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Neural and behavioral correlates of human pain avoidance in participants with and without episodic migraine

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Abstract

The innate motivation to avoid pain can be disrupted when individuals experience uncontrollable stress, such as pain. This can lead to maladaptive behaviors, including passivity, and negative affect. Despite its importance, motivational aspects of pain avoidance are understudied in humans, and their neural mechanisms vastly unknown. Rodent models suggest an important role of the periaqueductal grey, but it is unknown whether it sub-serves a similar role in humans. Further, it is unclear whether pain avoidance is associated with individual differences in pain coping.

Using functional magnetic resonance imaging (fMRI), networks underlying pain avoidance behavior were examined in 32 participants with and without episodic migraine. Pain avoidance behavior was assessed using an adaptation of the Incentive Delay Task. In each trial of the task, participants tried to avoid a painful stimulus and receive a non-painful one instead, while the difficulty to succeed varied across trials (three difficulty levels: safe, easy, difficult). After unsuccessful pain avoidance on the preceding trial, participants showed reduced pain avoidance behavior, especially in the difficult condition. This reduction in behavior was associated with higher helplessness scores only in participants with migraine. Higher helplessness in participants with migraine was further correlated with a stronger decrease in activation of cortical areas associated with motor behavior, attention, and memory after unsuccessful pain avoidance. Of these areas specifically posterior parietal cortex activation predicted individual's pain avoidance behavior on the next trial. The results link individual pain coping capacity to patterns of neural activation associated with altered pain avoidance in migraine patients.

Keywords: Pain avoidance, motivation, alertness, posterior parietal cortex, helplessness, fMRI, repetitive pain

1. Introduction

The ability to avoid pain is crucial for survival as it minimizes harm and injury [17]. While individuals typically have a strong urge to avoid/escape pain [32], pain avoidance behavior is promptly adjusted following recent pain experiences [43] and can even be disrupted when individuals repeatedly experience inescapable pain [33; 46]. Malfunctioning of pain avoidance is important, because it is associated with diminished quality of life and higher treatment costs [6; 26]. However, studies investigating changes in the ability to avoid pain and their underlying neural correlates in humans are still sparse.

The pre-clinical literature provides convincing evidence that the periaqueductal grey (PAG) plays a central role in pain avoidance [1; 12; 13]. Specifically the dorsal/dorsolateral aspect of the rodent PAG has been associated with risk assessment prior to defense behavior [12] and the consequential readiness to actively avoid physical threats and to show defense behaviors [12; 24; 25; 30; 31; 53]. Typical patterns of defense behaviors are established by the PAG via sensorimotor circuits [28], possibly regulating a cortical effector network associated with motor preparation and execution. Behavioral responses are accompanied by autonomic changes, such as increases in blood pressure, heart rate, respiration, and muscle tone [30; 39]. This suggests that the rodent PAG is essential for the preparation of the body to avoid or escape pain. Currently, it is unknown whether the PAG and its cortical effector network sub-serve a similar role in human pain avoidance.

In this study, we examined the neural networks underlying the influence of successful and unsuccessful pain avoidance on subsequent pain avoidance behavior, using functional magnetic resonance imaging (fMRI). Because (sub-conscious) behavioral decisions not only depend on the most recent experience, but are also influenced by the individual's learning history [35], participants with a broad experience in unsuccessful pain avoidance attempts previous to study

participation were included. Specifically, participants with episodic migraine were recruited as part of the sample – i.e. individuals who experience a frequent reoccurrence of unavoidable headaches as a key symptom of their condition (International Headache Society classification ICHD-II). While individuals with migraine generally report feelings of helplessness with respect to their migraine attacks, many still highlight a positive aspect of their pain condition and might even develop a psychological resilience to its negative consequences [36]. Therefore, a wide range of helplessness levels was expected across the participants with migraine. This would allow to assess the influence of individual differences in helplessness on pain avoidance behavior.

We hypothesized that (1) participants (i.e. individuals with and without migraine) show greater pain avoidance behavior subsequent to successful than unsuccessful avoidance attempts and (2) the readiness to avoid pain is driven by the PAG. Assuming that the experience of difficulties in coping with clinical pain can cause a generalized tendency to decrease pain avoidance behavior when having been unsuccessful on previous attempts, we further hypothesized that (3) reductions in pain avoidance behavior and in neural activation subsequent to unsuccessful avoidance attempts are greater with higher levels of self-reported helplessness in participants with migraine.

2. Materials and Methods

2.1. Sample size calculation

This was the first formal investigation on the interaction between unsuccessful pain avoidance and subsequent alterations in pain avoidance behavior, and therefore, the effect size was unknown. Consequently, we based the sample size calculation for a behavioral effect on a desired medium effect size. In the context of ANOVAs, effect size can be expressed as Cohen's f^2, and f^2=0.06 (f=0.25) is considered a medium effect size [9].

A repeated measure ANOVA with two within subject factors ('difficulty level' and 'outcome on preceding trial') with three-by-two levels and one between-subject factor (group) with two levels was conducted. In order to detect a medium interaction effect between the within and between factors, with a 5% probability of committing a Type 1 error (alpha=0.95) and a 20% probability of committing a Type 2 error (beta=0.8), a minimum of 28 participants were needed to be tested (GPower 3.1). To allow for potential data loss due to issues, such as technical difficulties with MRI or pain equipment, or potential incompliances of the participants, it was decided to recruit an additional 6 participants (20% extra), totaling in a sample of 34 participants.

2.2. Participants

Thirty-four participants were recruited for the study (6 males, 28 females; mean age 27±5 years). Half of the initially recruited sample were participants with episodic migraine; however, 2 of them were excluded because of incompliance with the experimental instructions. This resulted in a final study sample of 32 (6 males, 26 females; mean age 27±5 years, 15 participants with and 17 without episodic migraines).

Exclusion criteria included excessive smoking (more than 10 cigarettes a day), regular use of recreational drugs (more than once in three months), alcohol consumption of > 10 UK units per week, the presence or history of chronic pain conditions other than episodic migraine, major medical, neurological or psychiatric conditions, and MRI contradictions. Additional exclusion criteria for participants with migraine included less than 1 or more than 15 migraine attacks per month to ensure that they fulfilled the criteria for episodic migraine (International Headache Society classification ICHD-II), while excluding participants with an infrequent reoccurrence of migraine headaches. Participants could not have a headache (or any pain) at the time of testing to avoid the possibility that ongoing pain would affect their ability to focus on the tasks within the experiment or confound the fMRI signal. If pain was reported to be present on the day of testing, they were re-scheduled. All included participants with migraine reported taking acute pain medication on demand when migraine attacks commence. One participant reported the daily use of preventative migraine medication (Table 1), including the day of testing. The remaining participants (N=31) did not take any pain medication on the day of testing. All included participants with migraine met the criteria of episodic migraine [23]; four of them had migraines with aura and 11 had migraine without aura. All participants with migraine perceived their migraine attacks as unavoidable, aversive events, but as distinctive attacks with pain-free periods in between.

The study was approved by the local Ethics Committee and informed consent was obtained from all participants according to the revised Declaration of Helsinki (2013).

