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Controllability and hippocampal activation during pain expectation in fibromyalgia syndrome

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ABSTRACT

To examine the role of perceived control in pain perception, fibromyalgia patients and healthy controls participated in a reaction time experiment under different conditions of pain controllability. No significant differences between groups were found in pain intensity and unpleasantness ratings. However, during the expectation of uncontrollable pain, patients compared to controls showed higher hippocampal activation. In addition, hippocampal activity during the pain expectation period predicted activation of the posterior cingulate cortex (PCC), precuneus and hippocampus during pain stimulation in fibromyalgia patients. The increased activation of the hippocampus during pain expectation and subsequent activation of the PCC/precuneus during the lack of control phase points towards an influence of pain perception through heightening of alertness and anxiety responses to pain in fibromyalgia patients.

1. Introduction

Fibromyalgia syndrome (FMS) is a chronic pain condition where pain perception and neural responses to nociceptive stimuli are enhanced (Cook et al., 2004; Gracely et al., 2004; Staud, Vierck, Cannon, Mauderli, & Price, 2001). FMS patients tend to believe that they have a limited ability to exert control over their pain (Burckhardt & Bjelle, 1996; Jensen, Turner, & Romano, 2007; Santoro et al., 2014). Such negative, maladaptative appraisals about the situation and their personal efficacy may enhance the response to nociceptive stimulation (Flor & Turk, 2011; Nicassio, Schoenfeld-Smith, Radojevic, & Schuman, 1995). In healthy controls perceived lack of control over pain leads to increased pain perception, whereas the feeling of control over pain reduces it (Mohr, Leyendecker, Petersen, & Helmchen, 2012; Salomons, Johnstone, Backonja, & Davidson, 2004; Salomons, Johnstone, Backonja, Shackman, & Davidson, 2007; Wiech, Ploner, & Tracey, 2008). Wiech et al. (2006) showed that self-controlled stimulation in comparison to externally controlled pain led to higher activation in the dorsal anterior cingulate cortex (ACC) and anterolateral prefrontal cortex (PFC), which was accompanied by decreased pain and pain-related anxiety. Salomons et al. (2007) found that subjects with greater activation in the pregenual ACC, periaqueductal gray (PAG), and posterior insula in response to uncontrollable versus controllable pain reported more pain during the uncontrollable versus the controllable condition. In addition, activation in the ventral lateral PFC (vlPFC) in expectation of pain was negatively associated with pain intensity ratings. Activation in the vlPFC has been consistently observed when participants were instructed to use a reappraisal strategy to emotionally disengage from a threatening stimulus such as an impending noxious stimulation (Kalisch et al., 2005, 2006; Wiech et al., 2008). Thus, during pain expectation perceived control may modulate the magnitude of perceived pain by changing its emotional appraisal, so that it becomes less threatening when it is viewed as controllable (Salomons et al., 2007; Wiech et al., 2008). Perceived control over pain has been shown to be associated with reduced state anxiety, and this was related with increased functional connectivity of the amygdala and the nucleus accumbens with the ventrolateral and ventromedial PFC (Salomons, Nusslock, Detloff, Johnstone, & Davidson, 2014).

FMS patients consistently score higher in catastrophizing, anxiety and helplessness in pain questionnaires than healthy controls (Clauw, 2014). On a neuronal level, low perceived control and

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catastrophizing over pain have been found to be associated with increased activation in the amygdala and the hippocampus (Gracely et al., 2004; Lu et al., 2010; Salomons et al., 2014). The present study employed a novel paradigm to investigate the effects of perceived control over pain on the expectancy of pain and subsequent pain perception and the underlying brain activity in patients with FMS. We hypothesized that perceived uncontrollability would make pain more threatening and thus increase pain ratings and that this should affect FMS patients more than healthy controls. In addition, this difference should be reflected in higher activation of areas such as the amygdala and hippocampus and less activation in prefrontal control-related brain areas that are involved in the expectation of pain. We also assumed that activation during pain expectancy would predict brain activation during subsequent pain perception.

2. Materials and methods

2.1. Participants

Fifteen female patients with FMS (mean age = 52.07, standard deviation (SD) = 7.14 years, range 42–64 years) and 15 female healthy control subjects (mean age = 52.67, SD = 6.23 years, range 46–69 years), matched for age and educational level, participated in the study (see Table 1 for demographic and clinical details). All participants but one FMS patient were right handed (see Table 1). The patients reported a mean pain duration of 13.50 years (SD = 8.30, range 2–30). They were recruited through regional support groups and several outpatient pain clinics. The healthy controls were recruited via newspaper announcements.

