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DOI:

[10.1016/j.jpsychires.2017.09.026](https://doi.org/10.1016/j.jpsychires.2017.09.026)

Document Version

Peer reviewed version

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Citation for published version (APA):

Eitan, R., Fontaine, D., Benoît, M., Giordana, C., Darmon, N., Israel, Z., Linesky, E., Arkadir, D., Ben-Naim, S., Iserlles, M., Bergman, H., Hulse, N., Abdelghani, M., McGuffin, P., Farmer, A., DeLea, P., Ashkan, K., & Lerer, B. (2017). One year double blind study of high vs low frequency subcallosal cingulate stimulation for depression. *Journal of psychiatric research*. <https://doi.org/10.1016/j.jpsychires.2017.09.026>

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Accepted Manuscript

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

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PII: S0022-3956(17)30383-7

DOI: [10.1016/j.jpsychires.2017.09.026](https://doi.org/10.1016/j.jpsychires.2017.09.026)

Reference: PIAT 3223

To appear in: *Journal of Psychiatric Research*

Received Date: 3 April 2017

Revised Date: 12 September 2017

Accepted Date: 29 September 2017

Please cite this article as: Eitan R, Fontaine D, Benoît M, Giordana C, Darmon N, Israel Z, Linesky E, Arkadir D, Ben-Naim S, Iserlles M, Bergman H, Hulse N, Abdelghani M, McGuffin P, Farmer A, DeLea P, Ashkan K, Lerer B, One year double blind study of high vs low frequency subcallosal cingulate stimulation for depression, *Journal of Psychiatric Research* (2017), doi: 10.1016/j.jpsychires.2017.09.026.

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TITLE PAGE**Title:****One Year Double Blind Study of High vs Low Frequency Subcallosal Cingulate Stimulation for Depression****Corresponding author:**

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Key words:

Deep Brain Stimulation; Subcallosal Cingulate Area; Treatment Resistant Major Depressive Disorder; High Frequency Stimulation; Low Frequency Stimulation

Word count:

Main text - 4076, abstract - 247, references - 37, figures and tables - 8

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 ($\geq 40\%$ 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.

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 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, 2013; Eusebio et al, 2008; 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.

METHODS

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 Figure 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 ($\geq 40\%$ 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.

DBS System Implantation

The technique to insert bilateral DBS electrodes into white matter of Cg25 is detailed in the method section of the supplementary data. The target was planned as previously described [Mayberg et al, 2005; Lozano et al, 2008; Hamani et al, 2009]. An example of the specific target on a reconstruction of post-operative CT and pre-operative MRI is illustrated in Figure 2.

Stimulation Parameters

The initial stimulated contact was the second most distal contact on the lead, unless post-operative lead placement showed a different contact to be more optimal. The scans were reviewed by an expert team and recommendations made for the order of contact stimulation on each side. The initial device settings at the beginning of stimulation and after crossover were monopolar stimulation with amplitude 4mA, pulse width 91 μ Sec and frequency 130Hz for the high frequency group or 20Hz for the low frequency group.

For both groups, parameters of stimulation were fixed during the study and only minor adjustments in amplitude made to optimize clinical effects (as measured by the MADRS) were allowed at monthly evaluations. If a patient did not respond and did not improve according to the clinical evaluation and the MADRS (MADRS decrease <10% from previous evaluation), the amplitude was increased with 2mA up to 8mA (highest amplitude allowed). A change in contacts was made if there was either no response or worsening using higher (8.0mA) current. The new contact was the

second recommended contact and the settings were monopolar stimulation with current 4mA.

Concomitant Medications

All patients could maintain their anti-depressant medication regimen as well as any regularly scheduled psychotherapy. During the study (from the first baseline meeting to the end of the study) patients did not receive new medications (excluding sleep aids and other drugs to manage non-depression related conditions) nor increased current antidepressant medication doses.

Statistical Methods

Efficacy data are presented primarily on an intention-to-treat basis, meaning that all randomized patients were included in the analyses and data are presented as per the randomized treatment with last observation carried forward. Due to the small number of patients recruited to this study, statistical tests were not used and percent changes are simply compared to one another at face value.

RESULTS

The data for a total of 9 patients from 3 sites who participated in this study have been analyzed (see demographic details in Table 1).

