Concise report

Central neural mechanisms of interindividual difference in discomfort during sensorimotor incongruence in healthy volunteers: an experimental study

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Abstract

Objectives. It has been reported that disturbance in sensory and motor function may induce sensorimotor incongruence and produce pain, discomfort and other sensations in healthy volunteers. One study suggested that sensorimotor incongruent information to healthy subjects results in increased neuronal activity in the posterior parietal cortex (PPC) and dorsolateral prefrontal cortex; however, this study did not take into consideration the discomfort induced by sensorimotor incongruence. The present study attempted to characterize intracortical electrical activities for sensorimotor incongruence in the frequency domain. In our study, electroencephalogram (EEG) cortical sources were compared between sensorimotor congruence and sensorimotor incongruence. In addition, high and no discomfort subgroups were compared during sensorimotor incongruence.

Methods. Eighteen healthy female subjects participated in this study. Subjects were then asked to flex/extend both arms in a congruent/incongruent manner while viewing a whiteboard/mirror. EEG was performed to determine the cortical activation during sensorimotor congruence and incongruence.

Results. Alpha band activity in the right posterior parietal cortex during sensorimotor incongruence was significantly lower than that of sensorimotor congruence. The source activities induced in the anterior cingulate cortex (ACC) beta band activity and the posterior cingulate cortex (PCC) alpha band activity significantly decreased in the high-discomfort vs the no-discomfort subgroup.

Conclusion. The present findings suggest that the ACC and PCC are more activated in the high-discomfort subgroup than in the no-discomfort subgroup during sensorimotor incongruence. This method may evaluate the effectiveness of new medication therapy and/or rehabilitation by assessing the difference in the neuronal activity of chronic patients before and after treatment.

Key words: pain, discomfort, sensorimotor incongruence, quantitative electroencephalography, LORETA, cingulate cortex.

Introduction

It has been suggested that abnormal painful sensations in complex regional pain syndrome type 1 (CRPS-1) [1, 2] and phantom limb pain [3] may be related to the sensorimotor incongruence of motor intention, somatosensation and visual feedback. McCabe et al. [4] reported that disturbance in sensory and motor function may induce sensorimotor incongruence and produce pain, discomfort and other sensations in healthy volunteers. Sensorimotor incongruence is defined as a discrepancy between
were compared during sensorimotor incongruence. In addition, high- and no-discomfort subgroups were compared to the study. The study was conducted in compliance with the Declaration of Helsinki.

Bimanual coordination test

McCabe et al. [4] described the assessment apparatus and procedure employed in the current study in detail. After jewellery was removed, subjects were seated in an assessment chair. The assessment apparatus consisted of a double-sided board—a mirror as the intervention side and a whiteboard as the control side—that could be turned so that the mirror or whiteboard was positioned on the left or right side. The assessment apparatus was positioned on the subject’s anterior midline. Subjects were then asked to flex/extend both arms in a congruent/incongruent manner for 30 s while viewing the whiteboard/mirror and focusing on a reference point (a horizontal line at the level of the subject’s umbilicus). In a block design, after a baseline session of 30 s, each task was performed three times, alternating with 30-s rest periods. Throughout the assessment, nothing but the limb in front of the board was visible for the subjects. At the end of each session, two open-ended questions were asked: How did it feel? and Were you aware of any changes in either limb? When assessing the sensations of discomfort, the discomfort intensity was rated on a numerical rating scale (NRS) from 0 to 10 (0 = no discomfort and 10 = the worst possible discomfort). All the tasks were executed in a random order with at least a 5-minute rest period.

EEG measurement

EEG was performed to determine the cortical activation during the bimanual coordination test. The Discovery 24 E (BrainMaster Technologies, Bedford, OH, USA) was used with 19 electrodes arranged according to international conventions with FPz as a reference. EEG signals were obtained at 256 samples/s. During measurements, the impedance of all electrodes was maintained at <5 kΩ.

The EEG data were exported from storage and entered into Neuroguide (Applied Neuroscience, Petersburg, FL, USA) for analysis. EEG segments contaminated with eye blinking and eye movement artefacts were manually rejected by visual inspection. The EEG data were segmented into 2-s epochs. sLORETA is an algorithm used to address the inverse solution for source localization of the EEG produced on the scalp. Computation of the sLORETA algorithm is performed in a realistic head model using the MNI152 template. The solution space is restricted to cortical grey matter, which is partitioned into 6239 voxels at 5-mm resolution. The sLORETA algorithm can be performed either in the time domain to estimate underlying sources at any time instant or in the frequency domain to localize neuronal oscillators for different frequency bands. It has been demonstrated to be a useful and feasible tool for pain studies.