2.3. Experimental procedure

Individual data collection was performed in a single session. Upon arrival, informed consent was obtained, and the study aims, pain rating scale and tasks were explained. Once positioned on the scanner bed, pain sensitivity was tested (details below) to familiarize participants with the sensation of the electrical stimuli and to calibrate individualized stimulation intensities. Participants were reminded of the task instructions and practiced one trial of the pain avoidance task (details below) using visual feedback instead of electrical shocks. Before testing commenced, participants received one more painful and one more non-painful stimulus to confirm the calibrated stimulation intensities. During functional image acquisition, participants performed two tasks – first the 'pain avoidance task' and second a different behavioral task that is not further reported here. The behavioral tasks were followed by a high-resolution anatomical scan of the brain and finally another functional scan throughout which participants were engaged in a 'motor-visual control task'. After participants had been removed from the scanner, they completed the Beck's depression inventory [BDI-II, [2]], and the avoidance-endurance questionnaire (AEQ), of which only the hope- and helplessness subscale (HHS) was of interest here [20]. The HHS asks specifically for helplessness perceived when dealing with clinical/re-occurring pain. Thus, participants with migraine were asked to relate the questions to their migraine, whereas participants without migraine were instructed to think of common pains they may experience every once in a while, such as occasional headaches, tooth ache, or period pain (in females).

2.4. Electrical Stimulation

As part of the pain avoidance task, participants received transcutaneous electrical stimuli using pairs of 1 cm^2 MRI-compatible surface electrodes (Vermed®). Depending on the participant's task performance, stimuli were either painful or non-painful. *(i)* Painful stimuli were applied to degreased skin over the retromaleolar path of the right sural nerve using a Grass-S48 stimulator (Astro-Med Inc.). Each stimulation consisted of four repetitions of a 45 ms train (with 15 repetitions of 1-ms long pulses per train). The time in between the four repetitions was 500 ms. *(ii)* Non-painful stimuli were applied to degreased skin over the right anterior tibialis muscle using a Constant Voltage Isolated Linear Stimulator (STMISOLA, Biopac Systems, Inc.). Each stimulation consisted of three repetitions of three 1-ms long pulses. The time in between the three repetitions was 750 ms.

Stimulation intensities for painful and non-painful stimuli were individually determined prior to the scan. The painful stimuli were intended to be strongly aversive and painful, rated as 75 on a scale ranging from 0 ('no sensation') to 100 ('extremely painful/unpleasant') with 10 being the pain threshold ('just painful/unpleasant'). Stimulation intensities for the non-painful stimuli had to be perceivable (>0) but non-painful (<10). Stimulation intensities were determined using a staircase method. The intensity rated around 75 three consecutive times was used for the painful stimulation during the pain avoidance task. For the non-painful stimuli, the stimulation intensity that the participant rated consistently around 5 was used.

2.5. Behavioral tasks

2.5.1. Pain avoidance task

We used an adaptation of the Incentive Delay Task, which has previously been used to investigate motivated behavior in humans including by our lab [18; 27]. In the modified version (i.e. 'pain avoidance task'), the participants' goal was to avoid a painful stimulus and to receive a non-painful one instead. At the beginning of each trial, participants would see one of three words (safe; easy; difficult) displayed for 2-12 s (average 6 s). Then, a target cue would appear in the center of the screen (fig. 1). Participants were instructed to press a button on a button box as fast as possible when the target cue appeared. They were told that they had to press the response button quickly in the easy condition, and even more quickly in the difficult condition, to avoid the painful stimulus; in 'safe' trials participants knew they would receive the non-painful stimulus as long as they pressed the button eventually. Should participants not have responded (which did not occur), the trial would have automatically continued and initiated the non-painful stimulation after a maximum of 2 s. Despite being safe in 'safe' trials regardless of reaction times, we asked participants to respond to the target cue immediately in order to continue the task without delays. After their response, participants received a painful or a non-painful electrical stimulus, depending on their reaction time. Participants received the non-painful stimulus (i.e. they avoided the painful stimulus successfully) if they responded to the target cue within 310 ms for the easy, and within 230 ms for the difficult condition. Conversely, they received the painful stimulus if they failed to press the button within the allotted time window of each condition. To ensure that the safe, easy, and difficult condition were clearly distinguishable, we aimed for a success rate of 100%, 67%, and 33%, respectively. The order of the three conditions was pseudo-random, but identical for all participants. After the stimulation, a fixation cross appeared on the screen for 6-12 s (average 9 s), before the next trial commenced. Figure 1

shows a schematic illustration of one trial. In total there were 36 trials, with 12 repetitions per difficulty level ('safe', 'easy', 'difficult'). The duration of the task was approximately 11 minutes.

2.5.2. Motor-visual control task

The control task served the purpose to compare the hemodynamic responses between participants with and without migraine. Importantly, in this task behavior was not motivated by explicit threats or incentives and, thus, allowed us to assess potential differences in hemodynamic responses between the two groups that were unrelated to alterations in the neural correlates of pain avoidance. This seemed important, because migraine is a neurological disorder [5], including alterations in central processes such as increased blood flow [21], altered brain excitability, intracranial arterial dilation, and sensitization of the trigemino-vascular pathway [40; 52]. Such alterations might entail changes in neurovascular coupling and/or the hemodynamic response, albeit evidence to support this is still sparse [14].

During the control task, participants first saw a fixation cross projected onto a screen for one second. The fixation cross was followed by the presentation of a circular checkerboard that flickered at a frequency of 3 Hz for a duration of 1.7 seconds. The participants were asked to press a button on a button box using their right index finger once per trial, namely when they saw the presentation of the flickering checkerboard commencing. The two left-handed participants both reported daily use of a computer mouse with the right hand, so that the button presses in this task with their right (non-dominant) hand was similarly familiar to them as it was to the right-handed participants. The presentation of the checkerboard was followed by an inter-trial-interval of 6-20 seconds. During the inter-trial-interval a fixation cross was displayed on the screen again. There were 30 trials in total.

2.6. MRI data acquisition

Brain images were acquired using a 3 T Siemens Magnetom TRIO scanner (Siemens, Erlangen, Germany) with a standard 32-channel head coil. Functional MRI data were acquired using a blood oxygenation level-dependent (BOLD) protocol with a T2*-weighted multiband accelerated gradient echo planar imaging (EPI) sequence (TR=854 ms, TE=30 ms, flip angle 52°, resolution 2 × 2 × 2 mm, field of view 208 mm, matrix size 104 x 104, acceleration factor 6). Axial slices were oriented 30° from the line between the anterior and posterior commissure, covering the entire brain. After discarding the first three volumes to allow for steady-state magnetization, 721 volumes were acquired for the pain avoidance task, and 436 volumes for the control task. Anatomical images were acquired using a T1-weighted 3D magnetization prepared rapid acquisition by gradient echo (MP-RAGE) sequence (TR=2300 ms, TE=2.98 ms, flip angle 9°, field of view 256 mm, resolution 1 × 1 × 1 mm). Throughout the session, participants wore earplugs and their heads were stabilized.

2.7. Statistical analysis

Participants with migraine were included for their pre-existing experience with unavoidable pain and for the anticipated individual differences across this group in feeling helpless when dealing with their pain. Potential group differences were tested for by including ‘group’ as a between-subject factor in all analyses. To further assess whether observed group differences were associated with the extent to which participants feel helpless when dealing with their pain, individual helplessness scores were included in addition to ‘group’ to behavioral and imaging analyses as appropriate (see below).

2.7.1. Statistical analysis of the behavioral data

Only trials with reaction times greater than 150 ms and below 1000 ms were included, in order to exclude reaction times that were unlikely to reflect motivated, physiologically plausible behavior [57]. This resulted in the exclusion of ten trials across all participants (i.e. 10 out of 1152 trials in total).

