Brain responses to other people's pain in fibromyalgia: a magnetoencephalography study

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ABSTRACT

Objective. *We investigated whether the central pain symptoms in fibromyalgia syndrome (FM) are related to defective top-down sensorimotor regulation. The pain matrix was activated in a top-down manner by presenting pictures of painful situations while recording brain activity using magnetoencephalography (MEG). We investigated alpha desynchronisation in FM patients and healthy controls in response to pictures depicting pain.*

Methods. *19 FM patients and 14 age-matched healthy controls (age 20-60) were recruited. Participants were shown photographs of right hands and feet in situations depicting pain or of control situations with no depiction of pain. MEG was recorded in a whole-head 248-sensor system as subjects laid supine.*

Results. *In healthy controls exposure to pictures depicting painful situations elicited a decrease in alpha activity (10Hz) at 100–500ms post-stimulus, which was significantly more pronounced than the one elicited by non-painful content mostly on sensors above the right sensorimotor cortex. However, FM patients did not show significant differences in alpha activity between responses to pain and no-pain pictures.*

Conclusion. *Consistent with previous findings, healthy participants displayed stronger alpha desynchronisation for pain pictures, indicating automatic disinhibition of the sensorimotor cortices in response to the observation of pain in others. We found evidence for a deficient modulation of sensorimotor cortex in FM patients. The lack of differential response suggests that they perceived relatively neutral pictures as potentially painful, at least in this setting. Our findings suggest that defective top-down regulation may play a role in the pathogenesis of FM.*

Introduction

Fibromyalgia syndrome (FM) is a disorder characterised by widespread pain and tenderness, which is now believed to be, at least in part, a disorder of central pain processing producing hyperalgesia and allodynia and defective top-down sensorimotor regulation (1-6). Various studies have found abnormalities in brain activity in FM (7) as well as in functional (8) and anatomical connectivity (9). FM, as well as chronic pain in general, constitute a significant and often un-met therapeutic challenge (10) and carry significant socio-economic burden (11).

A possible way to investigate the central regulatory mechanism of pain in FM is by activating the pain matrix in a top-down manner via presentation of pain-related information without nociceptive stimulation, eliminating differences in bottom-up sensory processing. Such activation occurs, for example, when viewing other people in pain. It has previously been shown that similar regions are activated for pain and pain observed in others (12). Previous research has yielded some evidence implying that FM patients show abnormal brain activation when viewing the pain of others. Compared with healthy subjects, patients with FM showed a smaller fMRI response to pain-related versus neutral stimuli in several brain regions, including the thalamus, anterior cingulate cortex, dorsolateral prefrontal cortex, pre- and post-central gyrus, and supplementary motor area (13). The haemodynamic alterations observed in FM patients were interpreted as representing limited empathy with others who are in pain, in order to minimise arousal and aversive self-oriented emotions. However, others have shown increased heart-rate and event-related brain potential responses to facial expressions of other's pain in FM patients (14). In electrophysiologi-

cal recordings, mu/alpha suppression has been used as an index of sensorimotor resonance of vicarious pain (15, 16). Using Magnetoencephalography (MEG), previous studies with healthy participants have shown stronger event-related alpha (mu) desynchronisation in response to painful than to non-painful pictures over sensorimotor areas, indicating preparation to analyse incoming pain or somatosensory input (17). The response of the somatosensory cortex to the pain of others, as indicated by mu/alpha suppression, can be altered by top-down processes like perspective taking (16, 18) and even imagination (19). We hypothesised that FM patients would show defective top-down regulation manifested in altered alpha desynchronisation in MEG responses to pictures depicting others' pain.

Methods

Participants
Study participants included 19 FM patients [mean age=38.3 (10.6), 17 females] fulfilling 1990 ACR criteria for the classification of fibromyalgia (20) and 14 healthy controls [mean age=27.9 (6.6), 10 females]. Patients were recruited from the community as well as from a specialised fibromyalgia clinic. The study was approved by the Ethics Committee of the Department of Psychology at Bar-Ilan University, and all participants gave written informed consent.

