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Deep Brain Stimulation Modulates Gamma Oscillations and Theta–Gamma Coupling in Treatment Resistant Depression

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ABSTRACT

Background: Deep brain stimulation (DBS) in the subcallosal cingulate gyrus (SCG) is becoming an effective therapeutic option for treatment resistant depression (TRD).
Objective/hypothesis: Identifying the neurophysiological mechanisms altered by DBS may lead to more tailored treatment parameters and enhanced efficacy.
Methods: Twenty TRD patients with implanted DBS in the SCG were recruited. Patients participated in three EEG recording sessions, one with DBS ON, one with DBS randomized to ON or OFF, and one with DBS OFF. During each session, subjects performed N-back working memory tasks, namely the 0-back and 3-back. Fourteen subjects with valid EEG were included in the analysis. Changes in frontal gamma oscillations (30–50 Hz) and coupling between theta (4–7 Hz) and gamma oscillations as a result of DBS stimulation were quantified and correlated with depressive symptoms.
Results: DBS stimulation resulted in suppression of frontal oscillations in the ON state relative to the OFF state during the N-back tasks. Greatest suppression was demonstrated in beta and gamma oscillations and most pronounced during the 3-back. Suppression of gamma oscillations in the 3-back correlated with a reduction in depressive symptoms. DBS ON relative to OFF in the 3-back also resulted in an increase in theta-gamma coupling that correlated with a reduction in depressive symptoms.
Conclusion: Suppression of gamma oscillations and increased theta-gamma coupling through DBS is likely mediated by both SCG activation of inhibitory circuits and an enhancement of plasticity in the frontal cortex. Activation of both pathways may explain the therapeutic properties of DBS in TRD.

Introduction

Major depressive disorder (MDD) affects over 12% of men and 20% of women [1] with more than 30% of the patients being treatment resistant [2]. Deep brain stimulation (DBS) may be an effective therapeutic option for treatment resistant depression (TRD) [3,4]. DBS involves focal stimulation of specific brain regions via surgically implanted electrodes and can directly modulate key nodes involved in MDD pathophysiology. Several such nodes have been proposed [4–6], of which the subcallosal cingulate gyrus (SCG) is most well studied. In most clinical studies, which have been mainly open label, the effectiveness of SCG DBS for TRD has been well demonstrated [3,7,8], but response (35% after 1 month) and remission rates (10% after 1 month) [3,9] are still relatively low compared to ECT (70% remission within weeks of treatment) [10]. While randomized control trials have been discontinued due to lack of expected benefit with active versus sham stimulation, evidences still point to a therapeutic benefit of DBS and suggest that improved understanding of the neural mechanisms or biological targets of treatment response may lead to better outcomes in future studies [11,12].

Conflict of interest: The authors declare no competing financial interests.
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Electroencephalography (EEG) is a non-invasive measure of neuronal activity based on voltage fluctuations on the scalp and can be used to better understand DBS treatment. A confound for measuring the underlying cortical oscillations during DBS stimulation is the electrical artifact produced in the EEG recording. To overcome the problem, one can turn the stimulator off or design appropriate filters for examining recordings with the stimulator on. In this study, DBS artifacts were characterized and then filtered mathematically based on recently published methods [13]. In relation to the signal of interest, gamma oscillations (30–50 Hz) are critical for information encoding and are optimally evaluated in the prefrontal cortex during a working memory task [14,15]. Previous studies that applied repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex (DLPFC) showed suppressed gamma oscillations during working memory performance [16] and improved cognition in patients with schizophrenia [17]. These results suggest that suppression of gamma oscillations during working memory in patient populations may be beneficial. Additionally, the integrity of working memory circuitry has been associated with the degree of coupling between theta and gamma oscillations. Therefore, alterations in gamma oscillations and theta–gamma coupling may provide additional details about the therapeutic mechanisms of DBS [18–21].

The main objective of this study, therefore, was to examine the effects of DBS stimulation for both ON and OFF states on gamma oscillations and theta–gamma coupling during working memory performance. Another objective was to evaluate if DBS induced changes in EEG relate to antidepressant response. We hypothesized that during working memory performance, DBS would suppress gamma oscillations and potentiate theta–gamma coupling with the amount of change correlated to symptom improvement.

