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Pain catastrophizing is associated with altered EEG effective connectivity during pain-related mental imagery

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Pain catastrophizing – defined as a tendency to exaggerate the threat value or seriousness of experienced pain - has been shown to be a risk factor for pain chronification. However, the neural basis of pain catastrophizing remains unclear and requires thorough investigation. This study aimed to explore the relationship between pain catastrophizing and effective connectivity of the pain systems in healthy participants. EEG data were collected during an induced state of pain-related negative, depressive, positive and neutral mental imagery conditions, and pain catastrophizing tendencies were measured by the Pain Catastrophizing Scale. The Directed Transfer Function, a method based on Granger causality principles, was used to assess the effective connectivity. Linear mixed effects analyses revealed a negative relationship between pain catastrophizing and beta information flow from the right temporal cortex to the frontal regions and a positive relationship between pain catastrophizing and increased beta information flow from the right somatosensory cortices to the right temporal cortices when thinking about pain. These patterns were not found in other imagery conditions. Taken together, this study suggests that individual differences in pain catastrophizing might be related to an altered frontotemporal regulatory loop and increased connectivity between pain and affective systems. Our study reveals connectivity patterns related to pain catastrophizing tendencies that are detectable even in pain-free, healthy individuals.

Key words: pain catastrophizing, EEG effective connectivity, pain modulation, directed transfer function, emotional mental imagery

INTRODUCTION

The subjective experience of pain depends on various biopsychological factors, including pain catastrophizing (Melzack and Wall, 1965; Turk and Rudy, 1992). The tendency to catastrophize about pain was found to be one of the strongest predictors of negative pain-related outcomes leading to heightened pain intensity or lowered pain threshold (Beneciuk et al., 2010; Kjøgx et al., 2016), increased psychological distress in response to pain (Kjogx, 2016), inefficient disengagement from pain (Van Damme et al., 2004) and pain-related disability, e.g., pain interference and days missed from usual activities due to pain (Severeijns et al., 2001; Arnow et al., 2011). Although pain catastrophizing overlaps with other psychological constructs such as anxiety or depression (Rosenstiel and Keefe, 1983; Granot and Ferber, 2005), it was found to be the only psychological factor that is related to the distinctive pattern of altered brain activation in chronic pain (Malfliet et al., 2017). It has been characterized as a maladaptive response to pain, comprising three components: magnification (of the threat value or seriousness of experienced pain), rumination (compulsively focused attention on the symptoms of one's distress) and helplessness (inability to suppress pain-related thoughts and behaviors) (Sullivan et al., 1995). To date, the great majority of studies

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have focused on identifying brain changes related to pain-catastrophizing in clinical populations (especially individuals with chronic pain), suggesting deficient recruitment of the pain-inhibitory brain structures, e.g., the dorsolateral prefrontal cortex (Lorenz et al., 2003) as well as elevated activity in the emotional brain circuitry when experiencing (Gracely et al., 2004; Lloyd et al., 2008, 2014) or anticipating pain (Burgmer et al., 2011; Loggia et al., 2015). Moreover, connectivity analysis has revealed attenuated coupling between both of these systems during resting-state conditions (Kucyi et al., 2014; Jiang et al., 2016). However, as it has been suggested repeatedly that pain catastrophizing is a crucial risk factor for the development of chronic pain (Sullivan et al., 2001; Keefe et al., 2004; Edwards et al., 2006; Borkum, 2010), the examination of neural alterations associated with pain catastrophizing in a healthy yet predisposed population is a matter of great clinical importance.

To our knowledge, there are only a few studies addressing this issue in healthy individuals. Jensen et al. (2015) revealed that pain catastrophizing is related to greater activity in the right anterior brain regions as measured by alpha band power. This finding is consistent with the Anterior Asymmetry and Emotion model (Davidson, 1992), which associates this activity pattern with the tendency to engage in more withdrawal responses. Seminowicz and Davis (2006) showed that during mildly intense electrical stimulation, pain catastrophizing was positively correlated with activity in regions associated with affective, attentional and behavioral aspects of pain, such as the insula, the anterior cingulate cortex, the prefrontal cortex and the premotor cortex. However, during more intense pain, correlation with the prefrontal cortical regions, which are typically involved in pain inhibition, e.g., the dorsolateral PFC (Lorenz et al., 2003), reversed, thus implying that highly catastrophizing individuals could have difficulty disengaging from intense pain due to impaired top-down control. The results from Seminowicz and Davis (2006) are in line with results from individuals with chronic pain that exhibit pain catastrophizing tendencies (Loggia et al., 2015) or pain-related illness behavior (Lloyd et al., 2008; 2014), indicating that similar neural changes may already be present in healthy subjects. Although the study by Seminowicz and Davis (2006) identified changes in brain activation that are associated with pain catastrophizing tendencies, some relevant questions regarding the nature of this relationship remain to be answered. For instance, crucial questions include: At what stage of processing does this abnormal pattern of brain activity occur? What is the direction of information flow that becomes altered, e.g., information flow from or to the prefrontal cortical regions?

In the present study, we aimed to extend the existing findings by examining the information flow between brain regions and its relationship with pain catastrophizing tendencies. Although most of the previous studies explored fMRI-based connectivity, we chose to study EEG effective connectivity patterns. Methods for investigating complex interplay between brain regions using EEG have been carefully developed and have already begun to gain significant recognition in the field (Gómez et al., 2009; Leung et al., 2014; Li et al., 2017; Koelewijn et al., 2017). This progress may be related to several advantages of the technique. Firstly, EEG offers a noninvasive and easy-to-use method for measuring connectivity. For this reason, it has the potential to provide an objective tool for assessing pathophysiology as well as therapeutic outcomes in a clinical setting (Prichep et al., 2011). Another advantage of EEG is its high temporal resolution, which offers a unique opportunity to track brain networks over a very short duration. In comparison to BOLD, which is a slow measure of neural activity, EEG provides the possibility to track more dynamic changes during cognitive tasks or a resting-state (Hassan et al., 2015; Van de Steen et al., 2019). Finally, EEG-based connectivity measures represent a more direct way to make inferences regarding brain neurophysiology (Bandettini, 2009). Undeniably, connectivity research would benefit from the exploration of more EEG-based connectivity parameters.

Another novelty of this study is related to the use of pain-related mental imagery instead of physical pain stimuli. Mental imagery has been found to change neurophysiological responses to pain and, depending on the content of the imagery, provide hyperalgesic or hypoalgesic effects (Fardo et al., 2015). What is more, this relatively new line of research has demonstrated that pain can be induced not only physically, by applying painful stimuli, but also psychologically, when a nociceptive input is lacking. Specifically, it has been shown that pain-related mental imagery (Derbyshire et al., 2004; Krämer et al., 2008; Ushida et al., 2008; Cheng et al. 2010), recollection of pain-related memories (Ushida et al., 2008; Fairhurst et al., 2012) and hypnotic suggestion (Derbyshire et al., 2004; Raij et al., 2005) evoke patterns of brain activation similar to that of a real pain experience. Therefore, instead of administering painful stimulation, we introduced a pain-related mental imagery task, asking participants to imagine different situations associated with experiencing pain. This form of cognition in a healthy population may prove to be particularly interesting, as it was shown that individuals with chronic pain often experience spontaneously generated negative and intrusive mental images of their pain (Berna et al., 2011; 2012; Gosden et al., 2014). Furthermore, the

frequency of such occurrences appears to depend on pain-catastrophizing tendencies (Berna et al., 2011). Thus, the instructions that we used during the experiment were aimed at evoking ruminative-like thought patterns and highlighted pain-related unpleasantness, e.g., "Imagine having such a strong stomach ache that you start wondering whether something really serious might happen to your health". We expected that this task would provide a more sensitive way of revealing brain connectivity changes that depend on the pain catastrophizing tendency, rather than applying less ecologically valid experimental pain.