As shown in Table 2, four out of nine patients achieved the response criterion at the end of the study ($\geq 40\%$ reduction of the MADRS score compared to mean baseline values). The mean percent change from baseline of MADRS score showed an improvement in both high and low frequency groups after 3 and 6 months of stimulation, indicating that the degree of severity of depressive symptoms had decreased. After cross-over the MADRS scores improved further in both groups, with better results in the high frequency group.

Of the initial patients, only 6 out of 9 patients participated in the second phase of the study (6-12 months after stimulation was initiated) and only 5 out of 9 patients were crossed-over to the other frequency stimulation group. Two patients (no. 7 and no. 8) chose to withdraw after 6 months of active stimulation due to a lack of change in their clinical state. One patient (no. 3) that had a significant clinical improvement after 3 months of active stimulation was unable to comply with study requirements and withdrew. Patient no. 9 experienced a satisfactory functional improvement after 6 months and asked not to be crossed-over; she agreed to continue the blinded follow-up protocol. The study team accepted all these patients' requests.

The primary endpoint of the cross-over study was the percentage of change in the MADRS score after six months of active stimulation. In this analysis the results of 6 months of stimulation (the first period of the study) were compared to the mean baseline score while the results of 6 months of stimulation after cross-over (the second period of the study) were compared to the results at the time of cross-over (i.e., 7 months after surgery). As shown in Figure 3a, in the analysis of the cross-over study, the mean percent change of MADRS score showed an improvement in the all patients group as well as in each of the high and low frequency stimulation groups, after 6 months of active stimulation (-15.1 ± 20.2 ; -15.4 ± 21.1 and -14.7 ± 21.1 respectively).

This study could not demonstrate a significant difference in MADRS score change in high vs low frequency stimulation (Figure 3a). Hence, the primary endpoint of the study was not achieved. The HRSD showed a mild improvement with the low frequency stimulation while the QIDS, CGI and PGI showed a mild improvement with the high frequency stimulation (Figure 3b). The mean GAF score showed an overall

improvement in functioning of the patients after 6 and 12 months of stimulation, with better results in the high frequency group. The mean Q-LES-Q score showed improvement in the patient's overall quality of life after 12 months of stimulation but only for the high frequency group. According to the clinicians and patients' global impression scale the severity of illness score improved from "markedly ill" to "mildly ill" or "moderately ill" after 12 months of stimulation for the high frequency group but no improvement was demonstrated for the low frequency group. The same scale showed that the patients were 'minimally improved' for the low frequency group and 'much improved' for the high frequency group after 12 months of stimulation.

Comparison of the effect of stimulation in the first period of the study (prior to cross-over) and the second period of the study (after cross-over) yielded notable findings, as illustrated in Figure 4a. The mean effect at the end of the first period was less than the mean effect at the second period in all patients (-13.0 ± 22 and -23.4 ± 19.9 respectively). The mean effect of the first period was higher than mean effect of the second period in the low frequency group (-18.3 ± 25.5 and -7.7 ± 10.9 respectively). On the contrary, the mean effect of the first period was lower than mean effect of the second period in the high frequency group (-8.7 ± 20.6 and -31.3 ± 19.3 respectively). The mean percent change with high frequency stimulation after the cross-over was close to response criteria. Figure 4b shows that all the other tests (HRSD, QIDS, CGI and PGI) demonstrated similar results to the MADRS score.

For further evaluation, we divided the patients into a high then low frequency stimulation group versus a low then high frequency stimulation group, using intention to treat analysis. As illustrated in Figure 5, low followed by high frequency stimulation was more effective than high followed by low frequency stimulation (percent change of MADRS at the end of the study was -36.2 ± 23.5 and -6.4 ± 25.2 respectively). The mean percent change with low then high stimulation was close to the response criterion. All the other scales (HRSD, QIDS, CGI and PGI) demonstrated similar results to the MADRS scale.

Table 3 demonstrates the results of the cognitive tests (the CANTAB battery). Analysis of the cognitive tests reveals improvement after 12 months of stimulation in most tested cognitive aspects (one-touch stocking of Cambridge; spatial span; rapid visual information processing; affective go-no go) while partial or no improvement was demonstrated in two tests (delayed matching to sample; choice reaction time). Of note, similar to the improvement in the MADRS scale, the improvement in

cognitive tests in the “low then high” frequency stimulation group was greater than that in the “high then low” frequency stimulation group.

