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REVIEW ARTICLE

Deep brain stimulation of the brainstem

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Deep brain stimulation (DBS) of the subthalamic nucleus, pallidum, and thalamus is an established therapy for various movement disorders. Limbic targets have also been increasingly explored for their application to neuropsychiatric and cognitive disorders. The brainstem constitutes another DBS substrate, although the existing literature on the indications for and the effects of brainstem stimulation remains comparatively sparse. The objective of this review was to provide a comprehensive overview of the pertinent anatomy, indications, and reported stimulation-induced acute and long-term effects of existing white and grey matter brainstem DBS targets. We systematically searched the published literature, reviewing clinical trial articles pertaining to DBS brainstem targets. Overall, 164 studies describing brainstem DBS were identified. These studies encompassed 10 discrete structures: periaqueductal/periventricular grey ($n = 63$), pedunculopontine nucleus ($n = 48$), ventral tegmental area ($n = 22$), substantia nigra ($n = 9$), mesencephalic reticular formation ($n = 7$), medial forebrain bundle ($n = 8$), superior cerebellar peduncles ($n = 3$), red nucleus ($n = 3$), parabrachial complex ($n = 2$), and locus coeruleus ($n = 1$). Indications for brainstem DBS varied widely and included central neuropathic pain, axial symptoms of movement disorders, headache, depression, and vegetative state. The most promising results for brainstem DBS have come from targeting the pedunculopontine nucleus for relief of axial motor deficits, periaqueductal/periventricular grey for the management of central neuropathic pain, and ventral tegmental area for treatment of cluster headaches. Brainstem DBS has also acutely elicited numerous motor, limbic, and autonomic effects. Further work involving larger, controlled trials is necessary to better establish the therapeutic potential of DBS in this complex area.

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Abbreviations: DBS = deep brain stimulation; MFB = medial forebrain bundle; mRF = mesencephalic reticular formation; PAG = periaqueductal grey; PPN = pedunculopontine nucleus; PVG = periventricular grey; SNc/r = substantia nigra pars compacta/pars reticulata; STN = subthalamic nucleus; VTA = ventral tegmental area

Introduction

Deep brain stimulation (DBS) is a neuromodulatory therapy in which intracranial electrodes are used to deliver electrical impulses to targeted brain structures. Well-established as a safe and effective treatment for movement disorders such as Parkinson's disease, essential tremor, and dystonia (Anderson and Lenz, 2006; DeLong and Wichmann, 2012),

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DBS has also seen longstanding use for chronic pain (Hosobuchi, 1986; Levy *et al.*, 1987) and has been increasingly explored as a treatment for psychiatric and cognitive disorders such as obsessive-compulsive disorder (Greenberg *et al.*, 2006; Roh *et al.*, 2012), major depressive disorder (Mayberg *et al.*, 2005; Kennedy *et al.*, 2011), and Alzheimer's disease (Hamani *et al.*, 2008; Laxton *et al.*, 2010). However, the variable benefit observed in stimulating exploratory targets (Holtzheimer *et al.*, 2017), the evocation of undesirable side-effects (e.g. postural instability in Parkinson's disease) with traditional targets (Fasano *et al.*, 2015), and a continued desire to expand the therapeutic indications of DBS has prompted the exploration for suitable target alternatives outside the established cortico-basal ganglia-thalamo-cortical loop [e.g. subthalamic nucleus (STN), pallidum, and thalamus] (Lozano and Lipsman, 2013).

The brainstem is an intricate neuroanatomical structure that may hold therapeutic potential as a target for DBS, owing to its manifold fibre connections and functionally diverse nuclei. It is composed of grey matter, formed primarily by the cranial nerve nuclei, mesencephalic nuclei, reticular formation, and pontine nuclei, as well as ascending and descending white matter fibre tracts (Ángeles Fernández-Gil *et al.*, 2010; Benarroch, 2018). In addition to its role as a crucial conduit for numerous motor and sensory pathways, the brainstem performs vital vegetative functions—including cardiorespiratory and cardiovascular control (Benarroch, 2018) and maintenance/regulation of consciousness and sleep—and a pivotal role in coordination, posture, and locomotion (Drew *et al.*, 1986; Prentice and Drew, 2001). While the brainstem's importance, complexity, and diverse functionality present an attractive rationale for its targeting with DBS, these same factors mean that the consequences of operative complications in this area are particularly grave. Moreover, the brainstem's caudal positioning and susceptibility to physiological noise on imaging (e.g. movement artefact during breathing) impose significant technical challenges that have likely obstructed exploration of this structure (Jagannathan and Krovvidi, 2014; Sclocco *et al.*, 2018).

The brainstem DBS literature is spread over several decades and encompasses a wide range of substructures and indications. The present review was devised with the intent to provide an accessible and comprehensive summary of this literature, shedding light on how brainstem DBS has evolved, where it stands today with respect to both acute effects and long-term clinical consequences of stimulation, and what avenues for potential growth might be.

Literature search

We conducted a literature search of all published original research pertaining to DBS of brainstem targets in humans (Supplementary material). This review, performed in November 2019, consisted of an initial search of the NCBI PubMed database using the terms 'electric stimulation therapy'[MAJR], 'brain'[mesh], 'humans'[mesh], and 'english'[lang], which were combined with the boolean operator 'AND'. This generated 7632 papers. Two raters (G.J.B.E., A.N.) subsequently scanned each abstract to filter the results for relevance; a third (A.P.) resolved any disagreements. Reviews, animal studies, surgical technique papers lacking in clinical outcome information, and papers dealing with non-DBS stimulation modalities were excluded at this stage. From this selection, studies in which at least one patient received DBS of a brainstem structure were included for review. Information regarding sample size, patient clinical indication and demographics, stimulation target and stimulation parameters, clinical outcome, and any reported acute/peri-operative stimulation effects were extracted from each paper.