Pain catastrophizing is associated with exaggerated affective responses to pain and ineffective cognitive modulation of a pain experience. Thus, we hypothesized that pain catastrophizing would be related to altered connectivity patterns between the affective and inhibitory pain networks during pain-related mental imagery. The amygdala and insula, which are located in the medial temporal lobe, have been associated with affective responses to pain (Knudsen et al., 2011; Moayedi et al., 2011), while it has been proposed that the prefrontal cortices are involved in active control and top-down modulation of pain experience (Lorenz et al., 2003; Bushnell et al., 2013). Abnormal frontotemporal connectivity patterns that are related to pain catastrophizing tendencies were found in clinical studies on individuals with chronic pain (Kucyi et al., 2014; Jiang et al., 2016) and were identified as a risk factor for chronic pain development (Vachon-Presseau et al., 2016). We, therefore, expected decreased communication between the prefrontal cortices (left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex and medial prefrontal cortex) and the temporal regions. This would suggest ineffective prefrontal modulation of heightened emotional responses in healthy catastrophizing individuals, as has been previously put forward by Seminowicz and Davis (2006) in the context of physical pain.

Furthermore, we assumed that pain catastrophizing would be associated with altered connectivity patterns within the pain processing circuitry. In particular, we assumed that pain catastrophizing would be linked to the altered connectivity of the somatosensory cortex, as increased activity of this region has been reported in both healthy (Seminowicz and Davis 2006) and clinical (Gracely et al., 2004; Lloyd et al., 2008, 2014; Vase et al., 2012; Loggia et al., 2015) populations exhibiting catastrophizing tendencies. It has been speculated that the somatosensory cortex is involved in the attentional processing of pain and pain anticipation (Carlsson et al., 2000; Hauck et al., 2007; Worthen et al., 2011) and it was found to be activated when healthy subjects were imagining/recalling pain (Fairhurst et al., 2012). Interestingly, it was shown that the secondary somatosensory cortex was activated during imaginary pain induced by hypnotic suggestion, when no noxious stimulus was applied (Derbyshire et al., 2004). We expected the catastrophizing tendency to correlate with increased communication between the somatosensory cortex and the orbitofrontal cortex (OFC) and between the somatosensory cortex and temporal cortices. OFC cortical thickness was shown to be negatively correlated with perceived pain unpleasantness (Moayedi et al., 2011). Thus, along with the temporal lobe structures, the OFC may be responsible for processing emotional aspects of the pain experience. The increased outflow of the somatosensory cortex to these structures would imply stronger connections between the regions processing the sensory and attentional aspects of pain and those involved in affective responses to pain.

In summary, our study aimed to examine brain connectivity during pain-related imagery and its relationship with pain catastrophizing tendencies. Our primary hypotheses were: 1) there is a negative relationship between catastrophizing tendencies and information flow between frontal and temporal cortices, and 2) there is a positive relationship between catastrophizing and connectivity from the somatosensory cortices to the temporal and orbitofrontal cortices.

METHODS

Participants

First-year student volunteers from Radboud University (Nijmegen, the Netherlands) took part in the experiment. The prerequisites were right-handedness, no history of neurological or psychiatric conditions, no chronic pain, no hearing dysfunction and advanced English language skills. Thirty students participated in the EEG measurement (24F, 6M; average age=20.66), but the results from two students were not included in the analysis due to their high scores (>9) on The Patient Health Questionnaire (PHQ-4) (see description below). A high score on the PHQ-4 may indicate an ongoing depressive or anxiety disorder that could distort the results. In total, data from 28 individuals were analyzed (22F, 6M; average age=20.74).

The Patient Health Questionnaire (PHQ-4)

The Patient Health Questionnaire is an ultra-brief, self-administered screening tool for depression and anxiety disorders. Obtained scores are rated as normal (0–2), mild (3–5), moderate (6–8) or severe (9–12) and

can be an indicator of the presence of psychological distress (Löwe et al., 2010).

Pain Catastrophizing Scale (PCS)

The Pain Catastrophizing Scale was developed by Sullivan and colleagues (Sullivan et al., 1995). It measures a multidimensional construct of pain catastrophizing comprised of rumination (e.g., "I can't stop thinking about how much it hurts"), magnification (e.g., "I worry that something serious may happen") and helplessness (e.g., "There is nothing I can do to reduce the intensity of the pain"). It consists of 13 items describing pain-related thoughts and feelings. Participants reflect on past pain experiences and decide on a 5-point scale how often they experience each kind of thought/feeling (end points: (0) – not at all and (4) – all the time). Scores can range from 0 to 52. The PCS has high internal consistency with Cronbach's alpha for the whole PCS of 0.87.

EEG equipment and procedure software

Experimental data were collected with the use of a 64-channel BrainProducts EEG (DCC-customized 64-channel ActiCap; International extended 10-20 System; the BrainAmp DC amplifier) acquisition system, sampled at a frequency of 1000 Hz. The reference electrode was placed on the left mastoid. Four electrodes (Fp1, Fp2, FT9, FT10) were used to measure horizontal and vertical eye movements and one electrode was placed on the right mastoid (TP10) for offline re-referencing. The online filters were set for 0.016 Hz (high-pass filter) and 150 Hz (low-pass filter). All electrode impedances were kept in the recommended range during the recording (below 10 kΩ). The experimental procedure was programmed in PsychoPy version 1.82.01.

Experimental procedure

The procedure was compliant with the directives of the Helsinki Declaration and approved by the Ethics Committee Faculty of Social Sciences of Radboud University in Nijmegen, the Netherlands (ECG 2012-1301-005). Participants signed written informed consents and were informed that they could quit the experiment at any time. They were then asked to complete the PCS and PHQ-4. The EEG measurement took place in an air-conditioned and soundproof room. The experimental task was based on emotional mental imagery. There were four within-subject conditions in the main experimental procedure: (1) negative (depressive), (2) positive, (3) neutral and (4) pain-related. For each condition, 10 trials were implemented. The instructions used to induce each type of mental imagery were played by a synthesized English-speaking voice (IVONA program). For example, "Think about a mistake you have recently made" for the depressive ruminative state, "Think about an old wooden door" for the neutral, "Think about one of the happiest moments in your life" for the positive and "Imagine having such a terrible sore throat that it is too painful for you to speak" for the pain-related one. In total there were 40 statements, administered in a random order and intermingled across conditions. Participants listened to the instructions, which were followed by 40 seconds of silence during which the particular imagery task had to be performed. Each imagery task was ended with a beep sound. Participants were then asked to press a specific button to evaluate their performance on a three-point scale that ranged from 0–2 (0 – failure; 1 – completed task, but experienced problems with concentration; 2 – success). Trials rated as "failure" were not included in the subsequent analysis. Participants were instructed to keep their eyes closed during the imagery task and to open their eyes when asked to evaluate their performance. The scheme of the experimental procedure is presented in Fig. 1.

The effectiveness of our procedure to induce mental imagery was tested to ensure that the desired ruminative states were evoked in individuals. As mood changes might be an indicator of ongoing emotional mental imagery (Holmes and Mathews, 2005; Holmes et al., 2006; O'Donnell et al., 2017), we decided to verify that our experimental conditions (positive, depressive, neutral and pain-related) differed in subjective mood ratings. The verification of the procedure's effectiveness was performed in another sample of first-year student volunteers from Radboud University (18F, 3M; *N*=21; mean age=20.70). Participants evaluated their mood after each trial using the 10-point VAS scale (0 – extremely sad, depressed; 5 – neutral; 10 – extremely happy). They also evaluated their performance on 0–2 scale, as described previously.

DATA ANALYSIS

Manipulation check – mood induction procedure effectiveness

Ratings from each participant were averaged across different conditions. Out of 22 participants, 1 was re-

jected because more than 50% of the trials were rated as failures in the mental imagery task. Each dependent variable fulfilled normality assumptions as indicated by Shapiro-Wilk Tests (P>0.05), thus repeated measures ANOVA analysis was performed to verify that conditions differed in subjective mood evaluations. Trials with score 0 ("failure") in the performance rating were rejected from further analysis.

Behavioral analysis – performance measures and PCS relationship

Correlation analyses were performed on the PCS scores and the summed performance ratings in all conditions. As the normality assumption examined by Shapiro-Wilk tests (P>0.05) was fulfilled, the Pearson coefficient and 1-tailed significance were calculated.

