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Brief report

Immediate cerebral metabolic changes induced by discontinuation of deep brain stimulation of subcallosal cingulate gyrus in treatment-resistant depression

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ABSTRACT

Background: Positron emission tomography (PET) studies have shown that the antidepressant effect of chronic deep brain stimulation (DBS) of the subcallosal cingulate gyrus (SCG) may be consequence of modifications of brain metabolism at key structures involved in depression. Like clinical benefits, these metabolic changes may reverse when the stimulation is discontinued, even preceding clinical worsening. However no data on immediate effects of DBS discontinuation are available. The aim of this study was to determine immediate cerebral metabolism changes during a short switch-off of electrical stimulation in implanted patients with treatment-resistant depression (TRD) who had achieved clinical improvement after a period of chronic DBS.

Methods: Seven patients with TRD who had been previously implanted for DBS in SCG were included. After a period of clinical stabilization two consecutive FDG-PET were acquired, the first with active stimulation and the second after 48 h of inactive stimulation. A HAMD-17 to assess depressive symptoms was performed before both scans. Analyses were performed with SnPM8.

Results: Inactive stimulation was characterized by metabolism decreases in dorsal anterior cingulate (Broadmann Area, BA24), premotor region (BA6) and putamen with respect to active stimulation. No clinical changes according to HAMD-17 were detected.

Limitations: The main limitation of this study is the small sample size.

Conclusion: Our results point to immediate effects of DBS discontinuation on metabolism of brain depressive network which precede clinical changes, helping to disentangle the rationale behind DBS efficacy in TRD.

1. Introduction

Up to 33% of patients with major depressive disorder do not reach full remission after four sequenced pharmacological treatments (Rush et al., 2006), and some of these patients might experience disabling adverse effects or might not even improve with electroconvulsive therapy (ECT; Kellner et al., 2006; Dierckx et al., 2012). For this reason, alternative therapies for patients with treatment-resistant depression (TRD) are currently being tested, such as deep brain stimulation (DBS). This technique consists in high-frequency electrical stimulation of stereotaxically implanted electrodes in certain brain regions, such as the subcallosal cingulate gyrus (SCG) (Mayberg et al., 2005; Lozano et al., 2008; Holtzheimer et al., 2012; Lozano et al., 2012; Puigdemont et al., 2012; Merkl et al., 2013), the ventral capsule/ventral striatum (VC/VS) (Malone et al., 2009) or the nucleus accumbens (NAc) (Schlaepfer et al., 2008; Bewernick et al., 2010). Findings of DBS for TRD have shown promising outcomes, as most of the studies

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describe good remission rates (from 42% to 58% in SCG DBS) and tolerability appears to be high (Riva-Posse et al., 2013).

Although the exact mechanism underlying DBS efficacy in TRD is unknown, it is thought to modulate nerve transmission in cortico-striatal-thalamo-cortical loops (Mayberg, 2009). To shed light on this mechanism, studies on SCG DBS have used positron emission tomography (PET) to compare brain activity after chronic stimulation with pre-treatment baseline (Mayberg et al., 2005; Lozano et al., 2008). Mayberg et al. (2005) reported a reduction of blood flow in Cg25, adjacent frontal cortex (BA11), anterior insula, hypothalamus and medial frontal cortex (BA10), plus an increase in prefrontal dorsolateral (BA9/46), premotor region (BA6), parietal region (BA40), and dorsal anterior (BA24) and posterior (BA31) cingulate, after 6 months of stimulation (see a schematic representation in Fig. 1A). Lozano et al. (2008) obtained similar results with the same stimulation length: decreases of glucose metabolism in orbital (BA11), medial frontal cortex (BA 10/9/8) and insula, and increases in lateral prefrontal cortex (BA 11/47, BA 46/10/9), parietal (BA 40), anterior midcingulate (BA 24), and posterior cingulate areas (BA 23). In both studies changes at 3 months were restricted to medial and orbital frontal decreases. Overall, these findings show that chronic DBS modifies brain activity at key structures, and these changes may occur gradually. Whether these metabolic changes persist when turning stimulation off is unknown but clinical worsening has been reported within initial weeks of stopping stimulation in patients with chronic SCG DBS (Mayberg et al., 2005; Holtzheimer et al., 2012). Functional brain modifications caused by DBS withdrawal may occur even before clinical changes when stimulation is stopped, however there are no studies exploring this hypothesis.

The aim of this study was to determine immediate cerebral metabolism changes during a short switch-off of electrical stimulation in implanted patients with TRD who had achieved clinical improvement after a period of chronic DBS.

