Acute and chronic changes in brain activity with deep brain stimulation for refractory depression

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Acute and chronic changes in brain activity with deep brain stimulation for refractory depression

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Abstract:	<p>Deep brain stimulation (DBS) is a potential option for patients with treatment-refractory depression (TRD). DBS benefits have been reported when targeting either the subgenual cingulate (SGC) or ventral anterior capsule/nucleus accumbens (VAC/NAcc). However, not all patients respond and optimum stimulation-site is uncertain. We compared DBS of SGC and VAC/NAcc separately and combined in the same seven TRD patients, and investigated regional cerebral blood-flow (rCBF) changes associated with acute and chronic DBS. DBS-response was defined as reduction in Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline of $\geq 50\%$, and remission as a MADRS-score ≤ 8. Changes in rCBF were assessed using $[^{15}O]$water PET. Remitters had higher relative rCBF in the prefrontal cortex (PFC) at baseline and all subsequent time-points compared to non-remitters and non-responders, with PFC rCBF generally increasing with chronic DBS. These effects were consistent regardless of stimulation-site. Overall, no significant rCBF changes were apparent when DBS was acutely interrupted. DBS improved TRD severity in the majority of patients, with consistent changes in local and distant brain regions regardless of target stimulation. Remission of depression was reached in patients with higher baseline prefrontal rCBF. Because of the small sample size these results are preliminary and further evaluation is necessary to determine whether PFC rCBF could be a predictive biomarker of treatment response.</p>

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TITLE PAGE

Title: Acute and chronic changes in brain activity with deep brain stimulation for refractory depression

Short Title: Deep brain stimulation in TRD

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ABSTRACT

Deep brain stimulation (DBS) is a potential option for patients with treatment-refractory depression (TRD). DBS benefits have been reported when targeting either the subgenual cingulate (SGC) or ventral anterior capsule/nucleus accumbens (VAC/NAcc). However, not all patients respond and optimum stimulation-site is uncertain. We compared DBS of SGC and VAC/NAcc separately and combined in the same seven TRD patients, and investigated regional cerebral blood-flow (rCBF) changes associated with acute and chronic DBS. DBS-response was defined as reduction in Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline of $\geq 50\%$, and remission as a MADRS-score ≤ 8 . Changes in rCBF were assessed using [^{15}O]water PET. Remitters had higher relative rCBF in the prefrontal cortex (PFC) at baseline and all subsequent time-points compared to non-remitters and non-responders, with PFC rCBF generally increasing with chronic DBS. These effects were consistent regardless of stimulation-site. Overall, no significant rCBF changes were apparent when DBS was acutely interrupted. DBS improved TRD severity in the majority of patients, with consistent changes in local and distant brain regions regardless of target stimulation. Remission of depression was reached in patients with higher baseline prefrontal rCBF. **Because of the small sample size these results are preliminary and further evaluation is necessary to determine whether PFC rCBF could be a predictive biomarker of treatment response.**

1. INTRODUCTION

Major Depressive Disorder (MDD) is a common psychiatric disorder affecting an estimated 350 million people globally. It is severely debilitating and characterized by low mood, decreased energy, impaired cognition, and increased risk of suicide (World Health Organization, 2016). MDD can be effectively treated in the majority of patients with either antidepressant medication or psychotherapy (Mayberg et al., 2005). However, 20-30% of patients fail to respond to standard therapies (Mayberg et al., 2005; Morishita et al., 2014; Millet et al., 2014).

A possible alternative treatment for this treatment-refractory depression (TRD) is deep brain stimulation (DBS). DBS aims to modulate dysfunctional neuronal networks by surgical placement of stimulating electrodes (Krishnan and Nestler, 2010). Promising antidepressant effects of DBS have been reported when targeting either the subgenual cingulate gyrus (SGC), comprising Brodmann areas 25 (Cg25) and 24 (Cg24) (Berlim et al., 2014; Holtzheimer et al., 2012; Lozano et al., 2008; Mayberg et al., 2005; Puigdemont et al., 2012), or the ventral anterior capsule/nucleus accumbens (VAC/NAcc) (Bewernick et al., 2010; Bewernick et al., 2012; Millet et al., 2014; Nauczyciel et al., 2013; Schlaepfer et al., 2008; Kubu et al., 2013; Malone et al., 2009). These targets are in close anatomical and functional relationship, and data from neuroimaging studies can be used to argue for either of these targets (Schlaepfer and Bewernick, 2013).