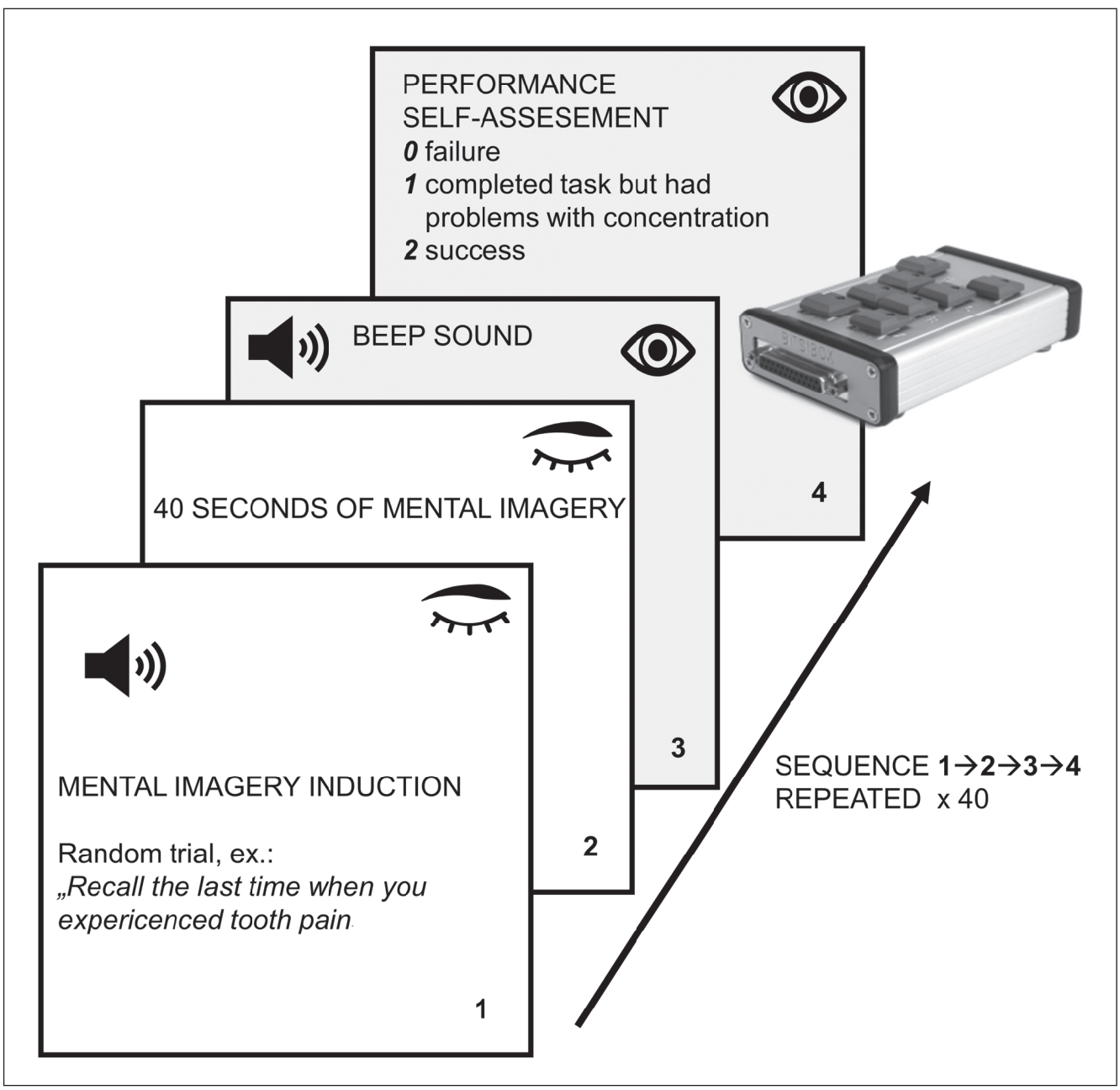

Fig. 1. Experimental scheme. The experiment consisted of a sequence that was repeated 40 times: 1 – mental imagery induction, trials were presented in a random order and intermingled across conditions, participants were listening to the audio instructions with their eyes closed; 2 – 40-second of mental imagery, participants were imagining each topic with their eyes closed; 3 – beep sound that ends the mental imagery period and was a cue to open the eyes; 4 – performance self-assessment – participants were evaluating themselves on a 0-2 scale using buttonbox and were asked to close their eyes afterwards.

EEG study: Preprocessing of EEG data

EEGLab toolbox version 14 (Delorme and Makeig 2004) was used for preprocessing of the EEG signal. The signal was first re-referenced to the linked mastoids, downsampled to 128 Hz, and then zero-phase filtered in the 2–40 Hz range. Since the signal subjected to the DTF analysis should not be excessively modified in order to preserve the original correlation data structure, we did not apply an artifact correction method. Instead, artifactual electrodes and signal fragments contaminated with artifacts were rejected. First, artifactual electrodes were rejected based on a visual inspection, and for three subjects several electrodes were qualified for removal (participant 1: AF7 AF8 FT8; subject 2: T7 TP7 and subjects 14: T8). To reject artifactual fragments of the signal, the 40-second-long recordings from each condition were divided into 2-second-long epochs. First, trials for which the subjects reported failure in completing the task were dropped, with the average number of "failure" trials being 3 out of 40 per person. Then, the automatic threshold for signal rejection was set to reject any epoch, where amplitude on any electrode exceeded 70 μV. Finally, in order to exclude remaining apparent artifacts related to the muscle activity, or undetected technical problems, visual inspection of the signal was applied. The average number of rejected epochs was 166 out of 1,000 per subject.

EEG study: Effective connectivity analysis

To assess the effective connectivity, the Directed Transfer Function (DTF) method was used (Kaminski and Blinowska, 2017; Kamiński et al., 2005). DTF is based on Granger causality principles and provides a multivariate estimation of the information flow rate and direction while controlling the familywise alpha level. The method is recommended for use on sensor space signals and not on reconstructed sources. Moreover, as DTF is based on autoregressive modelling, it is relatively insensitive to the volume conduction phenomenon (Kaminski and Blinowska, 2014; Wyczesany et al., 2015). In the multivariate autoregressive (MVAR) model, each data sample in *k* channels and at time *t* can be represented as a weighted sum of *p* previous samples with a random component added:

$$\mathbf{X}(t) = \sum_{j=1}^{p} \mathbf{A}(j)\mathbf{X}(t-j) + \mathbf{E}(t)$$

where X(*t*) is the data values vector and E(*t*) is the random component values vector at time t. A(*j*) is the MVAR model coefficients matrix and p is the model order which is equal to the number of past samples used to model the signal. We fitted the MVAR model to the EEG data. The MVAR model can be transformed into the frequency domain:

$$X(f) = A^{-1}(f)E(f) = H(f)E(f)$$

$$H(f) = (\sum_{m=0}^{p} A(m)\exp(-2\pi \mathrm{imf}\Delta t))^{-1}$$

where X(*f*), A(*f*) and E(*f*) are the Fourier transforms of X(*t*), A(*j*) and E(*t*) matrices, respectively. The matrix H(*f*)=A–1(*f*) is called the transfer matrix. The DTF function can be expressed as:

$$\gamma_{ij}^2(f) = |H_{ij}(f)|^2$$

where γij(*f*) describes the causal influence of channel j on channel i at frequency *f*. For a more detailed description of the DTF method, see Kaminski and Blinowska (1991) and Ligeza et al. (2016).

In our experiment, effective connectivity was measured between electrodes over the regions of interest as described in the hypotheses. Calculations were carried out using Multar software (Department of Biomedical Physics, University of Warsaw). Electrodes corresponding to the regions of interest were selected as follows: left DLPFC (lDLPFC: F3, F1), right DLPFC (rDLPFC: F4, F2), medial PFC (mPFC: Fz, FCz), left temporal area (lTmp: T7, TP7, FT7) and right temporal area (rTmp: T8, FT8, TP8), orbitofrontal cortex (OFC: AF7, AF8), left somatosensory cortex (lSi: C3, CP3, CP1) and right somatosensory cortex (rSi: C4, CP2, CP4). These were chosen on the basis of the EEG montage brain atlases (Okamoto et al., 2004).