The STN and structures within its immediate vicinity (e.g. zona incerta, fields of Forel, and dentato-rubro-thalamic tract) were considered to be beyond the scope of this review and papers involving these targets were excluded from analysis. The effects of stimulating these targets have been extensively catalogued in prior studies (Fytagoridis and Blomstedt, 2010; Welter *et al.*, 2014; Fenoy and Schiess, 2017).

DBS of brainstem structures

In total, we identified 164 clinical studies that reported on DBS of brainstem structures. Ten brainstem structures have been targeted using DBS: periaqueductal grey-periventricular grey (63 studies), the pedunculopontine nucleus (48 studies), ventral tegmental area (22 studies), substantia nigra (nine studies), medial forebrain bundle (eight studies), mesencephalic reticular formation (seven studies), red nucleus (three studies), superior cerebellar peduncle (three studies), parabrachial complex (two studies), and locus coeruleus (one study). Two studies involved two different brainstem targets; these were double counted for the purpose of tallying papers per target. A graph showing the cumulative number of studies involving each target over time can be seen in Fig. 1. The targets themselves are depicted in Fig. 2 (Edlow *et al.*, 2012; Glasser *et al.*, 2013).

Supplementary Table 1 details the clinical outcomes of these studies, organized by target, while Supplementary Table 2 presents acute effects that were observed during intra- and post-operative stimulation. Below, we summarize the salient patterns of outcomes and acute effects that have been reported for each target. This summary is ordered according to rostrocaudal convention (Fig. 2).

Substantia nigra

Situated in the ventral midbrain tegmentum just ventral to STN, the substantia nigra (SN) is a critical component of the basal ganglia circuit. This nucleus can be subdivided into the dopaminergic, neuromelanin-rich pars compacta (SNc) and

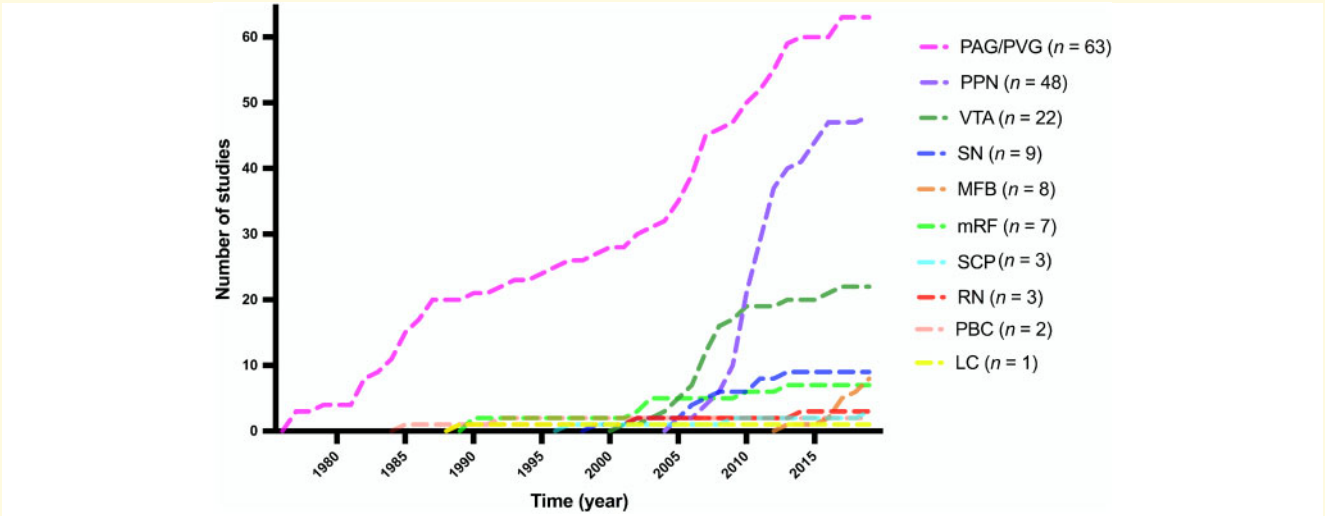

Figure 1 Cumulative number of brainstem DBS studies over time. Graph demonstrating the cumulative number of published studies for each brainstem target over time. LC = locus coeruleus; PBC = parabrachial complex; RN = red nucleus; SCP = superior cerebellar peduncle.

the GABAergic pars reticulata (SNr). SNc projects via the nigrostriatal pathway to the striatum, which then relays signals to SNr via the direct and indirect pathways. In turn, SNr projects nigrothalamic axons that disperse and terminate in the ventral (motor) and mediodorsal thalamus, exerting inhibitory GABAergic control over the thalamocortical network (Halliday, 2004). The degeneration of SNc neurons and subsequent diminution of nigrostriatal dopamine is a crucial element of Parkinson's disease pathophysiology (Ulla *et al.*, 2011), resulting in the cardinal Parkinson's disease symptoms related to dysfunction of motor control. More generally, dopamine is also implicated in widespread modulation of cognition, motivation, punishment and reward, prolactin inhibition, sleep, mood, attention, working memory, and learning (Calabresi *et al.*, 2007). Finally, animal studies have implicated the nigral system in epileptic neuronal transmission (Löscher *et al.*, 1998).