Procedure
Brain activity was measured using MEG in response to a well-validated set of colored photographs showing human right hands and feet in painful and non-painful situations (21) depicting familiar events that can happen in everyday life (*e.g.*, door closing on hand, knife cuts) representing various types of pain (mechanical, thermal and pressure). For each photograph depicting a painful situation, a corresponding one showed a neutral situation involving the same setting without any painful component. A total of 160 pictures (80 pain, 80 non-pain) were presented in two experimental blocks with a short break between them. Each block included 80 pictures (40 pain, 40 non-pain) in a random or-

der for each subject. Each stimulus was displayed for 200 ms, consistent with previous research (22, 23), followed by a fixation cross, during which the participants judged by pressing a button (using the right index finger) whether the photograph depicted a painful or a non-painful situation. Following the response, the fixation cross remained on the screen for a duration varying randomly between 1,000 and 1,600 ms. The stimuli were presented using the E-Prime software (Psychology Software Tools, Inc.) on a 17-in. screen located 60 cm in front of the participant. The size of all stimuli was 15.87 x 11.96 cm.

MEG data acquisition
MEG recordings were conducted using a whole-head, 248-channel magnetometer array (4-D Neuroimaging, Magnes 3600 WH) in supine position in a magnetically shielded room. Reference coils located a short distance above the head were used to remove environmental noise. Prior to data acquisition, five coils were attached to the participant's scalp for recording the head position relative to the 248 sensor-array. Head-shapes were digitised using a Polhemus Fastrak digitiser. The data were digitised at a sample rate of 1017.25 Hz and a 0.1-400 Hz online band-pass filter was used. An additional channel recorded the 50 Hz signal from the power outlet which was used to clean the mains noise and its harmonics by calculating the average 50 Hz cycle on every MEG channel and removing it from the data, hence allowing the cleaning of the line power noise without a notch-filter (24). A response box was used to record participants' responses.

Cleaning and preprocessing
Data was analysed with MATLAB 2012b (The Mathworks, Andover, MA) using Fieldtrip toolbox (25). Data was segmented into epochs starting 800 ms prior to stimulus to 1200 ms post stimulus onset. ERFs were measured relative to a 300 to 0 ms pre-stimulus baseline period. One malfunctioning sensor (A41) was discarded from all analyses. Heartbeat artifacts were removed using an event-synchronous cancellation al-

gorithm (24). Trials containing power jumps and/or muscle artifacts were manually rejected. Spatial Independent Component Analysis (26) was applied in order to clean eye movements and blink artifacts by visually identifying such components and reducing them from the data.

Time-frequency analysis was conducted for each condition (pain/no-pain) for the 2–40 Hz range in 2 Hz steps, using a hanning multi-taper method on the entire time segment (800ms pre-stimulus – 1200ms post-stimulus). Statistical analysis consisted of independent between-groups (FM/control) *t*-tests with the differential activity between pain and no-pain conditions as a dependent variable. A cluster based permutation test using the 'Monte Carlo' method was used to control for the multiple comparison problem, with 1000 iterations of the randomised data. The cluster (of neighbouring significant sensors) with the maximum/minimum sum of positive/negative *t*-values in each iteration was included in the permutation distribution ('maxsum'), and the values at the 95th percentile of the distributions were used as critical values. Analyses were performed with the fieldtrip toolbox (25).

