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Decoding the perception of endogenous pain from resting-state MEG

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ABSTRACT

Decoding the neural representations of pain is essential to obtaining an objective assessment as well as an understanding of its underlying mechanisms. The complexities involved in the subjective experience of pain make it difficult to obtain a quantitative assessment from the induced spatiotemporal patterns of brain activity of high dimensionality. Most previous studies have investigated the perception of pain by analyzing the amplitude or spatial patterns in the response of the brain to external stimulation. This study investigated the decoding of endogenous pain perceptions according to resting-state magnetoencephalographic (MEG) recordings. In our experiments, we applied a beamforming method to calculate the brain activity for every brain region and examined temporal and spectral features of brain activity for predicting the intensity of perceived pain in patients with primary dysmenorrhea undergoing menstrual pain. Our results show that the asymmetric index of sample entropy in the precuneus and the sample entropy in the left posterior cingulate gyrus were the most informative characteristics associated with the perception of menstrual pain. The correlation coefficient (ρ=0.64, $p < 0.001$) between the predicted and self-reported pain scores demonstrated the high prediction accuracy. In addition to the estimated brain activity, we were able to predict accurate pain scores directly from MEG channel signals (ρ=0.65, $p < 0.001$). These findings suggest the possibility of using the proposed model based on resting-state MEG to predict the perceived intensity of endogenous pain.

1. Introduction

Pain is a subjective, unpleasant experience consisting of sensory, affective, and cognitive dimensions (Merskey, 1986; Moisset and Bouhassira, 2007). The neural representation of nociception is distributed throughout numerous regions of the brain, each of which plays a distinctive role in the perception of pain (Apkarian et al., 2005; Brodersen et al., 2012; Duerden and Albanese, 2013; Hofbauer et al., 2001; Moisset and Bouhassira, 2007; Rainville, 2002). This greatly complicates the process of decoding the subjective perception of pain from brain activity.

A number of functional neuroimaging techniques have been used to investigate the mechanism of pain processing in order to establish signatures for pain in the brain (Apkarian, 2013; Peyron et al., 2000; Tracey and Mantyh, 2007). Positron emission tomography (PET) was used in conjunction with contact thermal stimuli to show that the bilateral activation of the cerebellum, putamen, thalamus, insula, anterior cingulate cortex (ACC), and secondary somatosensory cortex (S2) is correlated with the intensity of perceived pain (Coghill et al., 1999). Another PET study on menstrual pain found that activation in the orbitofrontal cortex is positively correlated with the level of subjective pain (Tu et al., 2009). In a magnetoencephalographic (MEG) study, Timmermann et al., (2001) calculated the equivalent current dipoles evoked by laser stimuli and found that the source amplitudes of contralateral primary somatosensory cortex and bilateral S2 were positively correlated with the intensity of the stimulation . Electroencephalographic (EEG) was used to calculate the source activity evoked by immersing one's non-dominant hand in cold water, the results of which showed a significantly negative correlation between subjective pain levels and source power at 4–8 Hz in the left medial frontal and left superior frontal cortex, 8–12 Hz in the ACC, and 12–18 Hz in the posterior cingulate cortex (Shao et al. 2012). Another study using EEG in conjunction with thermal contact-heat stimuli revealed that alpha-1 power recorded at the bilateral temporal lobe under noxious conditions and in a resting state was significantly negatively correlated with subjective pain scores (Nir et al., 2012). These results indicate a relationship between the subjective perception of pain and the characteristics of activity in specific regions of the brain.

Researchers have recently moved from univariate to multivariate analysis in decoding perceptions of pain from brain activity evoked by

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pain stimuli. Gaussian process models were applied to functional magnetic resonance imaging (fMRI) to predict subjective pain ratings from brain activation that occurred in response to thermal pain (Marquand et al., 2010). Sensitivity to laser-induced pain was predicted by applying multivariate pattern analysis (MVPA) to temporal and spectral patterns in neuronal activity measured using EEG (Schulz et al., 2012). MVPA was also applied to fMRI to facilitate the classification of responses associated with non-painful and painful experiences evoked by near-threshold laser pulses (Brodersen et al., 2012). The decoding results provide a neural representation of pain involving the spatial distribution of brain activity in pain-related regions of the brain. One practice-oriented study used EEG data evoked by radiant-heat stimuli in conjunction with a linear prediction model to predict the intensity of pain (Huang et al., 2013). The regions of the brain related to the perceived level of pain were identified by applying MVPA to fMRI data recorded during stimulation using noxious chemicals (Favilla et al., 2014). These studies focused on the sensory pain evoked by external stimuli. However, information related to endogenous pain may be embedded in the patterns of long-term brain activity, thereby complicating the selection of spectral and temporal features.