All patients were evaluated twice at 2 and at 4 weeks after the implantation, before randomization and at the start of stimulation. Only a small mean change of MADRS from baseline was found 2 weeks and 4 weeks post-operation (-9.8 ± 21.6 and -0.9 ± 11.3 , respectively). The patients who were responders at the end of the study had a higher improvement of the MADRS score at both 2 and 4 weeks post-operation (-15 ± 13.9 and -8.7 ± 12.1 respectively) compared to non-responders (-5.6 ± 27.2 and 5.2 ± 6.2 respectively).

Forty adverse events were reported and only one of these events was reported as a serious adverse event (SAE). 28 adverse events were reported as being possibly or definitely related to the device/procedure, of which 13 and 15 events were reported before the stimulation was activated and during active stimulation respectively, with no difference between high and low frequency stimulation groups. A detailed list of adverse events can be found in the result section of the supplementary data.

DISCUSSION

This study was designed as a prospective, multi-center, double-blind, randomized, and controlled study lasting 13 months from implantation, with 2 different treatment groups: subcallosal cingulate DBS with high frequency versus low frequency. This is the first study evaluating the most effective stimulation parameters for DBS in a TR-MDD population. Given the small numbers, detailed statistical analysis remains challenging. Nonetheless given that in most DBS for depression studies the number of patients is small (see meta-analysis by Nangunoori et al, 2013), the results of the study here present a significant contribution to the literature, being the largest published double-blind study of Cg25 DBS for depression.

As measured by a range of validated scales, depression, anxiety, daily functioning, symptom severity, severity of illness, quality of life and cognitive aspects all improved after DBS. Of note, the patients who were responders at the end of the study had a higher improvement of the MADRS score at both 2 and 4 weeks post-operation. Reduction of symptoms at this period is usually considered as an insertion effect, secondary to the mild edema as the electrode reaches the target [Mestre et al, 2016]. Our preliminary results suggest that the insertion effect might be a predictor for future clinical improvement.

Only one of the nine patients was responder after 6 months of stimulation, in contrast to previous open studies that reported 40-60% response rate after 6 months [Lozano et al, 2008; Holtzheimer et al, 2012]. Open label methodology has many disadvantages and a significant placebo bias effect. Although the patients/providers were blinded to stimulation parameters, they were aware that a procedure had been performed so a placebo effect in this study cannot be excluded. However, we believe that the lower response rate mainly reflects the double-blind methodology of our study.

Three out of six patients responded well to prolonged treatment at 12 months of stimulation. Increased response rate over time is in line with previous depression DBS studies [Lozano et al, 2008; Holtzheimer et al, 2012; Bergfeld et al 2016; Bewernick et al 2010; Kennedy et al 2011; Crowell et al, 2015]. This is also not unusual with other conditions treated with DBS, such as dystonia, where prolonged stimulation appears necessary to produce optimal clinical benefit. Long-term DBS probably causes neuroplasticity and CNS remodeling effects that are necessary for the treatment response [Timmermann et al, 2004]. Notwithstanding this, with

depression caution is warranted as even severe disease could be self-limiting and its natural history might yield similar results.

We did not demonstrate a significant difference in MADRS score percent change in high vs low frequency stimulation, but it was interesting that high frequency stimulation yielded better results than low frequency stimulation after 6 months of stimulation. The short term (first 6 months) effect of stimulation was better in the low frequency group while the long term (second 6 months) effect of stimulation was superior in the high frequency group. The lack of significance might be due to the small sample size. It should be mentioned that these differences could also be explained by differences in group composition (for example, the group that began with low-frequency stimulation may have been more responsive to the treatment). A longer duration of stimulation might be required to observe a change in symptomatic response, regardless of frequency. For both groups, figure 5 shows linear changes in MADRS over time that are consistent across both stimulation periods. However, our results may imply that long term brain plasticity is divergently influenced by stimulation frequency.

Differential effects of high and low frequency stimulation are also reported in other diseases. Most of the optimization protocols for subthalamic stimulation in Parkinson's disease recommend high frequency stimulation although some studies reported that low frequency subthalamic nucleus stimulation reduced side effects such as aspiration, axial instability, freezing of gait and word fluency [Xie et al, 2015; Vallabhajosula et al, 2015; Timmermann et al, 2004; Wojtecki et al, 2006; Hamani et al, 2010].

