Reduced limbic connections may contraindicate subgenual cingulate deep brain stimulation for intractable depression

Case report


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In this study, the authors performed deep brain stimulation (DBS) of the subgenual anterior cingulate cortex (SACC) in a patient with a history of bipolar disorder. After a right thalamic stroke, intractable depression without mood elevation or a mixed state developed in this patient. He underwent bilateral SACC DBS and died 16 months afterwards. Anatomical connections were studied in this patient preoperatively and postmortem using diffusion tractography (DT). A comparison of in vivo and high resolution ex vivo connectivity patterns was performed as a measure of the utility of in vivo DT in presurgical planning for DBS. Diagnostic measures included neuropsychological testing, preoperative and ex vivo DT, and macroscopic neuropathological assessment. Post-DBS depression rating scores did not improve. In vivo and ex vivo DT revealed markedly reduced limbic projections from the thalamus and SACC to the amygdala in the right (stroke-affected) hemisphere. A highly selective right mediothalamic lesion was associated with the onset of refractory depression. Reduced amygdalar-thalamic and amygdalar-SACC connections could be a contraindication to DBS for depression. Correspondence between preoperative and higher resolution ex vivo DT supports the validity of DT as a presurgical planning tool for DBS. (DOI: 10.3171/2009.2.JNS081299)

Key Words • deep brain stimulation • cingulate cortex • depression • bipolar disorder • diffusion tractography

Structural and metabolic brain abnormalities associated with depression have been noted in limbic, thalamic, and frontal lobe cortical regions.9 The SACC has been shown to be hypermetabolic in depressed patients11 with normalization following successful pharmacological treatment.10

Deep brain stimulation of the white matter underlying the SACC is emerging as an effective treatment for chronic, treatment-resistant depression.12 The mechanism of action of DBS remains unclear. However, mounting evidence suggests that the therapeutic effects of DBS in cases of major depression are mediated by stimulation of local cells and/or connecting white matter fibers linking the SACC to the orbitomedial prefrontal cortex, amygdala, hippocampus, striatum, and thalamus.4 The ability to map these pathways in vivo using noninvasive MR DT was recently demonstrated.6

Although some limited data exist concerning the efficacy of SACC DBS for the treatment of unipolar depression, ours is the first report of SACC DBS in a patient with a history of bipolar depression and also the first description of SACC DBS in a patient with a thalamic lesion. Thus, our experience with the patient described here provides rare insight into the role of the right thal-
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mus in the mood-regulating circuitry of the brain and the possible therapeutic mechanisms of SACC DBS. A comparison of in vivo and ex vivo DT emphasizes the value of DT in presurgical planning.

Case Report

History and Examination. At the age of 60, this right-handed man with diabetes and a 20-year history of medically controlled bipolar disorder presented with symptoms of stroke. Magnetic resonance imaging revealed an infarct affecting the right thalamus (dorsomedial nucleus). Although the stroke had no long-term impact on motor functioning, the patient reported the onset of severe depressive symptoms in the hours following admission. Psychiatric follow-up 9 months after the stroke confirmed severe depression (Beck Depression Inventory-II score 41, Beck Anxiety Inventory score 26), which proved refractory to multiple pharmacological and electroconvulsive therapies. Due to the severity of the patient’s symptoms, which included suicidal ideations, refractoriness to treatment, intolerance of combinations of antidepressant agents, and repeated requests to try alternative approaches, he was assessed for DBS at the Radcliffe Infirmary, Oxford ~ 3 years after the stroke. The patient gave written informed consent to take part in imaging research approved by the Research Ethics Committee at the University of Oxford.

Imaging. Diffusion-weighted MR images were obtained at 1.5 T, including 60 diffusion-encoding orientations with a b value of 1000 sec/mm² and 2 mm isotropic voxels. The T1-weighted images were acquired at 1-mm isotropic resolution allowing for infarct identification (Fig. 1a and d). The total scan time was 35 minutes. Multiorientation diffusion-encoded images permit voxel-wise estimation of the principal water diffusion orientation which corresponds to the orientation of white matter fiber bundles. Voxel-wise orientation estimates were used to map white matter pathways using probabilistic tractography.

Operation. The surgical technique used in this patient has previously been described. A stereotactic CT scan was obtained with the patient under sedation and local anesthesia and the image was fused to a preoperatively acquired MR image. A trajectory and bilateral coordinates for the SACC area Cg25 were calculated. Bilateral quadripolar Medtronic 3387 electrodes were implanted into both targets and the electrodes were plated to the skull. The system was internalized under the clavicle, connecting the deep brain electrodes to a subcutaneous Kinetra pacemaker and the wounds were closed. Bipolar stimulation across all 4 electrode contact points was used with a pulse width of 210 msec, amplitude of 5 V, and frequency modified up to and held at 150 Hz.

In Vivo DT. A T1-weighted image using preoperative scan parameters confirmed the location of the DBS sites (Fig. 1b, c, e, and f). Probabilistic DT was used to study anatomical connections between the SACC DBS sites and the rest of the brain, as well as amygdalar connections with the stroke and contralateral homolog. Masks of the left and right amygdala, right thalamic infarct, and a homologous contralateral region were drawn on the preoperative structural images. A mask including all 4 subgenual electrode contact sites in each hemisphere was drawn on the postoperative images. No pathways were found between the infarct and the right amygdala despite
clear pathways between the homologous, contralateral structures (Fig. 2a and b).