Nine studies to date have described SN-DBS. One study deliberately targeted both SNr and STN to treat resistant axial motor impairment in Parkinson's disease ($n = 12$); here, combined STN-SNr stimulation did not confer any significant improvement over STN stimulation alone. More encouraging results were observed across three studies ($n = 7$ in total) in which SNr—because of its putative connections with a dorsal midbrain anticonvulsant zone (Benabid *et al.*, 2001; Dinner *et al.*, 2002)—was stimulated alongside STN in epilepsy patients, leading to reports of reduced seizures in all patients. These papers primarily reported on progressive myoclonic epilepsy syndromes and tentatively support a role for STN-SNr stimulation in treating these indications. Paralleling STN-DBS for motor symptoms in Parkinson's disease, these findings suggest greatest improvement might be attained in patients with less severe disease. The utility of STN-SNr-DBS for other forms of epilepsy is largely unknown. Finally, six case reports/series described the acute effects of SN stimulation in Parkinson's disease patients undergoing STN-DBS. These primarily highlighted the ability of SN (possibly in combination with ventral STN given their proximity) stimulation to rapidly and reversibly induce pronounced limbic side-effects, including mania and depressive symptoms. Functional imaging studies conducted during these episodes have suggested that subcortically driven mania is accompanied by activation of areas such as dorsal anterior cingulate cortex (Ulla *et al.*, 2011), while acute depression during left SN-DBS on (contrasted with SN-DBS off) has been linked to increased regional cerebral blood flow in areas such as ipsilateral orbitofrontal cortex, amygdala, and anterior thalamus (Bejjani *et al.*, 1999).

Red nucleus

Lying dorsomedial to SN in the midbrain tegmentum, the oval-shaped red nucleus comprises caudal magnocellular and rostral parvocellular components. These provide efferents that contribute to the rubrospinal tract and central tegmental tract, respectively. Both cell populations also receive cerebellar and cerebral cortical inputs (Miller and Gibson, 2009). Additionally, at the level of the oculomotor nucleus, red nucleus is crossed by, but does not interact with, fibres of the oculomotor nerve (Paxinos *et al.*, 2012). Functionally, red nucleus is believed to supplement the dominant corticospinal tract in controlling gross trunk and limb movements. In clinical practice, this is reflected in the decerebrate posturing—a loss of flexion in the upper extremities—observed following red nucleus destruction (Mihailoff and Haines, 2018).

Only one case report has described prospective DBS targeting of red nucleus ($n = 1$); this was in a patient with

