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Antidepressant effects after short-term and chronic stimulation of the subgenual cingulate gyrus in treatment-resistant depression ☆

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ABSTRACT

Background: Deep brain stimulation (DBS) of the subcallosal cingulate gyrus (SCG) is an experimental approach in treatment-resistant depression (TRD). Apart from its potential long-term antidepressant effects acute stimulation effects have been described. We investigated putative neuroanatomical clusters in which such acute effects accumulate and followed patients over the long-term.
Methods: We assessed safety and efficacy of DBS in six patients with TRD receiving bilateral DBS with electrodes implanted in the SCG. First, high intensity 130 Hz stimulation was applied on five consecutive days after surgery for 24 h comprising a sham condition in a double-blind, randomized design. Acute stimulation was conducted at all four homologous electrode contacts on both sides. Afterwards, chronic stimulation was initiated and the clinical effect was evaluated at 24–36 weeks compared to baseline (50% reduction in HAMD scores). The primary outcome criterion was depression severity as assessed with the Hamilton Depression Rating Scale (HAMD-24); secondary outcome parameters were the Montgomery–Åsberg Rating-Scale and Beck Depression Inventory following DBS. The clinical effect over the three scores was compared to sham stimulation and was correlated to the anatomical localization of active contacts by stereotactically delimiting the cluster of most effective contacts in responding patients.
Results: Acute 24 h of stimulation showed only moderate reductions in mean HAMD-24, MADRS and BDI scores. At the last observation (24–36 weeks), two patients were remitters (HAMD-24 < 10) and the four other patients were non-responders.
Conclusions: Our results confirm that stimulation of the SCG is capable of exerting moderate acute and chronic antidepressant effects. The predictive value of these findings needs to be addressed in future studies.

Introduction

Treatment-resistant depression (TRD) has been described as the failure to respond to adequate treatment with antidepressant agents. TRD is a crucial public health burden, affecting 30–40% of those patients suffering from major depressive disorder (Nemeroff, 2007). Moreover, current relapse preventing therapies using combination pharmacotherapy (Sackeim et al., 2001) or continuation electroconvulsive therapy (ECT) (Kellner et al., 2006) are capable of significantly reducing relapse rates. However, at least 40% of the patients experience recurrence of depressive episodes within six months (Tew et al., 2007). Therefore, a high unmet need exists for both acute and relapse-preventing antidepressant treatment alternatives in TRD. Functional imaging has shown that major depression is associated with increased activity in the subcallosal cingulate cortex (SCC), a brain area involved in mood regulation and self-generated sadness (Damasio et al., 2000; Mayberg et al., 1999; Pardo et al., 1993). In detail, tractography based on diffusion tensor imaging (DTI) (Wakana et al., 2007) has shown corticostriatocortical (CSTC) projections from the ventral capsule/ventral striatum (VC/VS) and subcallosal cingulate white matter overlapping in areas of the brain associated with antidepressant responses (Gutman et al., 2009; Johansen-Berg et al., 2008). The subgenual cingulate gyrus (SCG), including Brodmann's area 25 and parts of 24 and 32, has shown abnormal metabolic activity in patients with depression (Mayberg et al., 2005). Differential interventions including pharmacotherapy,

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transcranial magnetic stimulation, or electroconvulsive therapy (Merkl et al., 2009) ameliorate the clinical features of depression and affect the activity of the SCG (Hamani et al., 2011). Furthermore, other potentially effective DBS targets in depression currently under investigation for treatment include the ventral striatum (Malone et al., 2009), the nucleus accumbens (Bewernick et al., 2010), the habenula (Sartorius et al., 2010) and the medial forebrain bundle (Coenen et al., 2011a,b; Schlaepfer et al., 2013), suggesting the involvement of a broader neural circuitry with different anatomical nodes as potential therapeutic targets. Current research on the efficacy and safety of DBS in the SCG for TRD has been limited to a few, promising open-label studies, anecdotal reports (Guinjoan et al., 2010; Lozano et al., 2008; Mayberg et al., 2005), one long-term follow-up study (Kennedy et al., 2011), an open-label trial which investigated efficacy after 12 months (Lozano et al., 2012) and a sham/open label long-term study of patients with unipolar and bipolar II disorders (Holtzheimer et al., 2012). Remission rates for DBS varied between 33% and 35% after three months, 50% and 60% after 6 months, up to 55% at 12 months and up to 75% after 24 months. Interestingly, there have been anecdotal reports on acute intraoperative effects (Holtzheimer et al., 2012; Mayberg et al., 2005). However, so far no studies systematically addressed the question of whether antidepressive effects can be elicited by short acute stimulation at high intensities (McIntyre and Hahn, 2010), thus allowing contact selection and adjustment of stimulation parameters on an anatomical basis. If effects are observed at an early time point at a stimulated electrode, this might serve as a valuable predictor for later response. It has been shown that depressive patients responding to chronic deep brain stimulation had electrodes within a cluster of Brodmann area 24, the head of the caudate nucleus and corpus callosum (Broadway et al., 2012). In this context, corresponding findings in neuroanatomical clusters of acute antidepressant effects may serve as the basis for future studies which investigate the predictive value (Broadway et al., 2012). In this study, we assessed the hypothesis that DBS to the SCG is efficacious in decreasing ratings of depression after short-term (24 h) and chronic stimulation and performed a neuroanatomical clustering for the most effective electrodes in this experimental setting.

