Neuromodulation in Psychiatric disorders: Experimental and Clinical evidence for reward and motivation network Deep Brain Stimulation: Focus on the medial forebrain bundle

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Funding information
Open access funding enabled and organized by ProjektDEAL

Abstract
Deep brain stimulation (DBS) in psychiatric illnesses has been clinically tested over the past 20 years. The clinical application of DBS to the superolateral branch of the medial forebrain bundle in treatment-resistant depressed patients—one of several targets under investigation—has shown to be promising in a number of uncontrolled open label trials. However, there are remain numerous questions that need to be investigated to understand and optimize the clinical use of DBS in depression, including, for example, the relationship between the symptoms, the biological substrates/projections and the stimulation itself. In the context of precision and customized medicine, the current paper focuses on clinical and experimental research of medial forebrain bundle DBS in depression or in animal models of depression, demonstrating how clinical and scientific progress can work in tandem to test the therapeutic value and investigate the mechanisms of this experimental treatment. As one of the hypotheses is that depression engenders changes in the reward and motivational networks, the review looks at how stimulation of the medial forebrain bundle impacts the dopaminergic system.

KEYWORDS
brain reward system, clinical and pre-clinical studies, DBS, major depressive disorder

Abbreviations: DBS, Deep Brain Stimulation; DSM, Diagnostic and Statistical Manual; FDA, Food and Drug Administration; HFS, High-frequency stimulation; MDD, major depressive disorder; MFB, medial forebrain bundle (primate including human); mfb, medial forebrain bundle (rodent); OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; sMFB, superolateral branch of the medial forebrain bundle; VTApp, projection pathway to/from VTA.

Edited by: Associate Editor: Dr. Michel Barrot

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1 | INTRODUCTION

Major depressive disorder (MDD, or depression) is a global disease with 300 million people affected—more so if we consider relatives, friends and caregivers—with a lifetime prevalence of 15%, impacting on quality of life, public health and multiple other socio-economic domains (DiLuca & Olsen, 2014; Sussman et al., 2019; WHO, 2017). A “disease of our civilization,” along with obesity, cardiovascular disease and cancer, the diagnosis of depression has increased by 20% between 2005 and 2015, probably due to population growth, ageing, changing life styles and diagnosis criteria (GBD 2015 DALYs and HALE Collaborators, 2016; WHO, 2017). If MDD is properly diagnosed and treated, the majority of patients will respond to the conventional sequential treatment strategy relying on medication, psychotherapy and electroconvulsive therapy. However, up to approximately one-third of the patients can end up being classified as Treatment-Resistant Patients (TRD), that is to say, they stay refractory to all currently approved treatments (Ruhé et al., 2012; Rush et al., 2006).

TRD today is not yet defined biologically, but more functionally and clinically: Patients are considered to be “treatment resistant” if they remain non-responsive to two antidepressant trials administered for a sufficient length of time, at an appropriate dose, with affirmation of treatment compliance (Akil et al., 2018; Kraus et al., 2019). On account of the heterogeneity of depression and the absence of clear biomarkers to aid with the stratification into appropriate subtypes (as well as due to the shortcomings of current therapies) less than 50% of the diagnosed MDD patients will go into remission after the first treatment, and then with each subsequent failure, the chances grow that the patient will not be helped by currently approved antidepressant treatments (Rush, 2007, 2011). Understanding is growing concerning the biology of MDD and why people might become treatment resistant (Akil et al., 2018; Drysdale et al., 2017; Williams, 2016). Nevertheless, there is a real need to identify new pathways, and develop and test novel treatment strategies such as neuromodulation, of which DBS, the focus of this paper, is one example.

The current review will describe in detail pre-clinical and clinical experience of investigating the therapeutic value of deep brain stimulation (DBS) of the superolateral branch of the medial forebrain bundle (slMFB; for human/primate the abbreviation “MFB” is used, but the rodent structure will be referred to as “mfb”). The results emerging from the series of clinical trials of our clinical group have been replicated independently by others (Fenoy et al., 2016, 2018). The slMFB appears to be a promising target for stimulation: it is a single target through which numerous projections pass through linking several regional hubs on the neurocircuitry associated with depression. In other words, stimulation of the slMFB can simultaneously modulate the activity in the nucleus accumbens (NAC), ventral tegmental area (VTA) or the prefrontal cortex (PFC), for example. One leading hypothesis that needs to be tested is that clinically slMFB DBS in part, particularly in the initial early stages, might act via modulating and “tuning up” of the mesolimbic and mesocortical dopaminergic pathways implicated in reward and motivation and which are suboptimal or dysfunctional in MDD (Berridge & Kringelbach, 2015; Castro & Berridge, 2014; Coenen et al., 2013; Döbrössy et al., 2015).

2 | NEUROMODULATION AND DBS

“Neuromodulation” typically refers to the alteration of nerve activity through targeted delivery of a stimulus, such as via a device or chemical agents, that results in the enhancement or the blocking of action potentials in the peripheral or central nervous system. The topic can be discussed in at least three contexts: (i) “Pre-clinical research,” it can be applied to study the function of neurons or networks by modulating their activity in health or disease models, for example, optogenetics, electrical stimulation; (ii) “Neuroprosthetics,” which are engineered and implantable devices that intend to replace or correct motor and sensory deficits, for example, cochlear or retinal implants; and, as is the case in this review, (iii.) “Therapeutic applications,” which are devices—such as DBS, Transcranial Magnetic Stimulation or Vagus Nerve Stimulation, used clinically to modulate the functions of organs or specific cortical or subcortical brain structures to achieve better physical or mental health, such as in the case of hypertension, or motor and psychiatric disorders (Luan et al., 2014).

DBS relies on implanting electrodes into selected brain structures and neuronal hubs associated with a given disease pathology. It is typically high-frequency stimulation (above 100 Hz). The electrodes are attached via a cable to an implanted impulse generator which sends electrical impulses into the targeted tissue area at a preprogrammed frequency, amplitude and pulse width (Figure 1). The electrical current around the contact area can depolarize and/or hyperpolarize neurons, thereby increasing and/or decreasing the neural activity. Electrical stimulation of the brain to modulate its function and shape human behaviour has been attempted during the 20th century by individuals applying questionable ethics (Baumeister, 2000; Delgado et al., 1952; Frank, 2018; Hariz et al., 2010; Oliveria, 2018). The “modern era” of DBS started in 1987 with Benabid and colleagues when they used high-frequency stimulation of the thalamus instead of the conventional thalamotomy and showed that it was as effective as the lesioning procedure to suppress tremor (Benabid et al., 1987, 1994). Since then DBS has become an integral part of treatment options.
of neurological disorders such as Parkinson's disease, Tremor and Dystonia, for example, with more than 160,000 patients implanted over the last 30 years, with the number of new implanted patients increasing by 12,000 every year (Lee et al., 2019).

3 | PSYCHIATRIC DISORDERS AND DBS

Following on the 1950s and 1960s with several controversial, unregulated and seemingly unscientific investigations of DBS, and the continual use of psychosurgery and the rise of pharmacological treatments, the late 1970s and 1980s saw little DBS involvement in psychiatric disorders. In 1999—12 years after Benabid and colleagues' paved the way for DBS therapeutics in motor disorders (FDA approval in Tremor since 1997, Parkinson's disease since 2002, and Dystonia since 2003)—the first small, but multidisciplinary trials investigating safety and efficacy of DBS in Obsessive Compulsive Disorder (OCD) and Tourette's took place (Nuttin et al., 1999; Vandewalle et al., 1999). These pioneering trials had precedents in psychosurgery and the selected stimulation targets corresponded to the areas that were previously irreversibly lesioned. The “historical” targets have been retained in the treatment of motor and movement disorders, but the “novel” DBS targets to treat psychiatric disorders that emerge are hypothesis based and driven by modern imaging approaches: they are chosen on the contemporary understanding of the stimulated area's role and contribution in health and disease pathology in the context of the disease in question (Coenen et al., 2011; Mayberg et al., 2005).

