Deep brain stimulation for chronic pain investigated with magnetoencephalography

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Deep brain stimulation has shown remarkable potential in alleviating otherwise treatment-resistant chronic pain, but little is currently known about the underlying neural mechanisms. Here for the first time, we used noninvasive neuroimaging by magnetoencephalography to map changes in neural activity induced by deep brain stimulation in a patient with severe phantom limb pain. When the stimulator was turned off, the patient reported significant increases in subjective pain. Corresponding significant changes in neural activity were found in a network including the mid-anterior orbitofrontal and subgenual cingulate cortices; these areas are known to be involved in pain relief. Hence, they could potentially serve as future surgical targets to relieve chronic pain. *NeuroReport* 18:223–228 © 2007 Lippincott Williams & Wilkins.

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Introduction

Recent developments in deep brain stimulation (DBS) of specific targets in the human brain have been successful in alleviating the symptoms of otherwise treatment-resistant disorders; mainly chronic pain [1–3], phantom pain [4], cluster headache [5], and motor disorders including Parkinson's disease [6], multiple sclerosis or essential tremor, dystonia and spasmodic torticollis [7] with some success also reported for unipolar depression [8]. The data so far suggest that low-frequency stimulation works particularly well for the treatment of pain, whereas high-frequency stimulation works best for movement disorders. The treatment and associated neurosurgical methods have shown remarkable promise [9]; however, the underlying neural mechanisms for DBS are not understood and, in particular, it is not at all clear how DBS of specific brain targets changes the neural activity in wider cortical and subcortical regions.

DBS has been successfully used for neuropathic pain and phantom limb pain with targets in the periventricular gray/periaqueductal gray (PVG/PAG) [1]. The analgesic effects of DBS remain largely unknown, but probably involve activation of thalamocortical pathways and changes in cortical activity [10]. DBS offers a novel and unique possibility for in-vivo investigation of the functional role of the underlying neural circuitry in humans by switching the stimulator on and off. The ensuing changes in whole-brain activity can then be mapped using neuroimaging methods. Owing to the danger that the strong magnetic field might induce movement or heating of the stimulator or electrode, it remains difficult to use functional magnetic resonance imaging (fMRI) to map DBS-induced cortical activity. Positron emission tomography (PET) has been used with some success to map the effects of DBS [11,12], but this method is not ideal given that PET only offers indirect measures of neuronal activity and has a very low temporal resolution on the timescale of minutes.

Here, we used for the first time magnetoencephalography (MEG) to investigate the whole-brain changes in neural activity induced by DBS in the PVG/PAG of a patient with severe phantom limb pain in the left leg. MEG directly measures the magnetic component of the electromagnetic signal from neurons and the current density of MEG sensors affords a spatial resolution comparable to fMRI (typically around 5 mm^3) but with much better temporal resolution (in milliseconds) [13]. Furthermore, neuronal activity in subcortical and even deeper sources such as in the brainstem can be measured with MEG [14]. To the best of our knowledge, it is the first time that MEG has been used to investigate the effects of DBS.

Methods

Brief case story

The 58-year-old right-handed male patient, R.M., was referred with a 4-year history of severe phantom limb pain

in the left leg stemming from fracturing his leg in May 2001 with subsequent complications including a methicillin-resistant *Staphylococcus aureus* infection culminating in an above the knee amputation in October 2001. Sympathectomy, spinal cord nerve stimulation, hypnosis and a wide variety of medications had provided little relief. Preoperative testing showed an abnormal neuropsychological profile with poor performance on all verbally mediated tests and at a level of 'caseness' for both anxiety and depression, probably linked to his level of medication, which was repeated prescriptions of morphine sulfate 380 mg over 24 h.

The patient R.M. was then implanted with a DBS in the right PVG/PAG, and he experienced excellent pain relief. The patient later fell, fracturing the deep brain electrode, and this caused immediate return of the pain. After surgical revision pain relief returned. Effective settings for stimulation in R.M. were 1.5 V, frequency 7 Hz and pulse width 300 μs. This has significantly decreased the level of chronic pain in the patient to a manageable level, reducing the patient's McGill pain score by 74%.

