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Review

What is the therapeutic mechanism of pedunculopontine nucleus stimulation in Parkinson's disease?

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ABSTRACT

Pedunculopontine nucleus (PPN) deep brain stimulation (DBS) is an experimental treatment for Parkinson's disease (PD) which offers a fairly circumscribed benefit for gait freezing and perhaps balance impairment. The benefit on gait freezing is variable and typically incomplete, which may reflect that the clinical application is yet to be optimised or reflect a fundamental limitation of the therapeutic mechanism. Thus, a better understanding of the therapeutic mechanism of PPN DBS may guide the further development of this therapy. The available evidence supports that the PPN is underactive in PD due to a combination of both degeneration and excessive inhibition. Low frequency PPN DBS could enhance PPN network activity, perhaps via disinhibition. A clinical implication is that in some PD patients, the PPN may be too degenerate for PPN DBS to work. Reaction time studies report that PPN DBS mediates a very specific benefit on pre-programmed movement. This seems relevant to the pathophysiology of gait freezing, which can be argued to reflect impaired release of pre-programmed adjustments to locomotion. Thus, the benefit of PPN DBS on gait freezing could be akin to that mediated by external cues. Alpha band activity is a prominent finding in local field potential recordings from PPN electrodes in PD patients. Alpha band activity is implicated in the suppression of task irrelevant processes and thus the effective allocation of attention (processing resources). Attentional deficits are prominent in patients with PD and gait freezing and PPN alpha activity has been observed to drop out prior to gait freezing episodes and to increase with levodopa. This raises the hypothesis that PPN DBS could support or emulate PPN alpha activity and consequently enhance the allocation of attention. Although PPN DBS has not been convincingly shown to increase general alertness or attention, it remains possible that PPN DBS may enhance the allocation of processing resources within the motor system, or "motor attention". For example, this could facilitate the 'switching' of motor state between continuation of pattern generated locomotion towards the intervention of pre-programmed adjustments. However, if the downstream consequence of PPN DBS on movement is limited to a circumscribed unblocking of pre-programmed movement, then this may have a similarly circumscribed degree of benefit for gait. If this is the case, then it may be possible to identify patients who may benefit most from PPN DBS. For example, those in whom pre-programmed deficits are the major contributors to gait freezing.

1. Introduction

Pedunculopontine nucleus (PPN) deep brain stimulation (DBS) is an experimental treatment for axial motor deficits in parkinsonian syndromes including Parkinson's disease (PD) (Thevathasan et al., 2018) Fig. 1. The PPN is a collection of neurons at the junction of the midbrain and pons (Jacobsohn, 1911; Jenkinson et al., 2009) Fig. 2. PPN neurons express a range of neurotransmitters, but the PPN has come to be identified by those that express acetylcholine (Jenkinson et al., 2009). The nucleus has widespread reciprocal connectivity with the cortex via the thalamus and with the basal ganglia, cerebellum, and spinal cord (Gut and Winn, 2016). A long history of research in animals suggests that the PPN may affect movement, states of arousal including sleep, the startle response, and even reward (Garcia-Rill et al., 1987; Jenkinson et al., 2004; Mena-Segovia et al., 2008a; Nandi et al., 2002a; Winn, 2008). Of relevance to gait, the PPN is considered a key component of the 'Mesencephalic Locomotor Region' (MLR) – an area where electrical stimulation in decerebrated animals can induce locomotor-like activity (Garcia-Rill et al., 1987; Orlovskii et al., 1966). This role in the MLR, as well as evidence that the PPN is degenerated and inhibited

Abbreviations: DBS, deep brain stimulation; GPi, globus pallidus internus; LFPs, Local field potentials; PD, Parkinson's disease; PPN, pedunculopontine nucleus; PET, Positron Emission Tomography; REM, Rapid Eye Movement; rCBF, regional cerebral blood flow; SRT, simple reaction time; STN, subthalamic nucleus

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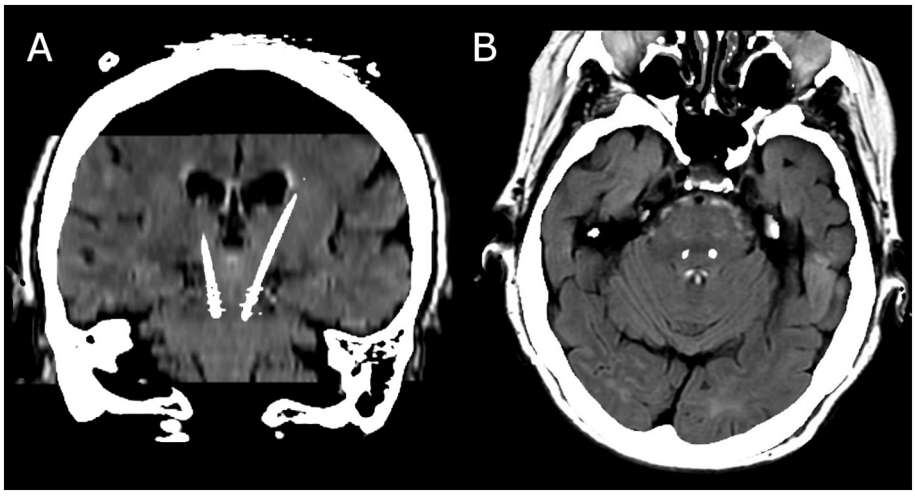

Fig. 1. Example images from a patient with PD implanted with PPN deep brain stimulators. These images represent fusion of the postoperative computed tomography (CT) with the preoperative Magnetic Resonance Imaging (MRI) scans (Fluid Attenuation Inversion Recovery sequence). These demonstrate the brain electrodes implanted in the PPN region in two planes: Coronal (A) and axial (B).