The use of DBS in psychiatric disorders today is regulated by consensual guidelines on ethical and scientific conduct developed by the leaders across several fields: psychiatrists, neurologists, psychologists, neuroscientists, neurosurgeons and ethicists (Nuttin et al., 2014). Clinical trials emerge from scientific data, designed and run by multidisciplinary teams and are hypothesis-driven. However, as the hypotheses concerning particular disorders vary, so do the stimulation targets: OCD (7 targets tested), MDD (7), Tourette's (6), anorexia nervosa (4), addiction (3), anxiety (2), obesity (2) and post-traumatic stress disorder (PTSD) (1) (Lee et al., 2019). To date, DBS treatment has been approved only for OCD (receiving a Humanitarian Device Exemption from the Food and Drug Administration (FDA) in 2008 to target the anterior limb of the internal capsule); stimulation in other psychiatric disorders, including Depression, fall under the “ investigational” trial category (for summary of results, see Cleary et al., 2015; Cormier et al., 2019; Graat et al., 2017; Lee et al., 2019).

4 | KEY SYMPTOMS OF DEPRESSION AND AETIOLOGY

Major depression is not a single disorder but a syndrome: a spectrum of associated behavioural symptoms that are
defined (and re-defined with time) in the Diagnostic and Statistical Manual (DSM) of Mental Disorders, American Psychiatric Association. Clinical depression is diagnosed if the person experiences five or more of the nine associated symptoms during a continuous 2-week period, with at least one of the symptoms being either depressed mood (reduced motivation) or loss of interest or pleasure (anhedonia; DSM-5 American Psychiatric Association, 2013). The other seven symptoms relate to unintentional changes in weight/apetite; insomnia/hypersomnia; psychomotor retardation; lack of energy; feelings of worthlessness, guilt; reduced capacity to think/concentrate or to make decisions and suicidal ideation. Given the nine criteria, 227 individual symptom profiles are possible that would qualify for depression diagnosis, and the numbers are even higher if one takes into account the bi-directionality of many symptoms (increase or decrease), or their sub-symptoms (Fried & Nesse, 2015).

There are multiple theories put forward concerning the aetiology of depression. One school of thought (described over 50 years ago; Beck, 1967) focusses around cognitive and behavioural theories of depression, meaning that the associated symptoms are rooted in maladaptive social constructs, negative thoughts and bad social models that people have acquired during their youth. According to these theories, depressed people did not learn or develop successful skills to cope with stressful experiences or traumatic events. However, the mainstream of scientists and medical professionals today accept that depression has significant biological components that can impact on a variety of factors such neurotransmitter systems, hormones, epi/genetics or inflammation (Dean & Keshavan, 2017). In other words, better understanding of the neural substrates of the disease—and their associated symptoms—should lead to improved, more rationale, and “customized” therapeutic strategies. The idea that depression has a strong biological component is not in contradiction with the cognitive theories of depression as these models can also be integrated with the biological knowledge of anatomy, neurochemistry and connectivity of the patient’s brain affected by depression (Disner et al., 2011).

5 | INDIVIDUAL DBS TARGETS IN DEPRESSION

Depression is now considered as a network disease with the symptoms emerging as a consequence of disorderly network connectivity, and not because of the dysfunction of a single given brain region. Four principle networks have been implicated in the clinical disorder: hyper-connectivity is reported within the “default mode” and the ventral limbic “affective” networks giving rise to symptoms such as rumination and dysphoria, respectively; and reduced activity is present within the dorsal “control/cognitive” and the frontal-striatal “reward” networks, producing disrupted cognitive control and anhedonia/reduced motivation, respectively (for a review, see Coenen et al., 2020; Li et al., 2018).

Numerous hubs—mainly on the “affective” and the “reward” networks—have been targeted by DBS in clinical trials in treatment-resistant MDD patients over the last 20 years (Figure 2). The first “hypothesis-led” DBS clinical trial in treatment-resistant depression patients was carried out by the neurologist Helen Mayberg and the neurosurgeon Andreas Lozano. Mayberg and Lozano targeted the subgenual cingulate gyrus (SCG, Brodman area 25; VCVS, ventral capsule ventral striatum; NAc, nucleus accumbens septi; BNST, bed nucleus of the stria terminalis; ITP, inferior thalamic peduncle; sLMFB, suprolateral branch of the medial forebrain bundle; lHb, lateral habenula)

![FIGURE 2 Deep Brain Stimulation in treatment-resistant depression (TRD). Numerous DBS targets have been tested in clinical trials to treat TRD. Legend: SCG, subgenual cingulate gyrus = cg25, Brodman’s area 25; VCVS, ventral capsule ventral striatum; NAc, nucleus accumbens septi; BNST, bed nucleus of the stria terminalis; ITP, inferior thalamic peduncle; sLMFB, suprolateral branch of the medial forebrain bundle; lHb, lateral habenula](image-url)
sections of the mfb also include components of the “reward” network, originating in the midbrain and passing through the mfb. The rationale for targeting the mfb (in rodents) or the MFB (in humans in clinical studies) with DBS is to modulate, either directly or indirectly, the pathways that regulate these functions and which become dysfunctional in depression.

6.1 Pre-clinical rationale

The majority of information we have concerning the role of the mfb has been obtained via pre-clinical, experimental research, mainly using rodents. The mfb is a complex and busy “information highway,” containing bi-directional, myelinated and unmyelinated projections of diverse neurotransmitter systems, including the monoamines, glutamate and GABAergic neurons (Nieuwenhuys, 1996; Nieuwenhuys et al., 1982). It is a not structure that can be visualized in its entirety using a specific staining, although subcomponents of it, for example the dopaminergic pathways, can be identified histologically. The descending and ascending fibres between the mesencephalon and the forebrain, connect different regions associated with multiple functions such as motor, cognition and emotion/mood processing. The fibres and hubs on the mfb also include components of the “reward” network such as the cingulate cortex, the NAC and the VTA (Russo & Nestler, 2013), structures which have been also implicated in depression. Sections of the MFB also pass through or are embedded in the lateral hypothalamic area, with collaterals projecting into this structure regulating metabolism and food intake.

The A9 dopaminergic neurons originating in the substantia nigra send projections through the mfb to dorostr striatal areas and are associated with motor control. Degeneration of these neurons is a key pathology in Parkinson’s disease. The ascending A10 midbrain mesocorticolimbic dopaminergic fibres start out from the VTA and project via the mfb to the NAC and dorsolateral prefrontal cortex (Alcaro & Panksepp, 2011; Ikemoto & Panksepp, 1999). There is ample evidence of that the mesocorticolimbic projection pathways contribute to positive emotional and euphoric behaviours that support exploration, and controls appetitive learning (Panksepp, 1998; Wise & McDevitt, 2018). Furthermore, these dopaminergic pathways are considered to underpin complex (human) emotions affected in depression such as “wanting,” “desiring,” “anticipating” and “hoping,” which in animal terms would translate into “motivation,” “anhedonia,” or “reward orientated behaviour” (Berridge, 2019; Berridge & Kringelbach, 2015; Howe et al., 2013). One hypothesis is that dysfunction of the dopaminergic projections running via the mfb on the limbic circuitry is responsible for symptoms observed in depression and in other psychiatric disorders (Heshmati & Russo, 2015). Dopamine’s contribution to key depressive-like symptoms has been further reinforced by lesion and optogenetic studies that recruit VTA dopamine neurons and have demonstrated that modulation of dopamine transmission changes the neural encoding of depression-related behaviours in the NAC and can also promote resilience (Friedman et al., 2014; Furlanetti et al., 2016; Heshmati & Russo, 2015; Lobo et al., 2012; Tye et al., 2013).

6.2 Clinical rationale

Non-invasive diffusion tensor tractography (fibre tractography) has been used to investigate the networks that were involved in the early lesion surgery approaches in psychiatric disorders such as depression (Schoene-Bake et al., 2010). The technique has also permitted better understanding of the fibre pathways that were affected by stimulation of Cg25, NAC and vclversus. During these investigations, it became clear that the DBS procedures all grouped around a single fibre pathway that had already been described as causative for hypomanic side effects when stimulating the subthalamic nucleus in Parkinson’s disease (Coenen et al., 2009). Coenen and colleagues went on to characterize the anatomy of a newly described superolateral branch of the medial forebrain bundle (sMFB; Coenen et al., 2012; Coenen et al., 2018). The rationale for this name (sMFB) at this moment was its positive affect mediating effect namely a pathological activation of the reward system. One would today rather speak of the VTApp (so projection pathway
out of/to the ventral tegmental area) to anatomically differentiate the structure from the trans-hypothalamic mfb of the rodent (Coenen et al., 2020). However, the authors strongly suggest an activation of the midline MFB (over slMFB DBS) as part of their working hypothesis. They later identified the MFB as a key regulator of the “reward” network. Since anhedonia is a clear dysfunction of the reward system, and it is a seminal symptom in depression, scientifically it was justified to stimulate what is considered as the main regulator of this system, the slMFB (or VTApp; Figure 3a–d; Döbrössy et al., 2015; Schlaeper et al., 2014).