Materials and methods

Patients

Six patients fulfilling the diagnostic criteria for severe major depressive disorder (MDD) (Association, 2000) who were treatment resistant and referred to our department, were enrolled from October 2007 to March 2012 in a pilot randomized controlled clinical trial (ClinicalTrials.gov NCT00531726). Referrals came from hospital and community psychiatrists who were aware of the protocol and were not involved in its implementation. All patients were in a current depressive episode as determined by the Structured Clinical Interview for DSM-IV Axis I disorders (First et al., 1996) with a minimum score of 20 on the HAMD-24 (Hamilton, 1960). Demographic and clinical characteristics of the six patients are shown in Table 1. Neuropsychological scores are reported as changes after 6 months (and if available 12 months) and compared to a pre-surgery baseline (Table 2). Concomitant medication was held stable for 6 weeks prior to and after surgery. Full details of inclusion and exclusion criteria are depicted in Supplementary Material (S1). Briefly, independent experienced psychiatrists established the diagnosis via a clinical interview following DSM-IV (Association, 2000) criteria for MDD. TRD was defined as failure to sequential treatment (see Thase, 2003; Thase and Rush, 1997). The Antidepressant Treatment History Form (ATHF) (Sackeim, 2001) was used to assess treatment history and to evaluate level of treatment failure to various antidepressants. After a detailed description of the study protocol to the patients, written informed consent was obtained. The local University Ethics Committee of the Charité — Universitätsmedizin Berlin approved the protocol, and the study was carried out in accordance with the declaration of Helsinki.

DBS surgical procedure

Patients with TRD received DBS with two electrodes (3387 lead, Medtronic, Inc., Minneapolis, MN, USA) implanted bilaterally in the SCC region with frame-based, magnetic resonance imaging-guided

Table 1
Clinical characteristics of six patients with unipolar depression.

Patient	P01	P02	P03	P04	P05	P06
Age at inclusion (years)	49	61	48	60	36	50
Gender (female/male)	f	f	f	f	m	m
Number of ECT lifetime (acute and maintenance)	>50	40	>100	32	0[#]	18
Onset of first episode (years)	33	23	16	20	16	34
Pharmacotherapy and psychotherapy[§] (y/n) (h)	y (90)	y (35)	y (48)	y (45)	y (45)	y (90)
Number of depressive episodes	8	10	20	4	10	5
Suicide attempts (lifetime)	2	0	10	0	1	0
Duration of index episode (months)	24	21	24	36	36	12
HAMD-24 at inclusion	37	31	28	36	42	30
MADRS at inclusion	38	32	27	16	35	36
Beck Depression Inventory (BDI) at inclusion	35	22	46	36	57	41
% HAMD-24 decrease at 6 months	41%	71%	4%	81%	21%	3%
% MADRS decrease at 6 months	16%	72%	−19%	75%	9%	17%
% (BDI) decrease at 6 months	9%	95%	22%	67%	9%	10%
ATHF	13	13	18	14	17	20
WST (IQ)	–	99	101	118	–	–
LPS (IQ)	–	99	103	91	108	–
Professional disability (%)	100	100	100	100	50	100

Abbreviations: HAMD = Hamilton Depression Rating Scale; ECT = electroconvulsive therapy; MDD = major depressive disorder; N = number; ATHF = medication resistance was measured with the ATHF (Modified Antidepressant Treatment History Form); Beck Depression Inventory = BDI; SD = standard deviation, values are mean ± SD if not otherwise specified; TCA = tricyclic antidepressant; IQ = intelligence quotient; WST = "Wortschatztest" (intelligence), LPS = "Leistungsprüfsystem" (LPS 3 and 4) (fluid intelligence), (y/n) = (yes/no); h = hours; P01 = patient; [¥]Patient 6 scored 144 from 144 (maximum score) in the Mattis Dementia Rating Scale (Mattis S., 1988). [§]Patients received concomitant medication at time of stimulation treatment, dosage being kept constant in all patients during active DBS period. Treatment comprised different antidepressants with add-on therapy; (SNRI) serotonin–norepinephrine reuptake inhibitors (100%), (SSRI) selective serotonin reuptake inhibitors (75%), tricyclic antidepressants (patient 2 and patient 3), non-selective alpha 2-adrenoceptor antagonist (patients 2 and 3) and/or atypical neuroleptics (50%, patients 3, 4 and 6). Two patients (patients 2 and 3) were augmented with mood-stabilizers (lithium, pregabalin) and non-hydrazine reversible MAO inhibitor (patient 4) and two patients (patients 2 and 6) had ketamine injections (0.5 mg/per kilo gram/body weight) in the past. Benzodiazepines were used in three (patients 1, 2 and 3) of the six patients. Patients were encouraged to apply the cognitive or behavioral skills that they had learned prior to DBS during psychotherapy. [#]Patient 05 had rejected ECT prior to inclusion to the study trial.

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