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Review

Role of pedunculopontine nucleus in sleep-wake cycle and cognition in humans: A systematic review of DBS studies

Lucia Ricciardi[a], Marianna Sarchioto[a,b], Francesca Morgante[a,c,*]

[a] Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, United Kingdom
[b] Department of Neuroscience "Rita Levi Montalcini", University of Torino, Italy
[c] Department of Experimental and Clinical Medicine, University of Messina, Italy

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ABSTRACT

Background: Animal studies have demonstrated that the pedunculopontine nucleus (PPN) is involved in the control of posture and gait, and that it is also a key structure in controlling basic non-motor functions such as sleep, attention and arousal. In this systematic review we aimed to evaluate all available studies assessing the role of PPN on cognition, nocturnal sleep and alertness in humans. Finally, we attempted to define a model in which PPN acts as an interface structure between motor control and behavior.

Methods: A systematic search of the computerized databases MEDLINE and PubMed was conducted to identify papers on PPN and cognitive functions, sleep and alertness. Key search terms included: 'PPN', 'arousal', 'sleep', 'cognition', 'memory', 'language', 'attention', 'alertness', 'PPN-DBS', 'Parkinson's and PPN', 'Parkinson's and PPN-DBS'.

Results: Twelve studies met our inclusion criteria and were included. All of them involved PD patients implanted with unilateral or bilateral PPN-DBS, most patients had concomitant DBS of another anatomical structure (subthalamic nucleus or Zona incerta). There is a lack of consistent evidences confirming the effect of PPN-DBS on specific cognitive functions, alertness or sleep in PD. There is heterogeneity between and within surgical centres of study protocols especially regarding DBS targeting, parameters of stimulation and experimental methods. Moreover, the available studies are limited by the small sample size and the short follow-up time. It has been suggested that low frequency stimulation (25 Hz) has a better effect compared to the high frequency one (60–80 Hz) on alertness, however this needs to be confirmed in further studies.

Conclusions: PPN-DBS is a promising but yet an experimental procedure. PD represents an encouraging pathological model for future studies aiming to shade light on the role of PPN in cognition, attention and alertness in humans.

1. Introduction

The pedunculopontine nucleus (PPN) is a neurochemically and functionally heterogeneous structure located in the dorsal tegmentum of the midbrain and upper pons. The involvement of PPN in the control of posture and gait has been proposed by several experimental studies (Garcia-Rill et al. 1987; Nandi et al. 2002), which led to testing the PPN area as a Deep Brain Stimulation (DBS) target for gait disturbances in Parkinson's disease (PD) (Ferraye et al. 2010; Moro et al. 2010; Stefani et al. 2007) and Progressive Supranuclear Palsy (PSP) (Scelzo et al. 2017). However, PPN area stimulation has produced heterogenous results due to difficulty in targeting a brainstem nucleus severely affected by neurodegeneration in PD; moreover, results have not been sustained at longer follow-up (Mestre et al. 2016).

Animal studies have also demonstrated how PPN is a key structure in controlling basic non-motor functions such as sleep, attention and arousal (Garcia-Rill et al. 2015; Garcia-Rill et al. 2018).

The amount of studies in humans about the role of PPN in such non-motor functions is small and comes from PD patients implanted with DBS. The aims of this systematic review were: 1) to evaluate available data on the effect of PPN-DBS on cognition, nocturnal sleep and alertness in patients with PD; 2) to review studies in humans which have assessed the role of PPN on these functions; 3) to suggest a model in which PPN acts as an interface structure between motor control and behaviour.

* Corresponding author at: Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, SW17 0RE, London, United Kingdom.
E-mail address: fmorgant@sgul.ac.uk (F. Morgante).

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Table 1
DBS studies testing the effect of PPN on non-motor outcomes.