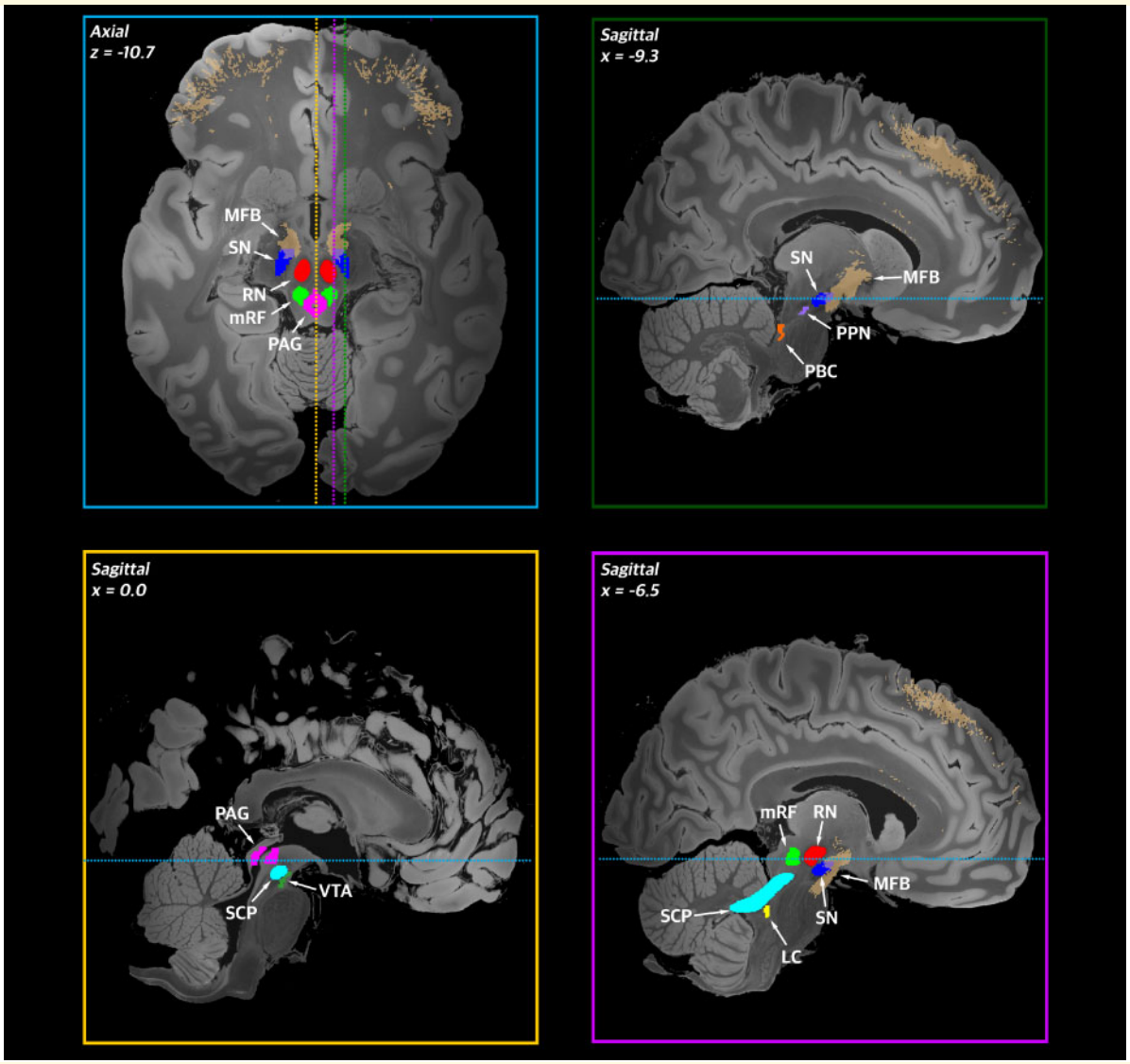

Figure 2 Brainstem regions and nuclei targeted by DBS. Brainstem regions and nuclei that have been targeted by DBS are shown on a high resolution brain template [7 T, 100-μm resolution brain in MNI152 (nonlin asym) space]. Brainstem targets (taken from the Harvard Ascending Arousal Network atlas or constructed from Human Connectome Project imaging data (http://www.humanconnectomeproject.org/) are shown in two planes (*top left:* axial; *top right* and *bottom*: sagittal). Dotted lines denote the anatomical level displayed in panels bordered by the corresponding colour (e.g. the blue dotted line denotes the level of the axial slice displayed in the *top left* panel). LC = locus coeruleus; PBC = parabrachial complex; RN = red nucleus; SC = superior colliculus; SCP = superior cerebellar peduncle.

cerebellar tremor, which is typically refractory to stimulation at conventional tremor targets. This study did not evince any benefits of red nucleus-DBS (Lefranc *et al.*, 2014). Another study reported on intra-operative effects of high frequency (130 Hz) stimulation at contacts that were localized to the white matter between red nucleus and SN in Parkinson's disease-STN patients ($n = 4$), while a third briefly described the effect of stimulating red nucleus alongside other targets (Feinstein *et al.*, 1989). Patients stimulated in this region experienced diplopia—likely due to stimulation of the nearby oculomotor nerve—as well as contralateral upper limb signs (dystonic posturing and tremor) that were consistent with the sequelae of red nucleus lesions (Bejjani *et al.*, 2002). Overall, red nucleus-DBS appears to be of limited therapeutic value.

Ventral tegmental area

The ventral tegmental area (VTA) is a dopaminergic midbrain structure that projects to the nucleus accumbens, amygdala, hippocampus, and prefrontal cortex (Corner and Swaab, 1976) via the mesolimbic and mesocortical pathways, thereby playing a key role in reward, executive function, and motivation (Alcaro *et al.*, 2007). May *et al.* (1998)

first implicated VTA in cluster headache, observing increased PET activation in this area during cluster headache attacks. Since then, numerous groups have performed DBS of the region, variously referring to it as the VTA or the posterior hypothalamic region (Leone *et al.*, 2001, 2013; Franzini *et al.*, 2003; Akram *et al.*, 2016). A detailed discussion of this anatomical debate is beyond this review's purview; for the sake of inclusiveness, we have gathered all studies targeting this general region under the umbrella of VTA-DBS.

Overall, 22 studies describing VTA-DBS were identified. Most patients received VTA-DBS for cluster headache, while smaller contingents underwent treatment for aggressiveness or atypical facial pain. Overall, cluster headache patients experienced improvements in headache symptoms, with many benefiting from sustained pain reduction at long-term follow-up (>5 years), and even years after the cessation of stimulation. In studies that provided clearly defined data on individual patients, we identified 20% of patients as being pain free or nearly pain free, 47% of patients as being responders ($>30\%$ reduction in headache severity or frequency), and 31% of patients as non-responders (no improvement, or transient improvement with subsequent relapse). While a randomized controlled trial did not report any benefit of VTA-DBS over placebo, methodological limitations of the study (Nowacki *et al.*, 2019), and the positive findings reported across multiple open-label studies suggest VTA-DBS is a potentially effective treatment for cluster headache, warranting further investigation. A handful of patients receiving VTA-DBS for aggressiveness ($n = 2$) experienced behavioural improvement, while treatment for atypical facial pain ($n = 1$) was not beneficial. Across all studies, acute side-effects of VTA stimulation included seizures ($n = 1$) and diplopia ($n = 3$), the latter of which could be avoided by adjusting stimulation parameters.

Medial forebrain bundle

The medial forebrain bundle (MFB) is a large white matter tract extending through the brainstem as a single main trunk, before bifurcating at the level of the VTA along divergent paths. The infero-medial branch (imMFB) traces the wall of the third ventricle anteriorly before terminating at the lateral hypothalamus. Conversely, the supero-lateral branch (slMFB) passes laterally beneath the thalamus, ascending to the anterior limb of the internal capsule and projecting to nucleus accumbens, orbitofrontal cortex, dorsolateral prefrontal cortex, and other regions via the mesolimbic and mesocortical pathways (Coenen *et al.*, 2012). Through these extensive dopaminergic connections, MFB is believed to be integral in mediating reward and motivation. Indeed, affective disorders such as melancholic depression have been associated with microstructural changes in these pathways (Bracht *et al.*, 2014). In the absence of histological descriptions of MFB in human brain specimens, possibly as a consequence of its complicated course and lack of myelin, the most comprehensive mapping of human MFB has come from diffusion tensor imaging studies (Coenen *et al.*, 2018*b*).