In a series of clinical trials in TRD patients initiated in 2011, bilateral and chronic DBS of the slMFB was started. To date, data have been analysed and published from approximately 30 patients: The slMFB DBS produced fast and long-term antidepressant effects with 75% responders and sustained remission in 50% of the previously treatment-resistant patients, and this state of remission was present even after the first 4-year follow-up (Bewernick et al., 2017; Coenen, et al., 2019; Schlaefer et al., 2013). Interestingly, the trials also suggest the importance of continuous slMFB stimulation because with the patients were stimulation was inadvertently or voluntarily discontinued, the symptoms returned (Kilian et al., 2019).

Trials of slMFB DBS in depression patients are under investigation at other sites (for a summary, see Table 1). In a small clinical trial with six patients, Fenoy and colleagues recently reported similar quick onset of antidepressant effects, and increase in energy and motivation, in previously treatment-resistant depression patients (Fenoy et al., 2016, 2018). The longitudinal trial is still ongoing, but the therapeutic effects have been sustained for at least 1 year (at the time of publication of the data). The primary outcome measure in all the cited clinical trials has been the Montgomery–Åsberg Depression Rating Scale. However, to obtain a more dynamic and detailed understanding of impact of treatment, it has been suggested to use additional read-outs such as a frequent computerized adaptive test (CAT) of depression severity (CAT-Depression Inventory) that the patients can carry out from home (Sani et al., 2017).

Single case studies of slMFB DBS with 1–2 patients have also been conducted in some centres but these tend to be explorative studies, focussing on technical/targeting issues (Blomstedt et al., 2017; Coenen, et al., 2019). Recently, Davidson, Hamani and colleagues published a brief communication based on MFB DBS of two severe treatment-resistant MDD patients and reported no clinical response as measured using the HAMD-17 scale (Davidson et al., 2020). However, with the patient numbers limited to a couple, the paper is hard to appreciate especially because of a lack of intraoperative verification of the target region with microelectrode recording, a lack of autonomic response during test stimulation and a lack of comprehensibility of the target structure in the presented tractographic imaging next to the unclear stimulation strategies chosen.

FIGURE 3  Bilateral Stimulation of the superolateral branch of the medial forebrain bundle (slMFB) in Treatment-Resistant Depression. The figure shows diffusion tensor images (giving indications of fibre orientations and axonal density) merged with MRI images. In clinical trials targeting the slMFB, the DBS electrodes are placed (only right side shown) in close proximity but outside the ventral tegmental area (a). The DBS electrodes are intercalated between the red nucleus (RN) and the STN (subthalamic nucleus)/SNr (substantia nigra) complex (b). An overview showing the projection of the slMFB projects from the midbrain to the frontal lobes. (c). Detail of the target region and the volume of activated tissue (VAT), the area affected by the electrical field created around the electrode’s contacts (d)
**TABLE 1**  Clinical studies, case series and case reports on deep brain stimulation of the slMFB in major depression

| Reference            | No. of patients | Design       | Clinical Characterization                                                                 | Outcome (ST)                                                                 | Outcome (LT)                                                                 | Stimulation parameters                        | Comment                                                                 |
|----------------------|-----------------|--------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------|
| Schlaepfer et al. (2013) | 7               | SC case series | 3 F; length of current episode mean 7.5 ± 5.0 yrs; mean MADRS at time of inclusion 29.9 ± 8; mean number of ECT (unilateral) 14.3 ± 14.3. | 6/7 (85%) responders @ 12–33 wks 4/7 (75%) remitters @ 12–33 wks.            | -                                                                            | 2.86 mA mean amplitude (130 Hz, 60 μs), bipolar. | First case series on slMFB DBS.                                      |
| Fenoy et al. (2016)   | 4               | SC case series | 2 F; 46.3 ± 8.9 yrs; MD; MADRS inclusion mean 34 ± 2.9; multiple major depressive episodes (mean 3.8 ± 1.5 episodes); mean current episode length 6.3 ± 2.1 yrs; mean number of antidepressant medication 2.8 ± 0.9; non-responders to ECT and PT. | 2/3 (67%) responders and remitters @ 26 wks 1 dropout.                      | -                                                                            | @ 6 m: bilateral 3.2 V, 130 Hz, 60 μs. | Preliminary analysis from ongoing series: n = 6.                      |
| Bewemick et al. (2017) | 8              | SC case series | Cf Schlaepfer et al., 2013: 5 M; 30–55 yrs of age; MADRS mean 30 ± 7.39; current depressive episode length 7.1 ± 4.48 yrs; before trial 18.8 ± 7.03 antidepressant medications; ECT and PT without response. | 6/8 (75%) responders @ 52 wks 4/8 (50%) remitters @ 52 wks.                 | 7/8 (87.5%) significant reduction in most months @ 200 wks (area under curve analysis). | -                                                                            | Further evaluation of first case series (Schlaepfer et al., 2013) plus n = 1 additional patient; long term favourable effects up to 49 m. |
| Blomstedt et al. (2017) | 1              | Case report   | F (56 yrs); MADRS 43.                                                                      | MADRS 26 @ 6m.                                                               | >10 m no sustained effects, side effects. Received bed nucleus of stria terminalis. | 2.8–3 V, 130 Hz, 60 μs. | Significant comorbidities besides MD (anorexia, OCD); no tractographic targeting of slMFB target. |
| Fenoy et al. (2018)   | 6               | SC case series | See Fenoy et al., 2016. Mean length of current depressive episode 5.7 ± 2.1 yrs; antidepressant medication at implantation time point 2.5 ± 1.0 non-responder to ECT and PT. | -                                                                            | 4/5 (80%) >70% MADRS reduction @ 52 wks.                                   | 3.8V ± 1.2 V (130 Hz, 64 μs (SD 8.4)). | Further analysis of (Fenoy et al., 2016).                                |
| Coenen, et al. (2019) | 16              | SC Phase I clinical trial; DB condition for 8 wks after surgery; follow-up until 12 m reported | 51.5 ± 10.2 yrs; MADRS mean 29.6 ± 4; current depressive episode duration 10.3 yrs; 18.9 (average) antidepressant medications; 20 (average) ECT, 70 hr (average) of PT. | Significant improvement but no separation of DBS versus sham condition in outcome (both groups improved). | Significant decrease in average MADRS from 29.6 (SD ± 4, baseline) to 12.9 (SD ± 9), mean MADRS during 12 m DBS (whole group analysis). | 2.1 mA (SD 0.5 mA) (130 Hz, 60 μs) at start; mean stimulation amplitude 3.0 mA (SD: 0.5 mA) during 12 m. | Indication for micro-lesioning effect.                                |

(Continues)
6.3 | Side effects of slMFB DBS

DBS has been used clinically for over 30 years and is considered to be safe with few undesired effects or complications (similar to any other surgical procedure). Despite initial concerns, slMFB DBS does not result in hypomania. Due to its anatomical position with respect to the oculomotor nerve (CNIII), it leads to a high incidence of habituating diplopia and blurred vision which is confined to the titration phase only and not a long-lasting effect of chronic stimulation. More so, oculomotor activation is a good hallmark for the antidepressant response. Authors do not report an excessive bleeding rate associated with this target region.

Along with Cg25 and vc/versus, slMFB remains a promising clinical target for DBS in TRD patients, but more clinical and experimental data are required to investigate efficacy and mechanisms of action.