Experimental setup

Patient R.M. gave written consent to participate in the MEG study in accordance with the principles of the Helsinki Declaration. He was initially scanned with MEG for 10 min with DBS switched on while resting. He was asked to continuously report his subjective experience of pain using a visual rating scale from 0 to 9 (where 0 is 'not painful' and 9 is 'very painful') every 20 s. This was then repeated three times with the stimulator switched off, during which his pain scores increased with time.

Data acquisition

MEG data 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 patient directly viewed the visual pain rating scale on a computer monitor.

Before and after surgery, the patient was scanned with MRI to get a high-resolution T1 volume with $1 \times 1 \times 1\,\mathrm{mm}^3$ voxel dimensions. Immediately after completing data acquisition in the MEG laboratory, the headcoils were registered to his MRI using a three-dimensional digitizer (Polhemus Fastrack; Polhemus Corporation, Colchester, Vermont, USA) to digitize the shape of the participant's head relative to the position of the headcoils with respect to the nasion, left and right ear on the headset.

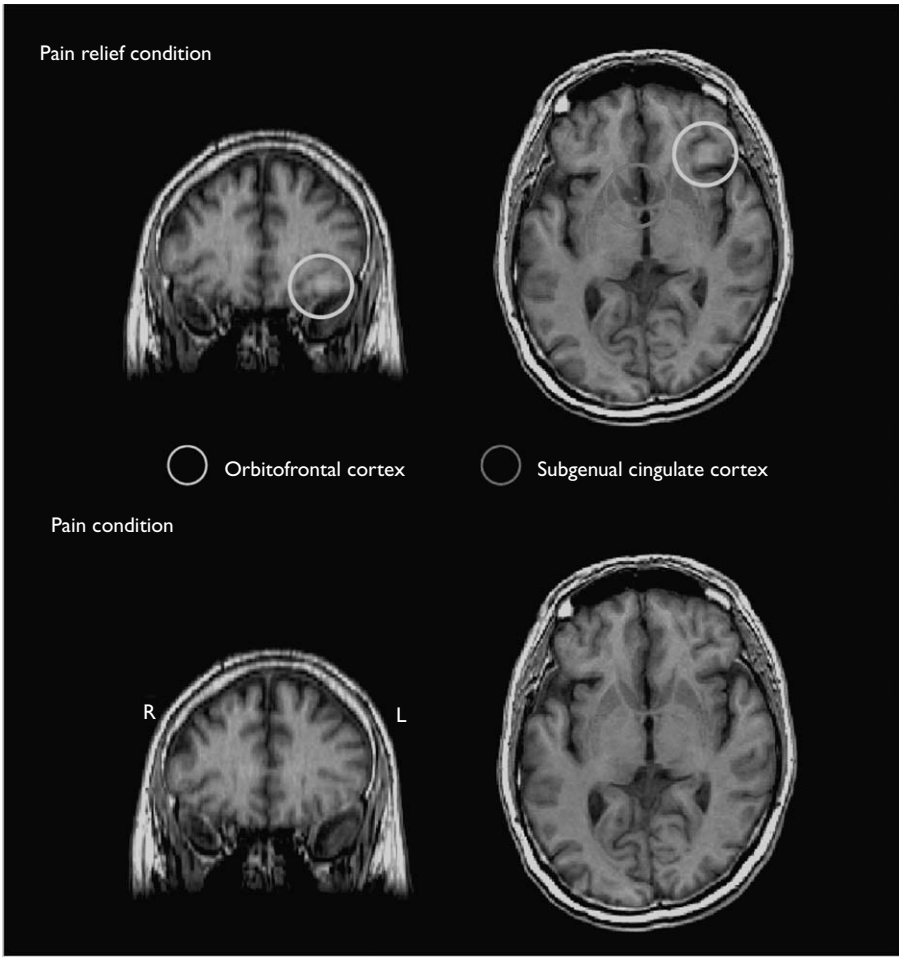

Fig. 1 Brain activity when the patient reported subjective pain relief (DBS on) and pain (DBS off). Top part of the figure shows that in the pain relief condition there was significant activity in the left mid-anterior orbitofrontal cortex and the right subgenual cingulate cortex. Activity in these regions was not found in the pain condition (bottom part of the figure).