Eight clinical studies have targeted MFB—specifically slMFB given its connections with mood-implicated prefrontal cortex—for psychiatric indications. The anatomical locus of stimulation along the slMFB for these trials was a triangle bound by the STN, SNc, and red nucleus (Coenen *et al.*, 2018*a*). Overall, most treated patients had treatment-resistant depression, while a far smaller number had obsessive-compulsive disorder, co-morbid treatment-resistant depression and anorexia nervosa, or bipolar depression. Open-label MFB-DBS trials for treatment-resistant depression, all of which used 130 Hz frequency, 60 μs stimulation with minor variation in voltage/current (3–4.3 V; 2.3–4.9 mA), have demonstrated reproducible improvements in depression symptoms. Antidepressant responses in these studies were typically notably rapid (within 1 week) and sustained, with multiple groups reporting a $\geqslant 50\%$ reduction in depressive symptoms at 12-month follow-up among most patients. It should be noted, however, that one randomized controlled trial comparing MFB-DBS stimulation against sham stimulation in a treatment-resistant depression cohort found no statistically significant differences between treatment arms (Coenen *et al.*, 2019). This pattern is similar to that seen in trials of another major target for treatment-resistant depression DBS, the subcallosal/subgenual anterior cingulate area; these demonstrated robust antidepressant responses ($\geqslant 50\%$ symptom reduction) in open-label studies but less convincing results in controlled trials (Kringelbach *et al.*, 2007; Lozano *et al.*, 2008; Holtzheimer *et al.*, 2012). Mitigating factors for the negative results of the MFB-DBS randomized controlled trial include its small size, relative short follow-up duration (8 weeks), potential microlesioning 'insertional' effects, and the difficulty of interpreting placebo responses in depression cohorts (Schatzberg and Kraemer, 2000). Moreover, acute relapse occurred in some patients after double-blinded battery failure (Bewernick *et al.*, 2017; Coenen *et al.*, 2019). Thus, the balance of evidence supports a promising role for MFB-DBS in treating treatment-resistant depression. MFB-DBS for the management of obsessive-compulsive disorder has also been reported to result in moderate improvements in overall symptoms, although confident conclusions are precluded by the small sample size to date. Reports of acute stimulation-induced strabismus and diplopia were common to all trials; these can be attributed to slMFB's proximity to the origin of the oculomotor nerve.

Mesencephalic reticular formation

The reticular formation is a loose collection of interconnected nuclei located in the central tegmentum that extends from the midbrain to the medulla oblongata (Horn and Adamczyk, 2012). Within the pons and medulla, the reticular formation can be divided into three columns: (i) the medial tegmental field with descending afferents involved in postural control; (ii) the raphe nuclei, which modulate firing rates in the sensory or motor spinal circuits; and (iii) the

lateral tegmental field, containing interneurons to various cranial nerve nuclei and to motor neurons in the spinal cord implicated in respiration, micturition, and blood pressure (Holstege, 1991). Pertinent to DBS studies of this region, ascending fibres from the mesencephalic reticular formation (mRF) contribute to the ascending reticular activating system, which serves to regulate states of consciousness (Edlow *et al.*, 2012).

While seven papers have described mRF-DBS, all were reported follow-ups of the same trial at varying time points. In part, this trial described a cohort of 21 persistent vegetative state patients, 19 of whom received centromedian/parafascicular (CMPf) thalamic DBS and two of whom received mRF-DBS. Low frequency stimulation (25–50 Hz) was used in all cases. At 24 months post-operation, eight DBS patients had progressed from persistent vegetative state and were able to obey simple verbal commands, while none of the untreated patients had progressed. Unfortunately, no distinction of outcomes between patients receiving mRF-DBS and CMPf-DBS was made, prohibiting any meaningful conclusions about the therapeutic value of mRF-DBS. Acutely, 'arousal responses' (e.g. eye opening) was observed following mRF and thalamic DBS. PET showed acute mRF was associated with increased regional cerebral blood flow while EEG demonstrated increased pain-related P250 (a measure of late positive component of cerebral evoked potential in response to painful stimuli) in response to stimulation, which could not be elicited in response to painful external stimuli (Tsubokawa *et al.*, 1990). While this points to possible mRF-mediated arousal and strengthens the case for further research in this field, it also highlights the potential ethical issues of performing DBS in a population unable to communicate distress or grant informed consent.

Periaqueductal and periventricular grey

The periaqueductal grey (PAG) is an area of grey matter within the midbrain that circumscribes the cerebral aqueduct until it reaches the third ventricle anteriorly, at which point it becomes known as the periventricular grey (PVG). Functionally, this continuous PAG/PVG region is involved in the coordination of autonomic and behavioural responses—especially to pain and other aversive stimuli—by integrating inputs from the prefrontal cortex, amygdala, reticular formation, hypothalamus, and nociceptive and sympathetic afferents (Green *et al.*, 2005). These responses, which include cardiovascular, respiratory, motor responses as well as central modulation of nociceptive signalling, are driven by the PAG/PVG's connections to other brainstem and hypothalamic nuclei (Benarroch, 2018). PAG/PVG DBS has a long and extensive history as a treatment for neuropathic pain under the premise that stimulation of this target engages endogenous, opioid-releasing neurons that are capable of inhibiting or altering nociceptive signals (Basbaum and Fields, 1978; Young *et al.*, 1993; Green *et al.*, 2009; Sims-Williams *et al.*, 2017). However, the PAG/PVG's more general role in the orchestration of autonomic responses has also prompted investigation of its relevance for purposes beyond analgesia.