Cg25 glucose metabolism is increased in MDD and remission is associated with normalization of this hypermetabolism (Schlaepfer and Bewernick, 2013). DBS of Cg25 has shown a response rate (i.e. at least 50% reduction in the Hamilton Depression Rating Scale) of 62.5% after 12 months (Puigdemont et al., 2012), 60% after three years, and 55% between 3 to 6 years (Kennedy et al., 2011) of DBS, and is associated with reduced Cg25 metabolic activity. The NAcc is involved in abnormal motivations

and reward processes in MDD, and NAcc DBS for 1 to 4 years has demonstrated sustained antidepressant effects in 45% of patients (Bewernick et al., 2012). VAC DBS for up to 4 years has shown a response rate of 40% at 6 months and 53.3% at last follow-up (Malone et al., 2009).

However, due to small sample sizes of <20 and relatively few studies, it is unclear which of these targets is most effective in producing a positive outcome. Furthermore, even though these targets seem promising, response to DBS does not occur in all patients. Since mood effects are not observed in all patients with either target, it might be possible that combined stimulation of both targets will achieve better clinical results in patients with insufficient response to stimulation of only one target. Additionally, previous studies have focused on either short-term chronic effects after 1 week of DBS in MDD (Schlaepfer et al., 2008), or long-term chronic effects after 3 months to 6 years (Bewernick et al., 2010; Bewernick et al., 2012; Lozano et al., 2008; Mayberg et al., 2005; Millet et al., 2014; Kubu et al., 2013; Malone et al., 2009). Comparison of acute effects that appear within hours with chronic effects would help to clarify possible differences in immediate and adaptive longer-term effects of DBS.

Positron emission tomography (PET) using [¹⁵O]water allows accurate quantification of regional cerebral blood flow (rCBF). As rCBF and regional metabolism are very closely coupled, [¹⁵O]water PET is an excellent method for assessing changes in brain-activity over time in circumstances where magnetic resonance imaging (MRI) is relatively contraindicated, such as pertains in DBS due to the presence of indwelling stimulator electrodes. A further advantage of [¹⁵O]water PET is that the very short (2 minutes) half-life of [¹⁵O] permits more frequent measurements over the same time duration than [¹⁸F]fluodeoxyglucose (FDG) PET for the same radiation exposure, permitting comparison of acute and chronic DBS effects.

The present study aimed to compare stimulation of SGC (Cg25 or Cg24), VAC/NAcc (VAC or NAcc), and a combination of these targets, in the same TRD patients using [^{15}O]water PET, focusing on chronic changes in rCBF and changes in rCBF associated with acute interruption of DBS for 2 hours. Choice of stimulation site (SGC or VAC/NAcc) was made in a block-randomized, single-blind fashion. Patients received stimulation of this site for at least 3 months before switching stimulation to the other single site for at least 3 months, then switching to the combination of both sites for at least a further 3 months. At each site, if remission occurred or clinical improvement was assessed as sufficient, stimulation site was not switched. Secondary outcome measures included clinical questionnaires to characterize effects of DBS on depressive symptoms and functional outcomes.

We hypothesized that: (i) either DBS target would produce a significant improvement in some TRD patients; (ii) combined stimulation would be effective in patients for whom one target was not sufficient; (iii) acute and chronic changes in rCBF associated with DBS would be prominent and would differ from each other; and (iv) clinical improvement would be associated with rCBF changes in brain regions relevant to depression.

2. METHODS AND MATERIALS

2.1 Patients

Eight patients were enrolled to the study, had pre-surgical measurement of baseline rCBF and implantation of DBS electrodes (see Table 1 for demographics and clinical characteristics). One patient required early removal of electrodes due to infection and was withdrawn from the study before first follow-up PET scan. Therefore, seven patients with treatment refractory unipolar MDD (5 male; age range 31-58 years; mean±SD: 48±9 years) received [¹⁵O]water PET (pre-surgical and three subsequent occasions during DBS). Patient-suitability was jointly assessed by a senior psychiatrist (ALM) and neurosurgeon (NKP) at the University of Bristol, UK. Referrals came from the patients' psychiatric team who were aware of the protocol but not directly involved in the study. If there were any doubts on inclusion criteria, further opinion was sought from one of a panel of three senior psychiatrists who interviewed patients separately.