Results
Time-frequency analysis at the sensor-level revealed a prominent alpha (and beta) desynchronisation at about 100-500 ms after stimulus presentation in response to both kinds of pictures (Fig. 1) in both groups. In healthy controls exposure to pictures depicting painful situations induced an event-related reduction in alpha activity (10Hz) which was significantly more pronounced than the one induced by non-painful content. This differential alpha activity appeared mainly in parietal sensors, mostly on sensors above the right sensorimotor cortex (Fig. 2), with a significant medial cluster of 6 sensors, cluster-*t*=-36.42, *p*=0.0019. FM patients did not show decreased alpha for pain relative to no-pain pictures (Fig. 2). The difference between groups in the pain-no pain subtraction was maximal at a significant posterior cluster containing 13 sensors, cluster-*t*=-36.42, *p*=0.04.
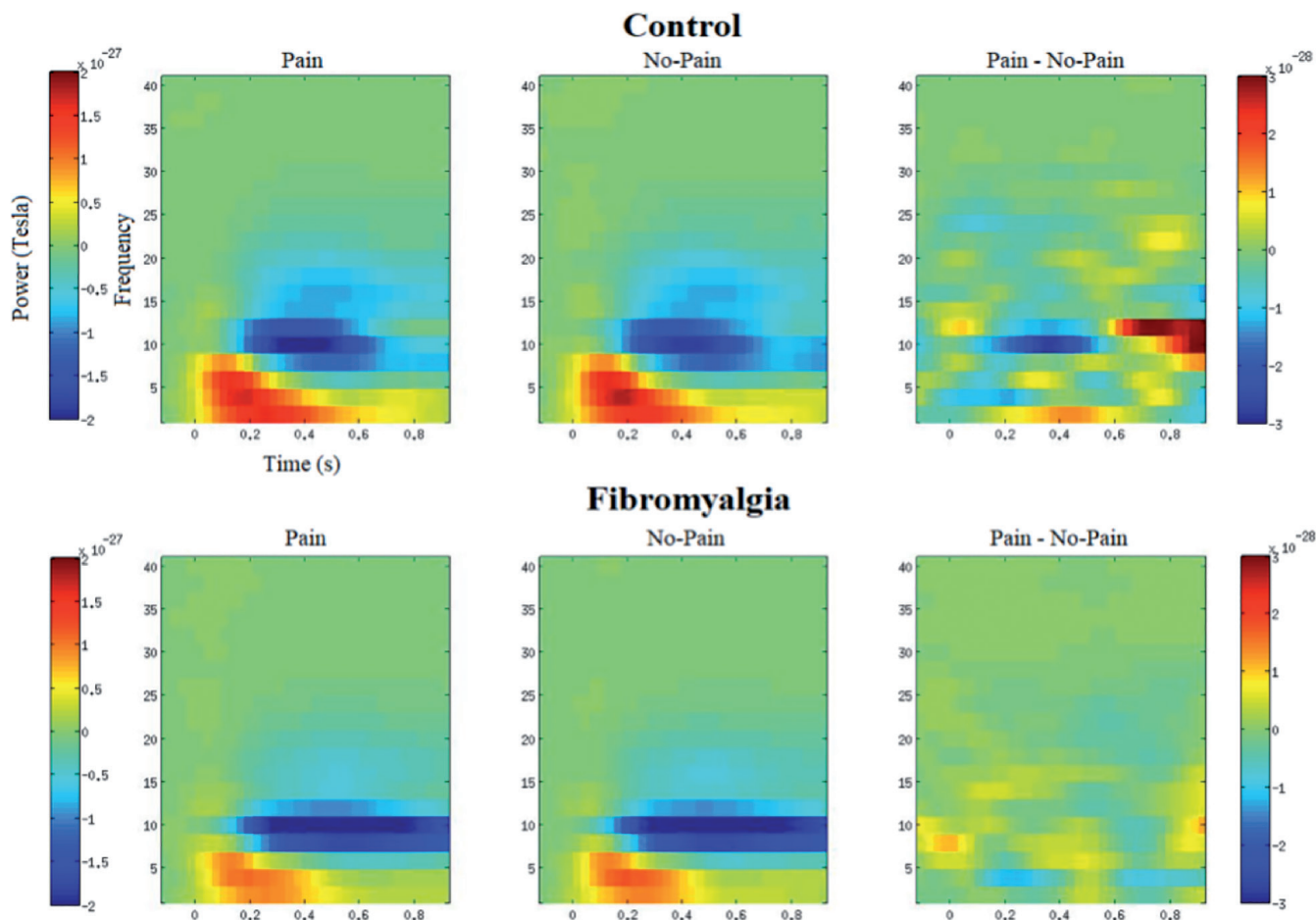
Fig. 1. Time-frequency analysis across all MEG sensors in the control (top) and FM (bottom) groups, of brain responses elicited by pain (left) and non-pain (middle) pictures.

The differential response pain-no-pain is shown on the right. Higher alpha suppression in the pain *vs.* no-pain condition is apparent in the control group (10 Hz, 100–500 ms) but absent in the FM group. No significant differences were found in other frequencies.

