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# One year double blind study of high vs low frequency subcallosal cingulate stimulation for depression

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## ABSTRACT

Subcallosal Brodmann's Area 25 (Cg25) Deep Brain Stimulation (DBS) is a new promising therapy for treatment resistant major depressive disorder (TR-MDD). While different DBS stimulating parameters may have an impact on the efficacy and safety of the therapy, there is no data to support a protocol for optimal stimulation parameters for depression. Here we present a prospective multi-center double-blind randomized crossed-over 13-month study that evaluated the effects of High (130 Hz) vs Low (20 Hz) frequency Cg25 stimulation for nine patients with TR-MDD. Four out of nine patients achieved response criteria (≥40% reduction of symptom score) compared to mean baseline values at the end of the study. The mean percent change of MADRS score showed a similar improvement in the high and low frequency stimulation groups after 6 months of stimulation (−15.4 ± 21.1 and −14.7 ± 21.1 respectively). The mean effect at the end of the second period (6 months after cross-over) was higher than the first period (first 6 months of stimulation) in all patients (−23.4 ± 19.9 (n = 6 periods) and −13.0 ± 22 (n = 9 periods) respectively). At the end of the second period, the mean percent change of the MADRS scores improved more in the high than low frequency groups (−31.3 ± 19.3 (n = 4 patients) and −7.7 ± 10.9 (n = 2 patients) respectively). Given the small numbers, detailed statistical analysis is challenging. Nonetheless the results of this study suggest that long term high frequency stimulation might confer the best results. Larger scale, randomized double blind trials are needed in order to evaluate the most effective stimulation parameters.

## 1. Introduction

Deep Brain Stimulation (DBS) is a relatively new therapy whose potential has been explored in the recent years for treatment resistant major depressive disorder (TR-MDD) (Delaloye and Holtzheimer, 2014; Coenen et al., 2015; Bewernick et al., 2017). The first reported brain

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target for stimulation is the subcallosal white matter, Brodmann's Area 25 (Cg25) (Mayberg et al., 2005). Cg25 stimulation has been reported to lead to beneficial responses in approximately 50% of patients suffering from severe TR-MDD; Lozano et al. (2008) and Holtzheimer et al. (2012) reported one year response rate of 62% and 36% respectively. The failure of the therapy in the remaining patients, however, indicates that this brain target or the mode of stimulation might not have a therapeutic relevance for all patients. While most research groups have examined the individual symptom profiles and the effects of stimulation in other areas of the brain or sub-locations within the Cg25 area, different modes of stimulation have hardly been studied (Holtzheimer et al., 2012; Schlaepfer et al., 2008, 2014; Hoyer et al., 2012; Riva-Posse et al., 2014; Bergfeld et al., 2016; Bewernick et al., 2010). Only one group reported that short term (one week) different frequencies (0, 5, 20, 50, 130 and 185 Hz) of Cg25 stimulation in four patients did not yield clinical change (Ramasubbu et al., 2013).

The initial DBS stimulating parameters (such as high frequency) used in clinical depression studies are in essence the same as those used for Parkinson's disease (Lozano et al., 2008; Bewernick et al., 2010). Few publications have described the impact of parameter settings on the efficacy of DBS in movement disorders such as Parkinson's disease and dystonia, recommending frequency optimization to balance efficacy and side-effects (Moreau et al., 2008; Eusebio et al., 2008; Sidiropoulos et al., 2013; Xie et al., 2015; Vallabhajosula et al., 2015). Preclinical studies explored the anti-depressant like effects of different stimulation settings at the parallel target of the Subcallosal Cingulate gyrus in both naïve rats and in a rat model of depression (Hamani et al., 2010; Lim et al., 2015). It was therefore considered possible that in patients with TR-MDD, different DBS stimulating parameters may have an impact on the efficacy and safety of the therapy.

There is no evidence-based data to support a protocol for optimization of stimulation in TR-MDD and adjustment of optimal stimulation parameters is guided by the clinician's knowledge and experience. Using a lower frequency may provide better efficacy as well as a health-economic advantage. Lowering the frequency from 130 to 20 Hz could extend the neurostimulator battery life by a factor of 5, avoiding the need for future multiple battery changes with all the associated surgical risks and costs. The goal of this double blind cross-over study was to investigate the impact of different DBS parameter settings (high (130 Hz) vs low (20 Hz) frequency) on the efficacy and safety of Cg25 DBS as an adjunctive treatment for patients with TR-MDD.