Reference	Type of design	NMS	Sample size	Outcome measures	Target	Frequency of DBS	Main findings
Romigi et al. 2008	Case Report, STN vs PPN stim	Sleep	1 PD	PSG	Bilateral STN + PPN	STN = 185 Hz PPN = 25 Hz	PPN DBS = ↑ REM stability and continuity of nocturnal sleep
Lim et al. 2009	Case series, ON vs OFF stim	Sleep	3 PD, 2 PSP	PSG	Unilateral PPN	Range: 5–70 Hz	↑ REM sleep time and REM percentage on PPN DBS.
Arnulf et al, 2009	Case reports, PPN ON vs OFF stim PPN LF vs HF*	Sleep and alertness	2 PD	PSG	Bilateral PPN	LF = 10 or 25 Hz HF = 80 Hz	LF induced alertness. HF induced NREM sleep episodes.
Alessandro et al. 2010	Cross-sectional, PPN ON vs OFF stim vs cyclic stim with STN ON stim	Sleep and Cognition	6 PD‡	Instrumental: PSG, FDG PET Clinical scales: ESS, PDSS, PSQI, CVLT, TMT, PF, naming test,	Bilateral STN + PPN	PPN: 25 Hz STN: 185 Hz	PPN ON: - ↑ REM sleep. - improve delayed recall, TMT and PF - ↑ metabolism of prefrontal areas and left ventral striatum ● STN-ON: - No effect on REM sleep ● - Improvement of sleep efficiency
Nosko et al, 2014	Double-blind randomised cross-over PPN LF vs HF with STN ON stim. - OFF MED/LF - ON MED/LF - OFF MED/HF - ON MED/HF	Alertness	9 PD	ESS	Bilateral STN + PPN (7); Bilateral PPN (2)	low-frequency (10–25 Hz) versus higher (60–80 Hz)	Daytime sleepiness lower under LF than HF
Ferraye et al. 2010	Prospective, open label, pre-op vs post-op (PPN + STN ON)	Cognition and apathy (secondary outcomes)	6 PD	MDRS, BDI, Starkstein apathy scale	Bilateral STN + PPN	Range = 15–25 Hz	No difference in MDRS, BDI and apathy compared to pre-DBS¥
Zanini et al. 2009	Cross-sectional, PPN + /STN + PPN-/STN + PPN + /STN- PPN-/STN-	Cognition	5 PD‡	Cognitive and Neurolinguistic assessment	Bilateral STN + PPN	PPN: 25 Hz STN: 185 Hz	Less grammar errors for STN ON - PPN ON
Costa et al. 2010	Cross-sectional, PPN ON vs PPN OFF with STN OFF and medication OFF	Cognition	5 PD‡	Cognitive assessment and computerized task for working memory	Bilateral STN + PPN	STN: OFF PPN: 25 Hz	Faster performance in computerized task for working memory in PPN ON vs PPN OFF
Ceravolo et al. 2011	Cross-sectional, PPN ON vs PPN OFF with STN OFF and medication OFF	Cognition and metabolic brain activity	6 PD‡	FDG PET and Cognitive assessment	Bilateral STN + PPN (redefined as PPTg)	STN: OFF PPN: 25 Hz	PPN ON – STN OFF: Improvement of verbal long-term memory, executive functions, verbal fluency. ↑ metabolism of dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate, superior frontal gyrus, parietal inferior lobule, supramarginal gyrus and left ventral striatum
Thevathasan et al. 2010	Cross-sectional, with ZI and medication OFF. PPN OFF, 5 Hz PPN, 10 Hz PPN and usual therapeutic frequency (20–35 Hz)	Attention	11 PD (8 PPN DBS, 3 PPN-ZI DBS)	SRT, Digit Vigilance task, Choice RTT, falls diary	Bilateral PPN: 10, unilateral PPN: 1	Therapeutic frequency range: 20–35 Hz. 5 and 10 Hz as per study protocol	Improvement of “Speed of Reaction” of SRT only during therapeutic stimulation. Falls score improvement correlated with changes SRT
Ricciardi et al. 2015	Case report, Pre-Op vs post-Op 6 m vs post-Op 4 y (OFF PPN vs ON PPN)	Cognition	1 PDD	Cognitive assessment	Unilateral PPN	30 Hz	Worsening of cognition in PPN OFF and improvement in PPN ON
Fischer et al. 2015	Cross-sectional, PPN- vs PPN-8 Hz vs PPN-20 Hz vs PPN-60 Hz vs PPN-130 Hz	Attention	8 PD	MDRS and 4 computerized tasks for attentional performance	Bilateral PPN = 5 Bilateral; STN + PPN = 3	8/20/60/130 Hz as per study protocol	Improvement of performance in a simple RT task when PPN-ON at 8 Hz and 20 Hz.