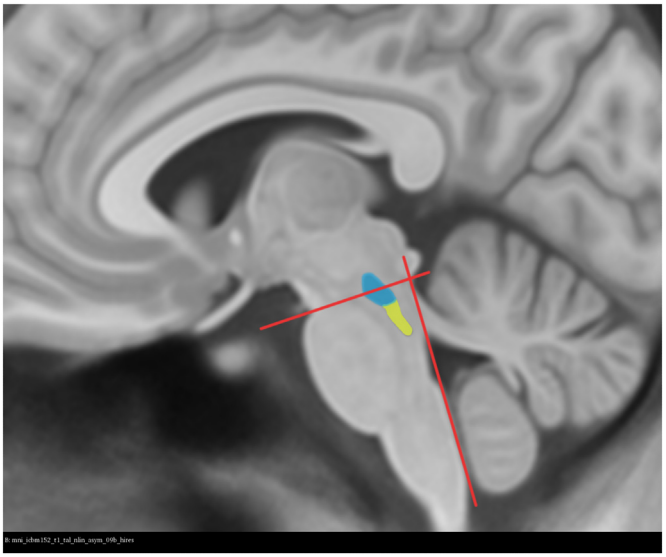

Fig. 2. The PPN region represented in Montreal Neurological Institute (MNI) space. The red lines are useful local landmarks which run, i) in the rostro-caudal axis parallel to the floor of the fourth ventricle and ii) from the inferior margin of the inferior colliculus to the pontomesencephalic (PM) junction (the PM line). The blue subregion is the approximate location of the rostral PPN (2 mm above and below the PM line) and the yellow subregion is the approximate location of the caudal PPN (between 2 mm and 6 mm below the PM line). It is usually possible to implant PPN electrodes to span both subregions, thereby permitting stimulation to be applied to either subregion. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in PD, led to the hypothesis that it could be a useful neuromodulation target for gait and balance (Aziz et al., 1998; Pahapill and Lozano, 2000). The subsequent finding that PPN DBS alleviated movement deficits in the MPTP non-human primate model of PD was rapidly translated to treat patients (Jenkinson et al., 2004, 2005; Mazzone et al., 2005; Nandi et al., 2002a, 2002b; Plaha and Gill, 2005).

Currently, less than 100 patients with PD implanted with PPN DBS have been published (Thevathasan et al., 2018). The combined experience suggests that low frequency PPN DBS offers to patients with PD a fairly circumscribed therapeutic benefit – particularly with respect to relief of gait freezing, including where refractory to conventional treatments such as levodopa, and subthalamic nucleus (STN) and globus pallidus internus (GPi) DBS·(Thevathasan et al., 2018) PPN DBS also reduces falls, and some have reported a benefit for balance deficits including postural instability (Welter et al., 2015). There is no accepted therapeutic benefit on akinesia, rigidity, tremor or levodopa requirements (Thevathasan et al., 2018). Importantly, the therapeutic impact on gait freezing has been variable and often disappointing, both within and between surgical centres (Ferraye et al., 2009; Khan et al., 2012; Moro et al., 2010; Thevathasan et al., 2011a; Welter et al., 2015). It is therefore unclear whether PPN DBS can improve quality of life in PD sufficient to make the risks of brainstem implantation worthwhile. The variable and typically incomplete impact of PPN DBS on gait freezing may reflect that the clinical application is yet to be optimised, or alternatively it may reflect a fundamental limitation of the therapeutic mechanism.

Thus, a better understanding of the therapeutic mechanism of PPN DBS is not simply of academic interest but it may also guide the further development of this novel therapy. Here we draw upon clinical and experimental studies of PPN DBS in patients with PD, in addition to selected insights from experimental work in animals particularly the nonhuman primate, to discuss potential therapeutic mechanisms. However, several limitations of the dataset need to be acknowledged. Firstly, only a few centres have generated the bulk of the published literature regarding PPN DBS·(Ferraye et al., 2009; Khan et al., 2012; Moro et al., 2010; Stefani et al., 2007; Thevathasan et al., 2011a) Secondly, patients with PD implanted with PPN DBS are a selected subgroup where gait freezing and postural instability are the dominant issues. Observations outside of the impact on movement have typically been incidental. Third, whilst the surgical target is the PPN, the impact of DBS may not necessarily reflect modulation of the PPN itself but could arise from its related networks or even from neighbouring regions. This is especially true of the pontomesencephalic area where nuclear boundaries and fibre connections can be indistinct. Thus, we always imply stimulation of the region of the PPN when discussing PPN DBS. Finally, it is important to note that in discussing the therapeutic mechanism of PPN DBS in PD, we do not necessarily assume that this relates to the normal function of the PPN– although one may well be informative on the other.

