)}$]								
SPC\IPC				52	-48	52	4.02*	60
PPI (positive expectancy $_{(control > pain)}$ > negative expectation $_{(control > pain)}$)								
Inferior occipital gyrus (BA37)	-52	-64	-14				4.2*	17

A)



B)