¥ Subjective Improvement of nocturnal sleep and increase in diurnal vigilance in 3 patients. ACC: anterior cingulate cortex; BDI: Beck's depression inventory; CVLT: California verbal learning test; DBS: deep brain stimulation; ESS: Epworth sleepiness scale; HF: high frequency; LF: low frequency; MDRS: Mattis Dementia Rating scale; PD: Parkinson's disease; PDSS: Parkinson's disease sleep scale; PF: phonological fluency; PI: postural instability; PPN: Peduncolopontine nucleus; PSG: polisomnography; PSQI: Pittsburgh sleep quality index; PSP: Progressive supranuclear palsy; Pts: patients; RBD: REM sleep behaviour disorders; REM: rapid eye movement; STN: sub-thalamic nucleus; TMT: trail making test.

2. Methods

A full search of MEDLINE and Cochrane (Ovid) database was performed up to June 2018, using the following key words: 'PPN', 'arousal', 'sleep', 'cognition', 'memory', 'language', 'attention', 'PPN-DBS', 'Parkinson's and PPN', 'Parkinson's and PPN-DBS'. Inclusion criteria of this systematic review were: studies on PD patients undergoing unilateral or bilateral PPN DBS, who have been specifically assessed for sleep and neuropsychological profile. We also included patients who underwent functional neurosurgery in more than one anatomical structure (such as PPN + STN DBS; PPN + DBS of the Zona incerta, ZI). Only articles published in peer-reviewed journals in English were included. Given the paucity of studies published on this topic, all study designs were included. Primary database searches were performed by two researchers (LR, MS) who compiled a list of non-duplicate studies according to inclusion and exclusion criteria. Relevant studies from the reference list of primary search results were identified and included in the review process.

3. Results

After abstract review and removal of duplicates, we retrieved 12 articles that met our review criteria, 3 of them were case reports. Most of the studies have included patients implanted with both STN and PPN DBS, often bilaterally. Heterogeneity among studies was due to different experimental designs, with PD patients being either ON or OFF STN DBS and dopaminergic medications during the assessments. Table 1 gives details of included studies.

3.1. Sleep and alertness

Four studies (Alessandro et al. 2010; Arnulf et al. 2010; Lim et al. 2009; Romigi et al. 2008) have evaluated the effect of PPN stimulation on sleep quality in patients with bilateral PPN, two of them with concomitant STN-DBS used as control (Alessandro et al. 2010; Romigi et al. 2008).

All DBS studies reported an improvement of sleep efficiency with PPN DBS when assessing sleep with polysomnography (PSG) and clinical scales. STN DBS improved sleep efficiency but it did not have any impact on REM sleep (Alessandro et al. 2010; Romigi et al. 2008). Only one study has evaluated sleep quality in PD patients with unilateral PPN-DBS (contralateral to the most affected side) using PSG (Lim et al. 2009). In this study, there was an improvement of REM sleep time and REM percentage when PPN-DBS was ON compared to when the stimulation was switched OFF. Moreover, 3 patients subjectively reported increased alertness or more refreshing sleep during the day time. Alertness was specifically evaluated respectively by polysomnography and a clinical questionnaire for daytime sleepiness by two studies (Arnulf et al. 2010; Nosko et al. 2015). Arnulf et al. compared the effect of low frequency and high frequency stimulation on sleep in 2 patients with a cross-over, double blind experimental design. They showed that low-frequency (10 or 25 Hz, unilateral or bilateral PPN) but not high-frequency (80 Hz) improved alertness. Indeed, when stimulated with low-frequency, patients were alert and spontaneously active while high-frequency stimulation determined marked feeling of sleepiness and could induce non-REM sleep (Arnulf et al. 2010). A double-blind randomised cross-over study in 9 PD patients comparing stimulation of PPN at low (10–25 Hz) versus high frequency found a significant reduction of daytime sleepiness by means of Epworth Sleepiness scale only in the low frequency stimulation condition (except for one patient) (Nosko et al. 2015). In this study, 7 out of 9 PD subjects had STN DBS active.

Recently, the role of PPN in sleep and balance control of PD patients has been highlighted by a rsMRI study which has demonstrated decrease connectivity in the arousal network between PPN and anterior cingulate cortex in patients with RBD (Gallea et al. 2017). Decreased connectivity correlated with daytime sleepiness, further suggesting a role for PPN in alertness control.