7 | EXPERIMENTAL MFB DBS

7.1 | mfb electrical stimulation in animals

Electrical brain stimulation in animal models emerged in parallel with the first clinical investigations in the 1950s and 1960s and the work was driven in large part by studies initially conducted by Olds and Milner (for a review, see Döbrössy et al., 2015). Over the years, two principal types of stimulation approaches of the MFB have emerged: the first decades have been dominated by animal models Intracranial Self-Stimulation (ICSS), with the last 15 years seeing a rise of pre-clinical exploration of DBS. Olds and Milner made an important observation: a brief electrical pulse delivered into deep brain structures via an electrode increased the likelihood of the rats revisiting the zone that coincided temporally with the stimulus. In a follow-up study, animals with electrodes implanted into areas associated with the lateral hypothalamic area—with MFB fibres passing through this zone—were shown to self-administer ad libitum electrical stimulation by lever pressing in a Skinner box (Olds & Milner, 1954). Their work was the first of many to discuss appetitive/reward/motivational behaviour in terms of neural substrates in the brain along the mfb axis, particularly in the septum, the cingulate and tegmentum areas.

7.2 | Health and safety issues of mfb DBS in rats

Pioneering mfb stimulation work by Routtenberg and colleagues suggested that chronic stimulation might not be a viable option if it activates the animals' reward network to
the detriment of the animals' health. Their studies concluded that given the choice between ad-lib mfb self-stimulation or food, the animals chose to ignore the food even if this led to self-starvation (Routtenberg, 1968; Routtenberg & Kuznesof, 1967; Routtenberg & Lindy, 1965). Hence, the feasibility of bilateral, chronic and continuous bilateral DBS in the mfb in rodents needed to be investigated.

Electrodes were implanted bilaterally into healthy control rodent mfb, approximate to but upstream from the VTA, targeting the zona carrying projections from the A10 midbrain ascending dopaminergic neurons (Furlanetti et al., 2015). The importance of placing the electrodes outside the VTA is that in the clinic, direct VTA stimulation is avoided as it causes oculomotor side effects (e.g., strabismus). The animals received continuous (24 hr/day) and chronic (up to 6 weeks) DBS with regular weight monitoring and intermittent behavioural assessment. The results showed that bilateral mfb stimulation (frequency 130 Hz, pulse width 100 µs, average current 290 µA) has a robust, reproducible, temporary and mild impact on welfare as shown by the rapid weight decrease, stabilization and subsequent weight gain despite of the ongoing, chronic electrical stimulation. A short-lasting (24–72 hr) increase in locomotion was observed which is consistent with the proposed role of this structure both in explorative behaviours (Alcaro & Panksepp, 2011). The study concerning the long-term viability of mfb DBS in rodents concluded that (i) continuous and chronic bilateral stimulation of the mfb in rodents was not detrimental to the animal's health and can be used as a platform to investigate the effects of mfb DBS in disease models and (ii) analysing c-fos expression as an indicator of neural activity, the mfb stimulation resulted in neuronal activation in infralimbic and prelimbic cortices, in NAC, and the dorsolateral thalamus, key areas implicated in the neurocircuitry of depression. The data confirmed that mfb DBS can modulate activity in distant neural structures.

7.3 | mfb DBS in a rodent model of depression: impact on behaviour

Choosing the appropriate model and behaviour tests in any area of research are important decisions as they impact on the validity and the relevance of the emerging data. An overview of animal models of depression is beyond the scope of this paper (for reviews, see Czéh et al., 2016; Overstreet, 2012; Wang et al., 2017). In our investigations, we use the Flinders Sensitive Line (FSL) rats that have been selectively breed over generation based on depressive-like phenotype, particularly reduced immobility in the Force Swim Test (FST; Overstreet & Wegener, 2013). FSL rats spontaneously display physiological changes including lower baseline levels of serotonin, dopamine and its metabolite DOPAC in the nucleus accumbens (Neumann et al., 2011; Wegener et al., 2012). Previous studies showed that antidepressive drug treatments of the FSL rats can correct behavioural deficits but also low basal dopamine levels in the NAC (Overstreet & Wegener, 2013; Roth-Deri et al., 2009; Zangen et al., 2001).

There is an over-reliance on the FST in the pre-clinical depression literature, with a tendency to over interpret the behavioural data emerging from this task (Hendrie et al., 2013; Trunnell, 2019). In our studies, we have diversified the tests and are using a broad spectrum approach to study depressive-like phenotype(s). An initial, and extensive behavioural characterization of the FSL described some of the phenotypes to be transient (i.e., not helpful in long-term studies), but others, such as weight change, reduced drive and motivation, and increased anxiety or cognitive, learning and memory deficits as long-term/robust impairments. Furthermore, FSL animals also exhibited bilateral chronic hypometabolism—as measured by 18-FDG PET—in the entorhinal cortex, a structure crucial in encoding spatial and non-spatial information and the formation of declarative memory (Thiele et al., 2016). Next, we assessed the range of behavioural modification achieved by mfb DBS in the FSL rats. The data showed that high-frequency continuous and chronic bilateral electrical stimulation of the mfb was safe, and lead to improvements in stress coping, exploration and cognitive behaviours like learning and memory performance (Figure 4a–c; Thiele et al., 2018). Importantly, shorter and fewer stimulation sessions of mfb DBS have also induced antidepressant effects in the FSL model (Edemmann-Callesen et al., 2015).

There are data from elsewhere that corroborate the behavioural effects of mfb DBS in other rodent models of depression. For example, in the chronic unpredictable mild stress model (CUMS), 7 days of mfb DBS had anti-anhedonic effects (when tested on the Froot Loops® consumption assay, a variant on the sucrose consumption test; Dandekar et al., 2019). However, antidepressant effects can be observed following shorter stimulation sessions already: animals receiving 4 hr of mfb DBS prior to testing showed increased mobility in the FST compared to unstimulated littermates in the FST, even though the stimulation had no impact on their general locomotor activity (Dandekar et al., 2017).

8 | BIOLOGICAL CONSEQUENCE OF MFB NEUROMODULATION: FOCUS ON DOPAMINE

The acute or chronic mechanisms of action of mfb DBS have been studied using pre-clinical models (for a summary, see Table 2 and Figure 5). As discussed in detail by others (Torres-Sanchez et al., 2017), due to the non-selective nature
of electrical stimulation, the intervention likely impacts diverse biological systems (monoamines, glutamate, GABA release, endocannabinoids, etc.) at multiple levels (gene expression, receptor density, neurotrophic factors), and in a temporally dynamic way (with different acute and chronic effects). The following sections will give an overview of how animal studies have contributed to our understanding of the biological consequences of mfb neuromodulation. As one of the hypotheses is that targeting the mfb impacts the reward and motivational networks, the focus in the next sections will be on the impact of stimulation on the dopaminergic system.

8.1 Rationale for studying dopamine's role in models of depression and neuromodulation

There are numerous ideas concerning the biological underpinnings of depression, including the monoamine hypothesis postulating that a dysfunctional monoamine system is a key contributor to major depressive disorder (Schildkraut, 1965). This is not to suggest that the monoamine hypothesis is the biological explanation for depression, but that a dysfunctional monoamine system likely plays a role in the emerging of certain key

**FIGURE 4** The FSL rodent model of depression. Typically, the Forced Swim Test is used to confirm the “depressive-like phenotype,” and the FSL animals show an increase in immobility (a). The Double-H Maze measures cognitive performance. On the Pre-Stimulation probe trial, FSLs showed a tendency to be slower to locate the escape platform; however, post-stimulation the FSLs were significantly faster suggesting a stronger encoding of the spatial information (b). The open field paradigm assesses locomotor activity and explorative behaviour. mfb DBS selectively eliminated the pre-stimulation freezing response—indicated by the time spent in Central Zone—in the FSLs compared to the Controls, suggestive of reduced anxiety in the experimental model (c). Micro-PET images of horizontal sections in the dorsal-ventral axis showing D2/D3 receptor ligand [18F]DMFP binding in the striatum (white arrows) prior to (d) and after (e) 11 days of raclopride administration in FSL animals. Raclopride reduced the binding potential of the D2/D3 receptor ligand [18F]DMFP. Moreover, the relative reduction of D2R receptor availability from baseline to post-MFB-DBS was 36%±5 (without DBS, FSL − group) and 25%±5 (with DBS, FSL + group) (f), indicating that the reduction was less in the group with MFB-DBS; in addition (data not shown), the raclopride-treated MFB-DBS animals had increased levels of D1R and D2R mRNA levels, suggesting that chronic and continuous MFB-DBS can act via the modulation of midbrain DA transmission, including an impact on post-synaptic DA receptor profiles. CA1 and CA3, hippocampal fields; MPA, medial preoptic area; mfb, medial forebrain bundle; PeFLH, perifornical part of lateral hypothalamus; AHA, anterior hypothalamic area; PH, posterior hypothalamicus; 3V (dorsal), third ventricle; MM, medial mammillary nucleus; cc, corpus callosum; SuM, supramammillary nucleus; VTA, ventral tegmental area; SNC, substantia nigra pars compacta; SRN, substantia nigra pars reticulate; AP, anterior-posterior; ML, mediolateral. Scale bar = 500 μm. Data are displayed as mean ± SEM. *p < .05; **p < .01. Panels (a–c) adapted from Thiele et al. (2020); (d–f) adapted from Thiele et al. (2018)
**Table 2** An overview of the parameters used in pre-clinical mfb DBS studies, with some of the main findings