Non-normalized DTF values were calculated for the beta band (14–25 Hz). As the original DTF estimates are in most cases lower than 0.1, we scaled them by a factor of 1,000 to increase their readability. The distributions of the DTF values were checked to identify and reject possible extremes, defined using boxplot 1.5 IQR (interquartile range).

Our choice of beta band was based on several factors. Most importantly, this frequency window covers an important part of middle and long-range cortical communication (Kuś et al., 2008; Wyczesany et al., 2015). Although it was suggested that gamma oscillations contribute to the local BOLD signal, alpha and beta

were found to be involved in inter-areal BOLD correlations and were thus considered the most suitable for studying connectivity between distant brain structures (Wang et al., 2012; Weinrich et al., 2017). Moreover, beta oscillations were shown to be related to executive functioning and top-down cortical signaling (Wang, 2010; Spitzer and Haegens, 2017). As our theory linked pain catastrophizing to specific attentional biases towards pain-related stimuli and impaired cognitive-emotional control, this band appeared to fit our hypotheses. Beta oscillations were also shown to be dynamically modulated in a content-specific manner (Spitzer and Haegens, 2017). As we were looking for pain-related specificity and were switching between four types of trials during the experiment, the beta oscillations' characteristics (short-lived, dynamic) made them the best candidate for our analysis. In this context, they appeared more appropriate than alpha oscillations. To confirm our choice, additional analysis for the alpha band was performed. As expected, there were fewer effects and these were less specific to the pain-related condition. Considering that this analysis did not add any meaningful insight to the discussion, we decided to present these results in Supplemental Material 1 only.

EEG study: Statistical analyses of DTF data

Linear mixed models analyses were conducted in R (R Development Core Team, 2015) with the lme4 library (Bates et al., 2015). We calculated separate models for all of the directions mentioned in the hypotheses (lTmp ↔ lDLPFC; lTmp ↔ rDLPFC; lTmp ↔ mPFC; rTmp ↔ lDLPFC; rTmp ↔ rDLPFC; rTmp ↔ mPFC; lSi ↔ OFC; rSi ↔ OFC; lSi ↔ lTmp; lSi ↔ rTmp; rSi ↔ lTmp; rSi ↔ rTmp).

Linear mixed effects models are comprised of both fixed and random effects. As fixed effects, we entered the interaction term of the PCS and valence, which are both independent factors; as random effects, we used individual subjects' intercepts and channels. By adding random effects we assumed that there were some baseline differences between participants and between channels (as there was more than one electrode assigned to each brain region). The R formula was as follows: DTF ~ PCS*val + 1|part + 1|chann; val – valence; part- participant; chann – channel. All of the values from each direction were pooled together as a factor in the mixed model analysis. Visual inspection of residual plots did not reveal any obvious deviations from normality. As the homoscedascity assumption was not fulfilled in all models, we applied a log transformation. P-values were obtained by comparing the full model with the effect in question against the model without the effect in question with the use of ANOVA. In our case, we compared the full model, which consisted of fixed effect interaction and random effects, with the null model containing the random effects only.

RESULTS

Manipulation check – mood induction procedure effectiveness

Repeated-measures analysis of variance revealed a significant condition effect ($F_{1.232,\ 25.868}$=71.122; P<0.001, Greenhouse-Geisser correction applied) in subjective mood ratings across the four experimental conditions. As shown by post-hoc pairwise comparisons with FDR correction, all conditions differed from each other at P<0.001 with the exception of the pain-related/depressive comparison at P=0.014. This manipulation check was carried out in a separate group of participants and their mood ratings in each experimental condition were assessed (Table I).

Behavioral analysis – performance measures and PCS relationship

The Pearson's correlation revealed a moderate negative relationship between the PCS score and summed performance ratings in the pain-related mental imagery condition (r_{26}=-0.32, P=0.050). Additional analyses of the relationship between the PCS and DTF in other conditions were performed. No significant relationship between the PSC score and the DTF in the depressive relationship was found (r_{26}=-0.11; P=0.293). Moderate,

Table I. Descriptive statistics of subjective mood ratings in each condition.

Condition	Mean	Std. Deviation	N
Depressive	3.59	1.00	21
Neutral	5.40	0.58	21
Pain-related	3.90	0.86	21
Positive	7.31	1.16	21

negative relationships were found between the PCS score and DTF both in the positive (r_{26}=-0.48; *P*=0.005) and in the neutral (r_{26}=-0.45; *P*=0.008) conditions. Scatterplots visualizing these relationships can be found in Supplemental Material 2.

EEG study: pain catastrophizing

There were 28 participants and their mean PCS score was equal to 18.79; standard deviation of the PCS score – 9.35; and variance – 87.43. The distribution of scores for the experimental group was similar to what has been reported in other samples of healthy, pain-free individuals (Seminowicz and Davis, 2006; Sullivan et al., 1995; Van Damme et al., 2004). Pain catastrophizing can be treated as a personality trait and, despite the fact that individuals with chronic pain usually score higher in pain catastrophizing, there is an overlap in the scores of healthy individuals and those suffering from chronic pain (Seminowicz and Davis, 2006).

Effective connectivity analysis

The interactive effects of the PCS and valence on information flow DTF values were significant in the following directions: rTmp → rDLPFC (*P*=0.007); rTmp → lDLPFC (*P*=0.018); rTmp → mPFC (*P*=0.001); rSi → rTmp (*P*=0.012); rSi → lTmp (*P*=0.026); rTmp → rSi (*P*=0.030). In four directions, the PCS was also found to be a significant predictor of the DTF value in the pain-related condition: rTmp → rDLPFC (*P*=0.007); rTmp → lDLPFC (*P*=0.009); rTmp → mPFC (*P*=0.003); rSi → rTmp (*P*=0.006). For a visual depiction of these directions see Fig. 2. Scatterplots of the PCS and DTF in the pain-related mental imagery conditions in these directions are presented in Supplemental Material 3. Detailed statistics of mixed effects models with reference to the pain-related condition are presented in Table II. Statistics of mixed effects models with reference to all conditions are presented in Supplemental Material 4. Descriptive statistics of DTF values averaged for each condition in the rTmp → rDLPFC, rTmp → lDLPFC, rTmp → mPFC, rSi → rTmp directions are shown in Supplemental Material 5. Statistics for the remaining directions are in Supplemental Material 6.

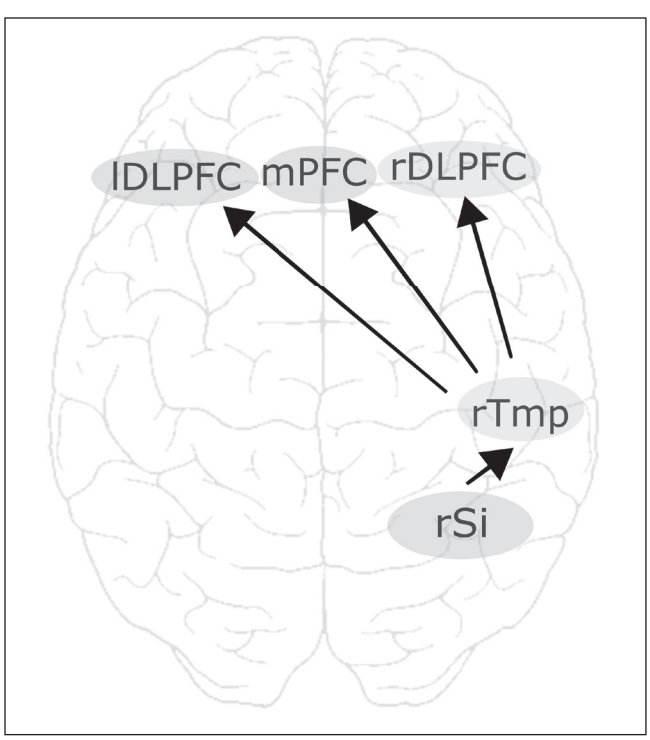

Fig. 2. The directions showing the correlation of pain catastrophizing scores on information flow rate (DTF) in the pain-related condition.