Trained clinical psychologists administered the German versions of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) parts I and II (Fydrich, Renneberg, Schmitz, & Wittchen, 1997; Wittchen, Zaudig, & Fydrich, 1997). Persons with a current major depressive episode (MDE) were excluded, however, FMS patients who had previously suffered from MDE or a remitted comorbid disorder were included (see Table 1 for the remitted diagnoses). No control subject reported any current or lifetime mental disorder or any recurring pain episodes (e.g. migraine, back pain). A pain specialist participating in the study diagnosed all patients. All FMS patients met the American College of Rheumatology's criteria for FMS (Wolfe, Smythe, & Yunus, 1990, Wolfe et al., 2010) that included a widespread pain index (WPI) score $\geq$7 and a symptom severity (SS) score $\geq$5 or a WPI score of 3–6 and an SS score $\geq$9. All patients participated in a standardized tender point examination (Okifuji, Turk, Sinclair, Starz, & Marcus, 1997). Fibromyalgia patients discontinued their usual pain medication after consulting with their physician, and were for at least two days without medication (6 patients were using the following medications each: Trimipramim 25 mg, Amitriptylin 0.25 mg, Amitriptylin 25 mg + Duloxetin 60 mg, Venlafaxin 75 mg + Pregabalin 75 mg, Citalopram 40 mg + Mirtazapin 15 mg, Citalopram 20 mg). All participants completed the German versions of the West Haven-Yale Multidimensional Pain Inventory (MPI) (Flor, Rudy et al., 1990), the Fibromyalgia Impact Questionnaire (FIQ) (Offenbaecher, Waltz, & Schoeps, 2000), the short form of the Center for Epidemiologic Studies Depression Scale (CESD) (Hautzinger & Bailer, 1993), the Spielberger State Trait Anxiety Inventory (Laux, Glanzmann, Schaffner, & Spielberger, 1981) and the Edinburgh Handedness Inventory (Oldfield, 1971). In order to explore pain-related cognitions and suffering related to pain, all subjects also completed the Pain-Related Self Statements and the Pain-Related Control Scales (Flor, Behle, & Birbaumer, 1993). The Pain-Related Self Statements Scale consists of the subscales catastrophizing and active coping and assesses situation-specific self-statements on pain. The Pain-Related Control Scale is composed of the two subscales, helplessness and resourcefulness, and assesses beliefs about uncontrollability and unpredictability. Given that healthy controls do not constitute a comparable sample to fibromyalgia patients for pain symptoms, scores of fibromyalgia patients in pain-related questionnaires (FIQ, PRCS, PRSS, MPI-D) where compared with published normative scores from chronic pain patients (indicated by * in Table 1). For the FIQ the patients reported a mean of 48.84 (SD = 8.68, range 36.36–61.00). Compared to the mean of 46.10 (SD = 13.7) of the validation study by Offenbaecher et al. (2000) this fits well within the normal range of FMS patients. In the MPI the patients obtained scale scores in the range of the FMS validation sample of Thieme, Gromnica-Ihle, and Flor (2003), but for the affective distress subscale our FMS patients reported a significantly lower score. Catastrophizing as assessed in the Pain-Related Self-Statements Scale, as well as helplessness and resourcefulness beliefs as assessed in the Pain-Related Control Scale were similar to the validation sample (see Table 1). For the FMS patients, the mean number of positive tender points was 13.79 (SD = 2.83, range 8–18) and the mean number of positive control points was 0.57 (SD = 0.76, range 0–2). Finally, the scores obtained in the CESD Depression Scale and the Spielberger State Trait Anxiety Inventory were compared with those of healthy controls to control for possible differences in mood state. The FMS patients had significantly higher scores on both questionnaires compared to the healthy controls (see Table 1). Individual comparisons to the normative samples showed that six and five patients were above the normative mean for the CESD (Hautzinger & Bailer, 1993) and the STAI (Laux et al., 1981), respectively. All patients and controls were interviewed by a trained psychologist using the SCID and showed no major depression or anxiety diagnosis. The high CESD and STAI results show only a higher impairment of the FMS patients.

The study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Germany. All subjects gave written informed consent to participate in the study.

2.2. Expectation and controllability task

The subjects were told that they would participate in a reaction time experiment and that they could reduce the intensity of painful laser stimuli depending on their performance. In the control condition, the subjects saw an image of a right hand with one of the five fingers colored in blue (see Fig. 1 for the design of the study). The task of the subject was to respond as quickly as possible with the indicated finger of their right hand on a response pad (LUMItouch, Photon Control Inc., Burnaby, Canada) after termination of the picture presentation. The subjects received feedback on their performance: If their response was fast enough, they saw a smiling face on a green background signaling that the subsequent train of laser stimuli would be of lower intensity (*low pain expectancy and control*). By contrast, if their response was too slow, they saw a frowning face on a red background signaling that the following stimulation would be of higher intensity (*high pain expectancy and control*). In the no control condition, the subjects were told that they would have no control over the intensity of the subsequent laser stimuli. These trials were indicated by the presentation of a picture of a right hand where no finger was colored. Subjects were told to just press any button in this phase. Then, they were either presented with a circle on a red (*high pain expectancy and no control*) or a green background (*low pain expectancy and no control*), indicating that the subsequent laser stimuli would be more or less intense. Before the experiment all subjects were familiarized with the task and the response pad.

Images of the hand with one finger in blue were presented and they pressed the corresponding button and received feedback. The