3.2. Cognition

More controversial are the results of the available studies on the effect of PPN DBS on cognitive functions in PD patients (Alessandro et al. 2010; Ceravolo et al. 2011; Costa et al. 2010; Ferraye et al. 2010; Fischer et al. 2015; Ricciardi et al. 2015; Thevathasan et al. 2010; Zanini et al. 2009)

A group of studies, performed on the same cohort of patients (Alessandro et al. 2010; Ceravolo et al. 2011; Costa et al. 2010; Zanini et al. 2009), assessed neuropsychological functions of PD patients with PPN-DBS using a battery of tests evaluating different cognitive domains. All patients had a concomitant STN-DBS which has been variably turned ON or OFF according to the study (Table 1). PPN stimulation ON/STN OFF compare to PPN OFF/STN OFF improved performance on tests for memory (delayed recall subtest of the California verbal learning test), and some aspects of executive functions (phonemic verbal fluency and Trail Making Test but not Stroop test) (Alessandro et al. 2010). One study specifically evaluated the effect of PPN stimulation on working memory with a task based on a N-back procedure for visual objects and verbal stimuli. As main finding, the average response times on the n-back task, calculated by subtracting the average simple motor reaction time, were significantly faster in the PPN-ON than in the PPN-OFF condition in both the visual-object and the verbal stimuli (Costa et al. 2010). There was instead no difference for accuracy of responses between the two conditions and there was no difference in response time in a task measuring simple motor reaction time, thus controlling for the effect of motor efficiency improvement after PPN stimulation.

One study investigated the effect of PPN stimulation alone or in addition to STN stimulation on language. Patients underwent a linguistic task consisting in a story generation with tape recording for neurolinguistic analysis in 4 experimental conditions: PPN + /STN +, PPN-/STN +, PPN + /STN, PPN-/STN-. There was no difference among conditions in phonology, lexical, semantic and speech characteristics. However, when patients had both STN and PPN stimulation ON made less grammar errors (Zanini et al. 2009).

We experimentally evaluated the effect of unilateral PPN-DBS stimulation on cognition and alertness in a patient with PD who had developed dementia over the years following surgery (Ricciardi et al. 2015). This subject was assessed with an extensive battery of neuropsychological tests while ON stimulation, 2 months after switching OFF the stimulator and again 2 months after turning the stimulator back ON. He showed a general worsening of all neuropsychological domains after switching OFF the stimulation and a clear return to baseline after switching it back ON. His family (who was blind of the status of stimulation during the whole study) reported a worsening of confusion, ability to perform activities of daily living and independency during the time when the stimulation was OFF and an improvement when it was turned back ON.

Few experimental studies have been conducted in PD patients with PPN-DBS using a computerized task measuring attentional reaction time and simple motor reaction time (Costa et al. 2010; Fischer et al. 2015; Thevathasan et al. 2010). Thevathasan and co-workers evaluated 11 PD patients implanted with PPN-DBS (bilateral in 10 out of 11 and associated to DBS of Zona Incerta in 3) with a task of simple motor reaction time and two tasks of attentional reaction time (digit vigilance task and Choice Reaction Time Task). Patients were tested OFF medication and in the following conditions: no stimulation, 5 Hz, 10 Hz and usual therapeutic frequency stimulation (20–35 Hz). They had a minimum 30 min 'washout period' between experimental conditions. Only the therapeutic frequency condition determined a significant difference for 'Speed of Reaction' but not 'Accuracy of Reaction'. The improvement was only demonstrated in the simple motor reaction time

but not in the digit vigilance task or choice reaction time task. These observations might suggest improved motor performance rather than augmentation of alertness or attention. However, authors commented that if this was a simple motor performance improvement, patients would have performed better in all tasks since the tasks required identical movements, and yet only the simple motor reaction time improved. Therefore, they speculated that there must have been some element of 'central' motor processing that differed between tasks and improved the simple RT during PPN stimulation. Also, the study by Costa et al. (Costa et al. 2010) assessed simple motor reaction time as part of a wider study protocol and showed no difference between PPN-ON and PPN-OFF conditions. Finally, in another study (Fischer et al. 2015), 8 PD patients with bilateral PPN-DBS (3 had concomitant bilateral STN-DBS) underwent a computerized task assessing attention (four subtests of the Testing System for Attentional Performance: the alertness task; the go/no-go task, and the divided-attention task). Patients were tested in five different stimulation conditions, one condition/day for 5 consecutive days: off-stimulation, 8 Hz, 20 Hz, 60 Hz, and 130 Hz. The main result of this study was an improvement of reaction time only in the alertness task (unwarned condition) in the study conditions with PPN ON and frequency of 8 Hz and 20 Hz.