PAG/PVG-DBS was identified as the most studied brainstem target. Sixty-three studies have reported on patients who received PAG/PVG-DBS for the management of medication-refractory pain, most commonly neuropathic pain secondary to stroke, trauma, or amputation. When all studies that reported individual patient outcome data were pooled, ~52% of patients experienced good-to-excellent pain relief (⩾50% improvement), 23% experienced mild relief (20–50% improvement), and 26% had poor or no benefit from stimulation. While 50% improvement has been argued by some to represent a benchmark for clinically useful pain relief (Owen *et al.*, 2006), the fact that treated patients are typically refractory to all other forms of therapy and that even moderate pain improvements in this context can lead to noticeable gains in quality of life (Farrell *et al.*, 2018), should be kept in mind. Overall, the available data—derived from a legacy of studies dating back to the 1970s—support a role for PAG/PVG-DBS in managing refractory pain conditions. PAG/PVG alone may represent a particularly useful target for treating refractory nociceptive pain; by contrast, best outcomes in the context of neuropathic pain were more often achieved using combined PAG/PVG and sensory thalamus stimulation.

In patients already receiving PAG/PVG-DBS for the treatment of chronic pain, more recent studies have also demonstrated associated changes in various autonomic functions. These include modulation of the cardiovascular system, with one group demonstrating clinical improvement in patients with hypertension or orthostatic hypotension. PAG/PVG-DBS has also been associated with increases in lung function (Hyam *et al.*, 2012*a*), and bladder capacity (Green *et al.*, 2012). These studies point to the potential of PAG/PVG-DBS as a tool for managing a broad range of autonomic dysfunctions (Hyam *et al.*, 2012*b*).

When reported, the frequency of PAG/PVG-DBS stimulation was typically low (<50 Hz), while the voltage and pulse width of stimulation varied between 0.6–7 V and 60–120 μs, respectively. The propensity for lower stimulation frequencies may relate to the acute adverse effects often observed with higher frequencies of stimulation (>100 Hz). These include eye bobbing and eye deviation—attributable to current spread to the nearby superior colliculus and oculomotor nerve—and anxiety. Autonomic side-effects including nausea and diaphoresis have been reported at relatively higher voltages (>3 V). By contrast, therapeutic stimulation parameters were often documented as producing warmth/cold sensations or paraesthesias acutely.

Pedunculopontine nucleus

Situated in the dorsolateral portion of the ponto-mesencephalic tegmentum at the level of the trochlear nucleus, the pedunculopontine nucleus (PPN) comprises part of the upper

brainstem's mesencephalic locomotor region (together with the cuneiform and subcuneiform nuclei). The two subnuclei of PPN, the pars compacta and pars dissipata, have widespread cholinergic, glutamatergic, and GABAergic bidirectional projections with the basal ganglia, cerebellum, cortex, thalamus, and spinal cord (Pienaar *et al.*, 2017). To date, studies have implicated PPN in the maintenance of posture, modulation of attention, arousal, sleep (as part of the reticular formation), and initiation of gait (Semba *et al.*, 1990; Fuller *et al.*, 2007; Boutin *et al.*, 2017). These processes are often impaired in Parkinson's disease patients, in whom the PPN is known to degenerate (Ricciardi *et al.*, 2015). Importantly, PPN has been studied for its relevance to freezing of gait (Nutt *et al.*, 2011)—characterized by sudden transient episodes of inability to move the feet forward—and balance. Progressive freezing of gait affects 40–50% of patients with Parkinson's disease and is frequently refractory to both pharmacotherapy and subthalamic or pallidal DBS (Perez-Lloret *et al.*, 2014; Amboni *et al.*, 2015; Forsaa *et al.*, 2015). As such, PPN has become an attractive DBS target for the improvement of freezing of gait in the subset of Parkinson's disease patients in whom it arises or persists following treatment via more conventional targets [i.e. STN or globus pallidus interna (GPi)] (Ferraye *et al.*, 2010).