2. What is the PPN and what does it do?

A detailed review of the anatomy, connectivity and functions of the PPN are beyond the scope of this paper and are dealt with elsewhere (Hamani et al., 2016; Mena-Segovia and Bolam, 2017). Here we address key concepts relevant to understanding the potential therapeutic mechanisms of PPN DBS.

The PPN is an ‘open’ reticular nucleus with indistinct boundaries. (Mannen, 1960; Ramon-Moliner and Nauta, 1966) PPN neurons are densely packed together at the ‘pars compacta’ whereas the PPN ‘pars

dissipata' is a reticular network of neurons with cells that intermingle with neighbouring structures including the cuneiform nucleus, superior cerebellar peduncle and locus coeruleus (Manaye et al., 1999; Mesulam et al., 1989). The PPN and laterodorsal tegmental nucleus form part of a complex of cholinergic neurons extending from the midbrain to mid pons (Manaye et al., 1999; Mesulam et al., 1989).

The PPN comprises part of the reticular activating system (RAS) in the tegmentum where stimulation can desynchronise the electroencephalogram (Moruzzi and Magoun, 1949). Such desynchronisation is a feature of both wakefulness and rapid eye movement (REM) sleep. The RAS includes the PPN, laterodorsal nucleus, locus coeruleus and raphe nucleus and likely mediates its effects via the intralaminar nuclei of the thalamus and thalamocortical projections (Garcia-Rill et al., 2008; Pahapill and Lozano, 2000). PPN neurons are the major source of cholinergic input to the intralaminar thalamic nuclei (Steriade et al., 1988).

The PPN is also considered important for movement. The PPN is reciprocally connected to the GPi, substantia nigra reticulata and the STN·(Bevan and Bolam, 1995; Devito et al., 1980; Lavoie and Parent, 1994b; Nauta and Mehler, 1966; Rye et al., 1996; Smith et al., 1990) These pathways provide a mechanism by which the basal ganglia could control movement separate to its impact on the thalamo-cortical circuit (Forman and Ward, 1957). Connectivity between the PPN and deep cerebellar nuclei raises the possibility that the PPN is where the basal ganglia and cerebellum can interact (Hazrati and Parent, 1992; Jenkinson et al., 2009). The PPN is also reciprocally connected with motor cortical areas and frontal eye fields (Matsumura et al., 2000).

The major descending projections from the PPN are to the reticular formation including the gigantocellular nucleus, nucleus reticularis pontis caudalis and oralis which may impact on the expression of the startle reflex. It is therefore relevant that the PPN receives fast 'unprocessed' auditory sensory input from the cochlear nucleus (Reese et al., 1995a, 1995b). The PPN modulates pontine nuclei that give rise to reticulospinal pathways which primarily innervate proximal and axial musculature (Grofova and Keane, 1991; Mitani et al., 1988). The PPN also projects to the spinal cord (Skinner et al., 1990). Of specific relevance to locomotion, the PPN and cuneiform nucleus are key components of the MLR, where electrical stimulation can produce stepping movements in decerebrated animals (Orlovskii et al., 1966; Reese et al., 1995c).

PPN cholinergic and glutamatergic neurons project to the substantia nigra compacta and the laterodorsal nucleus projects to the ventral tegmental area, providing pathways by which the PPN-laterodorsal nucleus complex can influence motor behaviour through motivation and reward (Hong and Hikosaka, 2014; Lavoie and Parent, 1994a; Mena-Segovia et al., 2008b; Mesulam et al., 1992; Xiao et al., 2016).

Thus, overall, the PPN receives rapid, unprocessed sensory information, could modulate startle, arouse and motivate the animal as well as rapidly influence movement via reticulospinal pathways including locomotion. There is an interface with the basal ganglia – suggesting the PPN may influence or be influenced by higher order action selection. One could therefore speculate a role in the fright/flight reaction and in rapidly modifying behaviour in response to environmental contingencies.

3. The PPN and PPN DBS in PD: degeneration/inhibition and excitation/disinhibition?

Several lines of evidence suggest that the PPN is underactive in PD due to degeneration and inhibition and that this underactivity relates to axial motor impairment. Furthermore, evidence is broadly consistent with the idea that low frequency PPN DBS could partly reverse this underactivity, yielding motor benefits.