Reaction times were corrected for non-normality by applying $f(x)=1/x$ (kurtosis and skewness <2 after correction). This measure will be referred to as 'response speed' throughout this article, with a high response speed indicating faster reaction to the target cue, and thereby increasing the chance to avoid the pain. To test the effects of difficulty level, preceding outcome and group on the response speed, a repeated measurement ANOVA design was used, using mixed model procedures with the between factor 'group' (2 levels: participants with migraine and participants without migraine) and the within-subject factors 'difficulty level' (3 levels: safe, easy, difficult), and 'outcome on preceding trial' (2 levels: painful vs. non-painful). The ANOVA analysis was followed by post-hoc ANOVA designs (i.e. 'group' by 'difficulty level', separately for 'outcome on the preceding trial'; and 'difficulty level' by 'outcome on the preceding trial', separately for the two groups) and/or pairwise comparisons, and calculation of Cohen's d as a measure of effect size [9] when appropriate.

To test for linear relations between different clinical characteristics of the participants with migraine and pain avoidance behavior, as well as between helplessness scores (HHS, log transformed) and (a) pain avoidance behavior for each group separately (participants with and without migraine) and (b) mean activation of brain regions identified within the fMRI analysis, Pearson's product-moment correlation coefficients (*Pearson's r*) were calculated between the respective variables.

The significance level was set to 5% for all analyses and results were Bonferroni-corrected to account for multiple testing. Outliers were defined as exceeding the group mean value by more than 2 standard deviations and were excluded from the analyses. All statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc. Chicago, USA).

2.7.2. Statistical analysis of fMRI data

BOLD fMRI analysis of the 'Pain avoidance task'

All image processing and statistical analysis was performed using the software package FSL 5.0.8 (FMRIB's Software Library; http://www.fmrib.ox.ac.uk/fsl; [48]). For one participant without migraine only 500 volumes (instead of 721) were available for the analysis of the pain avoidance task because the scan stopped early due to technical failure.

Subject level analysis. The following pre-processing steps were applied to each functional dataset: motion and distortion correction using MCFLIRT [22], denoising using the independent component analysis (ICA) MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) [4] and an automated algorithm to remove ICA components identified as motion-related noise (ICA AROMA, ICA-based Automatic Removal Of Motion Artifacts [42]), spatial smoothing (Gaussian kernel, full width at half-maximum: 5 mm), and temporal high pass filtering (Gaussian-weighted least-squares straight line fitting with sigma = 90 s). Susceptibility-related distortions were corrected using FSL field map correction routines. T1-weighted structural images were segmented into white matter (WM), grey matter (GM), and cerebrospinal fluid (CSF). WM and CSF maps were subsequently transformed to the individual's EPI space. Mean time series of WM and CSF were extracted from the individual EPIs and added to the first-level analyses for each participant as regressors of no interest.

A general linear model (GLM) was applied to each functional dataset, modeling the time of the display of the difficultly level in six conditions (safe subsequent to successful pain avoidance, easy subsequent to successful pain avoidance, difficult subsequent to successful pain avoidance, safe subsequent to unsuccessful pain avoidance, easy subsequent to unsuccessful pain avoidance, difficult subsequent to unsuccessful pain avoidance; 'basic GLM') in order to test the brain activation related to participants' preparatory state while waiting for the target cue, separately for each condition. This 'preparatory phase' corresponds to the 2-12 s (6s on average) when participants were presented with the cue indicating the difficulty level ('safe', 'easy', 'difficult') but before the onset of the target cue. The time points of the target cue, button press, electrical stimulation, and WM and CSF time series were included in the model as nuisance variables. A second GLM was applied to each functional dataset, modeling two conditions (preceding outcome non-painful and preceding outcome painful) with each trial weighted according to the level of difficulty (safe = 1, easy = 2, difficult =3; 'linear GLM') in order to test increasing brain activation with increasing task difficulty while waiting for the target cue. The resulting network of brain regions associated with a linear increase in task difficulty across the two conditions of the outcome on the previous trial will be referred to as the 'preparatory matrix'. The same nuisance variables as described for the basic GLM were included. In both GLMs, all regressors other than the CSF and WM time series were convolved with a gamma hemodynamic response function (phase = 0 s, standard deviation = 3 s, mean lag = 6 s) and the first temporal derivatives were included. Voxel-wise parameter estimates (PEs) were derived using the appropriate contrasts. Individuals' functional images were first registered to their own structural scan and subsequently to the International Consortium for Brain Mapping (ICBM) 152 *non-linear 6th generation* symmetric template in MNI standard space using linear [FLIRT; [22]] and non-linear transformations (FNIRT, warp resolution=6 mm).

Group level analysis. Second level analyses were performed using a mixed-effects model, implemented in FLAME [3]. Statistical inference was based on a voxel-based threshold of $z=2.3$, cluster corrected for spatial extent across the whole brain at $p<.05$.

To identify brain areas in which activation correlated with self-reported helplessness, a regressor was added to the second level analysis of the contrasts 'difficult subsequent to unsuccessful pain avoidance' and 'difficult subsequent to unsuccessful vs. successful pain avoidance' ('basic GLM + helplessness regressor'). This regressor coded the individual level of helplessness that participants reported via the HHS sub-scale of the AEQ. The aim of the analysis was to assess which brain areas were (positively or negatively) associated in their activation with the individual level of helplessness dependent on the success on the previous trial. It was assumed that helplessness would be associated with relatively reduced activation of brain areas relevant to prepare pain avoidance behavior, especially when previous avoidance attempts had been unsuccessful. The scores on the HHS were normally distributed following log-transformation. Log-transformed HHS scores were then demeaned across the sample before entered as regressor. Parameter estimates were extracted for areas that were associated with HHS-scores for trials following successful pain avoidance and for those following unsuccessful pain avoidance using FEATquery as implemented in FSL. Extracted parameter estimates for each of these regions were used to depict the correlation between them and change in response speed due to an unsuccessful pain avoidance attempt on the previous trial. Specifically, the mean differences in brain activation of the HHS-associated brain regions between trials following a successful vs. unsuccessful pain avoidance attempt in the difficult condition were correlated with the differences in response speed following a successful vs. unsuccessful pain avoidance attempt in the difficult condition.

Motor visual control task: estimation of the hemodynamic response function

Data from one female participant with migraine were included in the analysis of the visual responses but excluded from the analysis of the motor responses because she failed to give the required behavioral motor responses.

Using FSL 5.0.8 [FMRIB's Software Library; http://www.fmrib.ox.ac.uk/fsl; [48]], the following preprocessing steps were applied to each functional dataset: spatial smoothing (Gaussian kernel, full width at half-maximum: 5 mm), motion correction, and temporal high-pass filtering (Gaussian-weighted least-squares straight line fitting with sigma = 90 s). After this, a GLM was applied to each functional dataset, modeling one event (visual-motor) in order to test the pattern of brain activation related to participants' visual and motor responses while seeing the flickering checkerboard and simultaneously pressing the response button. Hereafter, we refer to this analysis as the 'initial GLM'.