Pathways were found between both SACC DBS masks and the unilateral amygdala, and extending further into the temporal lobe (Fig. 3a and b). However, amygdala-SACC pathways appeared reduced in the right hemisphere relative to the left. When tractography was constrained to paths between the SACC DBS sites and the amygdala, 193 and 117 paths were found in the left and right hemispheres, respectively. Bilateral pathways were also found between the SACC DBS sites and the frontal lobe (Fig. 3b and c).

**Postoperative Course.** The patient reported some reduction in subjective anxiety during intrasurgical stimulation on the left but not the right side. Although the patient did not have any adverse side effects subsequent to internalization of the electrodes, he continued to experience severe depression. Deep brain stimulation up to 150 Hz provided minimal or no effect. The patient’s case was reviewed 1 year postoperatively when the DBS battery was running low. Cessation of stimulation had no effect. We intended to replace the DBS after further neuroimaging studies were obtained, but the patient died in his sleep 16 months after the elective DBS surgery, at 65 years of age.

**Ex Vivo MR Imaging and High Resolution DT.** Permission to conduct a postmortem examination of the brain was obtained from the patient’s next-of-kin. Fixed brain diffusion-weighted imaging on a 3-T MR imager included 64 diffusion encoding orientations, a b value of 3000 sec/mm², and 0.73-mm isotropic voxels. Proton density–weighted images were acquired in 0.33-mm isotropic resolution. The total scan time was 99 hours.

The in vivo DT analyses were replicated on the high resolution ex vivo data. No evidence was found of any direct pathways between the affected right thalamus and amygdala despite a clear pathway on the left side (Fig. 2c–d).

From the SACC DBS sites, pathways were found to the amygdala and into the temporal lobe in the left hemisphere (Fig. 3d) but not to the frontal lobe. On the right, pathways to the amygdala were absent despite the presence of pathways to the frontal lobe (Fig. 3f). Although the in vivo
data revealed some paths between the right SACC DBS sites and the right amygdala and bilateral pathways to the frontal lobe, further tract degeneration may have occurred between preoperative imaging and death. It should also be noted that the ex vivo diffusion images were acquired at a much higher spatial resolution than the in vivo data (0.73 × 0.73 × 0.73–mm voxels compared to 2 × 2 × 2–mm voxels). Due to this increase in resolution the ex vivo tracts tend to appear thinner and suffer less from partial volume effects.

Neuropathology Report. A macroscopic assessment of the ex vivo brain and structural MR images showed no significant natural disease, recent hemorrhage, infarction, or swelling. No acute brain lesion was found to explain the cause of death. After imaging, the brain was cut into coronal slices, revealing a scar ~ 0.5 cm in length and 1-mm wide where the right thalamic infarct had occurred (Fig. 4).

Discussion

Deep brain stimulation for major depression is a nascent approach with little information available concerning large-scale success rates or therapeutic mechanisms. There is little reported experience of SACC DBS in patients with a history of bipolar depression: this will no doubt be remedied in due course. However, the phenomenology of bipolar depression overlaps substantially with that of unipolar depression, and chronic refractory depression is seen in both conditions. In the present case, mood elevation or a mixed state was not the problem following his stroke, just depression. Two fundamental questions arise from this case: 1) by what mechanism did the infarct induce a transition from recurrent but manageable bipolar disorder to severe, refractory depression? and 2) why did DBS fail to alleviate symptoms? Thalamic abnormalities have been observed previously in patients with depression and bipolar disorder, with elevated thalamic neuron counts relative to healthy control patients, and decreased blood flow in the left thalamus during a manic period. Additionally, there have been reports of thalamic lesions producing psychiatric symptoms.

The amygdala is believed to be a critical processing area for the identification of emotional significance and the subsequent tone of the affective state. Right mediothalamic input to the amygdala appears to have been disrupted (both on in vivo and ex vivo DT). It appears that this very selective lesion was sufficient to induce refractory depression in our patient with bipolar disorder. We had reasoned that stimulation of the SACC might compensate for this deafferentation, but in fact it did not. The apparent reduction in structural connectivity from the SACC back to the amygdala on the right side may have prevented effective treatment of depressive symptoms by SACC DBS. Projection to frontal areas was not clearly differentially disrupted.

Diffusion tractography is the only method for noninvasively probing white matter pathways. Clinical application of DT is hindered by the low resolution that can be achieved (~ 8 mm³) and lack of a viable method of validation. High-resolution (0.34 mm³) DT of ex vivo specimens, as presented here, provides a form of validation of in vivo results. The excellent correspondence between in vivo and ex vivo DT suggests that even at the resolutions possible in vivo, DT may have value in preoperative DBS planning for psychiatric conditions.

Disclosure

Funding for this work was provided by the Charles Wolfson Charitable Trust and the Oxford Centre for Science of the Mind. The authors report no other conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References


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Manuscript submitted October 9, 2008. Accepted February 23, 2009. Please include this information when citing this paper: published online March 13, 2009; DOI: 10.3171/2009.2.JNS081299. Address correspondence to: Jennifer A. McNab, M.Sc., Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom. email: jmcnab@fmrib.ox.ac.uk.