Clinical Study

Abnormal thalamocortical dynamics may be altered by deep brain stimulation: Using magnetoencephalography to study phantom limb pain

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Abstract

Deep brain stimulation (DBS) is used to alleviate chronic pain. Using magnetoencephalography (MEG) to study the mechanisms of DBS for pain is difficult because of the artefact caused by the stimulator. We were able to record activity over the occipital lobe of a patient using DBS for phantom limb pain during presentation of a visual stimulus. This demonstrates that MEG can be used to study patients undergoing DBS provided control stimuli are used to check the reliability of the data. We then asked the patient to rate his pain during and off DBS. Correlations were found between these ratings and power in theta (6–9) and beta bands (12–30). Further, there was a tendency for frequencies under 25 Hz to correlate with each other after a period off stimulation compared with immediately after DBS. The results are interpreted as reflecting abnormal thalamocortical dynamics, previously implicated in painful syndromes.

Keywords: Chronic pain; Phantom limb; Magnetoencephalography

1. Introduction

Phantom limb sensations, painful or otherwise, follow amputation surgery in around 60–75% of cases. These sensations can persist and become resistant to treatment. Several theories have been proposed to explain persistent phantom limb sensations. These theories include spinal mechanisms, central sensitisation, and somatosensory cortical rearrangement. It is likely that all of these may explain phantom phenomena to some extent.

Recently, chronic pain syndromes have been shown to be associated with increased electroencephalogram (EEG) and magnetoencephalogram (MEG) slow wave (theta and beta) activity. Persistent slow wave cortical activity is suggested to result from abnormal thalamocortical interplay, called thalamocortical dysrhythmia (TCD). In TCD hyperpolarised sensory thalamic neurons fire rhythmically at low frequencies, resulting in an imbalance of the usual cortical inhibitory and excitatory mechanisms. It is suggested that this abnormal activity causes painful sensations in the absence of a sensory input.

Deep brain stimulation (DBS) of the ventroposterolateral nucleus (VPL) of the sensory thalamus and/or the periventricular grey (PVG) or periaqueductal grey (PAG) is an effective treatment for neuropathic pain. However, it is not known if the effects of DBS are related to the pathology described in TCD. Unfortunately, it is difficult to study the mechanisms of DBS directly as the stimulation produces an artefact that has thus far precluded the use of...
the usual electrophysiological tools, and functional magnetic resonance imaging (fMRI) techniques are considered unsafe.

In the present study we addressed this problem by taking advantage of the fact that head geometry (and the location of stimulator hardware) with respect to the MEG sensors is different for each patient, hence some datasets will be less contaminated by artefacts than others, as the sensors are differently able to detect signals in different locations. To identify the least affected scans we asked patients to view a checkerboard stimulus, which in normal circumstances would give robust brain activations in stimulus defined frequency bands over the occipital lobe. One of the three patients we scanned showed brain activity resembling that of our control subject’s during this task. The patient rated his pain in the scanner while he was both off and on stimulation. Previous research has found greater power in the theta band in pain patients compared with controls. We therefore correlated subjective pain scores with power within these frequency bands. Finally, in order to determine if DBS alters the increased association between low and high frequencies characteristic of thalamocortical dysrhythmia, we computed correlations between frequencies.

2. Methods

2.1. Patient history

We studied three patients receiving DBS for chronic pain after amputation. The subject reported in depth here was 41 years old at the time of MEG. Traumatic injury to his left arm had resulted in above elbow amputation and partial brachial plexus avulsion 16 years earlier. Four stump revision procedures over the following six years, the last removing the humerus, failed to ameliorate phantom limb pain. Right PVG/PAG and VPL DBS electrodes were inserted seven years later. Our operative technique is detailed elsewhere. DBS settings at the time of the MEG scan were: frequency = 5 Hz, pulse width = 210 μs, amplitude = 1.0 v with subjective pain reduction from 8/10 to 4/10 with DBS.

The female control was aged 40 years at the time of MEG. Traumatic injury in the head was insufficient to explain the level of his pain.

2.2. Stimuli and procedure

2.2.1. Visual task

The patients and control subject each viewed a high contrast black and white flickering checkerboard displayed on a computer screen, alternating at 5 Hz. The patients viewed this while they were on (ON-STIM) and off stimulation (OFF-STIM). Each patient received their individual analgesic stimulation settings. The checkerboard stimulus was visible for 30 seconds, and was interspersed with a grey screen also lasting 30 seconds. This sequence was repeated 5 times, therefore lasting for a period of 5 minutes. In the centre of both stimuli there was a red fixation cross, on which the participants were asked to fixate.

2.2.2. Visual analogue scale (VAS) task

Patients viewed a horizontal bar on a computer screen. The length of the bar could be manipulated with a button box. At either side of the bar were the statements “no pain” and “very painful”. The left button caused the bar to decrease towards the statement “no pain”. If the patient pressed the button a second time, the bar would stop. The right button caused the bar to move towards the statement “very painful” and again a second press would stop the bar at the position the patient deemed indicative of the level of their pain.