Recent animal studies support the high frequency stimulation paradigm for depression. Hamani et al. (2010) studied the impact of different DBS stimulation settings such as amplitude and frequency (130 vs 20 Hz) in the ventromedial prefrontal cortex (vmPFC), the parallel target of the Subcallosal Cingulate gyrus that is used in clinical studies, in naïve rats. They found that the anti-depressant like effects of DBS varied as a function of stimulation settings and high frequency was more effective than low frequency stimulation. Lim et al (2015), found that high frequency (100 Hz) but not low frequency (10 Hz) stimulation of the vmPFC improved various depression-related behavior in both naïve rats and in a rat model of depression. The findings in these animal studies are therefore in keeping with what we found in our study here.

Over and above the direct findings of this study, there were important lessons to be learned from its scientific and organizational design which should help better plan future DBS studies for psychiatric indications [Fins et al, 2017].

Double blind DBS studies. DBS for depression is an experimental treatment. Until now most of the studies that evaluated the effectiveness of DBS for depression were not randomized controlled studies [Lozano et al, 2008; Holtzheimer et al, 2012; Bewernick et al, 2010; Nangunoori et al, 2013; Kennedy et al, 2011; Crowell et al, 2015; Loxano et al, 2012; Puigdemont et al, 2012]. Randomized controlled trials (RCTs) are considered to be the gold-standard to determine efficacy and safety. It is well known that in clinical studies for depression the placebo rate is high. The placebo effect and its moderators have been examined extensively in adult populations with major depressive disorder [Jakovljević, 2014]. It is important to mention that the placebo effect is related to the severity of depression. In the most severely depressed patients, the response to placebo and to active drugs is small and the drug-placebo differences are relatively modest [Licht et al, 2013]. The placebo response in depression is large in both pharmacological and non-pharmacological interventions [Brunoni et al, 2009]. It is also clear that the operation and electrode implantation have a high placebo rate and in the past, sham surgeries have demonstrated dramatic placebo effects [Tavel, 2014]. Therefore, it is extremely important to test the efficacy of DBS for TR-MDD using a double-blind design. Most recently, two reported studies used a double-blind design for Cg25 stimulation but had a small number of patients and short stimulation duration: Ramasubbu et al 2013 (4 patients; 3 months) and Puigdemont et al 2015 (5 patients; 6 months). A prospective, randomized trial of Cg25 stimulation for severe, medically refractory MDD (the BROADEN study) was discontinued after the results of a futility analysis predicted the probability of a successful study outcome to be low (no published data yet available). Another study used a double-blind design for Ventral Anterior Limb of the Internal Capsule stimulation (16 patients, 3 months) and found that during active DBS patients scored significantly lower on depression scales than during sham DBS [Bergfeld et al, 2016].

Number of patients. This study aimed to recruit of 60 patients over 2 years. The recruitment was prematurely stopped after 9 patients. Future studies should consider the difficulties in recruiting large numbers of TR-MDD patients for DBS treatment. These difficulties could be due to the perception of DBS as an invasive procedure by physicians and the patients as well as strict inclusion/exclusion criteria. In most centers, this study was the first to treat depression with DBS procedure in the city or

state. As DBS becomes more popular in psychiatry we hope that more physicians and patients would positively consider participating in DBS studies. Another important barrier in recruiting a large sample of patients is the high cost of DBS studies. In DBS studies, on top of the regular expenses of recruitment, evaluation and follow-up, the budget includes operation, device and long term programming follow-up. In addition to difficulties with patient recruitment, we faced a high rate of patient attrition; 3 out of 9 patients (33%) were unavailable for assessment at the 12 month follow-up. The attrition rate reported in long-term depression treatment studies is usually relatively high; 23% after 3-6 months of treatment and 47% after 12 months of treatment [Warden et al, 2009a; Warden et al, 2009b]. Other preliminary DBS studies for depression also reported a relative high patient attrition rate after 12 months (20% by Kennedy et al, 2010; 26% by Malone et al, 2009).

Multi-center DBS studies. This study aimed at recruitment from 8 centers. Actual recruitment was done only in 3 centers. DBS treatment requires a dedicated multidisciplinary team of psychiatrists, neurosurgeons, psychologists and neurologists. All expertise should be available in the same center to provide complete care. Split site working with patients receiving their psychiatric care in one center whilst undergoing neurosurgery at a different center is unlikely to encourage confidence and recruitment for this group of patients. Future studies should consider the ability and willingness of different centers to provide this expertise individually and then collaborate in a multi-center study.