Image analysis

The MEG data were analyzed using synthetic aperture magnetometry (SAM), which is an adaptive beam-forming technique for the analysis of electroencephalogram and MEG data [15]. SAM has been previously used in a variety of studies on the functions of the motor cortex [16], the human somatosensory cortex [17] and visual word recognition [18]. In addition, SAM has been shown to be able to unveil changes in cortical synchronization that are spatially coincident with the hemodynamic response found with fMRI [19].

The SAM analysis links each voxel in the brain to the detection array using an optimal spatial filter for that particular voxel [20]. The data from the MEG sensors are then projected through this spatial filter to give a weighted measure of current density, as a function of time, in the target voxel, which means that the time series for each voxel has the same millisecond time resolution as the original MEG signals. Fourier analysis was used to calculate the total amount of power in the specified frequency band within each of the active and passive time epochs of the time series. Thus, SAM is performed on the whole data set, not only the averaged data unlike some conventional electroencephalogram and MEG analyses. The jackknife statistical method is used to calculate the difference between the spectral power estimates for the active and passive states over all epochs to produce a true t statistic. A three-dimensional image of differential cortical activity is produced by repeating this procedure for each voxel in the whole brain.

In this experiment, the SAM analysis created a volume covering the whole brain in the patient with a voxel size of

