Medial Forebrain Bundle Deep Brain Stimulation for depression

Deep brain stimulation (DBS) to the superolateral branch of the medial forebrain bundle (MFB), as proposed by Schlaepfer et al. (2013), has led to rapid anti-depressant response.

The medial forebrain bundle-a white matter pathway projecting from the ventral tegmental area-is a structure that has been under a lot of scrutinies recently due to its implications in the modulation of certain affective disorders such as major depression. Fenoy et al. discussed major depression in the context of being a disorder dependent on multiple relevant networks, the pathological performance of which is responsible for the manifestation of various symptoms of the disease which extend into emotional, motivational, physiological, and also cognitive domains of daily living. They focused on the reward system, an evolutionarily conserved pathway whose underperformance leads to anhedonia and lack of motivation, which are key traits in depression. In the field of deep brain stimulation (DBS), different “hypothesis-driven” targets have been chosen as the subject of clinical trials on efficacy in the treatment-resistant depressed patient. The “medial forebrain bundle” is one such target for DBS, and has had remarkably rapid success in alleviating depressive symptoms, improving anhedonia and motivation. We will review what we have learned from pre-clinical animal studies on defining this white matter tract, its connectivity, and the complex molecular (i.e., neurotransmitter) mechanisms by which its modulation exerts its effects. Imaging studies in the form of tractographic depictions have elucidated its presence in the human brain. Such has led to ongoing clinical trials of DBS targeting this pathway to assess efficacy, which is promising yet still lack in sufficient numbers. Ultimately, one must confirm the mechanism of action and validate proof of antidepressant effect in order to have such treatment become mainstream, to promote widespread improvement in the quality of life of suffering patients [1)].

There is an urgent need for clinical trials exploring DBS-slMFB in treatment resistant depression (TRD). Further efforts should pursue measuring baseline pro-inflammatory cytokines, oxidative stress, and cognition as possible biomarkers of DBS-slMFB response in order to aid clinicians in better patient selection [2)].

It has been hypothesized that activation of the dopamine (DA) system contributes to this effect. To investigate whether DBS in the MFB affects DA release in the striatum, Klanker et al., combined DBS with fast-scan cyclic voltammetry (FSCV) in freely moving rats. Animals were implanted with a stimulating electrode at the border of the MFB and the ventral tegmental area, and a FSCV microelectrode in the ventromedial striatum to monitor extracellular DA during the acute onset of DBS and subsequent continued stimulation. DBS onset induced a significant increase in extracellular DA concentration in the ventromedial striatum that was sustained for at least 40s. However, continued DBS did not affect amplitude or frequency of so-called spontaneous phasic DA transients, nor phasic DA release in response to the delivery of unexpected food pellets. These findings suggest that effects of DBS in the MFB are mediated by an acute change in extracellular DA concentration, but more research is needed to further explore the potentially sustained duration of this effect. Together,

our results provide both support and refinement of the hypothesis that MFB DBS activates the DA system: DBS induces an increase in overall ambient concentration of DA, but spontaneous or reward-associated more rapid, phasic DA dynamics are not enhanced. This knowledge improves our understanding of how DBS affects brain function and may help improve future therapies for depressive symptoms [3)].

Little is known about the consequences of modulating the MFB in affective disorders. Döbrössy et al., reviews the relevant pre-clinical literature investigating electrical stimulation of regions associated with the MFB in the context of several models of psychiatric disorders, in particular depression. The clinical data is promising but limited, and pre-clinical studies are essential for improved understanding of the anatomy, the connectivity, and the consequences of stimulation of the MFB and regions associated with the neurocircuitry of psychiatric disorders. Current data suggests that the MFB is at a “privileged” position on this circuitry and its stimulation can simultaneously modulate activity at other key sites, such as the nucleus accumbens, the ventromedial prefrontal cortex or the ventral tegmental area. Future experimental work will need to shed light on the anti-depressive mechanisms of MFB stimulation in order to optimize clinical interventions. brain stimulation]] (DBS) of the medial forebrain bundle (MFB) was reported to reduce symptoms in psychiatric disorders [4)].

Twenty-two cerebral hemispheres in 11 patients were investigated to find standardised parameters for diffusion tensor imaging (DTI) based fibre tracking to reliably visualise the MFB. Three different regions of interest (ROIs) were defined as seed regions for fibre tracking: the ipsilateral and contralateral superior cerebellar peduncle (SCP) and the nucleus raphe dorsalis (NRD). From each seed region the fibres were followed separately through the ventral tegmental area (VTA = second ROI) and their further courses and volumina were documented and compared. Minimal fibre length was set at 30 mm and the FA threshold at 0.12.

The fibre tracts starting in seed regions in the ipsilateral SCP and the NRD follow a similar course along the lateral wall of the third ventricle (hypothalamus) and the anterior limb of the internal capsule (ALIC) to inferior fronto-medial brain areas. These fibres are in accordance with the course of the MFB as described in various anatomical atlases. Consistently, a branch leaves the main fibre tract laterally to take a course through the external capsule to the temporo-parietal cortex. Fibre tracts starting from the contralateral SCP follow a more superior and lateral course, including the dentato-rubro-thalamic and the pyramidal tract.

Deterministic fibre tracking with standardised ROIs provides constant and reproducible delineations of the medial forebrain bundle. Its visualisation might help to adjust targeting in DBS for psychiatric disorders [5)].

Bilateral chronic continuous MFB-DBS results in temporary increase in exploration, which could explain the initial weight loss and decreased food intake observed. The capacity of MFB-DBS to reverse depressive-like phenotype seemed to be a factor of the integrity of the ascending dopaminergic fibers and the stress associated with the behavioral task. Continued investigation on the network of depression using neuromodulation platforms in animal models is crucial to further elucidate mechanisms of the disease and of DBS in the treatment of neuropsychiatric disorders [6)].