Quantitative rating scales and cognitive assessment. While only one patient was a responder after 6 months of stimulation according to the MADRS scores, all the other scores (HRSD-17, QIDS-SR, Q-LES-Q, GAF, HAM-A, CGI and PGI) showed that the rating of depression, anxiety, daily functioning, symptom severity, severity of illness and quality of life *had* improved after 6 months of stimulation. Five out of seven cognitive tests revealed improvement after 12 months of stimulation. Future studies should consider how rating scales should be selected and completed and should be designed with both the patients' and clinicians' time in mind to eliminate unnecessary work and ensure data is collected completely. Specific rating scales should be chosen to focus the data collection within a specific area to minimize the amount of data that is collected.

In conclusion, our study suggests that Cg25 DBS is a promising therapy for treatment-resistant major depressive disorder. Based on our current data, long term high frequency stimulation is likely to confer the best results. Larger scale

randomized double blind trials are needed in order to evaluate the most effective stimulation parameters for Cg25 DBS.

ACKNOWLEDGEMENT:

The authors acknowledge Drs Helen S. Mayberg, Andres M. Lozano and Clement Hamani contribution to the study design and thank them for a series of helpful recommendations about patients' treatment.

CONFLICTS OF INTERESTS:

The study was organized and sponsored by the St Jude Medical LTD. The co-author Peichel DeLea is an employee of St Jude Medical LTD. No other conflicts of interests.

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FIGURE LEGENDS

Figure 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 ($\geq 40\%$ 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).

Figure 2: The Anatomic Target of Stimulation: Reconstruction of Post-operative CT and Pre-operative MRI.

An example of the location of the second most distal electrode contact is demonstrated in sagittal (a) and coronal (b) reconstruction images of post-operative CT and pre-operative MRI.

Figure 3: Mean Percent Change at 6 Months of Active Stimulation with High vs Low Frequency Stimulation

A. The mean percent change of MADRS (Montgomery and Asberg Depression Rating Scale) score at 6 months of active stimulation showed an improvement in all the patients (green) as well as in each of the high (blue) and low (red) frequency stimulation groups, after 6 months of stimulation. This analysis included both first and second episodes of patients # 1,2,4,5 and 6 but only first episode of patients # 3,7,8 and 9.

B. The mean ($\pm$ SD) percent change at 6 months of active stimulation of MADRS, Hamilton Rating Scale for Depression (HRSD), Quick Inventory of Depressive

Symptoms-Self Report (QIDS), Clinician and Patient Global Impression of Severity and Improvement (CGI, PGI).

Figure 4: Mean Percent Change with High vs Low Frequency Stimulation Before and After Cross-Over

A. The mean percent change in MADRS (Montgomery and Asberg Depression Rating Scale) score at the first period (prior to cross-over) in all patients (n=9, green), high frequency (n=5, blue) and low frequency (n=4, red), and at the second period (after cross-over) in all patients (n=6, green), high frequency (n=4, blue) and low frequency (n=2, red)

B. The mean ($\pm$ SD) percent change at the first period (prior to cross-over) and at the second period (after cross-over) in all patients (green), high frequency (blue) and low frequency (red), as measured by MADRS, Hamilton Rating Scale for Depression (HRSD), Quick Inventory of Depressive Symptoms-Self Report (QIDS), Clinician and Patient Global Impression of Severity and Improvement (CGI, PGI).

Figure 5: Mean Percent Change with High then Low vs Low then High Frequency Stimulation

A. The mean percent change in MADRS (Montgomery and Asberg Depression Rating Scale) score over time of all patients (green), low followed by high frequency stimulation (dark gray) and high followed by low frequency stimulation (light gray), with last observation carried forward. Patient no 9 did not cross over and was excluded from this analysis.

B. The mean ($\pm$ SD) percent change over time of all patients (green), low followed by high frequency stimulation (dark gray) and high followed by low frequency stimulation (light gray), as measured by MADRS, Hamilton Rating Scale for Depression (HRSD), Quick Inventory of Depressive Symptoms-Self Report (QIDS), Clinician and Patient Global Impression of Severity and Improvement (CGI, PGI).