For the actual evaluation of the hemodynamic response function (HRF) we performed a finite impulse response (FIR) estimation [11; 41] as implemented in the software NeuroLens2 (scripted in Python™). We applied this model-free analysis to estimate the shape of the HRF in the primary visual cortex (V1) in response to the onset of the visual stimulus, and in the hand area of the contralateral primary motor cortex (M1), as well as in the ipsilateral putamen in response to the button press. The coordinates of the RoIs were based on the respective peak activations resulting from the 'initial GLM'. Voxels exceeding a z-value of 2.3 were included in the RoIs and multiplied with anatomical masks of the left primary visual cortex, the contralateral primary motor cortex, and the ipsilateral putamen as defined by the 'Juelich Histological Atlas' implemented in FSL (using a probabilistic threshold of 10% for each anatomical mask). RoIs for

V1 and M1 were further manually restricted (based on anatomy) to avoid large RoIs exceeding the area of V1 and the hand area of M1, respectively.

To estimate the shape of the HRF for each RoI, an additional GLM was fitted for every individual dataset using 41 delta functions as regressors with one sample estimate per repetition time (TR = 854 ms, resulting in a time window of 41 x 0.854 s = 35 s), and a third order polynomial function as a regressor of no interest to control for slow drifts in the signal over time. The resulting HRF estimates were then further analyzed using a repeated measure ANOVA with 'trial number' as within-subject factor and 'group' (participants with and without migraine) as between subject factor, performed separately for the three RoIs. This analysis served the aim to compare the HRF shapes between participants with and without migraine and was carried out using IBM SPSS Statistics 25 (SPSS Inc. Chicago, USA).

3. Results

3.1. Participants with migraine had a wide spread of helplessness levels across the group and, overall, showed many similarities to participants without migraine.

In participants with migraine, helplessness scores on the HHS ranged from 0 to 48 (with 54 being the highest possible score on the HHS) and had a mean score of 21 (SD=13), thus showing the anticipated wide spread of perceived helplessness when dealing with their migraine pain. Helplessness scores correlated with the length of a typical migraine attack ($r=0.59$, $p=0.021$), meaning that patients who experience longer attacks feel more helpless.

Comparing participants with and without migraine showed that they were similar in age and gender and had comparable depression scores ($p's>0.09$, table 1).

We further tested whether the HRF was comparable between participants with and without migraine. The HRF was quantified in two cortical and one sub-cortical brain region (i.e. the primary visual cortex, the hand area of the contralateral primary motor cortex, and ipsilateral putamen) in response to a non-incentive, motor-visual control task (fig. 2a). We found no differences for the HRF between participants with and without migraine in any of the tested brain regions (fig. 2b). More specifically, a repeated measure ANOVA estimating the influence of time and group on the hemodynamic response function, revealed no significant effect of group and no significant interaction between time and group in any of the regions tested. Therefore, it can be concluded that participants with and without migraine studied here had a comparable HRF, indicating similarity of the neurovascular coupling.

3.2. Overall, success rates in the pain avoidance task and the electrical stimulation intensities were comparable for participants with and without migraine

Applied stimulation intensities did not differ between participants with and without migraine for neither painful (participants without migraine 6.5±2.8 mA (mean±SD); participants with migraine 7.3±3.5 mA; p=0.46) nor non-painful stimuli (participants without migraine 1.1±1.0 mA; Participants with migraine 1.1±1.0 mA; p=0.94), indicating that both groups received comparable physical input throughout the pain avoidance task.

Further, success rates for all three conditions (safe, easy, and difficult; independent of preceding pain avoidance success) were comparable between groups. Per default, the success rate in the safe condition was 100% for all participants and no painful shocks were received. In the easy condition participants with migraine received on average 4.00±0.68 and participants without migraine 3.65±0.51 painful shocks (p=0.677, Cohen's d=0.15); equivalent to an overall success rate of 68.25%, which was close to the 67% success rate aimed for. In the difficult condition participants with migraine received on average 8.07±0.81 and participants without migraine 8.17±0.69 painful shocks (p=0.919, Cohen's d=-0.04); equivalent to an overall success rate of 32.25%, which was close to the 33% success rate aimed for. Therefore, the goal of distinct success rates across conditions was achieved.

3.3. Response speed is altered following unsuccessful pain avoidance

Response speed was influenced by the difficulty level as well as by the outcome on the preceding trial. It should be noted that response speed is the inverse to reaction time (see section 2.7.1), meaning that higher response speed can be interpreted as an indication of greater alertness and/or motivation to avoid the painful stimulus. As depicted in Figure 3a (left panel), participants reacted faster with increasing difficulty for both types of preceding outcome (main effect of

'difficulty level' $F_{2,78}$=43.61, p<0.001). However, the response speed was altered when participants failed to avoid the painful stimulus on the preceding trial (main effect of 'outcome on preceding trial' $F_{1,614}$=6.79, p=0.009). Further, analysis revealed an interaction between 'difficulty level' and 'outcome on preceding trial' ($F_{2,692}$=3.48, p=0.031). Post-hoc pairwise comparisons between trials following unsuccessful versus successful pain avoidance showed a significant decrease for the difficult condition (mean difference -35.86 ms, p<0.001, Cohen's *d*=0.49, fig. 3a), but not for the safe or easy condition.

Response speed was altered in participants with migraine compared to those without migraine, but only after unsuccessful pain avoidance on the preceding trial (significant interaction between the outcome of the preceding trial and group, $F_{1,614}$=4.43, p=0.036). When pain avoidance attempts were successful on the preceding trial both groups showed comparable response speed (non-significant main effect of group; F1,215=1.34, p=0.249), independent of the difficulty level (non-significant interaction between group and difficulty level; F2,253=1.84, p=0.162, figure 3a, middle panel). Following unsuccessful pain avoidance on the preceding trial, however, response speed was slower in participants with migraine compared to participants without migraine (main effect of 'group' $F_{1,88}$=9.45, p=0.003). Post-hoc pairwise comparisons revealed a significant difference between groups for the difficult condition following unsuccessful pain avoidance on the preceding trials only (mean difference = 32.65 ms, p=0.007, Cohen's d=0.59), but not for easy and safe (figure 3a, right panel). However, the interaction effect for group and difficulty level was not significant ($F_{2,132}$=1.33, p=0. 269). Further, plotting the individual data points for all participants separately for all conditions (fig. 3a, middle and right panel) depicts that participants with and without migraine showed large overlaps in their response speed – even for the difficult condition following unsuccessful pain avoidance attempts. This implies that many participants with migraine reacted to changes in demand (indicated by the difficulty level) and in

previous experiences (modulated by previous pain avoidance success) in a comparable fashion to participants without migraine. The change in response speed following unsuccessful pain avoidance attempts on the previous trial was correlated to self-reported helplessness in participants with migraine ($r=0.67$, $p=0.007$, Fig 4a), where a greater reduction in response speed following unsuccessful versus successful pain avoidance attempts on the preceding trial was associated with higher helplessness scores. For participants without migraine, in contrast, there was no association between the change in response speed after unsuccessful pain avoidance on the previous trial and HHS scores ($r=-0.47$, $p=0.057$, Fig. 4a) (the scatterplot demonstrates that the trend for the negative association is related to an HHS score of 0 of many participants without migraine).

3.4. Diminished activation of posterior parietal cortex during pain threats underpins behavioral disruptions, especially in migraine patients reporting high helplessness

The brain activity was analyzed for the preparatory phase, i.e. during the time period *before* the actual avoidance behavior was performed. During this phase participants were presented with the cue indicating the difficulty level to avoid the upcoming pain stimulus (safe, easy, or difficult) and knew that they would have to react very promptly with a button press as soon as the presentation of the difficulty cue then switched to the presentation of the target cue. While they needed to prepare for the required motor behavior, no actual movement was performed during this phase yet. Therefore, brain activity observed during the preparatory phase is not only correlated to the observed behavior but can be interpreted as a predictor of the subsequent motor response.