| Reference            | Animal | Stimulation location | Amplitude (µA) | Frequency (Hz) | Pulse width (µs) | Duration | Main findings                                                                 | Comment |
|----------------------|--------|----------------------|----------------|----------------|------------------|----------|--------------------------------------------------------------------------------|---------|
| Ewing et al. (1983)  | M, SD  | UL (L), AP − 2.2, ML + 1.6, DV − 8.5 | 130            | 60             | -                | 10 s      | mfb stim induced DA release in CN.                                               | -       |
| Kuhr et al. (1984)   | M, SD  | UL (L), AP − 2.2, ML + 1.6, DV − 7 | 100            | 60             | 2 ms             | 2 s       | mfb stim induced DA release in CN, NAC.                                         | -       |
| Stamford et al. (1986)| M, SD  | UL (L), AP − 2, ML + 1.6, DV − 7.5–8.5 | 80–100          | 12.5–75        | -                | 10 s      | Verified the optimal stim parameters (50–62.5 Hz) for max DA release.           | -       |
| Stamford et al. (1987)| M, SD  | UL (L), AP − 2.2, ML + 1.6, DV − 7.5–8.5 | 80–100          | 25–200         | -                | 10 s      | Higher frequency stim led to shorter time period of DA and vice versa.          | -       |
| Kuhr et al. (1987)   | M, SD  | UL (L), AP − 2, ML + 2 | 300            | 60             | 2 ms             | 2 s       | mfb DBS resulted in SNC DA neuronal spiking accompanied by neostriatum DA release.| -       |
| Gonon (1988)         | M, SD  | UL (L), AP − 3.8, ML + 1.3–1.7, DV − 8.2–8.6 | 250            | 5 or 14        | 300              | 40 s      | Phasic stim was more potent in releasing DA compared to tonic stim.              | -       |
| Pillolla et al. (2007)| M, SD  | UL (L), AP + 0.1, ML + 2.0 (15°), DV − 8.0 | 690            | 20–80          | 300              | 1 s       | MFB DBS evokes an endocannabinoid-mediated short-term modulation of DA neuron activity.| -       |
| Friedman et al. (2012)| M, FSL| UL (L), AP − 5.3, ML + 0.4, DV − 8.3 | 300            | 10             | 1 ms             | 20 min    | VTA mfb restores VTA LFP in FSL rats to normal activity levels.                  | DBS “resets” networks to ameliorate phenotype. |
| Howard et al. (2013) | M, SD  | UL (L), AP − 4.6, ML + 1.4, DV − 7.0 | 300            | 5 pulses at 30Hz, DV − 60 s | 2 ms | 60 s trials within 45 min | Phasic mfb DBS Recovered DA depletion-induced dysfunctions. | Tonic stim showed no efficacy. |
| Furlanetti et al. (2015) | F, SD | BL, AP − 4.4, ML ± 1.2, DV − 7.8 | 250            | 130            | 100              | 24 h x 21 to 42 days | Chronic/continuous mfb DBS is safe. Increased c-fos expression NAC shell, PRL, md thalamic nuc, IHB. | No long-term welfare issues. |
| Furlanetti et al. (2015) | F, SD | BL, AP − 4.4, ML ± 1.2, DV − 7.8 | 250            | 130            | 100              | 24 h x 7 days | Recovery of anhedonic, depressive-like behaviours, Increased 5-HT in DRN & PRL, increased c-fos in PRL, NAC shell. | No change in 5-HT in NAC. |

(Continues)
| Reference                          | Animal | Stimulation location | Amplitude (µA) | Frequency (Hz) | Pulse width (µs) | Duration | Main findings                                                                 |
|-----------------------------------|--------|----------------------|----------------|----------------|-----------------|----------|-------------------------------------------------------------------------------|
| Bregman et al. (2015)             | M, SD  | BL, AP − 2.6, ML ± 2.2, DV − 8 | 100            | 130            | 90              | 1h microd. | Antidepressant-like response (FST), Increased activity in piriform ctx, PRL, NAC shell, VTA, anterior regions of caudate/putamen. |
| Furlanetti et al. (2016)          | F, SD  | BL, AP − 4.4, ML ± 1.2, DV − 7.8 | 250            | 130            | 100             | 24h x 21 days | mfb DBS rescues VTA DA lesion-induced depressive-like phenotype.                |
| Klanker et al. (2017)             | M, Wistar | UL (L), AP − 4.6, ML 1.0, DV − 7 | 200            | 120            | 80              | 30 min | Increased DA release in vm striatum following DBS onset.                      |
| Dandekar et al. (2017)            | M, Wistar | UL (L), AP − 2.5, ML + 1.7, DV − 8 | 200            | 130            | 90              | D1—8h D2—4h | Antidepressant-like response (FST), increased D2R in PFC, increase DAT in hippo. |
| Thiele et al. (2018)              | M, FSL | BL, AP − 2.8, ML ± 1.7, DV − 8.8 | 250            | 130            | 100             | 24h x 10 days | Recovery of depression-like phenotype, improved cognitive performance.         |
| Dandekar et al. (2019)            | M, Wistar | UL (L), AP − 2.5, ML + 1.7, DV − 8 | 200            | 130            | 90              | 8h x 7 days | Reverses anhedonic-like phenotype, regulates BDNF in plasma, CSF, hippo; differentially regulates cytokine levels. |
| Thiele et al. (2020)              | M, FSL | BL, AP − 2.8, ML ± 1.7, DV − 8.8 | 250            | 130            | 100             | 24h x 10 days | Rescued depressive-like phenotype, elevated D1R & D2R mRNA in NAC. Partial recovery of depression-induced reduction in D2R availability in striatum. |
| Ashouri Vajari et al. (2020)      | F, FSL | UL (L), AP − 2.8, ML + 1.8, DV − 7.8 | 250            | 130            | 100             | 5 s | mfb DBS evoked divergent DA release profiles across depressed v healthy models. |

**Abbreviations:** anterior–posterior; AP; BDNF, brain-derived neurotrophic factor; BL, bilateral; CN, caudate nucleus; CSF, cerebrospinal fluid; DA, dopamine; DAT, dopamine transporter; DRN, dorsal raphe nucleus; DV, dorsal-ventral; F, female; FSL, Flinders Sensitive Line; FST, forced swim test; hippo, hippocampus; L, left; lHb, lateral habenula; M, male; md, medial dorsal; mfb, medial forebrain bundle; ML, medial-lateral; NAC, nucleus accumbens; PFC, prefrontal cortex; PRL, prelimbic cortex; R, right; SD, Sprague-Dawley; SNC, substantia nigra pars compacta; UL, unilateral; VTA, ventral tegmental area.
symptoms associated with depression. The focus in this hypothesis has been mainly on serotonin and noradrenaline availability (Pereira & Hiroaki-Sato, 2018). However, there is strong clinical evidence that dopamine plays an important role in the aetiology of depression too, and in particular, in (i) the way it modulates the brain reward system (Gershon et al., 2007; Kapur & Mann, 1992); and (ii) its role in the two seminal symptoms of depression, anhedonia and reduced motivation (which are linked to reward system function). Furthermore, there is strong preclinical evidence that the A10 dopaminergic neurons projecting from the VTA to the NAC/dorsolateral PFC via the mfb are associated with motivation, exploration, appetitive learning and reward-driven behaviours (Heshmati & Russo, 2015; Ikemoto, 2007; Lobo et al., 2012; Wise & McDevitt, 2018).