3.1. Degeneration/inhibition

Post mortem studies report that PPN neurons, both cholinergic and non-cholinergic, degenerate in PD (Hirsch et al., 1987; Jellinger, 1988; Karachi et al., 2010; Rinne et al., 2008; Zweig et al., 1987, 1989). Interestingly, a recent study found that in PD, PPN neurons, like those of the substantia nigra, had abnormalities in mitochondrial function that may confer a specific vulnerability to neurodegeneration (Bury et al., 2017). Cholinergic PPN neuronal loss is prominent in PD compared to aged controls and Alzheimer's disease (Jellinger, 1988; Zweig et al., 1987, 1989). PPN cholinergic cells loss in PD is reported to be most prominent in the caudal PPN (Rinne et al., 2008).

In PD, PPN cholinergic cell loss can be related to axial motor impairment. For example, PPN cholinergic cell loss correlates with Hoehn and Yahr disease staging, of which gait and balance is an important determinant (Rinne et al., 2008). However, there is a lack of pathological evidence that PPN cholinergic cell loss in PD specifically relates to gait, balance and falls after controlling for disease stage. Nevertheless, in subjects without PD, bilateral infarction of the PPN area was reported to cause gait freezing (Kuo et al., 2008). In the MPTP non-human primate model of PD, PPN lesions caused 'akinesia' (Aziz et al., 1998; Matsumura and Kojima, 2001). This effect was more precisely determined in a study of normal and parkinsonian monkeys, where lesioning PPN cholinergic neurons specifically caused balance and gait disturbance (Karachi et al., 2010). A PET study in PD patients reported that falls correlated with reduced thalamic cholinergic activity, which largely derives from PPN projections (Bohnen et al., 2009). Interestingly, in that study, dopaminergic depletion did not, after controlling for cofactors of disease stage and cholinergic activity, correlate with falls (Bohnen et al., 2009).

In PD, excessive descending inhibition may also contribute to PPN underactivity. Increased activity in the indirect pathway of the basal ganglia in PD would be predicted to cause excessive GABAergic inhibition via projections from the GPi and substantia nigra pars reticulata – although this same model would predict increased glutamatergic influences from the STN (Aziz et al., 1998; Garcia-Rill et al., 2011). Connectivity with the parkinsonian basal ganglia could also cause the PPN to become engaged in abnormal beta band synchronisation (Hammond et al., 2007). In monkeys, the microinjection of the GABA agonist muscimol into the PPN and also high frequency PPN stimulation (considered inhibitory) was reported to cause motor impairment (Matsumura and Kojima, 2001; Nandi et al., 2002b).

3.2. Excitation/disinhibition

The possibility that PPN dysfunction may cause motor deficits in PD, which may be amenable to reversal through disinhibition, suggested the PPN as a target for neuromodulation (Aziz et al., 1998). In the MPTP primate model of PD, infusion of bicuculline (a GABA antagonist) into the PPN improved movement counts and postural stoop but not tremor (Nandi et al., 2002a). The effects of bicuculline were mimicked by low frequency PPN stimulation of around 5–10 Hz (Jenkinson et al., 2004). Dopamine added further benefits to low frequency PPN stimulation and together they restored normal movement to the MPTP monkey (Jenkinson et al., 2006). These findings were rapidly translated to treat patients with PD (Mazzone et al., 2005; Plaha and Gill, 2005). Emulating the MPTP monkey experiments, the application of lower frequencies (typically 20–40 Hz for bilateral stimulation) to the PPN has been found to be best in patients with PD (Thevathasan et al., 2018). This is much lower than the higher frequencies of around 130 Hz that are typically employed for STN DBS. Two studies have specifically investigated frequency effects of PPN DBS in PD. One study explored differing very low frequencies (5–35 Hz) on reaction time (Thevathasan et al., 2010). This study found that 20–35 Hz PPN DBS was superior to the very low frequencies found most beneficial in monkeys (5 Hz and 10 Hz stimulation) (Thevathasan et al.,

2010). Another study directly compared the impact of bilateral low frequency (10–25 Hz) versus higher frequency (60–80 Hz) PPN DBS on gait freezing, akinesia and sleepiness (Nosko et al., 2015). Seven of nine patients had less gait freezing with low frequency PPN DBS·(Nosko et al., 2015). Akin to the effects on monkeys, bilateral higher frequency PPN DBS was associated with worsened akinesia and sleepiness.

One argument which would seem to counter the claim that PPN DBS enhances PPN function is the seemingly paradoxical improvement in gait freezing due to the micro-lesion effect soon after PPN electrode implantation (Koop et al., 2006; Thevathasan et al., 2012b; Welter et al., 2015). The lesion-like properties of this microlesion effect would be predicted to further inhibit PPN function and thus worsen gait. However, in the caudal PPN, alpha activity persisted despite the apparent stun effect and correlated positively with gait performance (Thevathasan et al., 2012b). Accordingly, it is possible that stun effects in PPN surgery might arise from microlesioning inhibitory supraspinal influences along the electrode trajectory – supported by the temporary improvement in akinesia observed in some patients presumably by electrode passage through the subthalamic region (Welter et al., 2015).