Activation during the preparatory phase increased with increasing task difficulty and resulted in a vast ‘preparatory matrix’ activation. This ‘preparatory matrix’ included regions related to alertness, motor preparation/execution and cognitive control, such as bilateral dorsolateral prefrontal cortex (dlPFC), anterior insula, posterior parietal cortex (PPC), anterior cingulate cortex (ACC), pre-motor cortex, supplementary motor area, left primary motor cortex, basal ganglia, cerebellum, PAG, and superior colliculus (fig. 3b). Comparing brain activation following unsuccessful versus successful pain avoidance on the preceding trial showed significantly reduced activation of most areas of the preparatory matrix, including bilateral PPC, SMA, ACC, premotor cortex, secondary somatosensory cortex, and insula (fig. 3c). This suggests that alertness and motor preparation were decreased during the preparatory phase subsequent to unsuccessful pain avoidance. This is consistent with the behavioral result of a reduced increase in response speed with increasing difficulty following unsuccessful pain avoidance. Further, following unsuccessful pain avoidance on the previous trial, participants without migraine show a greater increase in right parietal cortex activation with increasing task difficulty compared to participants with migraine (fig. 3d). This is consistent with the behavioral finding of significantly reduced response speed in participants with migraine compared to those without following unsuccessful pain avoidance on the previous trial for the difficult condition, but not for easy and safe.

Being specifically interested in the question whether helplessness is associated with reduced brain activation and whether it might explain the decreased response speed in participants with migraine following unsuccessful pain avoidance, over and above a group difference, participants' HHS scores were added as regressor to the contrasts ‘previous avoidance attempt unsuccessful’, for the difficult condition only (Basic GLM). Using whole-brain analysis, a significant negative correlation between the activation magnitudes following unsuccessful pain avoidance and the

helplessness scores was found for participants with migraine in a network of cortical areas associated with motor behavior, attention, and memory, i.e. bilateral primary motor cortex, left posterior parietal cortex, bilateral secondary somatosensory cortex, and left hippocampus and parahippocampus (fig. 4b, left panel), with higher HHS scores being associated with less activation of these areas following unsuccessful pain avoidance on the previous trial. In participants without migraine, a significant negative correlation between the activation magnitudes following unsuccessful pain avoidance and the helplessness scores was found for PPC, occipital lobe, and right premotor cortex (fig 4b, middle panel). Comparison of participants with and without migraine showed that this negative association was stronger for participants with migraine for right posterior parietal cortex/posterior cingulate cortex, bilateral primary motor cortex, bilateral secondary somatosensory cortex, and right posterior insula (fig. 4b, right panel). This suggests that not only having clinical pain, but in addition feeling helpless about it, is associated with decreased brain activation relevant to prepare for pain avoidance.

Because of the positive correlation between HHS scores and a reduction in response speed due to unsuccessful avoidance attempts on the previous trial in the difficult condition that was found for participants with migraine only, it was next assessed whether the change in activation within the HHS-associated brain regions of participants with migraine (bilateral primary motor cortex, left posterior parietal cortex, bilateral secondary somatosensory cortex, and left hippocampus/parahippocampus) following successful versus unsuccessful pain avoidance was also correlated to changes in pain avoidance behavior. Changes in brain activation of the HHS-associated brain regions were indexed by the difference score of the extracted parameter estimates for each of the two contrasts, i.e. following successful minus unsuccessful pain avoidance in the difficult condition; accordingly, changes in avoidance behavior were indexed by the difference in response speed following successful minus response speed following

unsuccessful pain avoidance in the difficult condition. This analysis yielded a significant positive correlation (r=.53, p=0.042). Assessing each cluster of this network (fig. 4b, left panel) separately showed this association to be primarily driven by the posterior parietal cortex (r=.668, p=0.007, fig. 4c), with the correlations of change in response speed following successful versus unsuccessful pain avoidance and chance in activation of the other areas not being statistically significant (p's>0.49).

4. Discussion

In this study, pain avoidance behavior was increased with increasing task difficulty and compromised when previous attempts had been unsuccessful. While observed for both groups, participants with migraine were even more affected by preceding unsuccessful avoidance attempts as they showed greater reductions of their response speed in the difficult condition in trials following unsuccessful pain avoidance compared to trials following successful pain avoidance. Interestingly, patients' helplessness scores were associated with a greater reduction in response speed following unsuccessful attempts, suggesting that coping style is an important determinant of pain avoidance behavior.

Increasing task difficulty was reflected in increased activation of a large brain network during the preparatory phase, i.e. when participants prepared to react to the upcoming target cue, including areas associated with attention, motor behavior, cognition, and defense preparation (‘preparatory matrix’). In parallel to the reduction in response speed following unsuccessful compared to successful pain avoidance, preparatory matrix activation was also reduced. After unsuccessful pain avoidance, participants with migraine showed a reduced increase in right PPC activation with increasing task difficulty compared to participants without migraine, possibly causing the difference in response speed between the groups observed for the difficult condition. Out of several brain regions that were negatively associated with helplessness scores in participants with migraine, only left PPC activation predicted subsequent response speed, thereby highlighting its link to pain avoidance behavior. We conclude – in disagreement with the original hypothesis – that PPC rather than PAG plays a key role in human pain avoidance, with diminished PPC activation during pain threats underpinning behavioral disruptions, especially in migraine patients with elevated helplessness levels.

Pre-clinical studies describe a major role for the PAG in pain avoidance [12; 24; 25; 30; 31; 53]. While the present study identified a cluster spanning PAG/superior colliculus (SC) as part of the preparatory matrix and, thus, suggesting PAG/SC involvement in the preparation to avoid pain also in humans, no specific link of its activation to reduced pain avoidance behavior following unsuccessful pain avoidance attempts nor an association with helplessness scores was observed. This suggests that PAG/SC might be unaffected by immediate performance feedback as well as by long-term experiences with unavoidable pain. PAG stimulation in rodents leads to autonomic adaptations and changes in muscle tone [30; 39], the latter probably regulated via the cerebellum [28], likely to facilitate defense behavior. In the present study, the cerebellum was also part of the preparatory matrix, but – similar to PAG/SC – unaffected by the outcome of previous avoidance attempts as well as by clinical pain. These findings suggest that the PAG and its effectors consistently reacted to pain threats, implying unaltered PAG-dependent defense mechanisms even after unsuccessful attempts. The apparent discrepancy in findings between the current and pre-clinical studies is likely related to different experimental designs: In a majority of pre-clinical studies, the PAG was either stimulated directly to elicit defense behavior [1; 13; 53] or its neural activity was measured in response to noxious input [24; 25; 28; 30; 31].Thus, these studies rather assessed the role of the PAG in pain defense behaviors than in the avoidance of imminent pain, in contrast to the present study. One study in mice did provide evidence for PAG activation already during threat [12], which is more comparable to the current design. However, neural activity in PAG was recorded while the animals executed risk assessment behavior, while the participants here had to ensure not to miss the visual target cue during the preparatory phase in order to avoid pain, meaning that they had to be highly attentive and prepare for, but not execute any motor behaviors. This suggests that different threat processing networks are involved depending on the exact contextual and behavioral requirements.