In the present study, EEG source analysis was performed in the frequency domain. Cross-spectral matrices of the EEG epochs for each subject in each condition were first computed with the sLORETA software for five
frequency bands: 1–4, 4–8, 8–12, 12–18 and 18–30 Hz. The average cross-spectral matrices for each subject in each condition were given as the input for sLORETA source analysis. The sLORETA yielded the spectral density of the current density at each voxel. Subject-wise normalization (which takes the total power across all frequency bands and over all the 6239 voxels of the brain volume to unity) was performed on the sLORETA solutions before statistical analysis. Good reliability of sLORETA current source density and cross-spectral matrices analysis was shown [12].

Statistical analysis
After data preprocessing, the estimated EEG cortical sources were compared between a sensorimotor congruence and a sensorimotor incongruence test using voxel-by-voxel paired t-tests of the normalized and log-transformed sLORETA maps in the aforementioned five frequency bands. To identify brain regions that were activated more frequently in the high-discomfort subgroup, in reference to the study in subjective pain [9], the discomfort intensity was used to assign subjects to the high-(5 > NRS) or no-discomfort (0 = NRS) subgroup. The differences between the high- and no-discomfort subgroups during sensorimotor incongruence were assessed using unpaired t-tests. Voxel-by-voxel t-values in Talairach space are displayed as statistical parametric maps.

Results
Two (11.1%) and 12 subjects (66.6%) reported discomfort in sensorimotor congruence and sensorimotor incongruence, respectively. The average discomfort intensity in sensorimotor incongruence was 3.7 (s.d. 2.7). Alpha band activity (8–12 Hz) in the right PPC (Broadman area 7) during sensorimotor incongruence was significantly lower than that of sensorimotor congruence (Table 1 and Fig. 1). Subjects were divided into two subgroups representing the high-discomfort [mean NRS rating 6.3 (s.d. 1.5)] and no-discomfort subgroups (NRS rating = 0) of the sampled population. The source activities induced in the posterior cingulate cortex (PCC; Broadman area 30) alpha band activity (8–12 Hz) and the anterior cingulate cortex (ACC; Broadman area 32) beta band activity (12–18 Hz) significantly decreased in the high-discomfort vs the no-discomfort subgroup (Table 1 and Fig. 1).

### Table 1 Significant differences in alpha and beta activity congruence vs incongruence and high vs low discomfort

<table>
<thead>
<tr>
<th>Statistical value (t)</th>
<th>MNI coordinates, mm</th>
<th>Broadman area</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congruence vs incongruence</td>
<td>Alpha 0.806</td>
<td>29 −61 45</td>
<td>7 PPC</td>
</tr>
<tr>
<td>High vs low discomfort</td>
<td>Alpha 1.499</td>
<td>−5 −60 4</td>
<td>30 PCC</td>
</tr>
<tr>
<td></td>
<td>Beta 1.499</td>
<td>5 37 2</td>
<td>32 ACC</td>
</tr>
</tbody>
</table>

MNI: Montreal Neurological Institute.

Discussion
The present study was a first attempt to characterize the discomfort felt during sensorimotor incongruence at the cortical level by frequency-domain EEG source localization using sLORETA. Nociceptive processing is associated with inhibition of alpha and beta rhythms in the somatosensory cortex, ACC and PCC [13]. Alpha rhythms in the PPC were found to be associated with visuospatial attention tasks [14]. Decreases in oscillatory power classically indicate increases in sensory cortical activation. In this study, decreases in oscillatory power were found in the PPC alpha band in sensorimotor incongruence compared with congruence and in the ACC beta band and PCC alpha band in the high-discomfort subgroup compared with the no-discomfort subgroup during sensorimotor incongruence.

A reduction of alpha band activity was observed (increased cortical activation) in the right PPC during sensorimotor incongruence vs congruence. Our results are consistent with those reported by Fink et al. [8]. The PPC is generally considered to be a key region for the fusion of signals from different sensory modalities, body ownership and hand–eye coordination. Fink et al. [8] proposed that the PPC is activated as a result of increased attentional demands for the integration of vision and proprioception. In contrast, the primary and secondary somatosensory cortex, ACC and insula are known to be pain-related regions exhibiting no statistically reliable differences in activation between sensorimotor congruence and incongruence. This was seen in the present study as well as in the study of Fink et al. [8]. These findings confirm that the neural correlates of discomfort induced by sensorimotor incongruence are not known by comparing between sensorimotor congruence and incongruence.