4. The PPN and PPN DBS in PD: coupling therapeutic and network effects

A detailed discussion of the clinical impact of PPN DBS in PD has been the focus of a recent review paper (Thevathasan et al., 2018). Here we seek to clarify the precise nature of the clinical and network effects of PPN DBS in order to propose potential therapeutic mechanisms.

4.1. Movement, attention, startle and reward - interconnected mechanisms?

The benefit of PPN DBS on gait appears relatively circumscribed to the phenomenon of gait freezing without convincing impact on other spatiotemporal aspects of gait (Thevathasan et al., 2012a). Balance may also improve but there is no wider benefit on akinesia, rigidity or tremor (Thevathasan et al., 2018). This raises the question of which aspects of the pathophysiology of gait freezing are amenable to improvement by PPN DBS. Two candidates will be considered here - the motor block to gait adjustments and attentional deficits that impact on gait performance.

Gait freezing tends to occur at times of adjustments such as starting off, turning, avoiding obstacles and approaching destination (Almeida and Lebold, 2010; Chee et al., 2009). This suggests that gait freezing may involve failure to integrate adjustments to pattern generated gait. A role of the PPN in facilitating such movements could be supported by its proposed function in 'sensorimotor integration' (Winn, 2008). This could be seen as analogous to the relief of gait freezing by external cues (Praamstra et al., 1998).

Gait freezing may also be provoked when attention is divided or focussed away from locomotion (Camicioli et al., 1998; Giladi and Hausdorff, 2006; Peterson et al., 2015). For example, gait freezing can be precipitated by the performance of a second, unrelated task ('dual tasking') (Giladi and Hausdorff, 2006; Peterson et al., 2015). Dual tasking reduces gait speed, in healthy subjects and patients with PD (Hausdorff et al., 2003; Lamoth et al., 2011; Springer et al., 2006). In elderly subjects without PD, an inability to 'walk whilst talking' predicts falls (Lundin-Olsson et al., 1997). Such findings implicate 'attention' as a potentially important factor influencing the performance of gait and in the occurrence of falls and gait freezing. Importantly, with the term 'attention', we are not referring to level of arousal or alertness but rather the systems definition as the 'allocation of processing resources' (Wickens, 1991). Processing resources are finite and decline with age (Grady and Craik, 2000). In PD, attentional resources are even further diminished and yet processing demands are increased due to impaired automaticity of movement (Wu and Hallett, 2005; Wu and Hallett, 2008). Moreover, parkinsonian patients with gait freezing seem to have more attentional deficits than those without gait freezing (Amboni et al., 2008; Yogev-Seligmann et al., 2008). Implicating the PPN, one study reported that the degree to which dual task interference worsened gait in PD patients correlated with PPN structural connectivity (Peterson et al., 2015). Startling stimuli, heightened state of arousal and anticipated or actual reward are all capable of recruiting attention and enhancing movement (Anzak et al., 2011; Anzak et al., 2016; Mazzoni et al., 2007). Thus, the improvement in gait freezing with PPN DBS could implicate many of the proposed functions of the PPN such as modulation of alertness, startle and reward. This may be analogous to the mechanism of paradoxical kinesis – where an intense arousing stimulus can not only trigger the startle reflex and heighten attention but also temporarily relieve gait freezing (Glickstein and Stein, 1991).

Here we assess how these concepts have been explored in experimental studies in patients with PD implanted with PPN DBS using neuronal recordings from PPN electrodes and by assessing the impact of PPN DBS using imaging and neurophysiological and clinical techniques.

4.1.1. Neuronal recordings from PPN electrodes

Local field potentials (LFPs) recorded from PPN electrodes in PD patients have demonstrated peaks in both alpha and beta bands, coherent with the cortex (Androulidakis et al., 2008a; Androulidakis et al., 2008b; Fraix et al., 2013; Lau et al., 2015; Tattersall et al., 2014; Thevathasan et al., 2012b). Whilst beta band activity recorded from the basal ganglia and cortex has been linked to motor function, there is increasing evidence that alpha oscillatory activity has an important role in attention and the allocation of processing resources (Eusebio and Brown, 2009). The synchronisation of occipital alpha with eye closure was once interpreted to reflect passive 'idling' (Berger, 1929; Pfurtscheller et al., 1996). However, alpha activity is now considered to support active suppression of task irrelevant processes (Jensen and Mazaheri, 2010; van Diepen and Mazaheri, 2017). For example, during working memory tasks, cortical alpha power in visual and motor-sensory areas increases and the degree of synchronisation correlates with the number of items recalled (Haegens et al., 2010; Jensen et al., 2002). Correlation of performance with alpha oscillatory power in task irrelevant regions suggests suppression rather than mere idling. It has been proposed that within the motor system, alpha related suppression of competing processes could aid the smooth execution of motor programs (Pfurtscheller and Neuper, 1994; Suffczynski et al., 2001).