Table 1: Demographics

Demographics			
	High Frequency Stimulation Group*	Low Frequency Stimulation Group*	Overall
	n=5	n=4	n=9
Male n (%)	3 (60)	1 (25)	4 (44)
Female n (%)	2 (40)	3 (75)	5 (66)
Age, years (mean)	43	51	46
Weight, kg (mean)	78	94	85
Mean Baseline MADRS Score (mean $\pm$ SD)	34.7 $\pm$ 2.8	32.1 $\pm$ 2.6	33.5 $\pm$ 2.9

*Based on group assignment at the Initial Programming Visit (Week 4)

Table 2: Individual and Mean MADRS Scores Over Time

Individual and Mean MADRS Scores Over Time (months from start of active stimulation)					
Individual MADRS scores (% reduction of the MADRS score compared to baseline values)					
Mean MADRS scores (% mean reduction of the MADRS score compared to baseline $\pm$ SD)					
	Baseline	3 months	6 months	9 months	12 months
High Frequency Stimulation Group*					
Patient no 2	34	35 (2.94)	38 (11.76)	29 (-14.71)	38 (11.76)
Patient no 5 **	39	29 (-25.64)	26 (-33.33)	27 (-30.77)	22 (-43.59)
Patient no 7 #	35.5	37 (4.23)	36 (1.41)		
Patient no 8 #	31.5	37 (17.46)	33 (4.76)		
Patient no 9 **	33.5	21 (-37.31)	24 (-28.36)	13 (-61.19)	13 (-61.19)
Mean MADRS (% mean reduction compared to baseline $\pm$ SD)	34.7	31.8 (-7.7 $\pm$ 22.8)	31.4 (-8.8 $\pm$ 20.6)	28 (-22.7 $\pm$ 11.4)^	30 (-15.9 $\pm$ 39.1)^
Low Frequency Stimulation Group*					
Patient no 1	34.5	35 (1.45)	31 (-10.14)	34 (-1.45)	26 (-24.64)
Patient no 3 ** ##	33	15 (-54.54)			
Patient no 4 **	32.5	22 (-32.31)	28 (-13.85)	17 (-47.69)	14 (-56.92)
Patient no 6	28.5	31 (8.77)	30 (5.26)	11 (-61.40)	26 (-8.77)
Mean MADRS (% mean reduction compared to baseline $\pm$ SD)	32.1	25.7 (-19.2 $\pm$ 29.6)	29.7 (-18.3 $\pm$ 25.5)	20.7 (-42.9 $\pm$ 28.4)	22 (-37.9 $\pm$ 25.4)
All Patients					
Mean MADRS (% mean reduction compared to baseline $\pm$ SD)	33.6	29.1 (-12.8 $\pm$ 25.02)	30.75 (-7.8 $\pm$ 16.5)	21.83 (-36.2 $\pm$ 24.8)	23.1 (-30.6 $\pm$ 28.6)

Blue – Scores under high frequency stimulation, Red – Scores under low frequency stimulation, Bold – Scores that reached the response criteria ($\geq 40\%$ reduction of the MADRS score compared to mean baseline values).

* Based on group assignment at the Initial Programming Visit (Week 4)

** Patient achieved response criteria at the end of the study, i.e. $\geq 40\%$ reduction of the MADRS score compared to mean baseline values.

Patient chose to withdraw.

Patient was unable to comply with study requirements and withdrew.

^ Patient no 9 did not cross over and was excluded from this calculation.

Table 3: Results of Cognitive Tests

ACCEPTED MANUSCRIPT

Cognitive Test Description & Results					Unit	Sense	Ran
One-Touch Stockings of Cambridge (OTS)							
Problems solved on first choice The number of assessment problems on which the first box choice made was correct.					-	+ve	0-15
		All Patients **	High then Low **	Low then High **			
	Baseline	10	10.25	9.6			
	After 12 months	10.6	10.5	11			
	Delta change	0.6	0.25	1.4			
Median latency to correct The median latency, measured from the appearance of the stocking balls until the correct box choice was made, for assessment problems.					ms	-ve	0-∞
		All Patients **	High then Low **	Low then High **			
	Baseline	29456	23529	35026			
	After 12 months	18820	21199	14063			
	Delta change	-9636	-2330	-20963			
Spatial Span (SSP)							
SSP Span length (Forwards) The longest sequence successfully recalled by the subject.					-	+ve	0-9
		All Patients **	High then Low **	Low then High **			
	Baseline	5.71	6.25	5			
	After 12 months	5.85	5.75	6			
	Delta change	0.14	-0.5	1			
Rapid Visual Information Processing (RVP)							
A Prime A' (A prime) is the signal detection measure of sensitivity to the target, regardless of response tendency. In essence, this metric is a measure of how good the subject is at detecting target sequences.					-	+ve	0-1
		All Patients **	High then Low **	Low then High **			
	Baseline	0.88	0.91	0.85			
	After 12 months	0.89	0.91	0.86			
	Delta change	0.01	0.00	0.01			
Median response latency The median response latency during assessment sequence blocks where the subject responded correctly.					-	-ve	0-∞
		All Patients **	High then Low **	Low then High **			
	Baseline	510.62	527.75	493.50			
	After 12 months	477.36	469.37	488.00			