8.2 | Dopaminergic mechanisms following mfb DBS in pre-clinical depression models

We first studied the role of dopaminergic mechanisms in mfb DBS in a lesion model of depression (Furlanetti et al., 2016). Sprague Dawley rats were given bilateral injection of 6-OHDA into the VTA (to lesion dopaminergic neurons) or were left unlesioned. Later, all animals received bilateral microelectrode implantation into the mfb followed by chronic continuous stimulation for 3 weeks. Behavioural tests were performed as baseline and following mfb-DBS, along with histological analysis. Baseline testing of the VTA-lesioned animals indicated depressive-like phenotype in comparison with controls. Response to mfb-DBS varied according to (i) the degree of dopaminergic depletion: animals with severe mesocorticolimbic dopamine depletion did not, while those
with mild dopamine loss responded well to stimulation; (ii) environmental conditions and the nature of the behavioural tests, for example, stressful versus non-stressful situations. The data suggested that mfb DBS can act via both dopamine dependent and independent pathways.

It has been demonstrated in control (non-depression model) animals that mfb-DBS can produce an increase in protein levels of dopamine D2 receptors and DAT in the PFC (Dandekar et al., 2017). Dandekar and colleagues recently reported that mfb DBS rescued depression-induced reduction in BDNF levels in plasma, cerebrospinal fluid and in hippocampus. Further mfb DBS was also found to differentially regulate neuroimmune cytokine levels (Dandekar et al., 2019). In a recent study, we examined the role of the D2 receptors in mfb stimulation-mediated behaviour changes in the FSL rodent model of depression following chronic D2 selective antagonist administration using [18F]DMFP PET to monitor changes in dopamine receptor availability (Figure 4d–f). The pharmacological blockage of D2R dopamine receptors with raclopride enhanced some symptoms associated with depressive-like phenotype, and stimulation partially rescued social interaction and the exploratory behaviours. The raclopride-treated mfb DBS animals had increased levels of D1R and D2R mRNA suggestive of stimulation-mediated upregulation of dopamine receptors. The data indicate that one potential mechanism of chronic mfb DBS is via the modulation of the midbrain dopaminergic system, including its post-synaptic receptor profile (Thiele et al., 2020).

8.3 mfb DBS: Dopaminergic firing and release

Pioneering studies by Grace and colleagues reported that the dopamine neurons have two types of firing patterns categorized as (i) low-frequency “tonic firing” (1–8 Hz), and that this firing pattern was interspersed with (ii) high-frequency firing (>10 Hz) called “bursts” or “phasic firing” followed by a long duration of inter-spike intervals (ISIs) known as “pause” (Bunney et al., 1973; Grace & Bunney, 1983, 1984a, 1984b). Based on the distribution of bursts and pauses, the frequency with which the dopamine neuron fire varies which, in turn, primarily drives the postsynaptic dopamine release, thereby affecting the physiological role of the neuron in itself. Therefore, understanding how mfb DBS affects the dopamine firing and subsequent release could provide an insight into its mechanism of action.

In vivo monitoring of dopamine is relatively difficult because the concentrations are low, and the release and the clearing times from the extracellular space are fast (for reviews, see Ou et al., 2019; Si & Song, 2018). The two main methods available today to measure dopamine release as a consequence of mfb DBS are microdialysis and fast-scan cyclic voltammetry (FSCV).

Technological advancements in the 1980s paved the way for estimating in vivo dopamine transients in response to stimulation, and FSCV emerged as a method providing improved spatiotemporal resolution for detecting dopamine levels in vivo (Ewing et al., 1983). Pioneering studies by Wightman’s lab, employing FSCV, reported dopamine as a major biological substrate of mfb DBS (Millar et al., 1985).

Subsequent studies described that the presentation of a reward increased the activity of dopamine neurons in awake behaving animals (Spanagel & Weiss, 1999). Since then, the origin and implications of low-frequency tonic firing and high-frequency phasic firing in the context of reward and motivation has received great attention (Paladini & Roeppe, 2014). One such seminal study was done by Ewing and his colleagues, where they had reported an increased extracellular dopamine release in the caudate nucleus/dorsal striatum in response to 60Hz DBS of mfb (Ewing et al., 1983). By combining FSCV and single-unit recordings, for the first time, Kuhr and colleagues observed that 60 Hz mfb DBS increased the spiking activity of substantia nigra dopamine neurons leading to an increased extracellular dopamine release at neostriatum, indeed confirming the involvement of dopamine neurons in the neuromodulation attained by mfb DBS (Kuhr et al., 1987).

Different studies compared a range of stimulation frequencies of mfb and the optimum frequency was reported to be 50–65 Hz, as this led to a maximum dopamine overflow compared to other frequencies. It was also noted that the frequency response was largely dependent on the time-course of stimulation suggesting an optimal stimulation paradigm of shorter trains with higher frequency (high frequency, low pulse width) or longer trains with lower frequency (low frequency, high pulse width). Longer trains of stimulation with higher frequency were not found to be effective as neurons became potentiated and the rate of dopamine uptake was higher than the rate of dopamine release (Kuhr et al., 1984; Stamford et al., 1986, 1987). In addition to frequency (20–100 Hz)-related changes, Gratton and his team analysed the dopamine response to mfb stimulation at different current intensities (200–800 µA). They concluded that higher electrical intensity produced long-lasting and larger electrochemical signals, meanwhile higher stimulation frequency increased the magnitude but not the duration of electrochemical signals (Gratton et al., 1988).

Gonon and colleagues studied the influence of the tonic and phasic firing patterns on the dopamine release. They reported that high-frequency phasic mfb stimulation was found to be twice as effective as regularly spaced low-frequency tonic stimulation for evoking dopamine release in olfactory tuberculum (Gonon, 1988). A more recent study conducted in the awake behaving rats reported that the mfb DBS (at
120 Hz) induced an increase in dopamine release in the ventromedial striatum sustained for about 40 s, adding more evidence to the involvement of dopaminergic system in mfb DBS (Klanker et al., 2017).

FSCV offers a temporal resolution of milliseconds, permitting the monitoring of stimulation evoked dopamine release in a more detailed fashion. Studies using healthy control rodents and pigs (i.e., not experimental models of depression) have shown increased and sustained dopamine release (measured in minutes) in the NAC following acute electrical stimulation (measured in seconds) of the VTA in short-term experiments (Grahn et al., 2014; Klanker et al., 2017; Settell et al., 2017).

In a recent study from our laboratory, we explored the effects of varying mfb stimulation parameters on dopamine release in the NAC, and compared the dopamine release profiles—measured using FSCV—across the experimental depression model, FSL and healthy control animals. We, for the first time, have shown that clinically relevant mfb DBS stimulation (130 Hz frequency and 100 μs pulse duration) evoked a dopamine release in the NAC in both groups of animals, albeit, the induced dopamine response was larger and longer lasting in the FSL animals compared to the healthy controls (Ashouri Vajari et al., 2020). We have also investigated the dopamine release profiles with varying pulse widths of the stimulation. The different dopamine response across the groups with changing pulse durations suggested alterations in chronaxie between the pathological and healthy control models due to physiological and anatomical differences, such as differences in fibre types and density, or differences in dopamine neuron excitability. However, the study did not address whether the larger and longer-lasting dopamine response in the FSL animals following mfb DBS was due to increased release or to reduced removal of dopamine from the synaptic cleft in the NAC, although previously others showed that FSLs have similar levels of dopamine transporter in this structure compared to healthy controls (Roth-Deri et al., 2009). The enhanced excitability following mfb DBS in the FSL animals could be on the grounds of changes in the VTA dopaminergic neuron’s cellular machinery regulating neural transmission.