In summary, simple motor RT and in attentional RT tasks (Costa et al. 2010; Fischer et al. 2015; Thevathasan et al. 2010) showed only an improvement of reaction times, but not of accuracy of responses. These findings are difficult to interpret, and it is still not clear whether the improvement is due to an improvement of motor velocity ON stimulation or it is an effect of PPN on certain aspects of attention, determining attentional augmentation.

The effect of PPN on cognitive functions is still not clear, scanty data are available which do not allow us to draw any conclusion. In the available studies, authors have hypothesized that the improvement in cognitive functions (attention, working memory, executive functions and memory) might be mediated by activation of ascending cholinergic neurons to thalamus, determining a widespread activation mediated by the intralaminar thalamic nuclei. However, at the moment there is no evidence to support this hypothesis and the available studies results are limited by a number of methodological issues.

4. Integrating PPN in cognitive function and sleep control

A cluster of cholinergic, glutamatergic and GABAergic neurons spanning longitudinally in the mesopontine tegmentum constitutes the PPN (Wang and Morales 2009). The most striking feature of this nuclei is the amount of reciprocal connections with many cortical and subcortical areas as well as the brainstem (Fournier-Gosselin et al. 2013; Lee et al. 2000).

The PPN exchanges reciprocal connections with the ipsilateral prefrontal and motor cortex (Lee et al. 2000). Efferent connections are also established through glutamatergic and GABAergic neurons with the basal ganglia, and specifically with the subthalamic nucleus (STN), the globus pallidus pars interna (GPi) and the substantia nigra (SN); viceversa, these structures send efferents to PPN via GABAergic projections. It also receives afferent by the limbic system via the ventral striatum (Inglis and Winn 1995). The main efferent pathways of PPN project to most of thalamic nuclei and are cholinergic. Retrograde and anterograde tracing techniques in rats have also disclosed reciprocal connections between the lateral hypothalamus and the PPN. Specifically, the lateral hypothalamus sends projections from hypocretin/orexin and histaminergic neurons and PPN sends cholinergic fibres to the lateral hypothalamus (Hallanger and Wainer 1988). Finally, the PPN is connected with many brainstem structures, such as the medullary and pontine reticular formation, and the spinal cord (Jenkinson et al. 2009).

Insights from studies in animals and humans suggest that PPN represent a key structure integrating motor control with non-motor functions such as sleep-wake cycle, arousal, behaviour and cognition. Animal studies have shown that PPN integrates sensory and motor information via ascending and descending, afferent and efferent connections to all other parts of the central nervous system (Hazrati and Parent 1992; Lavoie and Parent 1994). A large amount of literature in animals has supported a role for PPN in some cognitive functions such as learning and reinforcement processes, updating of action–outcome associations, and decision making (Gut and Winn 2016). However, the association between specific neurological symptoms and neural networks involving the PPN in humans is still speculative. The few insights from DBS and functional neuroimaging studies (Ballanger et al. 2009; Ceravolo et al. 2011; Gallea et al. 2017; Stefani et al. 2010; Strafella et al. 2008) might suggest that PPN is not just involved in modulation of gait but also in some non-motor symptoms of PD.

Insights about the neural networks associated to PPN comes from few studies in DBS implanted patients with fluorodeoxyglucose positron emission tomography (FDG-PET) (Ballanger et al. 2009; Ceravolo et al. 2011; Stefani et al. 2010; Strafella et al. 2008) and local field potential (LFP) (Androulidakis et al. 2008; Anzak et al. 2016; Jha et al. 2017; Thevathasan et al. 2012) and from one large resting state (rs) MRI study in PD without DBS (Gallea et al. 2017).