Effective connectivity from rTmp to rDLPFC; rTmp to lDLPFC and from rTmp to mPFC

The right temporal cortex outflow to the bilateral dorsolateral prefrontal cortex and to the medial prefrontal cortex revealed similar effects. The PCS was found to be a significant predictor of the DTF value in the pain-related condition in all three directions; this relationship was negative (Table II). The PCS did not predict the connectivity DTF values in the positive, neutral and depressive conditions (Supplemental Material 4).

Moreover, relationships between the PCS score and rTmp → rDLPFC and rTmp → lDLPFC DTFs in the pain-related condition were significantly different from those in the positive, neutral and depressive conditions. For the rTmp → mPFC direction, the relationship between the PCS score and DTF in the pain-related condition was significantly different from the relationship of the PCS and DTF in the positive and depressive conditions. The difference between the neutral and pain-related conditions was not significant (although close to the significance level. The detailed statistics are shown in Table II and the interactive effects found in these 3 directions are presented in Fig. 3A-C.

Effective connectivity from rSi to rTmp

The PCS was found to be a significant predictor of the DTF value only in the pain-related condition; the relationship between the PCS score and DTF in the

pain-related condition was positive. The PCS did not predict DTF value in the positive, neutral and depressive conditions.

The relationship between the PCS score and DTF in the pain-related condition was significantly different from the relationship between the PCS and DTF in the positive and neutral conditions. The difference between PCS*DTF in the pain-related condition and PCS*DTF in the depressive condition was close to significance.

The detailed statistics are shown in Table II and the interactive effects found in this direction are presented in Fig. 3D.

Effective connectivity of OFC

We hypothesized that pain catastrophizing tendencies would be related to increased flow between the temporal and OFC in the pain-related condition. However, we did not find any significant relationship between the DTF in the pain-related condition and OFC connectivity. Interactive effects related to the information flow to the OFC were not significant (for more detailed statistics see Supplemental Material 6).

DISCUSSION

The goal of the present study was to identify the neuronal correlates of pain catastrophizing during a pain-related mental imagery task. Our study revealed the important role of the network consisting of the prefrontal cortex, the right somatosensory cortex and the right temporal cortex in pain catastrophizing tendencies. The effective connectivity of these regions was clearly and distinctively related to pain catastrophizing. As we found previously, the information flow of the right temporal and parietal cortices changes specifically with the emotional valence (Wyczesany et al., 2014). Thus, pain catastrophizing tendencies might be related to the altered emotional processing of pain-related stimuli.

A manipulation check was run in order to examine the effectiveness of our main experimental procedure. It revealed that each experimental condition induced a different subjectively perceived mood. As it was previously found that mental imagery can act as a mood amplifier (Holmes and Mathews 2005; O'Donnell et al., 2017; Burnett Heyes et al., 2017), significant changes in mood report may be an indirect indicator of successfully performed mental imagery. Our decision to verify the

Table II. Mixed levels analyses detailed statistics for the rTemp → mPFC, rTmp → rDLPFC, rSi → rTmp and rTmp → lDLPFC directions with reference to the pain-related condition: standardized Beta and *p*-value. Column ANOVA contains *p*-values of the null model / M model(log) comparison.

Direction	ANOVA: M(log) *vs.* null	Fixed effects	Ref=pain-related	
	p-value		std. Beta	*p*-value
rTmp → mPFC	0.001	PCS	-0.27	0.003
		PCS*neu	0.14	0.067
		PCS*pos	0.25	<0.001
		PCS*dep	0.23	0.003
rTmp → rDLPFC	0.007	PCS	-0.25	0.007
		PCS*neu	0.18	0.030
		PCS*pos	0.28	<0.001
		PCS*dep	0.22	0.011
rSi → rTmp	0.012	PCS	0.22	0.006
		PCS*neu	-0.21	0.006
		PCS*pos	-0.21	0.006
		PCS*dep	-0.14	0.068
rTmp → lDLPFC	0.018	PCS	-0.24	0.009
		PCS*neu	0.16	0.037
		PCS*pos	0.20	0.009
		PCS*dep	0.21	0.005

mood induction procedure in a different sample was to prevent the possibility of interference from self-assessment of the emotional state with the main mental imagery task. We also wanted to avoid a demand characteristics artifact, which could be induced by repetitive questions regarding the present emotional state.

Our behavioral analysis revealed a negative relationship between the PCS scores and summed performance scores for the pain-related, positive and neutral mental imagery conditions. Previous research has found a link between pain catastrophizing and executive function (Bell et al., 2018a; b). In particular, a high tendency to catastrophize was found to be related to impaired shifting and inhibition processes. Moreover, rumination was shown to be associated with worse inhibition of neutral memories (Fawcett et al., 2015). Thus, due to the nature of

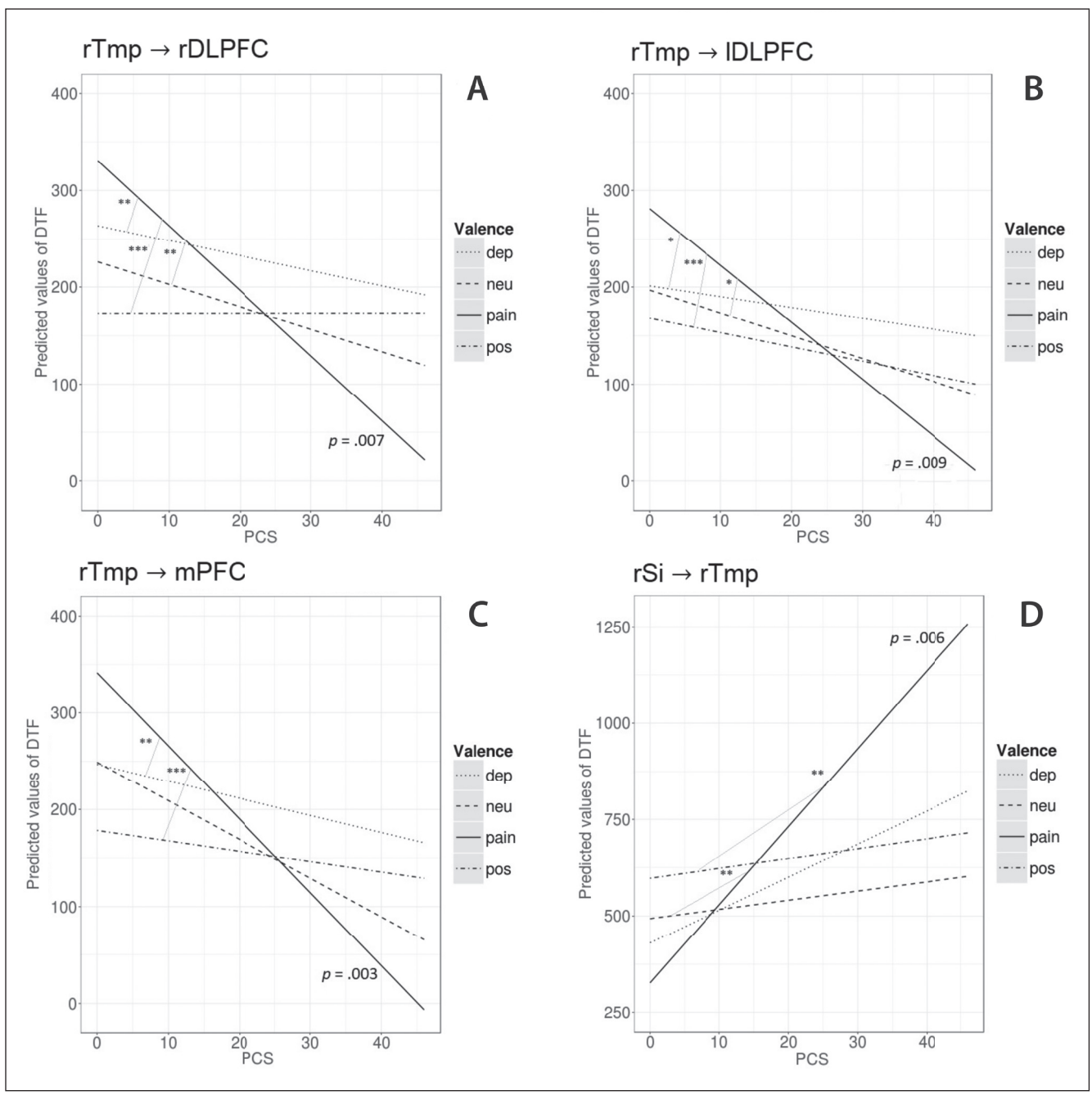

Fig. 3. PCS*valence interactive effects for rTmp → rDLPFC. (A), rTmp → lDLPFC (B) and rTmp → mPFC (C) and rSi → rTmp (D) directions; significant relationship between PCS and DTF in the pain condition are indicated by the *P* values next to the regression lines; Asterisks indicate significance level of differences between pain and other conditions : * *P*≤.05, ** *P*≤.01, *** *P*≤.001.

the repetitive thinking tendencies, catastrophizers might have been less effective in changing the topic of the mental imagery. This might have resulted in a general effect of worse self-evaluation of their performance.

