The impact of low-frequency stimulation of the pedunculopontine nucleus region on reaction time in parkinsonism

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ABSTRACT

Objectives Attentional augmentation and enhanced motor function are potential mechanisms by which stimulation of the region of the pedunculopontine nucleus (PPN) may improve gait in parkinsonism. Here, the authors assess the impact of stimulation of this region on attentional and motor aspects of reaction task performance in patients with parkinsonism.

Methods Eleven patients implanted with PPN stimulators underwent computerised assessment of simple, choice and digit vigilance reaction tasks. Patients were assessed 'off medication' during stimulation at different frequencies (0 Hz, 5 Hz, 10 Hz and 'therapeutic' 20—35 Hz). There were two primary endpoints: 'Speed of Reaction' (sum of the mean task reaction times) and 'Accuracy of Reaction' (reflecting omissions and percentage of correct responses). Baseline performance was compared with age- and sex-matched healthy controls. Clinical effects of stimulation were assessed using the Unified Parkinson's Disease Rating Scale and a falls frequency scale.

Results Compared with healthy controls, subjects had significant deficits in 'Speed of Reaction' and in all mean task reaction times. 'Accuracy of Reaction' was not different from healthy controls and did not improve with stimulation. 'Speed of Reaction' significantly improved with stimulation at therapeutic frequencies (20—35 Hz). Of the individual tasks, only simple reaction time improved significantly. Simple reaction time distribution analysis revealed a general speeding of responses rather than a selective reduction in outliers. Acute PPN stimulation improved gait and balance but not akinesia scores. Chronic PPN stimulation significantly improved falls frequency. Falls score improvement significantly correlated with changes to simple reaction time with therapeutic stimulation.

Conclusion The pattern of reaction time improvement with stimulation of the PPN area suggests a benefit on motor performance, rather than augmentation of attention.

INTRODUCTION

Pedunculopontine nucleus (PPN) stimulation is a novel therapy for freezing of gait and postural instability (FOG/PI) in Parkinsonian disorders.[1–3] The mechanisms of PPN stimulation for FOG/PI are unknown but potentially involve augmentation of attention or improved motor control.

In FOG/PI, attentional deficits may contribute to the final motor dysfunction.[4 5] For example, in PD, episodes of freezing can be triggered by external 'distracters,' and gait disturbance can emerge during dual task performance.[6 7] The PPN is considered a component of the 'reticular activating system' and may modulate states of arousal and attention.[8–10] Consistent with such a role, PPN stimulation in patients with Parkinson's disease (PD) increases rapid eye movement sleep, and there is PPN-cortical coherence in the α band during wakefulness.[11 12] However, the PPN is also proposed to be part of the basal ganglia and appears important to motor control.[13] For example, in the non-human primate, the microinjection of a γ-aminobutyric acid (GABA) antagonist into the PPN partially reverses the akinesia induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[14]

The aim of this study was to assess the impact of stimulation of the PPN region on attentional and motor aspects of reaction time (RT) performance, in patients with parkinsonism and FOG/PI.

SUBJECTS AND METHODS

Subjects and clinical evaluation

Twelve patients implanted with PPN stimulators were recruited from centres in Brisbane, Bristol and Oxford. Local ethics committee approval was obtained, and participants gave informed consent. One patient had significant cognitive impairment (Mini Mental State Examination Score=23) and could not reliably follow the study protocol, and so was excluded from further analyses. Clinical details of the 11 final study participants are shown in table 1. Three patients also had electrodes implanted in zona incerta (ZI).

All patients were diagnosed as having Parkinson's disease and had PPN stimulators implanted for severe FOG/PI that persisted in the 'on medication' state, causing falls. FOG/PI in PD is usually an 'off medication' phenomenon which becomes more common with disease progression, with an overall prevalence of approximately 50%.[15] However, severe 'on medication' FOG/PI as a dominant issue is unusual in PD and raises the question of atypical pathologies such as vascular disease and tauopathy.[16 17] Therefore, in the absence of a definitive test in life, we prefer to consider that patients in this study had the syndrome of parkinsonism and severe FOG/PI.