--- Table 1 ---

Patients were included if they had MDD and had not responded to treatments including: (i) cognitive behavioral therapy (CBT); (ii) antidepressants from three different classes in British National Formulary doses (Committee, 2015); and (iii) lithium augmentation. Furthermore, patients had to have failed to respond to two courses of electroconvulsive therapy (ECT), or to only have responded to maintenance ECT, or to not have responded to the first course of ECT and were unwilling to have a further course. ; and (iv) two courses of electroconvulsive therapy (ECT). They were required to have a MADRS score of ≥22 (moderately-severely depressed) on enrolment. Additional inclusion criteria were being physically fit, and having no suicidal intent, history of hypomania, mania nor psychosis. Exclusion criteria included: history of head trauma, dementia, cerebral infarcts, poor

~~physical health~~, incapacity to consent, inability to carry out the study, mood incongruent psychotic phenomena, and drug or and/alcohol addiction.

Enrolment and clinical procedures were conducted at the University of Bristol, and MRI and neurosurgery were conducted at Frenchay Hospital, Bristol. PET-scanning was performed at the University of Manchester's Wolfson Molecular Imaging Centre. The study was approved by the Bath Local Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee, and was carried out in compliance with the Declaration of Helsinki (1964), amended in Edinburgh (2000). Participants gave their written informed consent prior to study participation.

2.2 Surgical Procedure

The surgical procedure was performed under general anesthesia, using a modified Leksell stereotactic frame (Elekta, Stockholm, Sweden). Patients were implanted with four deep brain stimulating electrodes (Model 3387, Medtronic, Minneapolis, Minnesota): two electrodes were bilaterally positioned with all four contacts in the white matter of the SGC (Cg25 and Cg24), and two electrodes were bilaterally positioned with two contacts in the VAC and two distal contacts in the NAcc, 5mm anterior to the anterior commissure. Subclavicular programmable neurostimulators were implanted, either non-rechargeable (Kinetra; 7428) or rechargeable (Activa RC; 37601).

DBS electrode positioning and planning was made on high-resolution MRI. Implantable guide tubes and stylettes were stereotactically implanted to the planned coordinates. DBS leads were introduced down the implanted guide-tubes into the targets replacing the stylettes, whose position was verified on perioperative high-resolution MRI, enabling accurate knowledge of the electrode contacts within

the target (Khan et al., 2010; Patel et al., 2007) (Figure 1). Following the operation, a period of one-week recovery was allowed to minimize any effect from post-operative edema.

--- Figure 1 ---

2.3 Stimulation procedures

Overview of treatment-periods

For each patient, DBS was given in three sequential treatment-periods over a total period ranging from 16 to 45 months. The exact duration was determined by each patient’s clinical response and requirements. During each period (both sites singly and in combination) DBS was administered bilaterally for at least three months before switching (Table 2). More precisely, the treatment-periods were as follows:

Treatment-period 1: After post-operative recovery, appropriate stimulation contacts and frequencies were assessed for either SGC (selection of either Cg25 or Cg24) or VAC/NAcc (selection of either VAC or NAcc). The choice of SGC or VAC/NAcc as first stimulation site was made in a block-randomized fashion.

Treatment-period 2: After at least three months, stimulation was switched to the alternate site unless the patient had achieved remission (MADRS score ≤ 8 for at least two months). Specifically, if during the first stimulation block the SGC (either Cg25 or Cg24) was stimulated, stimulation would now be moved to either VAC or NAcc, and vice versa.

Treatment-period 3: After a further minimum of three months, patients received DBS of a combination of targets unless they had achieved remission in one of previous treatment-periods.

--- Table 2 ---

Criteria for determining stimulation sites and frequencies

Appropriate stimulation contacts and frequencies were assessed over a period of up to two weeks.

Each contact was tried in turn for up to two days. Final selection was the contacts showing most improvement on a mood-diary and a blinded mental-state examination. Stimulation was always bilateral. Patients were blind to order of stimulation, to contacts selected, and to any 'off' period in the contact selection-process.

2.4 Clinical assessments

Secondary outcome measures of depressive symptoms and function comprised the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), Hamilton Depression Rating Scale 17 items (HAM-D 17) (Hamilton, 1960), and Global Assessment of Function Scale (GAF) (Hall, 1995). Both the MADRS and HAM-D measure severity of depression, with lower scores indicating lower severity. For the GAF, higher scores indicate less impaired social, occupational, and psychological functioning.

Response to DBS was defined as a reduction in MADRS score from baseline of $\geq 50\%$, and remission as a MADRS score of ≤ 8 . The delay between clinical assessments and PET scans was as short as practicable, given that they were conducted in different cities, but not more than 72 hours.

2.5 Image acquisition

A baseline, pre-operative, high-resolution T₁-weighted image was acquired using a 1.5T Philips Achieva scanner. PET imaging was performed using a High-Resolution Research Tomograph

(Siemens). [¹⁵O]water PET scans were acquired at baseline and at the end of each treatment-period. At baseline, 4 repeat scans were acquired in each patient. For each of the other three PET scan visits, 3 repeat scans were acquired when stimulation was switched on and 3 when stimulation had been switched off for 120 minutes (Table 2).