Consistent with this premise, we identified 48 studies that described PPN-DBS—either alone or combined with STN-, GPi- or zona incerta-DBS—for improvement of postural stability and axial symptoms in patients with Parkinson's disease, as well as a small number of progressive supranuclear palsy, and primary progressive freezing of gait patients. Overall, Parkinson's disease studies tended to demonstrate statistically significant, although sometimes modest, post-operative improvements in Unified Parkinson's Disease Rating Scale motor component (UPDRS-III) score, particularly in axial metrics (items 27–30). These scores typically improved between 20% and 50% from baseline. The most robust axial benefit of PPN-DBS appeared to be improved freezing of gait, which has been documented across several case series and double-blind randomised assessments. The reported impact on balance as assessed by UPDRS-III item 30 (i.e. the 'pull' test, which may not accurately capture all aspects of balance) was more variable; however, reduced falls, which can be a function of many factors including balance and freezing of gait, was a common finding amongst studies. Conversely, improvements in bradykinesia, rigidity, and tremor rarely occurred with PPN-DBS alone. These findings suggest that PPN-DBS may be a useful therapy in Parkinson's disease patients for whom falls and freezing of gait are a particular concern, particularly if modest improvements in these areas might substantially benefit quality of life. Across identified studies, the stimulation frequency used was typically low (25–35 Hz), with a larger variation in pulse width and voltage (60–120 μs, 1.0–4.9 V). In line with these overall improvements in axial signs, improvements in verbal fluency were reported in several studies (Stefani *et al.*, 2010*a*, *b*; Mazzone *et al.*, 2012). PPN-DBS has also been linked to improvements in sleep quality and architecture (Lim *et al.*, 2009; Stefani *et al.*, 2010*a*, *b*), reaction time (Costa *et al.*, 2010), recall and executive function (Stefani *et al.*, 2010*a*), and visual perception (Strumpf *et al.*, 2016), which may be attributable to PPN's involvement in the ascending reticular activating system. These clinical findings have been supported by functional imaging, in which PPN-DBS has been associated with altered activation (both metabolic and regional blood flow) of brain areas implicated in movement (Strafella *et al.*, 2008; Ballanger *et al.*, 2009; Wilcox *et al.*, 2011)—specifically the cerebellum and mesencephalic locomotor region—as well as cortical areas implicated in executive function (Ceravolo *et al.*, 2011). The voltage used by PPN-DBS was often limited by unpleasant acute effects, particularly contralateral hemibody paresthesias—likely attributable to current spread to nearby medial lemniscus fibres—and oculomotor effects related to medial longitudinal fasciculus stimulation. Additionally, PPN-DBS induced involuntary urinary voiding in one patient, likely due to inadvertent stimulation of the pontine micturition centre.

Locus coeruleus

The locus coeruleus is a discrete cluster of noradrenergic neurons in the dorsal pontine tegmentum, lying close to the lateral floor of the fourth ventricle. The major source of noradrenaline in the brain, locus coeruleus projects extensively throughout the brainstem, cerebrum, cerebellum, and spinal cord (Counts and Mufson, 2012) and plays an important role in modulating memory function, arousal, attention, and 'fight or flight' responses (Foote *et al.*, 1980, 1983).

A single 1989 study used low frequency (50–60 Hz) locus coeruleus-DBS for the treatment of cerebral palsy ($n = 1$) and generalized tonic-clonic seizures ($n = 2$) with the intent of suppressing generalized neuronal hyperexcitability mediated through noradrenaline innervation (Feinstein *et al.*, 1989). An acute improvement in hypertonicity during stimulation was reported in the cerebral palsy patient (along with symptom worsening following double-blind battery failure), while decreased seizure frequency and severity was described in the epileptic patients. Continuous stimulation at night was associated with sleep disruption, possibly related to the role of the locus coeruleus in arousal. Locus coeruleus-DBS has not been described since in human trials, perhaps owing to the establishment of the more readily accessible GPi and anterior nucleus of the thalamus for the management of dystonia and epilepsy, respectively (Krauss *et al.*, 2002; Fisher *et al.*, 2010). Overall, the lack of reproducible findings or quantitative outcomes limit confidence in this region as a therapeutic target.

Parabrachial complex

The parabrachial complex is a cluster of neurons surrounding the superior cerebellar peduncles in the dorsolateral pons. Often divided into medial, lateral, and subparabrachial (or Kölliker-Fuse nucleus) subdivisions, the

parabrachial complex is known to play a role in cardiorespiratory homeostasis, pain, and aversion/avoidance, integrating ascending sensory signals with input from higher brain areas (Chiang *et al.*, 2019).

Two studies in the 1980s/90s (collective $n = 8$) described low frequency (10–60 Hz) parabrachial complex-DBS—in several cases in combination with PAG/PVG or thalamic DBS. All patients underwent treatment for chronic intractable pain of varied aetiologies, including post-herpetic neuralgia, spinal cord injury, and malignancy. Overall, parabrachial complex-DBS was reported to produce 'good' to 'excellent pain relief' in five patients without notable side-effects, although no quantitative measures of pain relief were provided (Katayama *et al.*, 1985; Young *et al.*, 1992). However, it should be noted that some of these patients received concurrent stimulation with other targets, such as PVG or sensory thalamus, making it difficult to ascribe benefit solely to parabrachial complex stimulation. Despite these seemingly promising outcomes and suggestions from animal studies that parabrachial complex-dependent analgesia, unlike PAG/PVG-dependent analgesia, may be partially opioid-independent (Katayama *et al.*, 1984), parabrachial complex-DBS has not been since pursued. This may reflect the structure's anatomical complexity as well as the fact that both nearby PAG-PVG and sensory thalamus were already well-established as 'classic' targets for treating refractory pain (Hosobuchi, 1983; Young *et al.*, 1992).

Superior cerebellar peduncle

One of the three white matter structures that connects the cerebellum to the brainstem, the superior cerebellar peduncle (SCP) attaches to the midbrain immediately below the trochlear nerve, conveying efferent cerebellar fibres—integral for ipsilateral arm and leg coordination—to the brainstem and diencephalon via the dentato-rubro-thalamic tract (DRTT) (Haines and Mihailoff, 2018).