Studies employing in vivo microdialysis also indicated the involvement of dopamine in mfb stimulation. Investigators reported increased dopamine release in the PFC with increasing frequency of stimulation and in addition, bursting mode stimulation was found to induce more dopamine release than tonic stimulation (Bean & Roth, 1991). Intracranial self-stimulation of mfb (100 Hz, 2 ms pulse width) was also found to increase the levels of dopamine and dopamine metabolites in NAC (Nakahara et al., 1989). In contrast, Bregman and colleagues reported that 130 Hz mfb stimulation (100 mA intensity and 90 μs pulse width) evoked an antidepressant-like behaviour in the forced swim test (FST) but they were unable to observe any significant dopamine release using microdialysis (although this is probably due to the limitations in temporal resolution of the method used; Bregman et al., 2015). These contradicting results clearly show the importance of choosing the pulse width of stimulation as longer pulse widths are considered to recruit more dopamine fibres when compared to shorter pulse widths due to the chronaxie of the fibre bundle (Kringelbach et al., 2007; Ranck, 1975). Moreover, the low temporal resolution of microdialysis could also affect the interpretation of the results as microdialysis is not sensitive to the transient dopamine release, which could be detected by FSCV.

### 8.4 Dopamine “ramping” theory

Development in the field of optogenetics helped researchers conduct pathway and cell-specific studies (Boyden et al., 2005). Using optogenetics, Tsai and colleagues studied the effects of selective stimulation of VTA dopamine neurons and reported that a high-frequency phasic stimulation induced higher dopamine transients in NAC when compared to tonic stimulation (Tsai et al., 2009). Interestingly, the dopamine transients produced by phasic stimulation was similar to natural reward-triggered dopamine release (Phillips et al., 2003), implicating that a researcher-guided stimulation of the mesolimbic pathway triggers a similar response to a natural reward. Optogenetic recruitment of VTA dopamine neurons was also found to alter the neural encoding of depression-like phenotype in NAC, in particular, phasic activation of VTA dopamine neurons reversed the depression-like phenotype induced by chronic mild stress (Tye et al., 2013). Chaudhury et al. reported that phasic activation of the VTA-NAC projection induced susceptibility, whereas inhibition induced resilience; and inhibition of the VTA-mPFC projection promoted susceptibility to social-defeat stress (Chaudhury et al., 2013). These studies indicate the complexity of the regulation of dopamine neuron firing, which could be dependent on the type of stressors or severity of the stress and suggests that it is highly context-dependent (Ungless et al., 2004; Valenti et al., 2012). Phasic optogenetic stimulation of VTA dopamine neurons was also reported to influence mPFC ensemble activity and behaviourally active states (grooming, rearing, locomotion), additionally enhancing beta-activity at a transient time scale (milliseconds) and high gamma activity at a prolonged time scale (minutes; Lohani et al., 2019).

Taken together, the literature suggests that phasic firing of dopamine neurons and dopamine release plays a vital role in the mechanism of action of mfb DBS. Howe and colleagues put forth a “dopamine ramping theory”: a
prolonged dopamine signalling (a 3rd mode, standing out from phasic and tonic signalling) in striatum that scales according to the distance and value of the reward, strongly suggesting that dopamine signalling plays a vital role in sustained motivational drive which is highly impaired in MDD (Howe et al., 2013). Recent reports also emphasize the role of dopamine in coding for “value”—estimating the available reward for investment of effort—thus contributing to the decision of whether or not to pursue a goal (Hamid et al., 2016). Different functional implications of dopamine firing and release has been reported as VTA dopamine firing was found to be involved in learning, whereas NAC dopamine release has been implicated in motivational drive and in encoding value of work (Mohebi et al., 2019). With our preliminary results reporting the prolonged dopamine release in response to mfb DBS in depressed rats compared to control rats (Ashouri Vajari et al., 2020), evidences point towards the involvement of dopamine release as a potential substrate of mfb DBS; however, further studies are required to delineate the underlying neural circuitry: mfb DBS at short pulse widths are unlikely to recruit dopamine fibres directly; hence, an indirect mechanism involving glutamatergic or GABAergic circuits may play a vital role as well (Ikemoto, 2010; Schlaepfer et al., 2013, 2014).

9 | DISCUSSION AND CONCLUSION

The aim of this review was to introduce the reader to deep brain stimulation (DBS) of reward and motivation network with focus on the medial forebrain bundle (mfb in the rodent; superolateral branch or slMFB in the human): an experimental therapeutic option currently being tested in clinical trials in major depressive disorder patients resistant to conventional treatment strategies. The review explored the idea that DBS in psychiatric disorders moved into the “modern” era once clinical trials became multi-disciplinary and hypothesis lead. We went on to introduce the slMFB as a DBS target in treatment-resistant depression, based on the rationale that it taps into the affect modulating network(s) responsible for motivation and hedonic behaviours. Among the many symptoms associated with depression, lack of motivation/interest and anhedonia are sine-qu-a-non requirements for the diagnosis, and it is thought that these functions—in large part—are regulated by dopamine.

The hypothesis that is being tested via clinical trials and experimentally as described in the review is that modulating the dysfunctional biological substrate for these traits will have antidepressant effects. Rapid onset and long-lasting clinical benefits of slMFB DBS have been reported by several groups from multiple clinical trials in treatment-resistant patients: is it important or essential to understand the mechanisms? After all, even today the mechanisms of action of DBS in PD are debated although it has been used for over 30 years as a symptomatic treatment. Trying to understand the mechanisms of action of slMFB DBS in depression is essential as it could improve outcome by better matching the therapy with particular patient subgroups, and improve our understanding of the dynamics and complexities of the biological consequences of electrical stimulation.

9.1 | How might mfb DBS work? What does the pre-clinical data suggest?

DBS is a form of non-selective electrical stimulation, that is, all biological matter within the “reach” of the electric current can be modified variably depending on the stimulation parameters (Jakobs et al., 2019). The rodent mfb is chemically and anatomically complex (Geeraedts et al., 1990a, 1990b; Nieuwenhuys et al., 1982), so it is highly likely that there are many concurrent events that occur when it is stimulated with DBS. Indeed, VTA DBS has been shown to modulate the BOLD signal in multiple regions including the ipsilateral dorsolateral prefrontal cortex, premotor/somatosensory cortex, anterior/posterior cingulate, insula and the striatum (Settell et al., 2017). However, the mechanisms of action of MFB DBS remain uncertain. In the following paragraphs, we will discuss some current ideas that are emerging from the “reward pathway modulating” school of thought.

Medial forebrain bundle DBS (in rodent or primates) very likely has different acute and chronic biological effects, but to date, mainly the acute changes have been studied, and the focus has been on modulation of neurotransmitter transmission. Studies targeting the ventromedial part of the prefrontal cortex have concentrated on serotonin-dependent mechanisms (Hamani et al., 2010; Rummel et al., 2016); similarly, the antidepressant effects described following mfb DBS focus on modulation of the mesolimbic dopaminergic midbrain reward system (Dandekar et al., 2017; Edemann-Callesen et al., 2015; Thiele et al., 2018). Targeting this network is justified as dopaminergic neurons in the VTA in the FSL model have reduced burst activity which is “corrected” by electrical stimulation (Friedman et al., 2007, 2008; Friedman et al., 2009, 2012), and dopamine release has been measured in the nucleus accumbens by voltammetry following mfb or VTA DBS by us and others (Ashouri Vajari et al., 2020; Klanker et al., 2017; Settell et al., 2017).

One possibility to consider is that mfb DBS initially activates the descending myelinated glutamatergic fibres from the PFC to the VTA, which, in turn, increases directly dopaminergic transmission, including in the NAC (Ikemoto, 2007, 2010). VTA dopamine neurons could also become more active indirectly due to the glutamatergic-mediated
rebound inhibition of VTA GABAergic neurons (Steffensen et al., 2001). Direct electrical stimulation of the PFC has been shown to result in increased dopamine in the NAC and this is thought to be independent of ionotropic glutamate receptors intrinsic within the NAC (Taber et al., 1995). However, direct intra-VTA application of the ionotropic NMDA and AMPA receptor agonists dose dependently increased dopamine release in the ventral striatum (Karrerman et al., 1996; Taber et al., 1995). A complementary mechanism can also be envisaged via the ascending mesocortical pathway where mfb DBS might antidromically modulate the PFC and enhance the activity of the descending glutamatergic projections to the VTA and produce increased dopamine release from the NAC as described above. Electrical stimulation of the mfb has been shown to have antidepressant effects, and reversed PFC volume loss and monoamine levels and metabolism in the neonatal clomipramine model of depression (Chakraborty et al., 2019). Very likely there are multiple cascades, and cross-talk between transmitter systems that electrical stimulation initiates, and this is further supported by the modulating role of endocannabinoids on VTA dopamine neuron activity following mfb DBS (Pillolla et al., 2007).