Neural data showed that pain catastrophizing is related to decreased information flow from the right temporal regions to the frontal regions (bilateral dorsolateral prefrontal cortex, medial prefrontal cortex). An fMRI study by Jiang et al. (2016) also revealed abnormal fronto-temporal connectivity patterns related to pain catastrophizing, showing perturbed amygdala connectivity to the Central Executive Network (which included the lateral prefrontal cortices). However, our experiment was the first attempt to demonstrate the direction of the disturbed connections with regard to pain catastrophizing. Anatomical studies indeed show that the temporal and frontal cortices are reciprocally connected (Banks et al., 2007; Lee et al., 2012). One of the functions of this communication is effective emotion regulation. It was shown that amygdala–prefrontal coupling underlies individual differences in emotion regulation (Lee et al., 2012) and that the strength of the connectivity of the amygdala and frontal cortices (OFC and dorsal medial dorsolateral cortex) can predict successful emotion regulation (Banks et al., 2007). It is possible that the regulatory loop between executive frontal regions and temporal structures does not function efficiently when individuals high on catastrophizing are processing pain-related stimuli. This may be related to repetitive rumination about pain, helplessness and exaggeration of the pain experience. Interestingly, decreased connectivity of prefrontal dorsolateral cortices was found to be related to tendencies which involve ruminating, such as depressive rumination (Brzezicka, 2013).

Moreover, frontotemporal alterations in connectivity might also be related to pain-related autobiographical memory retrieval. In order to become immersed in the pain-related experience, subjects might have referred to their own memories of specific situations when they felt pain. It was previously found that this process is associated with greater connectivity between the right inferior frontal and temporal lobe structures, such as the amygdala and hippocampus (Greenberg et al., 2005). The negative relationship between pain catastrophizing and connectivity between these regions might be explained by enhanced aversiveness of pain memories. However, as this interpretation is speculative, more detailed research is needed to explain these findings.

We did not find alternations in the top-down pain modulation system manifested by the altered information flow from the dorsolateral to the temporal cortices. It is possible that the top-down pain modulation function of the dorsolateral prefrontal cortex is not altered in healthy catastrophizing individuals or that the mental imagery was not strong enough for such changes to be observed. A reduction of grey matter in the frontal regions, as well as decreased activation of frontal regions and its decreased outflow, have been repeatedly observed in individuals with chronic pain (Blankstein et al., 2010; Seminowicz et al., 2013). A similar experiment in a clinical group would be needed to determine whether these mechanisms become disrupted in clinical pain states.

The relationship between the PCS and information flow from the right somatosensory cortex to the right temporal cortex was positive in the pain imagery condition. A role for the somatosensory cortices in pain catastrophizing was shown by Vase et al. (2012), who found that catastrophizing was positively correlated with activation of this region in phantom limb patients when non-painful stimuli were applied. The authors associated this pattern with increased anticipation, arousal and expectation resulting from an increase in catastrophizing. Additionally, the somatosensory cortex was found to be involved when healthy participants were recalling and imagining pain (Fairhurst et al., 2012). Our results suggest that the somatosensory pain system (through the somatosensory cortex) is more strongly connected to the affective pain modulatory system in the temporal cortex in highly catastrophizing individuals.

Contrary to our hypotheses, we did not find any effect of our manipulation for the OFC information flow. It is possible that this structure's effective connectivity patterns are not related to pain catastrophizing in a healthy population. Many studies have shown abnormalities in the frontal regions in individuals with chronic pain (May 2008; Rodriguez-Raecke et al., 2009; Valet et al., 2009). Thus, alterations in OFC effective connectivity might be associated with clinical pain states, rather than pain catastrophizing itself, or they could be a consequence of pain chronification. It is also possible that our method was not sensitive enough to detect OFC connectivity patterns. The OFC is a structure located at the bottom of the frontal lobes, therefore it is difficult to track its activity using the signal from EEG electrodes. Additional fMRI studies that would examine the connectivity of this structure with a better spatial resolution are needed.

CONCLUSIONS

Our study revealed that catastrophizing tendencies are related to increased beta information flow from the right somatosensory cortices to the right temporal cortices during pain-related imagery. This result might suggest that the somatosensory pain system is more strongly connected to the affective pain modulatory system in individuals with high catastrophizing

tendencies. Moreover, a negative relationship between pain catastrophizing and beta information flow from the right temporal cortex to the frontal regions was also found when imagining the pain. It is possible that catastrophizing is related to the ineffective regulatory loop between executive frontal regions and temporal structures when processing pain-related stimuli. Most importantly, our study revealed that there are detectable differences in EEG effective connectivity patterns that are related to pain catastrophizing even in a non-clinical, pain-free sample. These differences might precede symptoms observed by clinicians and, in some cases, may be a prelude to the development of chronic pain syndromes.

Relevance of this study

This study aimed to identify potentially altered directional connectivity patterns between brain regions involved in pain processing as a function of catastrophizing. The results clearly show distinct connectivity patterns among the pain modulatory systems that are related to catastrophizing behavior in healthy individuals. As pain catastrophizing is a strong predictor for the development of chronic pain, identification of markers such as altered connectivity patterns may be useful as an objective method to measure the risk of future chronic pain. Additional studies are needed to identify brain-based indicators for elevated risk of chronic pain development (for example after serious injury) that can then be applied in preventive interventions.

Moreover, the clinical relevance of this study is high as it was found that pain catastrophizing is an important mediator in the outcome of pain therapy; it mediates cognitive-behavioral changes in pain intensity, as well as changes due to pain education therapy (Turner et al., 2007; Burns et al., 2012). Pain catastrophizing has been acknowledged as an important variable in the cognitive and emotional aspects that are involved in the maintenance of chronic pain. This important role of catastrophizing has been widely acknowledged and is currently being incorporated into interventions, such as mindfulness-based treatment. This intervention, which is intended to increase, for example, the wellbeing of individuals with chronic pain, has been shown to reduce pain catastrophizing tendencies (Garland et al., 2012).

Limitations and Directions for Future Research

Several studies have shown that females score higher on the pain catastrophizing questionnaire (Sullivan et al., 2000; Sullivan, Bishop and Pivik 1995). Most of our participants were females, therefore our result may particularly apply to women. To what extent that this is the case remains unclear, as possible differences in effective brain connectivity between sexes with the same level of pain catastrophizing tendencies have not been studied. Future studies are needed to address this possible effect of gender.

Also, the DTF method is not influenced by the volume conduction phenomenon and the topography of the DTF results were shown to concur with previous anatomical, physiological and imaging studies (Ginter et al., 2001; Kaminski and Blinowska 2014; Kuś et al., 2006). However, the EEG method itself has limited spatial accuracy, which should be taken into account when interpreting the results. Thus, the proposed correspondence between electrodes and cortical areas should be treated as approximations (for example in the case of the OFC). The amygdala and hippocampus have dense connections with temporal cortex (Bickart et al., 2014). However, the signal collected on the scalp might not contain direct influences from the subcortical structures, but rather from the surrounding cortical areas.