Neural changes that did depend on unsuccessful pain avoidance on the previous trial were restricted to cortical areas in the current study and included the PPC, right insula, premotor cortex and SMA. While premotor cortex and SMA are typically associated with motor planning and preparing the motor system for exact movements [15], insula and PPC have been linked to regulatory and attention-related functions [34; 38; 47]. The right insula, specifically, has been suggested to link brain areas encoding task difficulty and attention [16; 49]; it has further been demonstrated to play a key role in evaluating task performance [16]. Accordingly, the reduction in right insula activation following unsuccessful versus successful pain avoidance might encode a perceived decrease in task performance, ultimately causing a decreased signal in PPC as one of the brain's attention areas [34; 47]. Functional connectivity between right insula and PPC has been shown specifically for visual attention tasks [7; 16; 37] during which participants have to react to visual cues in a similar way as in this study's paradigm. PPC has further been associated with generating nocifensive behaviors [29]. Taken together, alertness in the current study might have been diminished following unsuccessful pain avoidance attempts due to the perception of a poor task performance, leading to delays in the initiation of nocifensive behavior. This effect was greater in participants with migraine compared to those without, as they showed significantly reduced increases in PPC activation with increasing task difficulty after unsuccessful pain avoidance. This might have consequently led to the reduced response speed observed specifically in the difficult condition.

Interestingly, changes in left PPC activation following unsuccessful pain avoidance were associated with higher helplessness scores in participants with migraine, suggesting that helpless behavior within a pain context may be based on individual differences in the underlying neurobiology when facing threats. It has been described that, despite experiencing similar levels of pain, not everyone develops the same level of helplessness; some pain patients are even

resilient [36; 50]. In line with the current findings, studies in healthy individuals and pain patients showed that helplessness is associated with functional and anatomical brain measures [8; 44; 45; 56]. Extending these earlier studies, the present results link the relevant brain function that scales with individual helplessness scores to coping-relevant behavior (i.e. pain avoidance), as a reduction in left PPC activation following unsuccessful versus successful pain avoidance was also associated with a reduction in response speed.

The observation that participants with migraine were even more affected by previous unsuccessful avoidance attempts suggests that, on a cognitive level, they might have appraised the benefits/cost ratio as lower compared to participants without migraine, making it less favorable to exhibit strong efforts of staying attentive to avoid the next painful stimulus [19]. In addition to being associated with a stronger reduction in response speed after unsuccessful pain avoidance attempts, higher helplessness scores were related to a longer duration of migraine attacks. This reflects that patients with high helplessness scores experience a longer exposure to unavoidable pain with each migraine attack. This prior experience of uncontrollable pain can influence behavior in response to current threats [51]. It is thus plausible that patients with high helplessness appraise benefits/costs differently following unsuccessful preceding attempts [35]. This inaccurate appraisal of the benefit/cost ratio can explain the present findings, and can also resolve an apparent contradiction of the present results with previous literature that has pointed to increased tendencies of pain-avoidance behavior in chronic pain patients (e.g. [10; 54; 55]). Pain patients who avoid activities they had previously cherished out of fear to experience more pain might do so due to an overestimation of the involved cost (i.e. increased pain). In the present study, the inaccurate appraisal of the benefit/cost ratio might be more related to a

misjudgment of their own ability to avoid pain, leading to an underestimation of the potential benefit (pain avoidance) when the effort of doing so had previously remained unrewarded.

Limitations

The required sample size for this study was calculated for the anticipated behavioral effect. It is acknowledged that for a brain imaging study a sample of 32 participants (17 participants without and 15 with migraine) was relatively small. Nevertheless, strong effects within the fMRI analysis were detected, including interactions (e.g. between group and difficulty level following unsuccessful pain avoidance on the previous trial, and between difficulty level and previous outcome across the whole group), which often remain unobserved if statistical power is lacking. Further, the findings related to self-reported helplessness are based on the sub-sample of participants with migraine and, due to its relatively small number, are to be interpreted with caution. Nevertheless, the findings provide interesting insights into maladaptive coping with clinical pain and how this may influence attentional processing during pain threats that may be deemed difficult or even impossible to avoid dependent on individuals' previous experiences.

Conclusion

Individuals adjust pain avoidance behavior promptly, depending on their previous success in doing so. Participants with frequent unavoidable migraines were even more affected in their ability to quickly respond to pain threats when previously unsuccessful compared to participants without migraine. This behavioral group difference was underpinned by reduced PPC activation in participants with migraine, suggesting diminished alertness following unsuccessful pain avoidance. Helplessness in participants with migraine was related to both a greater reduction in PPC activation and in pain avoidance behavior following unsuccessful pain avoidance. This

implies that not only the mere experience of clinical pain compromises pain avoidance, but rather an interaction of it with the individual's coping capacity.

Acknowledgments

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Figure Captions

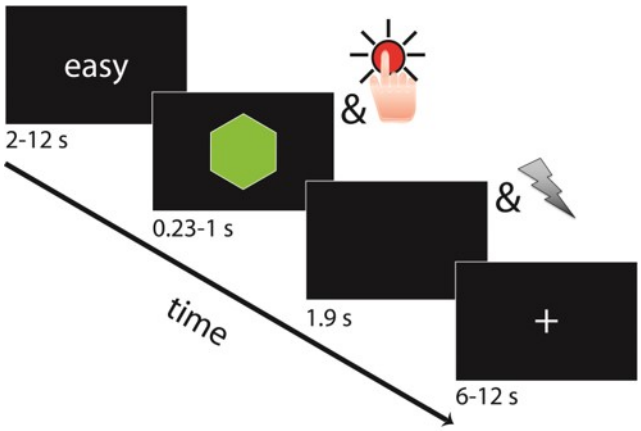

Figure 1 The pain avoidance task: outline of one trial including timeline.
Participants first saw how difficult it would be to avoid the upcoming painful stimulus (i.e. safe, easy, or difficult). We refer to this phase as the 'preparatory phase', during which brain activation was analyzed. After the preparatory phase, the target cue appeared. If participants reacted fast enough in response to the target cue, they avoided the painful stimulus and received a non-painful one instead. This was followed by the presentation of a fixation cross before the next trial commenced.