FDG-PET was assessed in 6 patients with bilateral PPN DBS and showed several areas of increase metabolism while ON stimulation (frequency of stimulations = 25 Hz) compared to OFF stimulation, including bilateral prefrontal areas such as the frontal inferior gyrus, the dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate, superior frontal gyrus, parietal inferior lobule and supramarginal gyrus. An increased cerebral metabolism was also showed in the left ventral striatum, left subgyral, right insula and right superior temporal gyrus. Instead, PPN stimulation decreased FDG uptake in the left cerebellar anterior lobe and right cerebellar posterior lobe. Stefani and coworkers also showed in these patients an improvement of long-term verbal memory, verbal fluency and trail making in the condition PPN-ON/STN-OFF compared to PPN-OFF/STN-OFF condition and how this improvement was linked to the widespread bilateral activation of the above regions at FDG-PET (Stefani et al. 2010). A different pattern of metabolic activation has been demonstrated by [^{15}O] H2O PET in few cases with unilateral PPN DBS (frequency of stimulations = 50–90 Hz). Strafella and collaborators described one patient with left PPN DBS who showed change in regional cerebral blood flow in ipsilteral GPi and bilateral thalamus (Strafella et al. 2008). In a subsequent study in 3 PD patients, the same authors showed an increased regional cerebral blood flow in the cerebellum and the thalamus bilaterally during the PPN ON condition (Ballanger et al. 2009). These data suggest that PPN stimulation recruits several ascending projections, which activate cortical and subcortical areas outside the basal ganglia. However, data are lacking about the correlations between these metabolic patterns and specific motor and non-motor functions.

Electrophysiological studies in human subjects have been carried out with LFP recordings from PPN implanted patients. Jha and coworkers have recorded magnetoencephalography and LFP from PPN in seven Parkinsonian patients undergoing surgery for PPN DBS (Jha et al. 2017). They showed a functional coupling between PPN regions and cerebral cortex. Coupling occurred in the alpha and beta bands, forming two spatially and spectrally distinct resting networks. The alpha band coupled with the subgenual cingulate cortex, which has been shown to modulate mood and autonomic arousal (Ressler and Mayberg 2007; Vogt 2005) and the beta band coupled with the supplementary motor area, a critical region for planning and execution of movement, and particularly suited to potentially modulate gait (Muthusamy et al. 2007; Sesack et al. 1989).

Despite the small sample size of these humans studies which poses a cautious interpretation, they suggest a role for the PPN as a structure at the junction between motor cortical planning areas and areas implicated in arousal and motor control (Garcia-Rill et al. 2016). This concept is further supported by a recent rsMRI study which has tried to make correlations between the functional networks associated to PPN and PD symptoms. The presence of REM behavioural sleep disorder

(RBD) was associated to decrease connectivity in the arousal network, comprising the PPN and the anterior cingulate cortex. This abnormality in the group with RBD was correlated with daytime sleepiness and also to the degree of connectivity in the locomotor network (Gallea et al. 2017).

The PPN, along with locus coeruleus (LC) and dorsal raphe nucleus (RN), is part of the reticular activating system (RAS) that modulates the maintenance of waking. The hallmark of the waking state is a shift in EEG power to higher frequencies with synchronized intracortical gamma activity, a process associated with high-level cognitive functions. The RAS, promotes this state and has been proposed as gamma wave generator (Munk et al. 1996). PPN, in particular, is the most active nuclei during waking and REM sleep and it has also recently been considered the major source of the "bottom-up" flow of gamma activity to the cortex (Garcia-Rill et al. 2018). REM sleep behaviour disorder, vivid dreams and a wide range of sleep and wakeful disturbances, such as insomnia, excessive daytime sleepiness and decreased slow wave sleep have been demonstrated in PD (Falup-Pecurariu and Diaconu 2017). These observations suggest that the RAS and especially the PPN, which is in charge of waking and REM sleep, might be overactive in PD. This hypothesis is supported by the evidence of an exaggerated response to sudden alerting stimuli in PD patients. In fact a wide range of hyperactive brainstem and cortico-spinal reflexes have been described in this subjects, such as blink reflex and stretch reflex (Nakashima et al. 1993; Penders and Delwaide 1971; Rothwell et al. 1983). The inability to maintain a steady waking state, interferes not only with sleep-wake cycle but also with cognitive functions. In general, it is known that gamma oscillations have a role in sensory perception, problem solving, and memory (Eckhorn et al. 1988; Phillips and Takeda 2009; Voss et al. 2009). Moreover, synchronous cortical gamma band activation is thought to contribute to the integration of information originating from separate regions. In fact, gamma oscillation deficits have been suggested as a pathophysiologic feature of diseases like AD (Stam et al. 2002). However, the role of gamma band activity in the RAS is still not clear. Garcia-Rill et al. proposed that "activation of the RAS generates the background of gamma activity necessary to support a state capable of reliably assessing the world around us on a continuous basis" (Garcia-Rill et al. 2013).