Each scan consisted of an intravenous injection of approximately 370MBq of [¹⁵O]water using a radio water generator (HIDEX, Turku, Finland). The data over the 90 second period following activity-arrival in the brain was acquired and reconstructed using 3D ordinary Poisson ordered subset expectation maximization (OSEM3D-OP) with 16 subsets and 4 iterations (Comtat et al., 2004). The images were subsequently used as a relative surrogate for rCBF. Scans were spaced a minimum of 10 minutes apart to ensure that radioactivity from the previous scan had decayed to background level.

2.6 Image pre-processing

Pre-processing was performed using SPM8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). For each patient, PET scan images were realigned to each other and used to create a mean image (rigid body, 5mm FWHM pre-registration smooth). This mean image was then used to co-register subjects PET data to the subject's T₁-weighted image (rigid body, normalised mutual information) which in turn was spatially normalised to the standard T₁-weighted MNI PET template in SPM8 (ICBM regularised affine + nonlinear (frequency cut-off=25, iterations=16, regularisation=1)). Subsequently each PET image was resliced into 2mm isotropic voxel MNI space images and smoothed with a 6mm FWHM Gaussian kernel.

2.7 Data analysis

Whole-brain analysis was performed within SPM8 using a flexible factorial design with interactions between target (Cg25, Cg24, VAC, NAcc, combination of >1 target stimulated) and activation state (baseline, stimulation on, stimulation off). Clusters of voxels were considered significant at a family-wise error (FWE) corrected cluster-size threshold of $pFWEc < 0.05$ and a height threshold of $pFWE < 0.05$. Follow-up analysis tested: (i) chronic effects of SGC (Cg25+Cg24), VAC/NAcc (VAC+NAcc), and combined target stimulation, regardless of whether stimulation was switched on or off; and (ii) changes in rCBF between baseline and last PET scan, irrespective of stimulation site and whether stimulation was on or off.

Furthermore, region data were visually inspected by focusing on intensity-normalized data, i.e. voxels which changed relative to average values in the brain (regional/global). More precisely, we inspected the mean concentration of radioactivity in the brain over a period of 90 seconds following its arrival, and used this as a surrogate for rCBF. Here, we will refer to this surrogate as rCBF. Regions of interest (ROIs) were derived from the n30r83 version of the probabilistic brain-atlas by Hammers et al. (2003) (Hammers et al., 2003; Rylands et al., 2012), and were selected based upon significant results found in the afore-mentioned whole-brain analysis.

3. RESULTS

3.1 Effects of DBS on rCBF: whole-brain analysis

3.1.1 Baseline versus stimulation on

Compared to baseline, significant rCBF decreases in the NAcc were seen after stimulation of both Cg25 [MNI coordinates x, y, z (in mm) = 14, 12, -1; cluster size (k) =31; pFWEc<0.001] and Cg24 [14, 10, -7; k=23; pFWEc<0.001]. With combined target stimulation, rCBF increased in the post-central gyrus [44, -24, 61; k=113; pFWEc<0.001] and parietal sub-gyral area [24, -42, 57; k=60; pFWEc<0.001].

3.1.2 Baseline versus stimulation off

Compared to baseline, significant rCBF increases were seen in the post-central gyrus [44, -24, 59; k=84; pFWEc<0.001] and parietal sub-gyral area [26, -40, 53; k=35; pFWEc<0.001] when combined stimulation was acutely switched off, similar to the findings in baseline versus stimulation on (3.1.1, above). A significant rCBF increase in the dorsal anterior cingulate (ACC) was seen when chronic VAC stimulation was acutely switched off [10, 32, 19; (k)=57; pFWEc<0.001].

3.1.3 Acute interruption of chronic stimulation: on versus off

When comparing rCBF on chronic stimulation with rCBF after stimulation had been turned off for 120 minutes (acute effects), only one statistically significant result was found: rCBF increased in the dorsal ACC when VAC stimulation was switched off [12, 30, 31; k=31; pFWEc<0.001]. This is similar to the rCBF increase in VAC seen between baseline and stimulation off (3.1.2, above).

Further details of all significant DBS effects comparing baseline with on and off, and on versus off, stratified by target stimulated (Cg25, Cg24, VAC, NAcc, and any combination of more than one target stimulated) are presented in Supplement 1. DBS signal changes compared to baseline on the normalized SPM glass brain are presented in Supplement 2.