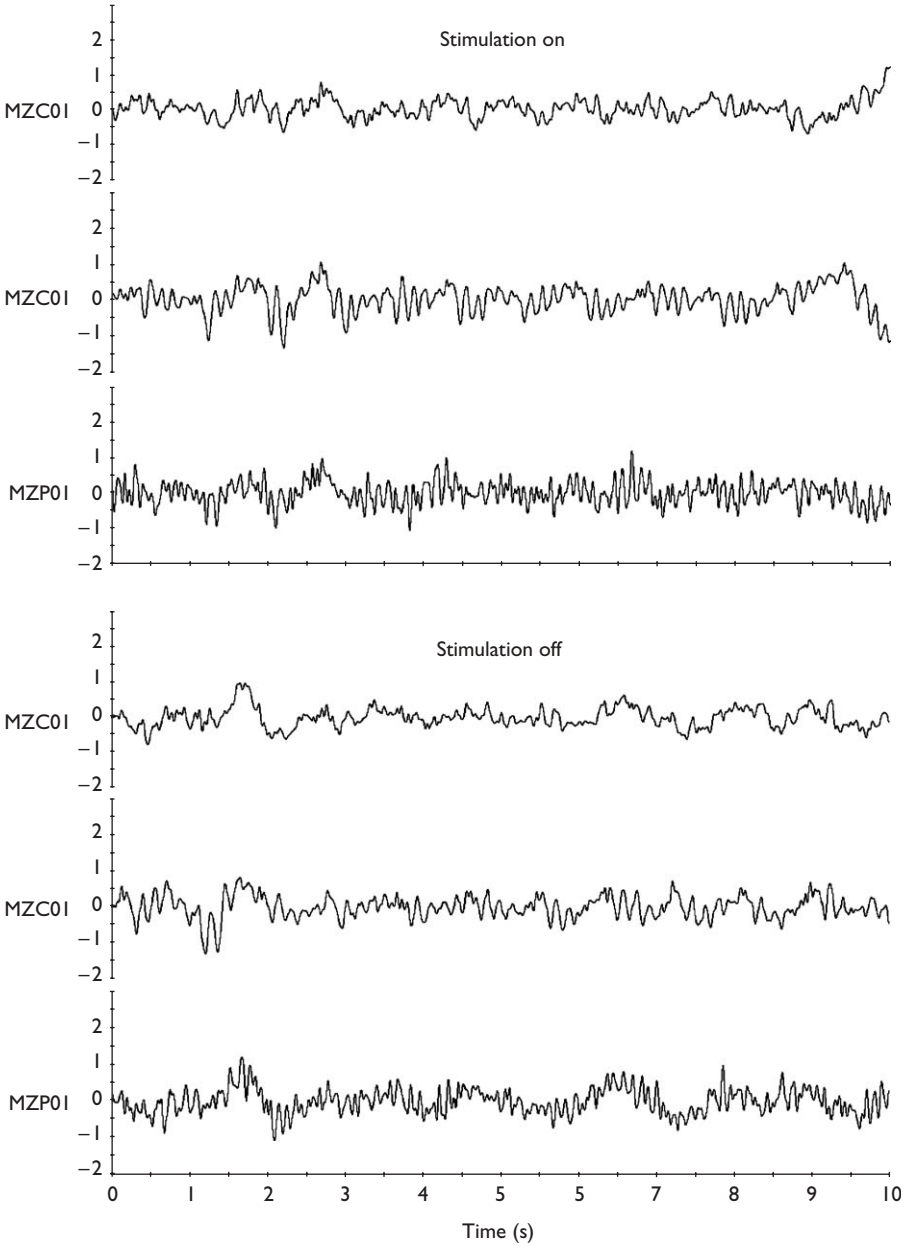

Fig. 2 Traces of three channels are shown with the brain stimulation on and off during 10 s of recording.

$5 \times 5 \times 5\,mm^3$. The passive state was defined as the time period between −1000 and 0 ms before pain rating; and the active state was defined as the time window from 0 to +1000 ms starting at each rating period. Power changes between the active and passive states were calculated in the frequency bands of 10–20, 20–30 and 30–60 Hz, for DBS on and off. Each *t*-map was thresholded at $t > 2.3$, except for a priori predicted regions of interest (e.g. the insula, cingulate and orbitofrontal cortices).

Results

Subjective pain experience

After the stimulator was turned off, R.M.'s subjective reports of pain on the visual rating scale significantly increased with time over the four scans. In the first run with the stimulator on, the ratings were 4.68 ± 0.25 (mean ± SE). With his knowledge, the stimulator was then turned off and in the second, third and fourth run the ratings were 4.68 ± 0.19, 4.97 ± 0.18 and 5.48 ± 0.20, respectively. Thus in the fourth run, starting 25 min after the stimulator was switched off, the level of reported subjective pain had significantly increased ($P < 0.009$) compared with the stimulator on and the first and second run with the stimulator off. It should be noted that during the short period that the stimulator was turned off pain levels did not approach preimplantation levels, and the stimulator was turned on as soon as the fourth run was completed.

Neuroimaging data

The DBS did not produce significant artefacts in the MEG recordings. This could be related to using unilateral low-frequency stimulation (7 Hz) as opposed to using high-frequency stimulation (e.g. 130 Hz), although we have not yet systematically tested this hypothesis. (Figs 1 and 2).

In the pain condition when DBS was switched off and when R.M.'s subjective pain ratings were significantly higher than that during the fourth period after the DBS had been switched on, significant activity was found in regions involved in the pain network that have previously been identified using fMRI and PET (see Fig. 1 and Table 1 for list of activations). These regions included the insula, and the primary and secondary somatosensory, lateral orbitofrontal and anterior cingulate cortices. Activity was also found in the motor networks related to the rating process. In the 10–20 Hz frequency band, significant

Table 1 Active brain regions

	Laterality	MNI *x*	MNI *y*	MNI *z*	*t* score
Deep brain stimulation off (pain)					
10–20 Hz					
Somatosensory cortices (SI, SII)	R	54	−38	56	2.8
Intraparietal cortex	R	4	−82	56	2.7
Motor cortex	R	58	−2	44	2.7
Left posterior insula	L	−38	−34	18	2.7
Occipital lobe	R	36	−94	16	−2.6
Premotor cortex	R	42	22	50	2.4
Middle frontal gyrus	R	6	6	66	2.3
Middle insular cortex	R	46	−10	16	2.0 *
20–30 Hz					
Motor cortex	R	58	4	28	3.9
Parietal cortex	R	46	−68	42	3.0
Anterior insula/lateral orbitofrontal cortex	R	48	36	−10	2.6
Occipital lobe	L	−30	−96	−4	−2.6
Fusiform cortex	R	22	−70	−10	−2.4
Anterior insula cortex	R	36	28	4	2.4
Rostral anterior cingulate cortex	R	2	−8	36	2.2 *
Motor cingulate cortex	R	12	−6	66	2.1 *
30–60 Hz					
Parahippocampal cortex	L	−12	−44	0	2.8
Motor cortex	R	66	−12	24	2.6
Fusiform cortex	R	46	−70	−10	2.4
Deep brain stimulation on (pain relief)					
10–20 Hz					
Somatosensory cortex (SI)	R	56	−36	54	2.4
Brainstem	R	12	−18	−40	2.3
Mid-anterior orbitofrontal cortex	L	−34	26	−10	2.0*
Subgenual cingulate cortex	R	4	6	−8	−1.8*
20–30 Hz					
Supplementary motor cortex	L	−56	12	30	2.8
Parietal cortex	R	28	−78	46	−2.5
Motor cortex	L	−48	−2	54	2.3
30–60 Hz					
Superior temporal gyrus	L	−54	−64	18	3.1
Middle temporal gyrus	L	−52	−40	−18	2.7
Occipital lobe	L	−18	−102	−10	2.5
Parietal cortex	L	−56	−58	40	2.4
Posterior cingulate cortex	R	8	−60	44	2.3