In conclusion, evidences from experimental studies in animals suggest that the PPN is a key structure in the control of arousal and alertness and it has a role in the regulation of cognition and behaviour. In humans, the majority of the available studies have been conducted in patients with PD who underwent PPN DBS. In these studies there is a lack of evidence confirming any convincing effect of PPN DBS on frontal functions, attention and alertness. Indeed, the few available studies do not employ any sensitive task specifically evaluating the role of PPN in these domains. Moreover, there is no consistency among studies protocols regarding the frequency of PPN DBS stimulation used. The available data seems to suggest that low frequency stimulation (25 Hz) has a better effect compared to the high frequency one (60–80 Hz) on alertness and reduces daytime sleepiness. This could be related to the fact that low frequency stimulation synchronizes the PPN cells at their physiological frequency. It has been suggested that PPN is underactive in PD because of both the neurodegenerative process and inhibition and that low frequency DBS may increase PPN activity and thus improve the motor symptoms of PD. Moreover, PPN DBS would improve "motor attention", allowing to redirect attention from one movement to another and to better allocate processing resources within the motor system (Johansen-Berg and Matthews 2002; Thevathasan and Moro 2018).

5. Limitations and knowledge gaps

The limited sample size represented the main limitation when interpreting the results of this systematic review. It is important to highlight that, due to the paucity of PD cases implanted in the PPN, a few studies have been conducted on the same case series. Another limitation when comparing studies relates to frequency of stimulation, which ranged from 5 to 80 Hz, with frequencies of 20–30 Hz being most frequently associated to improvement of sleep and cognitive outcomes. A fundamental point to consider when dealing with PPN-DBS relates to targeting of this area which is made of clusters of neurons longitudinally spanning the mesopontine tegmentum. It has been suggested that the caudal portion of PPN, which is linked to the mesencephalic locomotor area, might be involved in gait control, but is unknown which portions of the PPN are more closely related to sleep and alertness control. Moreover, the short follow-up of PPN DBS in most of reports hastens our understanding of the long-term effect of PPN on alertness and cognition. The only available case study with a long-term follow-up suggests that the effects of PPN stimulation over time are maintained (Ricciardi et al. 2015).

6. Conclusions and lines for future reaserch

Summarizing, there is still no clear and convincing evidence on the role of PPN in cognition, attention and alertness in humans, however PD represents a promising pathological model for future studies on this matter, since PPN is involved in the neurodegenerative process in this disease. It is = important to highlight that one of the reasons for the heterogenous results of PPN DBS both for motor and non-motor symptoms of PD might be due to the high cellular heterogeneity of this region, the different degree of atrophy in subgroups of PD patients and the lack of knowledge on which specific neurotransmitter should be modulated to produce a clinical change. Hopefully, optogenetics and chemogenetics (Kroeger et al. 2017) studies might help to tackle these issues as well as to clarify the role of PPN in the pathophysiology of specific non-motor symptoms of PD. Future researches are needed to shade light on the best targeting of DBS in the PPN area and to clarify the best stimulation frequency in order to achieve a good effect on both motor and cognitive/behavioural domains. Moreover, there is a need for designing experimental protocols employing specific and sensitive tasks for cognitive functions and more specifically for attention in healthy subjects and PD patients. PPN DBS has been suggested as a possible surgical option for PD patients with gait disorders, especially freezing of gait. The role of attention in FOG pathophysiology has been showed in previous studies (Shine et al. 2013) and it has also been suggested a strong association between gait impairment and cognition decline in healthy elderly people and PD patients (Montero-Odasso et al. 2012; Ricciardi et al. 2014). However, to date no study has evaluated the effect of PPN DBS on this interplay between gait and cognition in PD patients with FOG. Future studies are encouraged to specifically look at the effect of PPN on attention and other cognitive functions and how this modulates FOG in PD.

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