3.1.4 Effects of chronic stimulation of each area

In the whole-brain results above, similar findings were apparent when comparing stimulation on and off with baseline, and few effects were seen when chronic stimulation was acutely interrupted. We therefore decided to run additional analyses, focusing on effects between: (i) baseline and SGC stimulation (Cg25+Cg24); (ii) baseline and VAC/NAcc (VAC+NAcc) stimulation, and (iii) baseline and combined target stimulation, all regardless of whether stimulation was on or off. Please see Table 3 for the results.

--- Table 3 ---

3.2 Region data on NAcc

The most consistent finding after visually inspecting the ROI data was a decrease in rCBF (regional/global CBF) in TRD patients in the NAcc. This decrease was apparent irrespective which target was stimulated. Also, differences between both baseline and on, and baseline and off were overall more pronounced than differences between on and off (Figure 2).

--- Figure 2 ---

We also see a decrease in NAcc rCBF when inspecting the data over time (from baseline to visit 4), regardless of target stimulation (Figure 3). Furthermore, post-hoc whole-brain SPM analysis of DBS

signal-changes between baseline and visit 4, when target stimulation is optimized, showed a similar decrease in NAcc, and a decrease encompassing Cg25, ACC (ba32) and the interpeduncular region of the ventral midbrain (Figure 4).

--- Figure 3 ---

--- Figure 4 ---

3.3 Effects in PFC and clinical outcomes

Over the course of the study, 3 patients remitted, 2 responded but did not remit (non-remitters), and 2 were non-responders. When visually inspecting the ROI data over time, there was an increase in rCBF bilaterally in the PFC. The data indicated that remitters had higher rCBF in the PFC both at baseline and all subsequent visits compared to non-remitters and non-responders (Figure 5a-b).

Although less clear, when looking at the raw data of clinical outcome measures, remitters also seemed to have lower MADRS and HAM-D scores at baseline (indicating less severe depression) (Figure 5c-d). They also had higher GAF scores (indicating less impaired social, occupational, and psychological functioning) during baseline (Figure 5e).

--- Figure 5 ---

4. DISCUSSION

The present study was conducted to compare stimulation of SGC (Cg25 or Cg24), VAC/NAcc (VAC or NAcc), and a combination of these targets in the same TRD patients, focusing on both acute and chronic changes in rCBF using [^{15}O]water PET. DBS was associated with decreased rCBF at the sites of stimulation and in a range of distant regions including frontal and orbitofrontal cortical regions and thalamus (Table 3). Most prominently, a decrease in NAcc was seen with all three stimulation conditions. Acute interruption of chronic stimulation was not associated with prominent rCBF changes (Supplement 1). Five of seven patients responded to DBS and of these, three remitted. These results are similar to previous studies (Lozano et al., 2008) (Bewernick et al., 2010). Remitters had higher rCBF in PFC before and throughout DBS (Figure 5).

4.1 Acute effects

The lack of prominent changes after acute interruption of chronic stimulation might be caused by the relatively short time (2 hours) that stimulation was switched off before scanning. A previous study suggests that beneficial DBS effects in dystonia may persist after stimulation is switched off, with only a slow worsening of symptoms returning to pre-operative levels after 48 hours of stimulation (Grabli et al., 2009). In agreement, a case-report of a TRD patient under DBS of the lateral habenula showed that after stimulation was accidentally switched off, relapse occurred a couple of days later (Sartorius et al., 2010). One might however expect that stimulation interruption would cause acute changes in rCBF even when not apparent in behavioral response. But in this study, in general, this was not observed. Nonetheless, such acute rCBF changes may still occur when switching stimulation acutely on.

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4.2 Effects by area of stimulation

4.2.1 Effects on frontal regions and thalamus

Local rCBF decreases were apparent in Cg25 after SGC stimulation and in NAcc after SGC, VAC/NAcc, and combined stimulation. Increases in both glucose metabolism and rCBF in SGC have been seen in MDD, which normalize with remission and antidepressant treatment (Sacher et al., 2012; Drevets et al., 2008; Mayberg et al., 1999). In more distant regions, decreases in medial frontal gyrus and thalamus were seen with SGC and combined stimulation, and in the MFG with SGC and VAC/NAcc stimulation. Decreases in the orbitofrontal cortex were present after combined stimulation. In keeping with this, decreases in the medial frontal gyrus and orbitofrontal cortex after DBS have previously been reported with both Cg25 (Lozano et al., 2008; Mayberg et al., 2005) and NAcc stimulation (Bewernick et al., 2012; Millet et al., 2014). Similar effects have also been observed after CBT, suggesting that SGC and combined DBS target a mood-regulatory network involved in depression (Mayberg et al., 2005). Additionally, the effects seen in the MFG are consistent with past studies regarding Cg25 stimulation (Lozano et al., 2008), and in the thalamus regarding NAcc stimulation (Bewernick et al., 2010; Schlaepfer et al., 2008).