Activations are significant at $t > 2.3$, uncorrected; unless indicated with * for a priori predicted regions. All brain coordinates are in the standard space of Montreal Neurological Institute.

differences in activity were found in the somatosensory cortices (SI, SII), intraparietal cortex, motor cortex, premotor area, middle and posterior insula cortices, occipital lobe, and middle frontal gyrus. In the 20–30 Hz band, significant differences were found in the motor, parietal, insula, fusiform and motor cingulate cortices as well as lateral orbitofrontal cortex/anterior insula. In the 30–60 Hz band, we found significant differences in the parahippocampal, motor and fusiform cortices.

In the pain relief condition, during the fourth period after the DBS had been switched on, significant activity was found in brain regions previously identified with fMRI as the pain relief network (see Table 1 for list of activations). In the 10–20 Hz band, significant differences in activity were found in the SI, brainstem, mid-anterior orbitofrontal cortex and subgenual cingulate cortex. In the 20–30 Hz band, there were differences in activity in a motor network comprising the supplementary motor area, and parietal and motor cortices. In the 30–60 Hz band, significant differences were found in the superior and middle temporal gyri, occipital lobe, parietal and posterior cingulate cortices.

Discussion

To the best of our knowledge, this is the first study to show that it is feasible to use MEG to map whole-brain changes in neural activity induced by DBS. We have been able to show significant changes in brain activity in a patient with implanted DBS in the right PVG/PAG for severe phantom limb pain in the left leg. This patient reported significantly more pain relatively soon after the DBS was turned off than when the DBS was switched on. The MEG artefacts induced by unilateral low-frequency stimulation of the right PVG/PAG would appear to be minimal, although the presence of the magnetic battery can induce long-term data drift (which is present regardless of whether the stimulation is on or off). It should be noted, however, that the reported findings are preliminary and will need further confirmation in more participants.

The obtained changes in brain activity are consistent with previous results reported with fMRI and PET [21]. Testifying to the utility of our method, irrespective of DBS, we also found activity in brain regions that are part of the motor network related to the patient using button presses to rate his pain.

Pain-specific activity was found when DBS was switched off and the subjective pain scores were significantly higher than in the pain relief condition (with DBS on). Significant activity was found in the well-documented extended pain network including insular, SI, SII, lateral orbitofrontal and anterior cingulate cortices [21].

Importantly, in the pain relief condition, we found activity in the subgenual cingulate and mid-anterior orbitofrontal cortices, which are the two regions previously implicated in pain relief. The subgenual cingulate cortex has been strongly implicated in depression [22], and recent DBS stimulation in this region has shown significant improvement in patients with treatment-resistant depression [8]. The mid-anterior orbitofrontal cortex has been shown to be more active in placebo-responders than in placebo-nonresponders [23], and it has also been shown to correlate with the subjective pleasantness of various primary and secondary reinforcers [24,25].

Conclusion

The results of this study have for the first time demonstrated the feasibility of using MEG to map changes in the whole-brain activity induced by DBS. The findings have highlighted the mid-anterior orbitofrontal and subgenual cingulate cortices as potential future candidates for DBS in patients with chronic pain.

Significantly, this study introduces a combination of techniques that allow us to investigate the underlying neural changes caused by DBS in its various applications, and thereby directly investigate functions of the human brain.

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