Discussion

In the current study, we have demonstrated the utility of MEG, as a novel tool for exploring differential patterns of brain activity among patients suffering from FM, a condition considered to represent a prototype of chronic centralised pain. This non-invasive modality, linked with a paradigm of empathetic – pain analysis, may provide new insight into the underlying mechanisms of augmented pain processing in FM. Consistent with previous findings (17), healthy participants displayed stronger alpha desynchronisation for pain pictures, indicating automatic disinhibition of the sensorimotor cortices in response to observation of pain in others. In contrast, FMS patients did not exhibit such a differential response, showing similar alpha suppression to both pain and no-pain pictures, indicating deficient modulation of the sensorimotor cortex in FM patients. This finding is similar to the lower differential fMRI activation to pain *versus* no-pain pictures reported by Lee *et al.* (13). Importantly, it should be noted that the effect reported in our study does not appear to result from lesser responsiveness of FM participants to the pain-related stimuli, since their response to others' pain was as strong as that of healthy controls. The
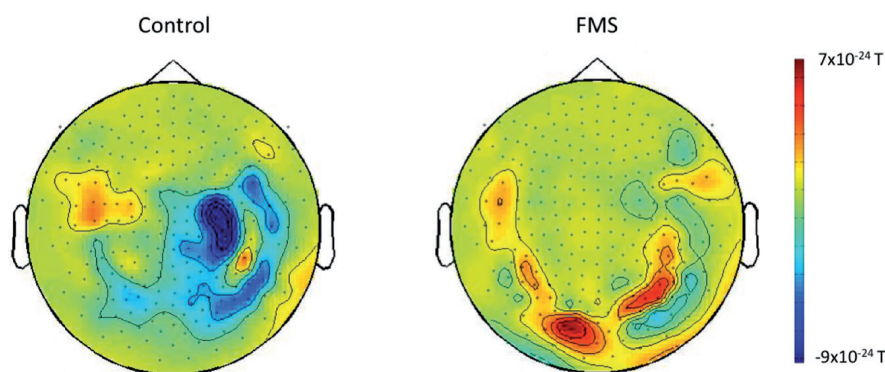
Fig. 2. Spatial distribution of alpha activity (10 Hz) of the differential response (pain-pictures minus no-pain-pictures, during the 100–500 ms time window.

In the control group (left), higher alpha suppression in response to pain vs. no-pain stimuli is located across parietal areas, mostly above sensorimotor cortex. In the FM group (right) no such difference between responses to pain *vs.* no-pain pictures in alpha suppression is apparent over parietal regions.

source of the effect seems to be an enhanced response of FM patients to the supposedly non-painful stimuli as well. This was not tested in the fMRI study (13), which analysed only the pain-no-pain contrast. Thus, the lack of differential response between pain and no-pain conditions in FM patients, suggests that they do not lack empathy to others' pain but that, instead, they perceived the relatively neutral pictures as potentially painful. Notably, such a finding might be clinically construed as analogous to allodynia, *i.e.* the perception of innocuous stimuli as being painful. A similar finding of increased amplitude of the LPP component in event-related potentials in response to non-pain pictures has been reported (27).

A similar finding has been reported in veterans who were previously exposed to extreme pain in others during combat (23). Pain-exposed veterans also exhibited a normative response to others' pain pictures, but no pain-to-no-pain differentiation. It was suggested there that previous pain-related experiences led to enhanced salience of the neutral stimuli and to increased attention to their potential threat. Such enhanced responses to neutral stimuli may reflect over-processing related to the survival importance of both pain and potential pain to combat-trained veterans. It is possible that for patients with FM as well, painful and neutral pictures may both be perceived as potentially threatening, especially within an experimental context in which painful and nonpainful stimuli appear interchangeably. In order to test this interpretation, further studies would need to include baseline measures of responses to neutral stimuli in a neutral context. Notably, FM is known to have clinical, epidemiological and possibly some pathogenetic overlap with Post Traumatic Stress Disorder (PTSD) (28, 29), a condition clinically characterised by extreme hypervigilance and similarly associated with central sensitisation (30). Thus, prior exposure to pain in others may serve as a defining event in the pathogenesis of chronic pain and trauma-related disorders.

A number of limitations of the current study should be noted. First, the number of participants was relatively small, and thus many fine differences in processing between FM patients and healthy controls may have been undetected. In addition, the number of participants was insufficient in order to stratify patients according to various clinical parameters such as severity, length of disease and treatment, which may have important effects regarding heterogeneity of brain function. Further research will require replicating our results in larger groups of patients as well as performing sub-group analyses. Acquiring bio-physical data regarding the processing and modulation of pain, *e.g.* Quantitative Sensory Testing (QST) and evaluating Conditioned Pain Modulation (CPM), which is assumed to be defective in many FM patients (31, 32), could also add significant and complementary dimensions to those obtained in the current study.

Despite these limitations, our results indicate overall that defective top-down regulation may play a role in the pathogenesis of FM. Future applications of both MEG and empathy-based pain paradigms may further our understanding of the neuroscience of FM and eventually pave the way to the design of novel therapeutic interventions.

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