The patient’s stimulators were set to cycle on and off for five minutes. The above stimuli were timed to appear on the screen so that each was viewed in both the ON-STIM and OFF-STIM conditions. Each of the patients were therefore presented with the checkerboard for 5 minutes ON-STIM, then the VAS for 5 minutes OFF-STIM, then the VAS for 5 minutes ON-STIM, followed by the checkerboard for 5 minutes OFF-STIM, finally the VAS for 5 minutes ON-STIM and the VAS for 5 minutes OFF-STIM.

2.3. Data collection and analysis

The recordings were collected using a 275 channel CTF Omega system (CTF systems Inc., Port Coquitlam, Canada) at Aston University. Data were sampled at 2400 Hz with an antialiasing cut-off filter of 200 Hz.

The data were analysed using Fieldtrip (F.C. Donders Centre for Cognitive Neuroimaging, Radboud University Nijmegen) and in-house matlab® scripts (for the frequency analysis procedures outlined below). For all analyses the data were band pass filtered between 5 Hz and 500 Hz. Fast Fourier transforms (FFTs) with a Hanning window (1 second) were used to obtain a power spectrum for frequencies between 6 Hz and 60 Hz during the 30 seconds grey screen and checkerboard stimuli. Power for each frequency while subjects viewed the checkerboard was then divided by the power for each frequency while they viewed the grey screen. This gave a ratio of activity during the checkerboard stimulus versus the grey screen stimulus.

As described and validated below, one patient’s response to the checkerboard stimuli resembled that of the control subject’s during the visual stimulus. Hence this patient’s data has been used for the remainder of the study. The patient rated his pain once every 22 seconds. We computed power (using FFTs with a 1 second Hanning window) for the data collected in the five seconds before each rating. Power within the following frequency bands was calculated: Theta (6–9 Hz), beta (12–30 Hz) and gamma (30–60 Hz). For both the ON-STIM and OFF-STIM conditions, power within each of these frequency bands was correlated with the corresponding pain ratings.

Finally, to assess the degree of correlation between frequencies we followed a similar procedure to Jeanmonod
et al.\textsuperscript{5} FFTs with a Hanning window (1 second) were used to compute power for each frequency between 6 Hz and 60 Hz. The time series of each frequency was then correlated (using Pearson’s correlation coefficient), with the time series of all other frequencies. Since we could not determine the effect of stimulation on correlations we did not use data collecting in the ON-STIM conditions in this analysis. Instead we used 20 seconds of data collected immediately before and immediately after each ON-STIM condition. After removing trials containing excessive movements, we obtained 2 trials in each condition (labelled from here on as AFTER-STIM for the data collected immediately after stimulation, and BEFORE-STIM for the period immediately before stimulation).

3. Results

3.1. Visual stimuli

For all patients we obtained the ratio of activity during the checkerboard versus the grey screen in both the ON-STIM and OFF-STIM conditions. Activity measured across all sensors in one of the patients resembled that of the control. To verify this, correlations were calculated between the control subjects and the patient’s ratio of power at 10 Hz (the expected response of the visual system to 5 Hz alternating stimuli). This was found to be significant ($r = 0.49$ [ON-STIM] $r = 0.46$ [OFF-STIM] $p < 0.0001$). The other 3 patients’ data did not significantly correlate with that of the controls\textsuperscript{5}. The power ratios are shown in Fig. 1.

Fig. 1 shows 10 Hz activity in the posterior sensors in the control and in one patient. The other patients did not show reliable activations of this kind, and their data was not correlated with the controls’ data. We have not presented data for other frequencies, which are flat topographies as expected. The data for the patient looks similar in the on and the off DBS conditions, suggesting that some analyses may be possible even during stimulation.

3.2. Correlations between theta, beta and gamma power and subjective pain scores

The patient was asked to rate his pain every 22 seconds in the ON-STIM and OFF-STIM condition. We were not expecting differences between ratings on and off stimulation, as we have previously found that the VAS is inappropriate for comparing periods that cycle on and off stimulation (unpublished observation: A. Green, Nuffield Department of Surgery, John Radcliffe Hospital, clinical observation during patient monitoring). This is probably because pain ratings made in such close succession to each other are influenced by the previous ratings, rather than being a judgment of the level of pain being experienced at that time. Nonetheless, they have been used here to gain a rough estimate of the patients’ experience of pain fluctuations.

Fig. 2 shows the percentage of significant correlations with pain ratings in sensors divided into left and right frontal, central, parietal, temporal and occipital regions. We found a similar profile for theta activity across sensors in both the ON- and OFF-STIM conditions. However, there were fewer beta correlations and more gamma correlations in the ON-STIM condition.