	Delta change	-33.28	-58.37	-5.50	
Delayed Matching to sample (DMS)					
Percent correct The percentage of assessment trials during which the subject selected the correct box on their first box choice.				%	+ve 0-100
	Baseline	All Patients ** 82.5	High then Low ** 87.5	Low then High ** 77.5	
	After 12 months	79.3	82.5	75.0	
	Delta change	-3.2	-5.0	-2.5	
Median correct latency The Median latency from the available choices being displayed to the subject choosing the correct choice on assessment trials where the subject's first choice is correct.				ms	-ve 0-∞
	Baseline	All Patients ** 4389.4	High then Low ** 4465.5	Low then High ** 4313.2	
	After 12 months	4381.4	4685.6	3975.8	
	Delta change	-7.9	220.1	-337.4	
Probability of error given error This measure reports the probability of an error occurring when the previous trial was responded to incorrectly.				-	-ve 0-1
	Baseline	All Patients ** 0.194	High then Low ** 0	Low then High ** 0.292	
	After 12 months	0.269	0.276	0.262	
	Delta change	0.074	0.276	-0.029	
Choice Reaction Time (CRT)					
Median latency The median latency of response (from stimulus appearance to button press) on assessed trials that were responded to correctly.				ms	-ve 0-∞
	Baseline	All Patients ** 361.9	High then Low ** 360.6	Low then High ** 363.2	
	After 12 months	399.0	417.8	373.8	
	Delta change	37.1	57.2	10.6	
Affective Go/No Go (AGN)					
Median affective response bias		The Median time taken to respond correctly to each target word stimulus in the positive blocks minus the Median time taken to respond correctly to each target word stimulus in the negative blocks		ms	cx 0-∞
	Baseline	All Patients*** 76.1	High then Low*** 137	Low then High*** 55.8	

	After 12 months	37.7	125.5	-6.25			
	Delta change	-38.4	-11.5	-62.1			
Median correct latency (positive)		The median time taken to respond correctly to each target word stimulus in the blocks with positive targets			ms	-ve	0-∞
	Baseline	All Patients***	High then Low***	Low then High***			
	After 12 months	584.2	551	595.3			
	Delta change	-63.4	-21	-79.1			
Median correct latency (negative)		The median time taken to respond correctly to each target word stimulus in the blocks with negative targets			ms	-ve	0-∞
	Baseline	All Patients***	High then Low***	Low then High***			
	After 12 months	540.5	484	559.3			
	Delta change	-45.8	-26.5	-46.1			

* The sense of each measure is indicated by +ve (higher is better) or -ve (lower is better). Cx indicates complex score types where such correspondences cannot be stated.

** All patients (n=8); High then low frequency (n=4); Low then high frequency (n=4)

*** All patients (n=4); High then low frequency (n=1); Low then high frequency (n=3)

HIGHLIGHTS

High (130 Hz) vs low (20 Hz) frequency Cg25 deep brain stimulation for depression

Effect at 6 months after cross-over was higher than first 6 months of stimulation

MADRS scores improved more in high than low frequency groups

Long-term high frequency stimulation might confer the best results

Larger scale trials are needed to evaluate the most effective stimulation parameters

ACKNOWLEDGEMENT:

The authors acknowledge Drs Helen S. Mayberg, Andres M. Lozano and Clement Hamani contribution to the study design and thank them for a series of helpful recommendations about patients' treatment.

CONFLICTS OF INTERESTS:

The study was organized and sponsored by the St Jude Medical LTD. The co-author Peichel DeLea is an employee of St Jude Medical LTD. No other conflicts of interests.