Three studies describing high frequency (200 Hz) SCP-DBS were identified. In both studies, investigators sought to exploit SCPs connection to DRTT in the treatment of hypertonic conditions, namely cerebral palsy ($n = 31$) and dystonia refractory to previous pallidal intervention ($n = 1$). Decreased post-operative hypertonicity was reported in the cerebral palsy cohort, albeit in the absence of quantitative measures (Galanda and Hovath, 1997; Harat *et al.*, 2009). By contrast, notable quantitative improvements in muscle tone, pain, and quality of life were noted in the dystonia patient at 6 months follow-up (Horisawa *et al.*, 2020), suggesting that further work on the role of SCP-DBS as a treatment for refractory dystonia may be warranted. Acutely, high voltage stimulation (8.5–10 V) was associated with both oculomotor effects as well as forced laughter (Horisawa *et al.*, 2020), and subjective pleasure and fear (Galanda and Hovath, 1997). These phenomena may reflect infringement on the trochlear nerve and white matter pathways relevant to the cerebellum's role in emotional regulation and expression (Damasio *et al.*, 2000; Parvizi, 2001), respectively.

Limitations

Several limitations of the literature reviewed here should be acknowledged given their potential to inform future study design. First, many of the studies described in this paper were open-label and uncontrolled, making them susceptible to performance and detection biases. More generally, the well-recognized bias towards reporting and publishing positive results should be kept in mind when reviewing any case studies or case series, as it can lead to an overrepresentation of efficacious DBS cases in the literature (Schlaepfer and Fins, 2010). Another limitation is that comparison across the reviewed studies is challenging because outcome measures were often non-standardized. Additionally, some of the case series reported clinical outcomes as aggregate group measures, which can be heavily skewed by individual outliers when sample size is small and can also obscure specific target-outcome relationships if patients with different stimulation targets are grouped together. Finally, technological limitations in older studies reduce the accuracy and reliability with which implanted electrodes can even be said to be stimulating the purported targets.

Summary and future directions

DBS of the brainstem remains a relatively unexplored field. We identified 164 unique clinical studies on this topic that have been published to date; for context, prior work has shown there were over 500 DBS-related publications per year by the latter part of the 2000s (Lozano and Lipsman, 2013). Indeed, in a recent survey of past and present DBS clinical trials that were registered on clinicaltrials.gov, only 21 (4%) of the total 485 trials identified involved brainstem targets (Harmsen *et al.*, 2020). Data on several targets—namely locus coeruleus, parabrachial complex, reticular formation, and superior cerebellar peduncle—are fairly sparse, primarily deriving from decades-old case series that lack information on follow-up, stimulation parameters, and standardized outcome measures. Charitable interpretations of these areas could tentatively suggest potential avenues of further investigation in disorders such as chronic pain, hypertonic conditions, and disorders of consciousness; however, the paucity of high-quality evidence necessitates a conservative interpretation. SN-DBS may have a role to play in controlling progressive myoclonic epilepsy, although reports on this indication are outnumbered by studies describing acute limbic consequences (mania or depression) of stimulation in this area. This side-effect profile could prove problematic for any future applications of SN-DBS to epilepsy treatment. The most promising targets for therapeutic stimulation within the brainstem appear to be the PPN, PAG/PVG, VTA, and slMFB, in which studies have respectively demonstrated reproducible improvements in axial stability, pain/autonomic dysfunction, cluster headache severity, and depressive symptoms. Of these targets, PAG/PVG has been utilized since the

late 1970s, while VTA and PPN have seen increased interest since the early 2000s. However, the number of new DBS studies involving these structures has plateaued in recent years. Conversely, slMFB has emerged as a target of interest for psychiatric indications in the last half decade and continues to be explored in contemporary work (Fig. 1). In addition to positive results, studies investigating these targets have also been more consistent in reporting recognized outcome measures and long-term follow up, increasing their reliability and reproducibility. These factors have likely contributed to the relatively large quantity of studies in these areas when compared to other brainstem substructures. Despite this, there is a clear absence of double-blinded randomized control trials, suggesting that further work is needed in order to validate these areas as reliable and efficacious treatment targets.

The technical challenges of performing DBS in a region as constrained and anatomically complex as the brainstem may be mitigated by advances in stimulation delivery. The arrival of directional leads has allowed for the possibility of greater stimulation precision (Schüpbach *et al.*, 2017), while endoscopic 'stentrode' devices may render certain brainstem targets, such as the slMFB, more accessible to stimulation (Neudorfer *et al.*, 2020). Increased focus on the development of closed-loop systems, which offer the prospect of recording neuronal or peripheral activity and adapting stimulation accordingly (Habets *et al.*, 2018), may also be beneficial for brainstem DBS. By allowing stimulation to be fine-tuned in real time based on physiological dynamics, these systems may improve the utility of DBS for brainstem functions such as arousal and autonomic function. In concert with advances in stimulation technology, improved imaging—such as that delivered by ultrahigh-field (e.g. 7 T) MRI—has potential to enhance the visualization of brainstem structures and relevant circuitry (Sclocco *et al.*, 2018).

In summary, we comprehensively reviewed the existing human literature on brainstem DBS, cataloguing the long-term clinical outcomes and acute effects of stimulation as they have been reported. It is hoped this work serves as a concise account of what is known about this field to date in addition to providing a helpful launch-point for future research.

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Competing interests

A.M.L. is the co-founder of Functional Neuromodulation, is a consultant for Boston Scientific, Medtronic, and Abbott (all of which produce DBS devices), and holds intellectual property in the field of DBS. The other authors report no conflicts of interest.

Supplementary material

Supplementary material is available at *Brain* online.

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