Increases in rCBF were only observed after combined DBS, with effects in MFG, pre-and postcentral gyrus, and inferior- and superior gyrus. Increases in MFG are comparable to previous Cg25 and NAcc stimulation (Lozano et al., 2008; Schlaepfer et al., 2008). Precentral-, and superior gyrus increases are similar to NAcc stimulation in earlier studies (Bewernick et al., 2010; Millet et al., 2014). Increases in prefrontal regions, such as the inferior frontal gyrus, have been reported with Cg25 stimulation and are similar to antidepressant patterns seen with medication (Mayberg et al., 2005; Mayberg et al., 2000).

Taken together, our data are consistent with previous studies and indicate that abnormalities observed in MDD, such as hypo- and hyperactivity in brain regions (Morishita et al., 2014), are

reversed by DBS. Our results show that the targets used have more commonalities than differences between them with an overlap in effects between stimulation targets, which is also present when comparing Cg25 and NAcc literature, suggesting a similar response-pattern irrespective of target area.

4.2.2 Effects on NAcc

A decrease in NAcc rCBF is also apparent in the region data with all target stimulations (Figure 2), consistent with the NAcc results of our whole-brain analysis (Table 2). Furthermore, no clear difference between stimulation on or off can be seen which is again consistent with earlier analysis (Appendix 1). When looking at the response pattern over time, the rCBF decrease in the NAcc remains (Figure 3) which is also consistent with whole-brain analysis (Figure 4). This decrease in NAcc rCBF does not appear to differ between responders and non-responders, suggesting that this decrease is either not directly linked to improvement of MDD symptoms, or on its own is insufficient for response.

Previous DBS studies do not report NAcc decreases. In fact an increase in NAcc metabolism has been reported after 1 week of NAcc DBS (Schlaepfer et al., 2008). However, this increase did not remain after chronic DBS suggesting that it might have been a short-term response to the surgical procedure (Bewernick et al., 2012).

4.3 Frontal cortical changes predictive for response and marker for response

Our stimulation procedures were designed to ensure that patients received appropriate DBS of either SGC or VAC/NAcc during treatment-period 1 and 2. During treatment-period 3, patients

received combined DBS treatment or, when remission occurred in previous periods, the best treatment so far. It was therefore expected that improvements should be most prominent after the third treatment-period. Indeed, inspecting the region data over time shows increases in PFC between baseline and last PET scan (Figure 5). MDD is associated with decreased PFC activity and increases after DBS are consistent with past studies, as well as similar to effects of antidepressant medication (Mayberg et al., 2000; Mayberg et al., 2005; Schlaepfer et al., 2008). Activity changes in the PFC thus seem to be a marker of antidepressant response (Riva-Posse et al., 2014).

Our data show that remitters had higher rCBF levels in the PFC during all visits, including baseline, compared to non-remitters and non-responders. Remitters also had relatively better clinical outcome measures at baseline and at the last PET visit. Higher frontal cortical rCBF might thus be predictive for response. However, even though non-responders failed to cross the clinical threshold, effects of DBS were apparent. It might therefore be that DBS on its own is insufficient or that more time on stimulation is required to reach clinical response in these patients, which are in this study characterized by low PFC rCBF.

4.4 Limitations

A limitation of our study is the small sample size that provides insufficient power to clearly determine clinical efficacy, making our findings preliminary. Nonetheless, 5 of 7 patients responded to TRD and 3 of 7 reached remission. Given the documented low and poorly sustained response rates in TRD (Dunner et al., 2006; Luijckes et al., 2013), these are encouraging results. In this study, patients were required to have failed to respond to two courses of ECT, or responded only to maintenance ECT, or did not respond to a first course of ECT and were unwilling to have a further course. Our cohort of patients therefore represents a particularly treatment-refractory group.