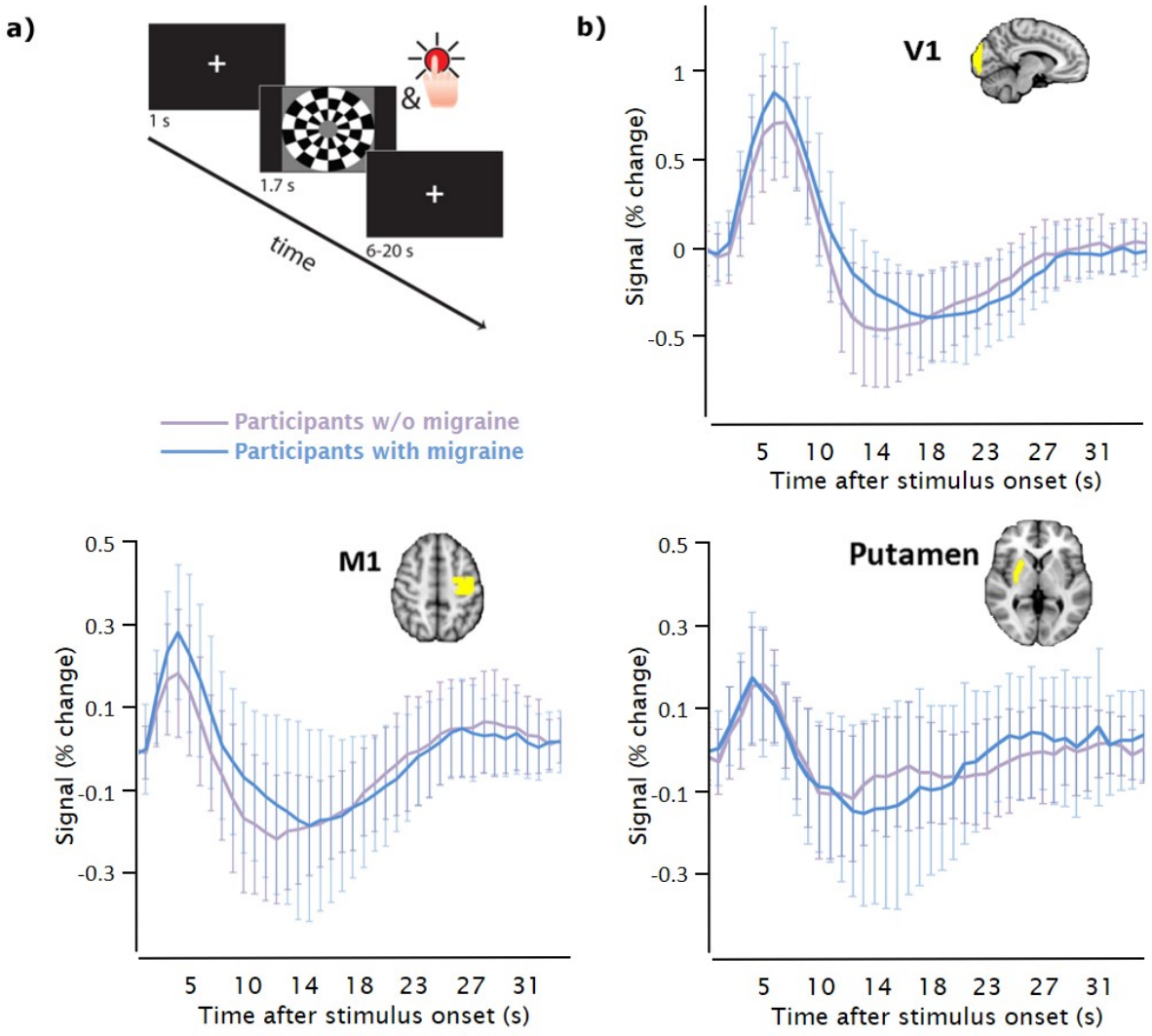

Figure 2 Estimation of the hemodynamic response function (HRF) in response to visual and motor stimuli. a) Outline of one trial of the motor-visual control task. When participants saw the flickering checkerboard (visual stimulus) they were instructed to react with a single button press on the response unit (motor stimulus). b) No differences were observed between participants with migraine (blue lines) and without migraine (purple lines) w.r.t. their HRF in response to the visual stimulus assessed in the visual cortex or associated with the button press in contralateral primary motor cortex and ipsilateral putamen. The regions of interest are depicted in yellow on the standard brain. Lines show the mean across the group and the error bars the standard deviation; N=32 (n=17 participants without migraine, and n=15 participants with migraine).

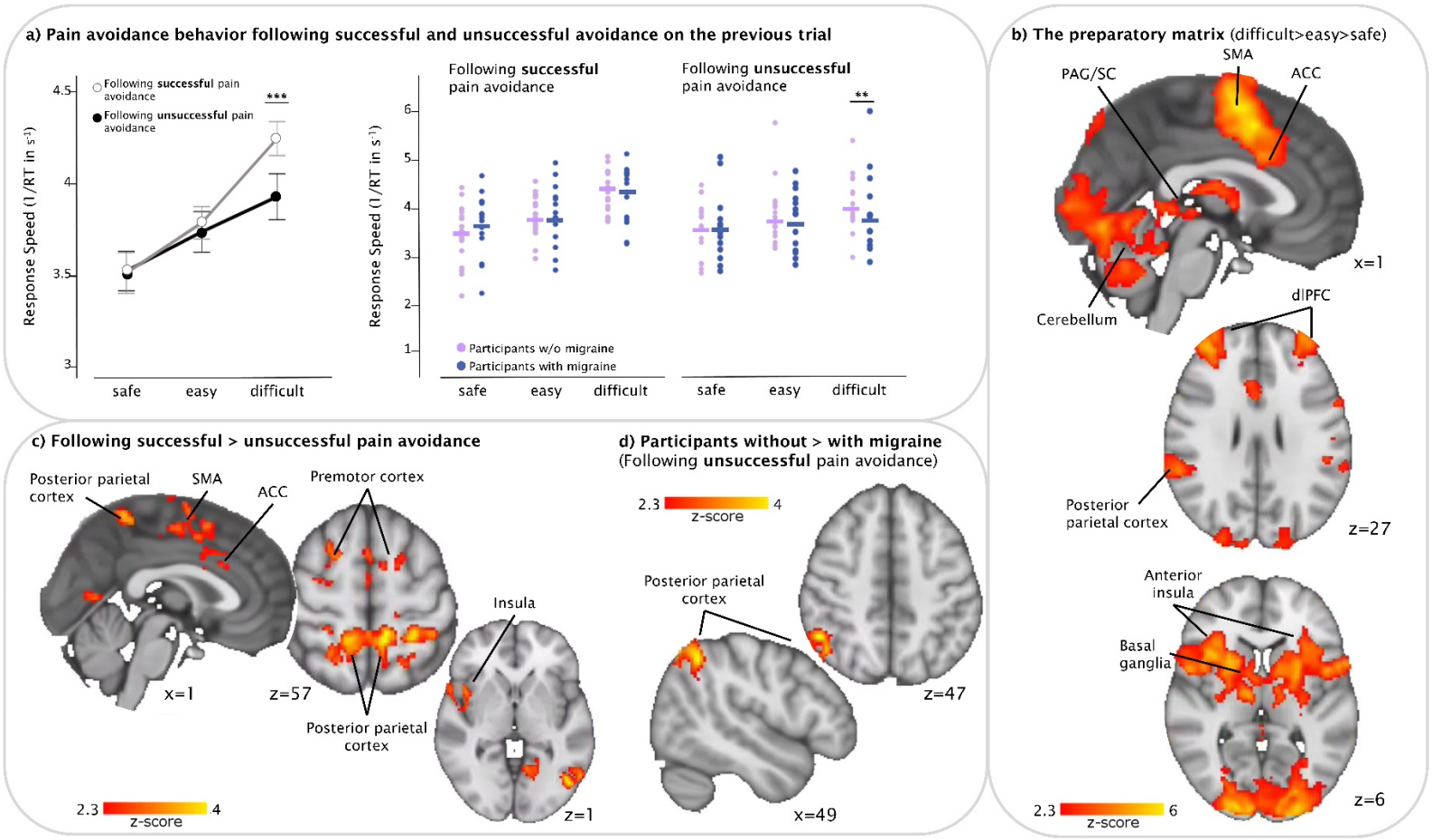

Figure 3 Linear increases in neural activation with increasing task difficulty and corresponding pain avoidance behavior.

a) Response speed generally increased with increasing task difficulty (main effect of 'difficulty level', $p<0.001$). Pain avoidance behavior (i.e. response speed) was reduced following unsuccessful compared to successful pain avoidance attempts (main effect of 'outcome on preceding trial', $p=0.009$); post-hoc tests revealed a significant difference for the difficult condition. While participants with migraine (blue dots, middle and right panel) were more affected in their pain avoidance behavior following unsuccessful preceding attempts compared to participants without migraine (purple dots), generally considerable overlap was found between the groups in their pain avoidance behavior.

b) Activation in a large network of brain areas during the preparatory phase linearly increased with increasing task difficulty ('preparatory matrix'). This network encompassed brain areas associated with attention, such as the anterior insula and the posterior parietal cortex, as well as motor-preparation areas, including the cerebellum, basal ganglia, and supplementary motor area.

c) Significant differences in the activation of the 'preparatory matrix' between trials subsequent to successful pain avoidance compared to unsuccessful pain avoidance were observed in various brain regions, including posterior parietal cortex, right insular cortex, SMA, ACC and pre-motor cortex.

d) Following unsuccessful pain avoidance on the previous trial, the linear increase in activation with increasing difficulty was significantly reduced in the right posterior parietal cortex for participants with migraine compared to those without migraine.