The central processing of pain within the cortex has often been referred to as the pain matrix. The primary (S1) and secondary (S2) somatosensory cortex, insula, ACC, PCC, PFC, thalamus, amygdala and brainstem are included in the pain matrix. Sensory-discriminative aspects of pain perception are often thought to be independently and specifically represented in S1, S2 and the insula, while the affective-cognitive-evaluative aspects of pain perception are represented in medial brain structures such as the ACC, PCC and PFC. In chronic pain patients, including CRPS, phantom pain and back pain,
Discomfort during sensorimotor incongruence

**Fig. 1** Electroencephalogram activity during sensorimotor congruence and incongruence tests

sLORETA differences in the (a) alpha band comparing EEG activity during sensorimotor congruence and incongruence tests and in the (b) alpha band and (c) beta band for the high- and no-discomfort subgroups during sensorimotor incongruence tests.
reorganization in the primary motor and sensory homunculus maps occurs. In irritable bowel syndrome, defined by continuous or remittent abdominal pain and/or discomfort, increasing levels of discomfort and/or pain are associated with activation of the ACC, insula, parietal and ventral medial frontal regions during ramp distension.

Cerebral cortical regions such as the ACC and PPC, considered to be key pain-related regions, exhibited more activation in individuals who were highly sensitive to discomfort vs individuals who were insensitive to discomfort induced by sensorimotor incongruence. The ACC is an essential cerebral region in sensory cognition and the affective process of pain [15]. Brain imaging studies have revealed significant changes in pain-evoked activity within the ACC, consistent with an individual’s perceived unpleasantness, while primary somatosensory cortex activation is unrelated [16]. Many studies identify a role for the PCC in negative emotion and the pathological state of pain [17, 18]. Therefore increased activation in the ACC and PCC may reflect negative emotion and incongruous physical states induced by sensorimotor incongruence.

Individuals with FM feel more discomfort during sensorimotor incongruence than healthy volunteers [5]. There is vast evidence for brain dysfunction in patients with FM, and it is possible that central plasticity is critical for chronic pain. ACC responses to sensory stimuli in FM may play a key pathophysiological role in chronic pain syndromes. Experimental temporal summation inducing hyperalgesia in FM confirmed the altered pain processing by increased activation of the ACC [19]. Positive relationships between physical activity and brain responses to experimental pain have been observed in the PPC in individuals with FM [20]. In individuals with FM, the ACC and PCC react to stimuli more easily than in healthy individuals. Our results showed that ACC and PCC activation were increased in the high-discomfort subgroup during sensorimotor incongruence. We speculate that the reason individuals with FM sense discomfort more during sensorimotor incongruence is that the ACC and PCC are easily activated by stimuli.

There is still no gold standard for the evaluation of chronic pain patients, including those with FM and CRPS. The present study may provide an important step in the implementation of an objective measurement method, although there is a long way to go. EEG measures during sensorimotor incongruence may evaluate the effectiveness of new medications and/or rehabilitation by assessing the difference in ACC and PCC activities during sensorimotor incongruence in chronic pain patients before and after treatment.

Two limitations of our study should be considered. The first limitation is that we selected only healthy female subjects for this study. We decided on this population because the mean prevalence is a female: male ratio of 3:1 in patients with FM. Those with FM feel more discomfort induced by sensorimotor incongruence than healthy volunteers. We revealed the relationship between discomfort and ACC and PCC activity in healthy women. However, our findings may not apply to patients with FM. Therefore a second study on patients with FM is needed to arrive at a definite conclusion. The second limitation is that we could not perform a functional connectivity analysis, which would allow us to understand more clearly the regulatory functionality of the cingulate cortex during sensorimotor incongruence, as more electrodes are needed in order to perform a functional connectivity analysis. Therefore, in a future study, increasing the number of electrodes from 19 to 64 may provide a more detailed analysis.

Conclusions
The present findings suggest that the ACC and PCC are more activated in the high-discomfort subgroup than in the no-discomfort subgroup during sensorimotor incongruence. These findings may provide an understanding of discomfort during sensorimotor incongruence.

Rheumatology key messages
- Neural correlates of discomfort are not known by comparing sensorimotor congruence and incongruence.
- The cingulate cortex is more activated in the high- than in the no-discomfort subgroup.
- These findings may provide an understanding of mechanisms of discomfort during sensorimotor incongruence.

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References