In this work, we developed a decoding method for the prediction of perceived pain intensity associated with menstrual pain (endogenous visceral pain), from MEG sensor signals and estimated cortical source activity data. Sensor-level analysis is crucial to clinical applications, whereas cortical-level analysis is helpful in investigating the mechanisms involved in the perception of pain. We began by extracting features from the frequency and time domain of brain activity data, including relative band power (RP) and multiscale entropy, which has previously been used for the quantification of regularity in biomedical signals (Costa et al., 2005, 2003; Liang et al., 2012; Yang et al., 2013). The perception of pain is strongly related to the affective dimension; therefore, we also calculated hemispheric asymmetric indices with which to assess the lateralization of emotional processing (Alves et al., 2008; Davidson, 1992; Wheeler et al., 1993). Next, we determined the combination of essential features and associated regions of the brain required for decoding the perception of pain based on nested cross-validation (CV). Our decoding results were then evaluated according to the correlation coefficient between the predicted and self-reported pain scores as well as the accuracy of classification between high and low pain states. Accurate predictions related to the level of pain could be highly valuable in the objective assessment of pain for clinical applications, particularly for the patients with severe illnesses or injuries, preverbal toddlers, or elders with advanced dementia, who might be unable to report their pain verbally, in writing, or by other means (Herr et al., 2006, 2011). One such research would also involve the establishment of pain-related brain signatures by identifying the regions of the brain useful in pain level prediction.

2. Materials and methods

2.1. Participants

Primary dysmenorrhea (PDM) patients were clinically examined and diagnosed by a gynecologist and were recruited according to the following inclusion criteria: (1) females 20–30 year-old; (2) regular menstrual cycle of 27–32 days; (3) PDM history longer than six months; (4) menstrual pain in the previous six months, rated higher than 4 on a numerical rating scale (0=no pain, 10=the worst pain imaginable); and (5) right-handedness confirmed by the Edinburgh Handedness Inventory. A total of thirty-three subjects participated in this study (mean age of 23.3 ± 2.2 years, menarche: 12.3 ± 1.3 years, cycle: 29.5 ± 1.7 days, PDM history: 8.3 ± 2.8 years). No analgesics were taken within 24 hours before data acquisition. The quality of life, the psychological status, and the menstrual pain experience of all patients were assessed by the Short-Form Health Survey (Ware et al., 2000), the Spielberger's State-Trait Anxiety Inventory (Spielberger, 2010), the Beck Anxiety Inventory (Beck and Steer, 1990), the Beck Depression Inventory (Beck et al., 1996), the Pain Catastrophizing Scale (Sullivan et al., 1995), and the McGill Pain Questionnaire (MPQ). In MPQ assessment, the participated PDM patients were asked to recall their pain experiences during the current menstrual cycle. Before MEG signals were recorded, each subject verbally rated the currently perceived pain intensity using a numerical rating scale from 0 (no pain) to 10 (the worst pain imaginable). All subjects gave informed consent and received payment in exchange for participation in the study. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital. Data of three subjects were excluded due to the high rejection rate of trials in the data preprocessing.

2.2. Data acquisition

MEG data were measured using a 306-channel whole-head system (Vectorview system, Neuromag Ltd., Finland) in a magnetically shielded room at Taipei Veterans General Hospital, Taiwan. The MEG signals were recorded at a sampling rate of 1001.6 Hz and a band-pass filter with cutoff frequencies of 0.03 and 330 Hz. Among all channels, the signals from 204 gradiometers were used for further processing. Vertical and horizontal electrooculograms were also recorded for the detection of eye movements. Three-dimensional T1-weighted magnetic resonance imaging (MRI) with the MP-RAGE sequence was performed using a Siemens scanner with TR=2530 ms, TE=3.03 ms, TI=1100 ms, FOV=224×256×192 mm^3, matrix size=224×256×192, and voxel size=1×1×1 mm^3. Coordinate systems between the MRI volume and MEG device were co-registered by locating three landmarks (nasion, left and right pre-auricular points) in both systems.

Spontaneous MEG signals were recorded for 180 s in the menstrual phase, occurring between day 2 and day 4 of the menstrual cycle. During MEG recording, the subjects relaxed quietly with their eyes closed but in an awake state. The electrocardiographic (ECG) signals were also recorded at a sampling rate of 512 Hz with frequencies of 0.05 and 40 Hz using a portable device (Yang Ying Inc., Taiwan).

2.3. Data Preprocessing

The 180-s recordings were first segmented into eight-second epochs without temporal overlap. Epochs with an amplitude exceeding 2000 fT/cm at any time point and in any channel of the gradiometer were eliminated. To prevent contamination of MEG recordings with noise from eye movement or blinks, epochs with an amplitude exceeding 150 μV in any channel of the electrooculography recordings were also rejected. Four subjects were excluded from this study due to their high epoch rejection rate in which fewer than five epochs remained. The mean number of epochs after elimination was 14.1±5 across all remaining twenty-nine subjects. MEG signals associated with each epoch were projected onto a signal subspace using the signal space projection method (Uusitalo and Ilmoniemi, 1997). The projected signals were then passed through a 0.5–90 Hz band-pass filter for subsequent analysis followed by a 55–65 Hz band-stop filter for the elimination of powerline interference. Zero-mean adjustment was also applied to each channel to remove drift from the recordings.

2.4. Overview of proposed decoding method

Fig. 1 illustrates the framework of the decoding method proposed in this study. For sensor-level analysis, we used the resting-state MEG signals after data preprocessing for feature extraction. For cortical-level analysis, source activity in each position of the brain was estimated using maximum contrast beamformer (MCB) (Chen et al., 2006). The temporal and spectral features associated with each position or sensor were extracted from the brain signals. Features within the same brain