Voxel-based threshold $z>2.3$, cluster corrected for spatial extent across the whole brain at $p<0.05$. Images are displayed in radiological convention, i.e., right side of the brain is on the left. The statistical parametric maps are overlaid on the non-linear ICBM-152 template. Coordinates are given in MNI space. The line graph depicts the response speed for all three difficulty levels in the pain avoidance task in trials following successful (open

circles) versus unsuccessful pain avoidance on the preceding trial (closed circles); shown are means±SEM; *** p≤0.001; ** p≤0.01; N=32 (n=17 participants without and n=15 with migraine); ant INS: anterior insular cortex; SMA: supplementary motor area; ACC: anterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex; PAG: periaqueductal grey, SC: superior colliculus.

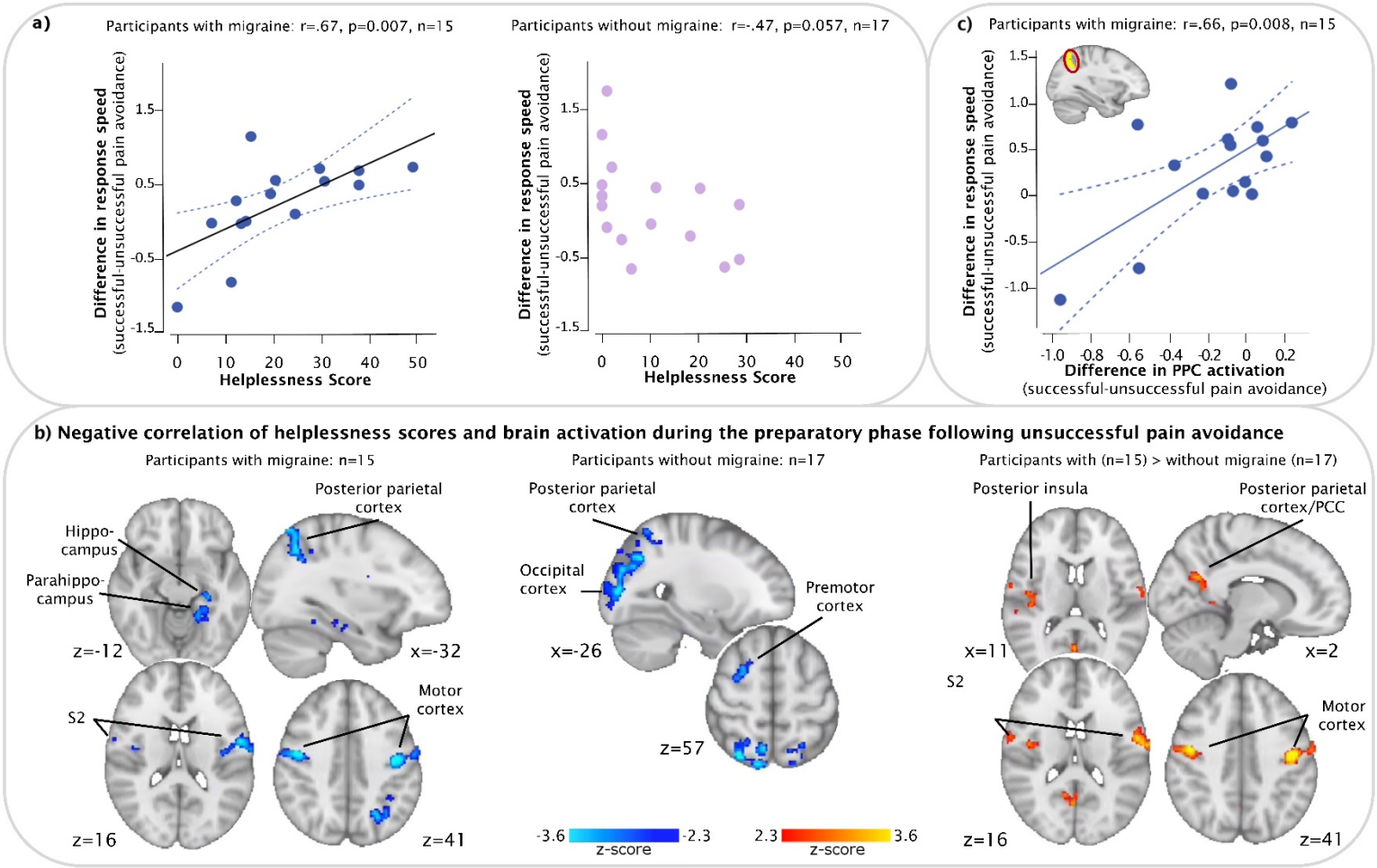

Figure 4 Associations between helplessness, pain avoidance behavior, and PPC activation

a) In participants with migraine (n=15, left panel), self-reported helplessness was positively correlated with a greater reduction in response speed in difficult trials following unsuccessful pain avoidance on the previous trial (delta response speed in the difficult condition for previous avoidance attempt successful versus unsuccessful). This positive association was not observed for participants without migraine (n=17, right panel).

b) Following unsuccessful pain avoidance on the previous trial, a negative association was found between helplessness scores of participants with migraine and activation of several brain areas, including left posterior parietal cortex, bilateral motor cortex, secondary somatosensory cortex (S2), and left hippocampus/parahippocampus (left panel). This indicates that the more helpless an individual perceives him-/herself, the lower the activation in the identified brain areas. For participants without migraine (middle panel) a negative association was found between helplessness scores and activation of brain areas, including posterior parietal cortex, occipital cortex and right premotor cortex. When comparing the two groups (right panel) this negative association is stronger in participants with migraine than for those

without migraine for posterior parietal /posterior cingulate cortex, right posterior insula, bilateral motor cortex, and bilateral secondary somatosensory cortex.

c) Out of the identified brain regions associated with self-reported helplessness in participants with migraine, only changes in activation of posterior parietal cortex following successful versus unsuccessful pain avoidance on the previous trial correlated with changes in response speed. Precisely, a greater reduction in posterior parietal cortex activation following unsuccessful pain avoidance predicted a greater reduction in response speed in participants with migraine.

Voxel-based threshold $z>|2.3|$, cluster corrected for spatial extent across the whole brain at $p<0.05$. Images are displayed in radiological convention, i.e., right side of the brain is on the left. The statistical parametric maps are overlaid on the non-linear ICBM-152 template.
N=32 (n=17 participants without and n=15 with migraine); S2: secondary somatosensory cortex; PPC: posterior parietal cortex.