Recently proposed standardised definitions of TRD, including “Stage II treatment-resistant depression” (Conway et al., 2017) and “Multiple-therapy-resistant-Major Depressive Disorder” (MTR-MDD) (McAllister-Williams et al., 2017 (in press)), which may warrant more invasive or higher-risk antidepressant treatments such as surgical interventions, either do not include the need for prior ECT (Stage-II TRD) or require non-response to one adequate trial of ECT (MTR-MDD). Standardisation of inclusion criteria should improve the comparability of future studies. Additionally, it might have been better to determine the ideal stimulation sites and frequencies for each patient over a longer period than two days per contact, since it may take longer to see the ideal effects of DBS. However, we did notice differences in improvements between stimulation sites and frequencies after trying each contact in turn for up to two days, making this approach nonetheless an improvement and appealing approach for future DBS studies. Another limitation is that stimulation was always switched off after chronic stimulation, though acute changes might occur if stimulation were to be acutely switched on after being off. Global intensity-normalization was used, meaning that rCBF changes in one direction could be due to changes in the opposite direction of the complementary region. Furthermore, no sham stimulation phase was used because of possible symptom aggravation. Indeed, previous studies have changed their design after study-initiation leaving out sham conditions because of significant worsening of symptoms (Bewernick et al., 2010; Bewernick et al., 2012; Holtzheimer et al., 2012). Moreover, there is evidence that placebo response rates are lower in patients with severe depression (such as in our cohort) compared to patients with mild depression (Schatzberg and Kraemer, 2000). Also, for each of our patients different stimulation contacts and frequencies for stimulation were most effective, arguing for specificity of stimulation (Lozano et al., 2008).

4.5 Conclusion

We conclude that DBS improves TRD in the majority of patients. Acute effects of short-term DBS interruption are small compared to chronic stimulation effects, indicating that acute effects are more subtle than hypothesized. A consistent decrease in rCBF is observed in the NAcc with DBS regardless of stimulation site, suggesting that this may be a common pathway mediating effects of DBS in TRD, although it is not clearly linked to improvement in severity of depression. Our data additionally suggest that treatment response is reached in patients with higher baseline prefrontal rCBF. Further evaluation is necessary to confirm whether higher frontal rCBF could be a predictive biomarker of treatment response, which might help to optimize patient selection for DBS in MDD.

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For Peer Review

CONFLICTS OF INTEREST

S.C. has been a consultant for Bayer HealthCare LLC. N.K.P. has been medical advisor to Boston Scientific and has held consultancies to Medtronic, St Jude Medical (now Abbott) and Nevro; and he is the chief medical officer at Bioinduction Ltd (Bristol, United Kingdom). PST has received consultancy fees as an Advisory Board member for the following companies: Galen Limited; Sunovion Pharmaceuticals Europe Ltd; myTomorrows; Cyberonics Europe BVBA (now LivaNova UK Ltd). J.C.M. and J.A. have no conflict of interest.

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Nucleus Accumbens

Variable	Value
Age at Implant (mean ± SD)	48.6 ± 11.7 years
Sex (n)	2 male / 6 female
Duration illness (mean ± SD)	19 ± 14 years
Length current episode (mean ± SD)	11.5 ± 10 years
Recurrent MDD (n)	5 of 8
Mean lifetime episodes (n)	3.5
Mean previous hospitalization (n)	6.5
Previous responders (n)	8 of 8
Family history MDD (n)	7 of 8
Carer (n)	4 of 8
Retirement from work preoperatively (n)	8 of 8
Mean different pharmacological treatments received (n) ^a	18.5
Mean current psychotropics (n)	4.5
Received ECT treatments (n)	43
Received vagus nerve stimulation (n)	2 of 8
Prominent anxiety (n)	8 of 8
Panic disorder (n)	2 of 8
Agoraphobia (n)	1 of 8
Obsessive Compulsive Disorder (n)	1 of 8

	Visit 1 (baseline)	Stereotactic surgery	DBS 1 > 3 months	Visit 2	DBS 2 > 3 months	Visit 3	DBS 3 > 3 months	Visit 4
Implant electrodes								
PET scan
Stimulation on	n/a							
Stimulation off	n/a							
Site			Cg24, Cg25, NAcc or VAC		Cg24, Cg25, NAcc or VAC*		Cg24, Cg25, NAcc, VAC, or combo*	