Although our choice to focus on beta band connectivity was well documented, it should be noted that our connectivity findings were most strongly related to these particular frequencies.

Using correction for multiple comparisons decreases the risk of type I errors. Therefore, in our DTF analyses, we included all electrodes in each single MVAR model to control for multiple connections at the level of the DTF estimation. However, we decided not to use another correction for multiple mixed models in order to avoid compromising the power of the statistical testing. This was also justified by the fact that specific hypotheses were formulated on the basis of previous research on catastrophizing individuals. We believe that the conclusions would benefit from replication using a similar set of variables and larger experimental groups.

In future studies, it would be interesting to administer the same experimental procedure to individuals suffering from chronic pain. A comparison with the results of the current study would shed more light on the role of pain catastrophizing in the development of chronic pain states, for example with regard to potential differences in catastrophizing-associated prefrontal, top-down driven processes.

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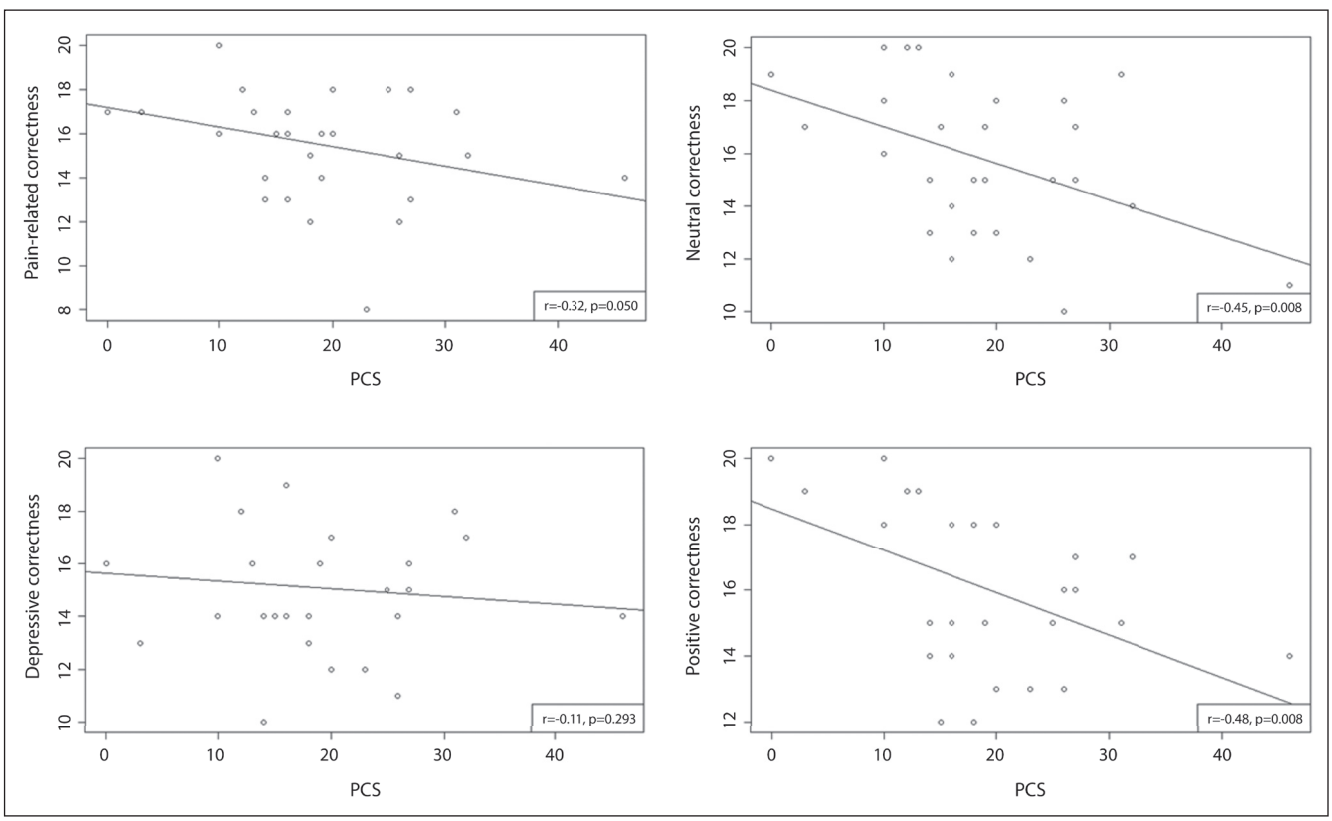
SUPPLEMENTAL MATERIAL 1

Mixed effects statistics for all directions in alpha band.

	ANOVA:	PCS predicts DTF in specific condition							
	M(log) *vs.* null	Pain-related		Depressive		Neutral		Positive	
	p-value	std. Beta	*p*-value	std. Beta	*p*-value	std. Beta	*p*-value	std. Beta	*p*-value
lDLPFC → lTmp	0.051	0.02	0.856	-0.05	0.691	-0.08	0.474	-0.10	0.384
lTmp → lDLPFC	0.001	-0.15	0.241	-0.14	0.248	-0.03	0.826	-0.04	0.742
rDLPFC → rTmp	0.050	-0.04	0.746	-0.13	0.245	-0.23	0.045	0.03	0.791
rTmp → rDLPFC	0.047	-0.26	0.011	-0.24	0.015	-0.15	0.123	-0.06	0.554
lDLPFC → rTmp	0.591	0.02	0.882	-0.07	0.512	-0.11	0.327	-0.10	0.385
rTmp → lDLPFC	0.048	-0.25	0.013	-0.25	0.015	-0.18	0.066	-0.08	0.390
rDLPFC → lTmp	0.057	0.03	0.818	-0.07	0.160	-0.04	0.772	0.16	0.235
lTmp → rDLPFC	0.017	-0.12	0.334	-0.17	0.162	-0.13	0.282	-0.06	0.626
mPFC → lTmp	0.415	-0.04	0.754	-0.16	0.212	0.03	0.844	-0.10	0.754
lTmp → mPFC	0.022	-0.07	0.563	-0.07	0.524	-0.05	0.670	-0.07	0.570
mPFC → rTmp	0.223	-0.04	0.735	-0.07	0.547	-0.06	0.610	-0.09	0.406
rTmp → mPFC	0.018	-0.27	0.007	-0.28	0.006	-0.20	0.043	-0.08	0.401
OFC → lSi	0.008	-0.18	0.159	-0.15	0.257	-0.31	0.020	-0.36	0.007
lSi → OFC	0.751	0.19	0.232	0.02	0.900	0.09	0.565	0.04	0.823
OFC → rSi	0.002	-0.23	0.074	-0.23	0.081	-0.39	0.004	-0.48	0.001
rSi → OFC	0.012	-0.05	0.789	-0.03	0.854	-0.07	0.702	-0.12	0.496
lSi → lTmp	0.658	-0.14	0.282	-0.10	0.429	-0.07	0.552	-0.13	0.300
lTmp → lSi	0.018	-0.13	0.219	-0.08	0.435	-0.02	0.868	-0.03	0.741
rSi → rTmp	0.585	0.04	0.641	-0.02	0.856	-0.02	0.792	-0.04	0.673
lSi → rTmp	0.937	0.04	0.768	0.04	0.753	0.02	0.890	-0.07	0.632
rTmp → lSi	0.002	-0.24	0.008	-0.23	0.009	-0.25	0.006	-0.08	0.351
rSi → lTmp	0.001	-0.03	0.831	0.02	0.903	-0.05	0.595	-0.06	0.672
lTmp → rSi	0.010	-0.13	0.226	-0.17	0.101	-0.06	0.528	-0.08	0.446
rTmp → rSi	<0.001	-0.35	0.001	-0.39	0.023	-0.14	0.145	-0.06	0.546