Supportive of the idea that alpha and beta band activity recorded from the PPN may serve different functions, a study employing magnetoencephalography found that these two PPN oscillatory bands have distinct connectivity – with the beta band network coherent with the supplementary motor area and alpha network coherent with the cingulate including the posterior mid-cingulate which has been linked with integrating sensorimotor feedback during movement. (Jha et al., 2017; Vogt, 2005) Divergence in the roles of alpha and beta oscillations in the PPN is also supported by the topographic oscillatory spectral arrangement in the PPN reported now by several studies - with beta power most prominent in the rostral PPN and alpha power in the caudal PPN. (Jha et al., 2017; Tattersall et al., 2014; Thevathasan et al., 2012b) Fig. 2. It appears that alpha band activity in the PPN may have greatest relevance for gait. For example, alpha activity in the caudal PPN is increased with walking compared with sitting or standing (Thevathasan et al., 2012b). PPN alpha increases along with gait speed (real and imagined) and drops out just prior to episodes of gait freezing (Lau et al., 2015; Thevathasan et al., 2012b). In the rostral PPN, alpha power increased when stepping in place on levodopa compared with sitting off levodopa (Fraix et al., 2013). This corroborated earlier studies which reported that PPN alpha power increases with levodopa (Androulidakis et al., 2008a; Androulidakis et al., 2008b).

However, neuronal recordings suggest that the PPN is not only of relevance to locomotion but also to movement in general. PPN neuronal firing responds to ipsilateral and contralateral voluntary limb movements in monkeys and patients with PD (Matsumura et al., 1997; Weinberger et al., 2008). LFPs recorded from PPN electrodes in PD

patients are responsive to self-paced joystick movements (Androulidakis et al., 2008b). Event related synchronisation occurred in the alpha band many seconds prior to movement (Androulidakis et al., 2008b). This interval is too long for immediate motor preparation but would be consistent with the focussing of attention (Androulidakis et al., 2008b; Tsang et al., 2010). As found in STN LFPs, beta desynchronisation also occurs in PPN LFPs just before and during movement (Tsang et al., 2010). One study compared neuronal firing between STN and rostral PPN recordings – and found that both PPN and STN neurons were modulated by motor tasks (Lau et al., 2015). But unlike the STN, a majority of PPN neurons were also specifically activated by multiple phases of imagined gait (Lau et al., 2015). Some PPN neurons were also activated by visual stimuli. Thus, the authors posited that the PPN would be well placed to have a role in integrating sensory stimuli into gait (Lau et al., 2015). It should be noted that recordings dorsal to the PPN, in the cuneiform region, have also demonstrated neuronal firing in time with imagined stepping in PD patients intraoperatively (Piallat et al., 2009). This would be consistent with the idea of the cuneiform nucleus being part of the MLR.

Taken together, these data suggest that the PPN may be important for movement in general but also has a particular role in the regulation of locomotion. Furthermore, the PPN can interact with other distant nodes including the cingulate, such as with alpha oscillations, and is well placed to integrate sensory information such as visual input. That PPN alpha activity increases with levodopa across studies and reduces with gait freezing raises the hypothesis that alpha power in PD may be pathologically decreased, and this may contribute to impaired attentional processing and gait freezing. The increase in PPN alpha with levodopa has therefore raised speculation that low frequency PPN DBS could somehow support or emulate PPN alpha (Thevathasan et al., 2010). Furthermore, that PPN alpha is most prominent in the caudal PPN has also raised speculation that the caudal PPN may be a more relevant target for gait (Windels et al., 2015). However, currently there is a lack of direct evidence supporting these hypotheses (Fu et al., 2014; Thevathasan et al., 2012b).

4.1.2. PPN DBS assessed with imaging

Relatively few papers have been able to assess the network effects of PPN DBS using Positron Emission Tomography (PET), seeking changes in regional cerebral blood flow (rCBF) (^{15}O-H_2O PET) or brain glucose metabolism (^{18}F-FDG PET)(Ballanger et al., 2009; Ceravolo et al., 2011; Khan et al., 2012; Strafella et al., 2008). A common finding has been that PPN DBS increases activity in local (e.g. to cerebellum and within the brainstem) and cortical motor sensory areas.

In a case report, unilateral PPN-DBS increased rCBF bilaterally in the thalamus, and in other subcortical areas (Strafella et al., 2008). In three PD patients with unilateral PPN stimulation, rCBF increased in several cortical regions, particularly in the prefrontal areas, along with thalamus, cerebellum, and midbrain (Ballanger et al., 2009). In four patients, bilateral PPN stimulation increased rCBF in subcortical areas including thalamus, cerebellum, and midbrain and a decreased rCBF in the left Brodmann area 5 (Khan et al., 2012). Concomitant PPN and caudal zona incerta stimulation resulted in an additive effect on cerebral blood flow, combining the rCBF changes induced by the stimulation of the individual targets (Khan et al., 2012). In one study of six patients, bilateral PPN was reported to increase glucose utilization in bilateral prefrontal areas, left ventral striatum, and right temporal areas and bilateral decreases in cerebellar glucose utilization (Ceravolo et al., 2011).

Taken together, PET studies suggest that PPN DBS increases rCBF locally in the brainstem, and in the cerebellum and thalamus – regions with well described connectivity with the PPN. Across studies, there is less consistency regarding the network effects of PPN DBS on cortical areas.