	Region	Side	pFWEc	k	x	y	z
BL > SGC	Nucleus accumbens/ subgenual anterior cingulate (ba25)	-	0.000	1160	14	12	-3
	Medial frontal gyrus (ba10)	R	0.000	50	18	58	5
	Middle frontal gyrus (ba8)	L	0.000	62	-46	22	47
	Medial frontal gyrus (ba10)	L	0.000	44	-2	60	1
	Thalamus	R	0.000	46	4	-12	1
BL > VAC/NAcc	Subgenual anterior cingulate (ba32)	R	0.000	32	10	12	-9
	Nucleus accumbens	L	0.000	57	-4	28	-9
	Nucleus accumbens	L	0.000	60	-8	16	-11
	Middle frontal gyrus (ba8)	L	0.000	30	-36	22	43
BL > combination	Nucleus accumbens	-	0.000	135	10	12	-9
	Thalamus	L	0.000	66	-4	-10	11
	Orbital gyrus (ba11)	R	0.000	91	4	44	-27
	Medial frontal gyrus (ba11)	L	0.000	42	-8	30	-13
	Rectal gyrus (ba11)	R	0.000	30	6	14	-23
BL < combination	Postcentral gyrus (ba3)	R	0.000	730	44	-24	59
	Postcentral gyrus (ba1)	L	0.000	174	-48	-22	59
	Precentral gyrus (ba6)	R	0.000	264	58	-2	27
	Precentral gyrus (ba6)	R	0.000	92	14	-16	67
	Inferior frontal gyrus (ba46)	R	0.000	103	46	34	3
	Superior frontal gyrus	L	0.000	42	-26	50	1
	Middle frontal gyrus (ba10)	R	0.000	72	36	44	15
	Middle frontal gyrus (ba10)	L	0.000	38	-34	42	21

Supplement 1

S1. Overview of DBS effects compared with baseline, and on versus off, divided by area of stimulation. DBS effects were measured after area was stimulated for > 3 months (electrode switched on), and after the electrode was switched off for 120 minutes after stimulation (electrode switched off). On = electrode switched on for at least 3 months. Off = electrode switched off for 120 minutes after stimulation. BL = baseline, Cg25 = subgenual cingulate 25, Cg24 = subgenual cingulate 24, VAC = ventral anterior capsule, NAcc = nucleus accumbens, Combination = any other combination of more than 1 target stimulated. ba = brodmann area. k = number of voxels. The data represent clusters ($k > 30$ unilateral or $k > 15$ bilateral) of $p = 0.05$, family-wise error (FWE) threshold, at a peak-level threshold of $p = 0.05$ (FWE).

		Region	Side	PFWE	k	x	y	z
Cg25	BL > on	Rectal gyrus (ba11)	L	0.000	61	-2	22	-21
		Nucleus accumbens	R	0.000	31	14	12	-1
	BL > off	Anterior cingulate (ba32)/subgenual cingulate (ba24)	L	0.000	206	-2	28	-9
		Medial frontal gyrus (ba25)	R	0.000	65	10	12	-13
Cg24	BL > on	Nucleus accumbens	R	0.000	23	14	10	-7
		Nucleus accumbens	L	0.000	26	-8	16	-11
	BL > off	Middle temporal gyrus (ba39)	L	0.000	43	-52	-74	31
VAC	BL > on	Cingulate gyrus (ba31)	R	0.000	62	10	-40	41
		Middle temporal gyrus (ba39)	L	0.000	38	-48	-82	23
	BL > off	Middle occipital gyrus (ba19)	L	0.000	163	-58	-70	7
		Middle occipital gyrus (ba18)	L	0.000	36	-42	-90	11
		Superior temporal gyrus (ba22)	L	0.000	58	-66	-34	17
	BL < off	Dorsal anterior cingulate (ba32)	R	0.000	57	10	32	19
	On < off	Dorsal anterior cingulate (ba32)	R	0.000	31	12	30	31
NAcc	BL > on	Superior frontal gyrus	R	0.000	49	22	58	15
Combination	BL < on	Precentral gyrus (ba6)	R	0.000	79	58	-2	27
		Postcentral gyrus (ba3)	R	0.000	113	44	-24	61
		Postcentral gyrus (ba1)	L	0.000	38	-48	-22	59
		Parietal sub-gyral (ba40)	R	0.000	60	24	-42	57
		Precentral gyrus (ba4)	R	0.000	35	32	-18	53
		Inferior frontal gyrus (ba46)	R	0.000	33	46	34	3
	BL > off	Sub-lobar	R	0.000	149	10	12	-9
	BL < off	Postcentral gyrus (ba3)	R	0.000	84	44	-24	59
		Parietal sub-gyral (ba40)	R	0.000	35	26	-40	53
		Middle frontal gyrus (ba10)	R	0.000	38	36	44	13

Supplement 2

S2. DBS signal changes compared to baseline on the normalized SPM glass brain. Divided into 4 regions of activation: (a) subgenual cingulate 25 (Cg25), (b) subgenual cingulate 24 (Cg24), (c), ventral anterior capsule (VAC), (d) nucleus accumbens (NAcc), and (e) any other combination of more than 1 region stimulated (Combination). L = left.