Methods and materials

Participants

Twenty TRD patients (mean age: 48 ± 7; 14 female, 6 male) with implanted DBS in the SCG were recruited at the University Health Network (UHN) in Toronto. All participants gave their written informed consent and the protocol was approved by the ethics committee at UHN and the Centre for Addiction and Mental Health. The average age of onset for the patients was 22 ± 8 and the average age at the time of surgery was 45 ± 7. All participants were right handed. The patients had an average of 4 ± 2 major depressive episodes (MDEs) and were hospitalized 3 ± 2 times. Fourteen subjects had attempted suicide before. All patients had failed at least four adequate antidepressant trials and have received psychotherapy in the past. All patients except for one have been treated with ECT. Six patients have also received repetitive transcranial magnetic stimulation treatment before. Table 1 contains data for the individual subjects. Before the DBS surgery, patients had a mean score of 25 ± 3 for the 17-items Hamilton Depression Rating Scale (HDRS-17). At the time of this study, patients had a mean HDRS-17 score of 11 ± 7; 60% of them were treatment responders (i.e., >50% decrease from baseline HDRS-17), while 40% of them were remitters (i.e., current HDRS-17 < 8). Time from DBS surgery to completion of the study varied between 4 and 76 months. Patients had one of two types of DBS stimulators: Medtronic (13 subjects) or Advanced Neuromodulation System (ANS; 7 subjects). The Medtronic stimulators maintained a constant voltage, while the ANS stimulators maintained a constant current. The stimulation frequency for both types of stimulators was set to 130 Hz. Other stimulator settings (i.e. pulse width, voltage or current) were optimized on an individual basis. Please refer to Table 2 for subject specific results. Medication information of the subjects at the time of the current study are provided in Table 3.

Experimental setup

Patients underwent three EEG recording sessions in one day. In the first session, the DBS stimulator was kept ON at the therapeutic setting. In the second session, the stimulator was randomized to either ON or OFF. In the third session, the stimulator was turned OFF. The duration of each session is around 1 h and 20 min, which includes a 15 min break. During each session, patients performed the 0-back and 3-back tasks in a randomized order.

During the N-back task, participants were visually presented with letters on a computer screen one at a time for 250 ms and then given 3000 ms from the letter onset to respond whether the current letter matches the one *N* steps back. A fixation '+' is presented on the screen at the end of the response period for 1500 ms before the

Table 1
Subject clinical history.

ID	Age of onset	Age at time of surgery	Gender	Duration of pre-DBS MDE (mo.)	Number of MDEs	History of suicide attempts	Number of hospitalizations for psychiatric reasons	Received rTMS	Received ECT	Received psychotherapy
1	17	42	M	26	7	No	6	No	No	Yes
2	21	45	F	72	6	Yes	4	No	Yes	Yes
3	34	48	F	12	5	No	0	Yes	Yes	Yes
4	16	29	M	36	4	Yes	1	Yes	Yes	Yes
5	16	38	F	108	3	Yes	0	No	Yes	Yes
6	26	50	M	288	2	No	0	Yes	Yes	Yes
7	16	49	M	36	3	Yes	2	No	Yes	Yes
8	9	57	F	82	6	Yes	3	No	Yes	Yes
9	15	49	F	60	7	Yes	8	No	Yes	Yes
10	22	39	F	120	2	No	3	No	Yes	Yes
11	19	44	F	36	4	Yes	2	No	Yes	Yes
12	22	53	F	39	4	Yes	3	No	Yes	Yes
13	21	55	F	192	4	Yes	4	No	Yes	Yes
14	25	42	F	156	8	Yes	9	Yes	Yes	Yes
15	34	44	F	108	2	Yes	2	No	Yes	Yes
16	16	43	M	120	2	Yes	2	No	Yes	Yes
17	38	48	F	120	2	Yes	1	No	Yes	Yes
18	33	53	F	58	2	No	2	No	Yes	Yes
19	17	40	F	36	5	Yes	1	Yes	Yes	Yes
20	22	39	M	36	4	No	3	Yes	Yes	Yes