4.1.3. PPN DBS assessed with clinical and neurophysiological tools

Clinical studies employing cross sectional assessments have failed to reveal any convincing impact of PPN DBS on frontal lobe function, attention or alertness. For example, two studies found no consistent change in the Mattis Dementia Rating Scale or a composite assessment of frontal lobe function in six patients with PPN DBS·(Ferraye et al., 2009; Welter et al., 2015) Several studies from the Rome group reported substantial improvements with PPN DBS on frontal lobe cognition in small numbers of patients. For example, two such studies suggested improvements in performance on various tasks of executive functioning but with relatively limited information regarding the methodology (Alessandro et al., 2010; Costa et al., 2010). One case report found that PPN DBS improved measures in all tested cognitive domains including attention, memory and language, although this effect may have been due to intercurrent factors (Ricciardi et al., 2015). Dedicated sensitive testing seeking an impact of PPN DBS on reward in controlled experiments or using dopamine labelled PET studies has not been performed. However, small clinical studies that performed neuropsychiatric assessments before and after PPN DBS have not detected any obvious impact on mood or apathy using clinical rating scales (Ferraye et al., 2009; Welter et al., 2015). Many other clinical studies did not formally assess psychiatric outcomes (Moro et al., 2010; Stefani et al., 2007; Thevathasan et al., 2011a).

Several studies of at least seven patients used reaction time to seek and discriminate any impact of PPN DBS on alertness, attention and motor performance (Fischer et al., 2015; Thevathasan et al., 2011b; Thevathasan et al., 2010). These studies reported a benefit of PPN DBS most prominent in simple reaction time (SRT) tasks (Fischer et al., 2015; Thevathasan et al., 2011b; Thevathasan et al., 2010). PPN DBS did not uniformly improve the motor component of response times, as occurs with levodopa and STN and pallidal DBS·(Brown et al., 1999; Temel et al., 2006; Thevathasan et al., 2010) However, neither was there convincing evidence from these studies that PPN DBS improves alertness or global attention. For example, PPN DBS did not improve reaction time in a vigilance or divided attention task (Fischer et al., 2015; Thevathasan et al., 2010). One study reported that PPN DBS improved simple reaction time without a warning cue and a strong trend for also improving SRT with a warning cue ($p = .07$) (Fischer et al., 2015). On the basis that this latter result was not significant, the authors argued that PPN DBS might improve phasic arousal. Though, with only eight patients in the study, this may simply reflect insufficient power. The specific benefit of PPN DBS on SRT was further analysed using reaction time distribution which found that PPN DBS affected all reaction times rather than having a disproportional benefit on outliers (which are considered to reflect attentional lapses) (Thevathasan et al., 2010). This consistent benefit across all trials suggests a motor effect – albeit one that seems restricted to SRT and not choice reaction time (Thevathasan et al., 2010).

But what sort of motor effect only occurs in SRT as opposed to across all tasks? A key feature of SRT tasks is that unlike choice and Go/No-Go tasks, the motor output is known and can be prepared in advance, ready for triggered release. That is, pre-programmed motor responses may be uniquely responsive to PPN DBS. A useful probe for this hypothesis has been the Start-React phenomenon, where a startling stimulus such as a very loud sound can involuntarily trigger or accelerate the release of pre-programmed movement (Valls-Sole et al., 1999). Using the StartReact probe, it was found that patients with PD and severe gait freezing had absent Start-React, tested in a ballistic elbow flexion task, which was restored by PPN DBS·(Thevathasan et al., 2011b) Moreover, acceleration of pre-prepared movement by loud sounds correlated with the severity of gait freezing in this cohort (Thevathasan et al., 2011b). The lack of Start-React in PD has since been corroborated by others – and associated with gait freezing (Carlsen et al., 2009; Nonnekes et al., 2014, 2015). Interestingly, the startle reflex was also absent in patients with PD and severe freezing – consistent with neurodegeneration affecting this region of the

brainstem (Thevathasan et al., 2011b). However, PPN DBS did not restore the startle reflex. Thus, the impact of PPN DBS on pre-programmed movement was dissociated from the startle reflex.

The benefit of PPN DBS on pre-programmed movement in PD could be viewed as a facilitation or disinhibition of reflexic, event triggered action such as those required to adjust continuous motor patterns such as locomotion and sway. It would not be inconsistent with this idea that PPN DBS has also been observed to facilitate the spinal H reflex, a potential down-stream consequence of such disinhibition of reflexic action (Pierantozzi et al., 2008). The proposed 'unblocking' of pre-programmed movement with PPN DBS could be seen as analogous to the improvement in gait freezing observed with external cues (Glickstein and Stein, 1991; Keefe et al., 1989; Nieuwboer et al., 2007).