3.3. Correlations between frequencies

In TCD there is an increased coherence between frequencies\textsuperscript{7} which is thought to account for the positive symptoms associated with the various neurological disorders described within a TCD framework. If DBS is interfering with these correlations, there should be greater correlation between frequencies on DBS compared with off DBS. We felt that correlating between frequencies in the on DBS condition...
had not been justified by the checkerboard task because the time series of the FFT is used for the correlations rather than the absolute power. Therefore, the data in Fig. 3 were obtained during 20 second periods immediately after and immediately before an ON-STIM period.

Fig. 3 shows a tendency for weaker correlations between the lower frequencies in the after DBS condition than in the after no DBS condition. T-tests revealed that these differences were significant at the $p = 0.05$ level.

4. Discussion

Using MEG to study patients undergoing DBS is an intriguing prospect and may eventually help elucidate how the brain responds to DBS. However, the artefact from the stimulator is considered too large for MEG to be used while patients’ stimulators are turned on. We have minimised this problem by assessing the integrity of the recordings using a simple visual task. Occipital lobe activations to a visual stimulus were reliably measured in one of the three patients. We therefore considered data from this particular patient to be suitable for further analysis.

On the basis of experimental evidence, and the clinical finding of low threshold spikes in pain patients, Llinas et al. proposed a TCD account of neuropathic pain. In TCD, cells become hyperpolarised due to deafferentation or excessive inhibition. This causes activation of a low threshold Ca$^{2+}$ current, resulting in spontaneous low threshold spiking activity and bursts of fast Na$^+$-dependent action potentials that fire rhythmically at low (theta) frequencies. When these low frequencies are present alongside higher frequency gamma, an “edge effect” due to lateral inhibition occurs, similar to that observed in the retina. This results in aberrant gamma activity that signals painful experiences in the absence of painful stimuli.

The TCD process begins with a lowered excitatory input to the sensory thalamus. It is therefore interesting that the patient studied here had DBS implants in PAG/PVG. This suggests that even DBS at a site away from thalamus, but with connections to it, can override...
thalamic hyperpolarisation and remove the abnormal oscillations. Stimulation in PAG/PVG is also suggested to improve pain via endogenous opioid release, suggesting a dual mechanism of action for DBS in this area.

Supporting a TCD model of neuropathic pain, Sarnthein et al. found that patients with neuropathic pain have increased EEG power in the theta and beta bands. Stern et al. found a spontaneous presence of enhanced theta and beta activations in the pain matrix of pain patients compared with controls using EEG and functional low resolution electromagnetic tomography. In the present study theta and to some extent beta, measured over frontal and central sensors was shown to correlate with the subjective experience of pain. This finding fits with studies that have shown that prefrontal cortex activity follows experimental or clinical pain conditions. Frontal lobe activity during pain is generally related to the cognitive and attentional processing of painful stimuli. Our data suggest that the strength of this activity can be measured as power in the theta and beta bands, which can also be associated with subjective pain intensity.

Excessive theta and beta activity during pain suggests that any treatment for pain should aim to reduce activity in these bands. It is possible that DBS directly interferes with theta rhythms by releasing thalamic cells from hyperpolarisation, and therefore limiting the deinactivation of the low threshold calcium currents. While our data cannot determine whether low frequencies are reduced during DBS, it does suggest that it is possible to use MEG to measure theta activity off and during DBS that correlates with pain intensity. This would greatly benefit the study of DBS for pain.

Although pain in the TCD framework is proposed to occur because of aberrant gamma activity, previous work has not found increases in gamma in patients compared with controls. Similarly, aside from the central and parietal correlations with pain scores during DBS (which are difficult to interpret in a single case), we did not find that gamma correlated with pain intensity. It has been suggested that studies fail to associate increased gamma with pain groups or conditions because of methodological issues concerning frequency analysis techniques, or because the edge of gamma-range activity is too narrow to be detected.

Under the assumption that the effects of DBS do not wear off instantly after termination of stimulation, we chose to compare time periods immediately after DBS or before DBS. Finding that correlations between frequencies (Fig. 3) in the BEFORE-STIM condition were greater than those in the AFTER-STIM condition suggests that DBS might improve pain by interfering with these correlations. This is an intriguing prospect and studies with larger samples and longer periods off and on DBS are needed to ascertain if this effect can be measured in other patients.

In summary, after taking steps to ensure our data was minimally affected by the artefact from stimulation, we found that abnormal oscillations previously reported in TCD fluctuated with subjective pain scores. These correlations were strongest in the frontal sensors, and were also detectable in the DBS on condition. This suggests that MEG is an appropriate technique for studying DBS for pain. We also found that correlations between frequencies were reduced immediately after stimulation compared with before stimulation. This suggests that DBS might interfere with these correlations to produce pain relief.

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References