Outcome

Deep brain stimulation (DBS) of the supero-lateral branch of the medial forebrain bundle (slMFB) in treatment-resistant depression (TRD) is associated with acute antidepressant effects.

OBJECTIVE: Long-term clinical effects including changes in quality of life, side effects and cognition as well as long-term data covering four years are assessed.

METHODS: Eight TRD patients were treated with DBS bilateral to the slMFB. Primary outcome measure was a 50% reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) (response) and remission (MADRS <10) at 12 months compared to baseline. Secondary measures were anxiety, general functioning, quality of life, safety and cognition assessed for 4 years. Data is reported as conventional endpoint-analysis and as area under the curve (AUC) timeline analysis.

RESULTS: Six of eight patients (75%) were responders at 12 months, four patients reached remission. Long-term results revealed a stable effect up to four years. Antidepressant efficacy was also reflected in the global assessment of functioning. Main side effect was strabismus at higher stimulation currents. No change in cognition was identified. AUC analysis revealed a significant reduction in depression for 7/8 patients in most months.

CONCLUSIONS: Long-term results of slMFB-DBS suggest acute and sustained antidepressant effect; timeline analysis may be an alternative method reflecting patient's overall gain throughout the study. Being able to induce a rapid and robust antidepressant effect even in a small, sample of TRD patients without significant psychiatric comorbidity, render the slMFB an attractive target for future studies [7)].

Reports of changes in patients' social behavior during deep brain stimulation (DBS) raised the question whether DBS induces changes in personality. This study explored if (1) DBS is associated with changes in personality in patients suffering from treatment-resistant depression (TRD), (2) how personality dimensions and depression are associated, and (3) if TRD patients' self-ratings of personality are valid.

METHODS: TRD patients were assessed before DBS (n = 30), 6 months (t2, n = 21), 2 (t3, n = 17) and 5 years (t4, n = 11) after the initiation of DBS of the supero-lateral branch of the medial forebrain bundle (slMFB-DBS). Personality was measured with the NEO-Five-Factor Inventory (NEO-FFI), depression severity with Hamilton (HDRS), and Montgomery-Åsberg Depression Rating Scale (MADRS).

Personality dimensions did not change with slMFB-DBS compared with baseline. Extraversion was negatively correlated with HDRS28 ($r = -0.48$, $p < 0.05$) and MADRS ($r = -0.45$, $p < 0.05$) at t2. Inter-rater reliability was high for the NEO-FFI at baseline (Cronbach's $\alpha = 0.74$) and at t4 ($\alpha = 0.65$). Extraversion [$t(29) = -5.20$; $p < 0.001$] and openness to experience [$t(29) = -6.96$; $p < 0.001$] differed statistically significant from the normative sample, and did not predict the antidepressant response.

slMFB-DBS was not associated with a change in personality. The severity of depression was associated with extraversion. Personality of TRD patients differed from the healthy population and did not change with response, indicating a possible scar effect. Self-ratings of personality seem valid to assess personality during TRD [8)].

Case series

10 enrolled patients throughout one year post-implantation, showing sustained antidepressant effect up to 5 years. The primary outcome measure was a 50% reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) score, which was interpreted as a response. Deterministic fiber tracking was used to individually map the target area. An insertional effect was seen during the 4-week sham stimulation phase (29% mean MADRS reduction, $p = 0.02$). However, after 2 weeks of initiating stimulation, five patients met response criteria (47% mean MADRS reduction, $p < 0.001$). One patient withdrew from study participation at 6 weeks. Twelve weeks after initiating stimulation, six of nine remaining patients had a >50% decrease in MADRS scores relative to baseline (52% mean MADRS reduction, $p = 0.001$); these same six patients continued to meet response criteria at 52 weeks (63% overall mean MADRS reduction, $p < 0.001$). Four of five patients who achieved the 5-year time point analysis continued to be responders (81% mean MADRS reduction, $p < 0.001$). Evaluation of modulated fiber tracts reveals significant common prefrontal/orbitofrontal connectivity to the target region in all responders. Key points learned from this study that we can incorporate in future protocols to better elucidate the effect of this therapy are a longer blinded sham stimulation phase and use of scheduled discontinuation concomitant with functional imaging [9].

In a interim analysis of an ongoing pilot study of ten subjects, Fenoy et al., assessed the efficacy of MFB-DBS in a cohort of four TRD patients over a 52-week period using the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary assessment tool. Implanted patients entered a 4-week single-blinded sham stimulation period prior to stimulation initiation. Deterministic fiber tracking analysis was performed to compare modulated fiber tracts between patients.

Intraoperatively, responder patients displayed immediate increased signs of energy and motivation upon stimulation at target. There was no significant mean change in mood during sham stimulation phase. Three of 4 patients had >50% decrease in MADRS scores at 7 days post-stimulation initiation relative to baseline. One patient withdrew from study participation. At 26 weeks, two of 3 remaining patients continue to have >80% decrease in MADRS scores. One patient failed to have response; evaluation of modulated fiber tracts revealed reduced frontal connectivity to the target region.

LIMITATIONS: This is an interim report, with limited conclusions.

This study of MFB-DBS shows similar rapid anti-depressant effects within the first week of stimulation as initially reported by Schlaepfer et al. (2013). Implementation of anhedonia measurements would greatly augment characterization of the striking motivational effects observed. We urge others to pursue this target to further prove efficacy. ClinicalTrials.gov (identifier: NCT02046330) https://clinicaltrials.gov/ct2/show/NCT02046330 [10].

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