2. Methods

2.1. Participants

Seven patients with TRD who had been previously implanted for DBS in SCG in Hospital de la Santa Creu i Sant Pau and had achieved clinical remission were included. Remission was defined as a fall of the HAMD-17 mean score below a cut-off of 8. Inclusion criteria for DBS can be found elsewhere (Puigdemont et al., 2012). All patients gave informed consent to participate in the study and did not receive any economic retribution. The study was approved by the hospital ethical committee and the Agencia Española de Medicamentos y Productos Sanitarios (Spanish regulatory drug agency).

2.2. Procedure

After a period of clinical stabilization with chronic stimulation (9 months on average), two FDG-PET scans were acquired from each patient, in a 48 h period. The first scan was done with the implants set to active stimulation ('on'), then the stimulator was turned off and a second scan was carried out after 48 h of non-stimulation ('off'). Afterwards, the stimulator was turned on again. Stimulation parameters were specific for each patient and were kept the same before and after the brief discontinuation (in particular, each patient achieved clinical stabilization with these parameters): subject 1: 0–1+, 4–5+, 5 V, 180 μs, 135 Hz; subject 2: 0–2+, 4–6+, 3.5 V, 180 μs, 135 Hz; subject 4: 0+1−, 5+6−, 4 V, 150 μs, 135 Hz; subject 5: 1–2+, 6–7+, 3.5 V, 180 μs, 135 Hz; subject 6: 0–1+, 4–5+, 5 V, 210 μs, 135 Hz; subject 7: 0–2+, 4–6+, 3.5 V, 120 μs, 135 Hz; subject 8: 1+2−, 5+6−, 5 V, 210 μs, 135 Hz. Details of such values can be referred elsewhere (Puigdemont et al., 2012). Pharmacological treatment was not modified during this 48 h period. Clinical ratings were performed before the first and the second scan by means of the Hamilton Depression Rating Scale_17 items (HAMD-17). Patients were fully advised of the whole procedure during the trial.

2.3. PET imaging

FDG-PET scans were performed on a Siemens ECAT EXAT HR+ PET/CT scanner at Hospital del Mar in Barcelona, in 3-D mode (Biograph; Siemens Medical Solutions Inc., software version 6.5.9.1) with a 15.8-cm axial field of view. Blood glucose measured before tracer injection was 96.93 mg/dl (mean). Scans were performed 30 min after intravenous injection of 7.78 mCi (on) and 7.99 mCi (off) of fluorine-18-fluorodeoxyglucose PET (18FDG-PET). The acquisition time was 20 min per position. Sixty-three slices 2.4 mm thick were acquired (matrix dimensions = 128 × 128 × 63, voxel size = 2.57 × 2.57 × 2.43 mm^3).

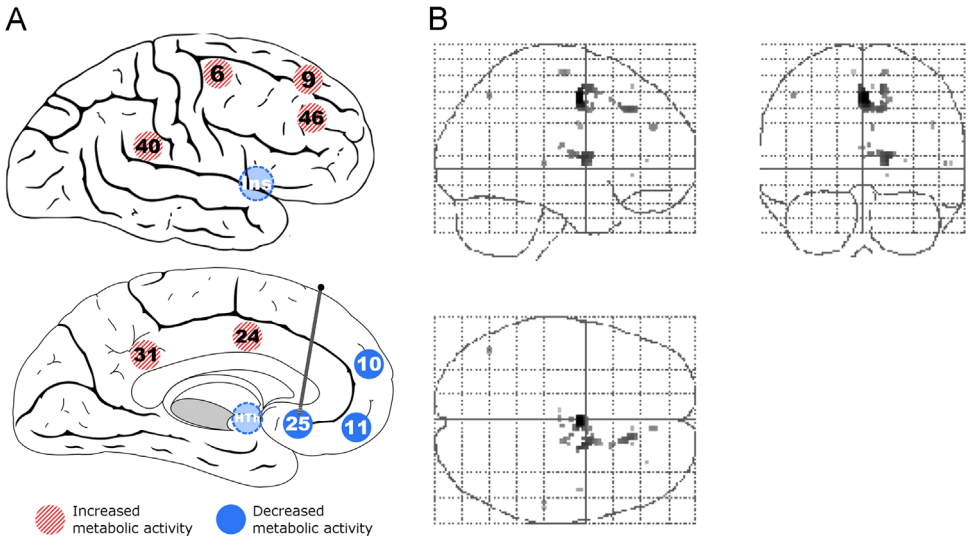

Fig. 1. A: schematic representation of brain metabolic changes after 6 months of deep brain stimulation of the subcallosal cingulate gyrus in treatment resistant depression (as measured by Mayberg et al., 2005). Numbers indicate Brodmann's areas; Ins = Insula; Hth = Hypothalamus. **B:** SnPM8 results of Off < On contrast showing decreased metabolic activity in BA24, BA6 and putamen when stimulator was turned off for 48h.