## 2. Methods

### 2.1. Study design

This clinical study was designed as a prospective, multi-center, double-blind, randomized, 13-month study to evaluate the effects of high (130 Hz) vs. low (20 Hz) frequency Cg25 DBS as an adjunctive treatment for single or recurrent episode TR-MDD. The study design is illustrated in Fig. 1. After having 2 baseline evaluations by 2 separate psychiatrists, eligible patients were implanted with the Libra® DBS System. All patients underwent a 4 week surgical recovery period during which the system was not activated. One month after implantation, patients were randomized (1:1) to 2 different treatment groups (high vs low frequency) and their system was activated. Once activated, patients returned to the clinic for efficacy and safety evaluations every month. Both the evaluating psychiatrists as well as the patients were blinded to which stimulation group they were randomized. Each patient's device was programmed by one clinician and the information regarding the device was not given to the evaluating psychiatrists. The evaluating psychiatrists were the same throughout the patient study treatment and follow-up visits, in order to reduce variability in the evaluators' scoring.

After 6 months of active stimulation (i.e. at the 7-month post-implant visit) patients were evaluated based on their MADRS (Montgomery and Asberg Depression Rating Scale) score as either being a responder or non-responder: responders (≥40% reduction of the MADRS score compared to mean baseline values) continued with their treatment in the same frequency group for another 6 months; non responders crossed over to the other frequency group, still in a double-blind way, for the following 6 months. A threshold for response of 40% reduction in MADRS had been used in previous DBS studies (Lozano et al., 2008) and adopted for this cross-over design to enable patients with a prominent clinical improvement after 6 months of active stimulation to continue with their probable effective treatment.

The primary objective was to evaluate the effect of two different frequency settings of Cg25 DBS on mood, measured as the percentage of change from baseline value in the MADRS score after six months of active stimulation.

The secondary objectives were to evaluate the safety and efficacy of the same two frequency settings for DBS on mood after 3, 6, 9 and 12 months of active stimulation as measured by MADRS, Hamilton Rating Scale for Depression [HRSD-17], (Quick Inventory of Depressive Symptoms-Self Report [QIDS-SR]), quality of life (Quality of Life and Satisfaction Questionnaire [Q-LES-Q]), functioning (Global Assessment of Functioning [GAF]), anxiety (Hamilton Anxiety Rating Scale [HAM-A]), Clinician and Patient Global Impression of Severity and Improvement (CGI; PGI) and cognitive function (CANTAB battery). Safety measures included the incidence of depression related and device related adverse events (i.e. hospitalization due to worsening depression, suicidal ideation, or behavior, medical treatment, and device related events) that occur over study duration.

The clinical investigation plan, screening and subject selection procedures and description of the investigational device are detailed in the method section of the supplementary data.

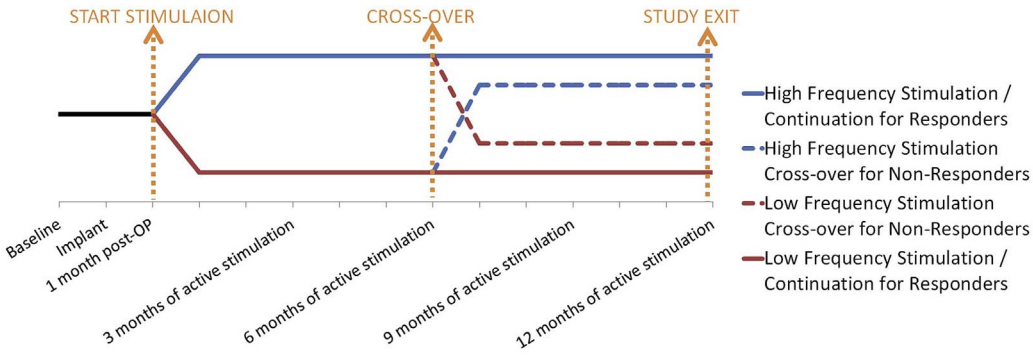


**Fig. 1. The study Design: One year double-blind cross-over study of high vs low frequency stimulation.**
One month after implantation, patients were randomized (1:1) to 2 different treatment groups (High (130 Hz) frequency (solid blue line) vs Low (20 Hz) frequency (solid red line)) and their system was activated. After 6 months of active stimulation patients were evaluated based on their MADRS Score as either being a responder or non-responder: responders (≥40% reduction of the MADRS score compared to mean baseline values) continued with their treatment in the same frequency group for another 6 months (blue and red solid lines); non responders crossed over to the other frequency group, still in a double-blind way, for the following 6 months (blue and red dashed lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)