Most of the speculation concerning the mechanisms of mfb DBS looks towards the direct or indirect modulation of the mesocorticolimbic dopaminergic reward/motivational systems; however, it could equally well modulate the hippocampal formation and associated structures via connections between the VTA and the entorhinal cortex. We have shown using 18-FDG microPET that FSL rats have a robust and long-term bilateral hypometabolism in this structure, and the entorhinal cortex has been implicated in clinical depression too (Gerritsen et al., 2011; Thiele et al., 2016). The entorhinal cortex sub-serves spatial navigation, acquisition and consolidation of declarative memory by encoding spatial/ directional/temporal data and the hippocampus integrates this information within the given spatial and temporal context (Jacobs et al., 2010; Knierim, 2015; Witter et al., 2017). The antidepressant effect of mfb DBS could be via modulation of this pathway in multiple ways. VTA projects directly to the entorhinal cortex (Akil & Lewis, 1994), and midbrain dopaminergic input to the lateral entorhinal cortex can regulate the output activity of this structure (Caruana & Chapman, 2008). But the entorhinal cortex also sends glutamatergic projections to the NAC which modulates VTA dopamine transmission, as discussed previously and elsewhere (Blaha et al., 1997; Todd & Grace, 1999).

Pre-clinical studies can help generate ideas about novel target regions and ideas about the pathology in depression based on their response to stimulation. There is evidence that healthy control animals respond differently to mfb DBS, in terms of behavioural response or inducing dopamine release, suggestive of physiological and anatomical differences in the mfb in the depression model and the healthy controls. For example, in our voltammetry study, the FSL animals showed longer and larger mfb-DBS-mediated dopamine responses which could be related to a combination of reasons (that needs to be tested experimentally), such as differences in the number of descending glutamatergic fibres recruited by the stimulation; the number or distribution of ionotropic glutamate receptors on VTA dopaminergic neurons; the proportion of myelinated/unmyelinated ascending dopaminergic axons, or the excitability of the dopaminergic neurons in the FSL/healthy control animals (Ashouri Vajari et al., 2020). Dopamine transmission from the VTA is tightly modulated by the inhibitory inputs from the tail of the VTA, which is regulated by the lateral habenula (Bourdy & Barrot, 2012). Biophysical divergence across the depression model and the healthy controls, such as differences in the regulation of VTA activity by these upstream structures, could also explain why the groups respond differently to mfb DBS and give insights into the disease pathology.

In short, continuous and chronic mfb DBS most likely produces a spectrum of temporal, spatial, biological and behavioural responses. One hypothesis for the symptom relieving clinical application of slMFB DBS is that stimulation initially modulates the suboptimally performing reward and motivational network by modulating dopamine transmission and glutamatergic pathways. However, this is only a starting point. Future studies will need to focus on the dynamic action of MFB DBS, and in particular how continuous and chronic stimulation modulates multiple biological systems, such as the dopaminergic and other transmitter systems—including the serotonergic, the noradrenergic and the glutamatergic—over time.

9.2 Conclusions and outlook

DBS as applied to psychiatric disorders is at the beginning of the learning curve in many ways, and it is facing many challenges. In movement disorders, dystonia and tremor, DBS has been used for 30 years and today is recognized as a crucial therapeutic option and its application is not questioned. However, in the case of psychiatric disorders many medical professionals today would not even refer TRD patients to a neurosurgeon as they see DBS as too invasive, do not accept the biological basis of the disorder or simply do not judge the clinical data as being “promising.” It must be emphasized that DBS has only been applied to the most treatment-resistant patients, who are by definition, the most difficult cohort of patients to treat. Many of these patients have had conventional treatments for years, some for decades, without a satisfying resolution. If we consider that slMFB DBS produced fast and long-term antidepressant effects with response rate of 85% after 3 months of treatment, with 75% responders and sustained remission in 50% of the
previously treatment-resistant patients sustained even after a 4-year follow-up (and still going), then this could be regarded as “promising” (Bewernick et al., 2017; Coenen, et al., 2019; Kilian et al., 2019; Schlaepfer et al., 2013).

DBS in MDD (and other psychiatric disorders) is in the early days of its evolution, and this therapeutic option should be looked at within the so-called “technology-life-cycle framework” (Widge et al., 2018). The initial Cg25 trials published in 2005 by Mayberg and colleagues (Mayberg et al., 2005) were “dramatic” leading to immediate and “great expectations” initially, but further assessments and follow-ups by multiple groups targeting multiple sites produced variable results, leading to the “valley of disillusionment.” The two pivotal industry sponsored clinical trials investigating DBS Cg25 and vc/versus were stopped after futility analysis showed that during the sham-controlled phase no clear distinction could be made between active stimulation and sham and that by the end of the studies primary endpoints would not have been met (Dougherty et al., 2015; Holtzheimer et al., 2017). With the emergence of novel targets, like the slMFB, improved surgical implantation, contact selection and shaping of the electric field, DBS in psychiatric disorders is entering into the “slope of enlightenment,” a period of slower, but steadier advancement of knowledge. This is where we are now. Along with Cg25 and vc/versus, the slMFB—as we attempted to demonstrate in this review—remains a hypothesis driven DBS target with growing pre-clinical and more importantly, clinical data supporting it as therapeutic option in TRD. Small- and medium-sized single-centre trials are now focusing on issues of patient selection and targeting. The field is in search of biomarkers for optimal response, and focusing on improving implantation procedures (Coenen, et al., 2019; Coenen, et al., 2018; Mayberg et al., 2016). Targeting is getting more precise based on connectomic approaches and customized tractographic planning (Coenen, et al., 2018; Coenen, et al., 2019; Coenen, et al., 2019; Riva-Posse et al., 2018), and knowledge about biological substrate of psychiatric disorders, including depression, is growing (Dean & Keshavan, 2017).

Finally, a key component of the treatment that is also evolving is the technological aspect. DBS is a prime and exciting example of technology interacting with biology (and physiology and psychology), and the Brain–Machine Interface area is in the early stages of a boom that will certainly revolutionize medical treatment in the 21st century. Next generation of DBS in psychiatric disorders will likely contain “smart” components that—based on customized preloaded algorithms—will adapt stimulation parameters and strategies based on the patient's individual phenotype and immediate needs in a closed-loop, semi-autonomous fashion. If early diagnosis, prevention and the conventional treatments for depression would improve, reducing or eliminating the treatment resistant depression population, there would be much less need or justification for experimental treatments like DBS. However, unfortunately, global trends and predictions point towards growing number of people—especially among the young—being diagnosed with depression (Weinberger et al., 2018), and for a sub-population of those patients DBS of the slMFB, or other clinically validated targets, could be a therapeutic option that significantly improves their quality of life.

ACKNOWLEDGMENT

Open access funding enabled and organized by ProjektDEAL.

CONFLICTS OF INTEREST

The authors declare no conflict of interest. The funders had no role in the design of any of the studies mentioned; nor in the collection, analyses or interpretation of data; nor in the writing of the manuscript, nor in the decision to publish the results. VAC and TES are receiving an ongoing grant from Boston Scientific (USA) for an IIT concerning slMFB DBS in major depression, FORESEE III.

AUTHORS’ CONTRIBUTIONS

MDD developed and wrote the manuscript, but all the authors contributed significantly to the various sections. TES and VAC contributed to section III (Psychiatric disorders and DBS), to section V (Individual DBS targets in depression) and section VI (The Medial Forebrain Bundle as a DBS target in TRD: What is the rationale?). CR, DAAV and YT worked on section VIII (Biological consequences on mfb neuromodulation: focus on dopamine). VAC helped with the proofreading of the document.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.14975

DATA AVAILABILITY STATEMENT

All data used in Figure 4a–f are available on request.

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How to cite this article: Döbrössy M, Ramanathan C, Ashour Vajari D, Tong Y, Schlaepfer T, Coenen VA. Neuromodulation in Psychiatric disorders: Experimental and Clinical evidence for reward and motivation network Deep Brain Stimulation: Focus on the medial forebrain bundle. Eur. J. Neurosci. 2021;53:89–113. https://doi.org/10.1111/ejn.14975