4.2. State of arousal including sleep – related to movement?

Three studies have specifically assessed whether PPN DBS affects sleep in parkinsonian patients (Arnulf et al., 2010; Lim et al., 2009; Romigi et al., 2008). Two studies assessed patients using overnight polysomnography, and both reported that PPN DBS roughly doubled the proportion of REM sleep (Lim et al., 2009; Romigi et al., 2008). In one study, unilateral PPN DBS increased nightly REM sleep time (mean 35 to 61 min) compared with no stimulation (Lim et al., 2009). Importantly, this study found that the increased REM sleep was due to an increase in frequency rather than duration of REM sleep episodes. Non-REM sleep was unchanged by PPN DBS. Two patients experienced REM sleep behavioural disturbance, and this persisted with PPN DBS. A further study detected phasic potentials during and before REM sleep from externalised PPN electrodes consistent with ponto-geniculo-occipital waves which have been classically associated with REM sleep in animal research (Lim et al., 2007).

The increased REM sleep episodes with PPN DBS suggest that there may be an underlying impact on switching between states of arousal including sleep. Further supporting this notion, one study reported two patients in whom PPN DBS could provoke sleep from a state of wakefulness, assessed clinically and with electroencephalography (Arnulf et al., 2010). The patients were alert during therapeutic low frequency PPN DBS (10 Hz or 25 Hz). In one patient, abrupt withdrawal of low frequency PPN DBS reproducibly triggered REM sleep. In both patients, high frequency PPN DBS (80 Hz) could precipitate non-REM sleep (Arnulf et al., 2010).

It is unclear if these findings suggesting an impact of PPN DBS on sleep relate to the motor benefit of PPN DBS on gait. REM sleep may decline in some patients with PD (Peeraully et al., 2012). REM sleep is postulated to improve memory consolidation, including procedural learning (Plihal and Born, 1997). This could suggest a mechanism by which PPN DBS could improve any motor skill via increased REM sleep. This could account for the long latencies of days or longer between activation of PPN DBS and improvement in gait, from anecdotal observations (Ferraye et al., 2009; Moro et al., 2010; Thevathasan et al., 2011a). On the other hand, studies employing objective techniques report that PPN DBS can improve gait within minutes (Thevathasan et al., 2012a). Furthermore, there is a lack of current evidence that increase in REM sleep with PPN DBS correlates with the beneficial impact on gait freezing.

5. Discussion

The available data regarding the impact of PPN DBS in patients is limited, variable and rather inconclusive. Whilst we acknowledge these limitations, we believe it remains worthwhile to speculate on potential therapeutic mechanisms of PPN DBS – as this may offer suggestions of how the clinical application can be progressed.

The available evidence, preclinical and clinical, support that the PPN is underactive in PD due to a combination of both degeneration and excessive inhibition. Low frequency PPN DBS may enhance PPN network activity, perhaps via disinhibition. One clinical implication is that in some patients, the PPN is too degenerate for PPN DBS to work. It may therefore be worth exploring if PPN DBS may be best deployed in patients in whom excessive inhibition rather than degeneration is most contributory. Structural and functional imaging could offer the tools to identify such patients (Boisgontier et al., 2017).

The prominent finding of alpha activity in the PPN recorded from patients with PD which declines with gait freezing and increases with levodopa, raises the hypothesis that PPN DBS could support or emulate this activity and consequently enhance the allocation of attentional resources. However, studies assessing the impact of PPN DBS have not convincingly detected a pervasive increase in alertness or any benefits that may arise from a general increase in attention, at least with the parameters of stimulation currently applied clinically. Instead, reaction time studies have reported that PPN DBS appears to mediate a very specific benefit on pre-programmed movement. This seems relevant to the pathophysiology of gait freezing, which can be argued to reflect impaired release of pre-programmed adjustments to locomotion.

Despite the lack of evidence that PPN DBS increases general attention, the allocation of processing resources cannot be discounted as an important factor in the therapeutic mechanism of PPN DBS. But how could attention relate to the circumscribed benefit on pre-programmed movement from PPN DBS? A speculative proposal could be that alpha band activity recorded from the PPN and the action of PPN DBS may enhance the allocation of processing resources within the motor system, or "motor attention" (Johansen-Berg and Matthews, 2002). For example, this could facilitate the 'switching' of motor state between continuation of pattern generated locomotion towards the intervention of pre-programmed adjustments. This is not so dissimilar to the recent proposal that the normal function of the PPN is to "simultaneously restrain obsolete actions while it facilitates new contextual associations" (Mena-Segovia and Bolam, 2017). If so, then this raises the possibility that PPN DBS could facilitate other types of 'switching' where connectivity between the brainstem and cortex is important, as suggested by its impact on sleep state.

However, if the downstream consequence of PPN DBS on movement is limited to a circumscribed unblocking of pre-programmed movement, then this may have a similarly circumscribed degree of benefit for gait. If this is the case, then it may be possible to identify patients who may benefit most from PPN DBS. For example, those in whom pre-programmed deficits are the major contributors to gait freezing. Such patients could potentially be identified using the Start-React protocol. Furthermore, such a marker of therapeutic mechanism may aid the choice of stimulation contact and parameters.

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Conflict of interests

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