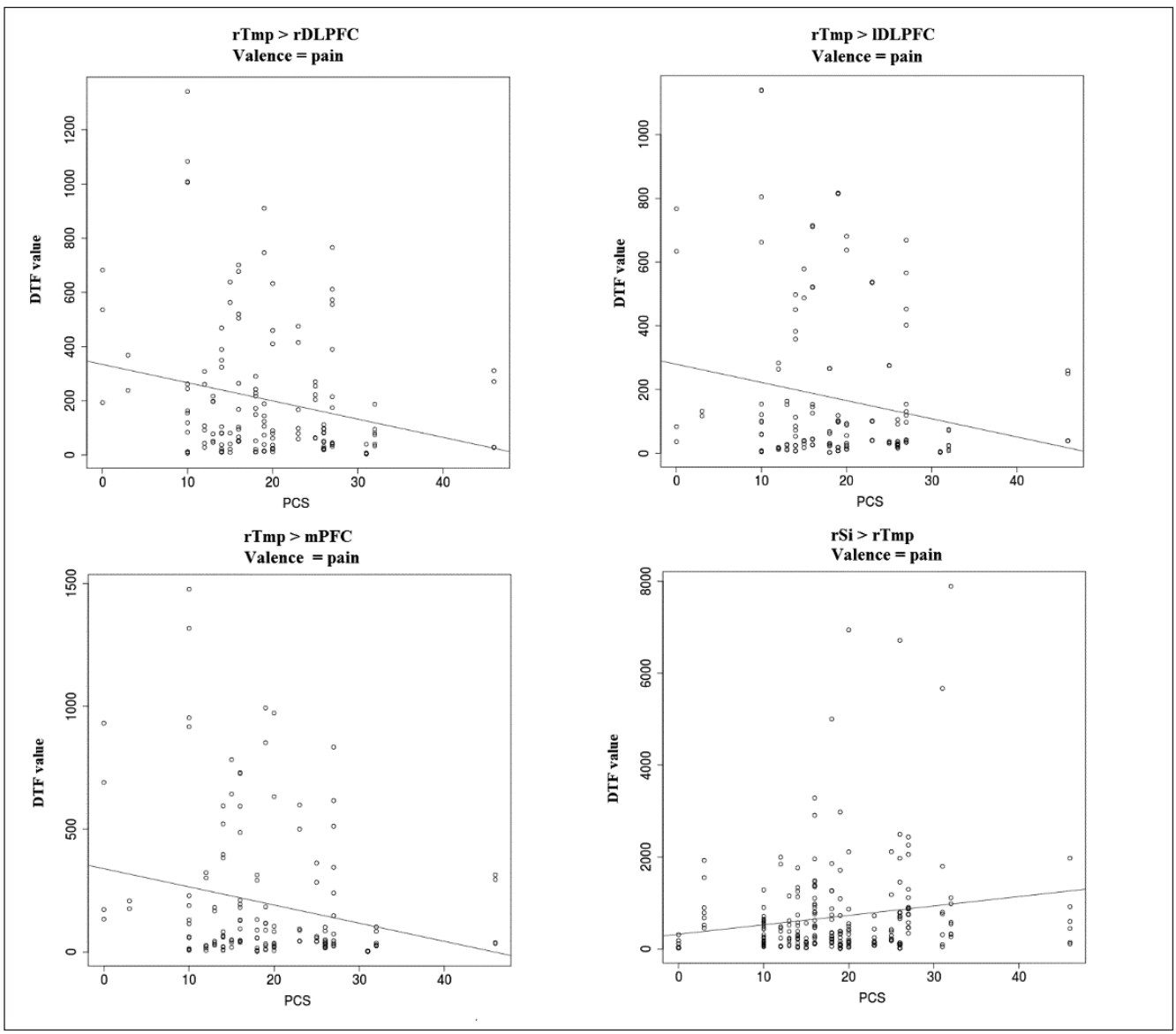
SUPPLEMENTAL MATERIAL 2

Scatterplots of relationships between correctness in each experimental condition (pain-related; depressive; neutral; positive) and PCS.



SUPPLEMENTAL MATERIAL 3

Scatterplots of significant relationships between PCS and DTF in the pain-related mental imagery conditions. Each point represents the DTF of one pair of electrodes.



SUPPLEMENTAL MATERIAL 4

Mixed levels analyses detailed statistics for the rTmp → mPFC, rTmp → rDLPFC, rSi → rTmp and rTmp → rDLPFC directions, with reference to all conditions (pain-related, depressive, positive, neutral): standardized Beta and p-value. Column ANOVA contains p-values of the null model / M model(log) comparison.

Direction	ANOVA:	PCS * valence interactive effects								
	M(log) *vs.* null		Ref = depressive		Ref = positive		Ref = neutral		Ref = pain-related	
	p-value		std. Beta	p-value	std. Beta	p-value	std. Beta	p-value	std. Beta	p-value
rTmp → mPFC	0.001	PCS	-0.06	0.463	-0.04	0.655	-0.14	0.101	-0.27	0.003
		PCS*neu	-0.09	0.252	-0.11	0.131			0.14	0.067
		PCS*pos	0.03	0.722			0.11	0.134	0.25	<0.001
		PCS*dep			-0.03	0.772	0.09	0.249	0.23	0.003
rTmp → rDLPFC	0.007	PCS	-0.06	0.523	0.00	0.998	-0.09	0.342	-0.25	0.007
		PCS*neu	-0.03	0.706	-0.10	0.247			0.18	0.030
		PCS*pos	0.07	0.439			0.10	0.250	0.28	<0.001
		PCS*dep			-0.07	0.439	0.03	0.704	0.22	0.011
rSi → rTmp	0.012	PCS	0.09	0.235	0.03	0.722	0.03	0.741	0.22	0.006
		PCS*neu	-0.07	0.339	-0.00	0.979			-0.21	0.006
		PCS*pos	-0.07	0.347			0.00	0.979	-0.21	0.006
		PCS*dep			0.07	0.353	0.07	0.338	-0.14	0.068
rTmp → lDLPFC	0.018	PCS	-0.05	0.609	-0.06	0.499	-0.09	0.284	-0.24	0.009
		PCS*neu	-0.05	0.464	-0.04	0.602			0.16	0.037
		PCS*pos	-0.02	0.832			0.04	0.604	0.20	0.009
		PCS*dep			0.02	0.831	0.06	0.642	0.21	0.005

SUPPLEMENTAL MATERIAL 5

Descriptive statistics of DTF values for the rTemp → mPFC, rTmp → rDLPFC, rSi → rTmp and rTmp → lDLPFC directions; results of all pairs of electrodes within each direction were averaged.

Direction	neutral		positive		depressive		pain-related	
	M	SD	M	SD	M	SD	M	SD
rTmp → mPFC	173.63	831.02	159.07	856.14	214.37	850.62	196.66	839.46
rTmp → rDLPFC	182.28	716.65	173.84	732.90	234.37	730.63	200.81	709.62
rSi → rTmp	538.00	2319.51	646.40	2305.36	589.89	2300.63	703.95	2333.33
rTmp → lDLPFC	152.72	729.18	140.54	748.69	181.06	743.84	168.37	729.15

SUPPLEMENTAL MATERIAL 6

Mixed effects statistics for all directions.

Direction	ANOVA: M(log) *vs.* null	PCS predicts DTF in the pain condition
	p-value	p-value
lDLPFC>lTmp	0.343	0.491
lTmp>lDLPFC	0.437	0.559
rDLPFC>rTmp	0.061	0.946
rTmp>rDLPFC	0.007**	0.007**
lDLPFC>rTmp	0.184	0.486
rTmp>lDLPFC	0.018*	0.009**
rDLPFC>lTmp	0.502	0.876
lTmp>rDLPFC	0.883	0.868
mPFC>lTmp	0.712	0.845
lTmp>mPFC	0.692	0.762
mPFC>rTmp	0.750	0.322
rTmp>mPFC	0.001***	0.003**
OFC>lSi	0.021*	0.392
lSi>OFC	0.385	0.231
OFC>rSi	0.022*	0.108
rSi>OFC	0.356	0.705
lSi>lTmp	0.914	0.959
lTmp>lSi	0.469	0.579
rSi>rTmp	0.012*	0.006**
lSi>rTmp	0.092	0.916
rTmp>lSi	0.190	0.031
rSi>lTmp	0.026	0.352
lTmp>rSi	0.333	0.767
rTmp>rSi	0.030	0.127