In all cases, the electrodes implanted in the PPN region were model 3387 (Medtronic, Minneapolis, Minnesota). This electrode is configured with four active contacts, each 1.5 mm in diameter and separated from the adjacent contact by 1.5 mm. The surgical technique used to implant the PPN has

Table 1 Baseline clinical characteristics of patients

Subject no	Centre	Age (years)	Mini-Mental State Examination	Disease duration (years)	Unified Parkinson's Disease Rating Scale Off/On Meds (Off Stim)	L-Dopa equivalent dose(mg)	Deep brain stimulation targets	PPN stimulation: frequency (Hz), voltage (V), pulse width (μs)	Postop duration (months)
1	Brisbane	71	30	17	26*/22	1700	Bilateral PPN	30/3.3/60	13
2	Brisbane	74	29	5	37/21	300	Bilateral PPN	30/2.2/60	8
3	Brisbane	60	30	8	42/26	800	Bilateral PPN	30/3.1/60	5
4	Brisbane	69	26	4	56*/47	1300	Bilateral PPN	30/3.7/60	3
5	Brisbane	71	28	8	37/20	1200	Bilateral PPN	30/3.3/60	6
6	Oxford	54	30	12	46/29	1800	Bilateral PPN	20/2.3/60	13
7	Oxford	63	27	12	75/29	2100	Bilateral PPN	20/2.0/60	12
8	Oxford	54	30	20	53/19	800	Bilateral PPN	20/2.5/60	2
9	Bristol	61	27	12	56/20	1300	Bilateral PPN/ZI	35/2.5/60	4
10	Bristol	67	28	15	29/24	1200	Unilat PPN/bilateral ZI	30/3.3/60	36
11	Bristol	65	29	15	54/43	1000	Bilateral PPN/ZI	20/3.5/60	38

*Off medication Unified Parkinson's Disease Rating Scale likely underestimated due to use of long-acting ergot dopamine agonists.
PPN, pedunculopontine nucleus; ZI, zona incerta.

been described previously.[1 18 19] Targeting the PPN has been controversial.[20–22] We therefore adopt the conservative position that 'PPN electrodes' in this study lie within the region of the PPN. The optimal parameters for therapeutic PPN stimulation (without confounding ZI stimulation, if present) established by the usual clinical teams prior to our study were as follows: frequency range 20–35 Hz, voltage range 2.0–3.7 V and pulse width 60 μs.

The acute motor effects of stimulation of the PPN area with clinical stimulation parameters were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) and compared with the unstimulated state on the same day as RT testing. Clinical evaluations were performed both off and on dopaminergic medication. After changing stimulation parameters, there was a minimum 30 min 'washout' period before clinical assessment. Off medication assessments occurred after overnight withdrawal (>12 h) of dopaminergic therapy. The primary assessment tool was the motor subsection (Part III) of the UPDRS (maximum score=108, with a higher score indicating worse motor function). Items 27–30 of the motor UPDRS specifically address gait, posture and balance. The item 27–30 subscore was calculated as a separate entity (IT27-30; maximum score=16). Items 1–26 assess akinesia, rigidity and tremor. The item 1–26 subscore was also calculated as a separate entity ('Residual UPDRS'; maximum score=92). All clinical assessments were performed unblinded by the same neurologist specialised in movement disorders (WT). The chronic efficacy of stimulation of the PPN area was judged by comparing the frequency of falling before and after PPN surgery. Falls frequency was determined using an item of the 'gait and falls questionnaire' constructed by Giladi *et al*.[23] This meant that the frequency of falls was estimated to be very often (daily or more), often (about weekly), rarely (about monthly), very rarely (about yearly) or never. Patient responses were recorded prospectively (patients 1–8) or assigned by the assessor based on falls diaries (patients 9–11). For statistical analysis, responses were converted to scores as follows; daily=3, weekly=2, monthly=1, less than monthly=0.

Tasks

Reaction times were assessed using components of the Cognitive Drug Research Ltd (CDR) Computerised Assessment System.[24–29] Three RT tasks were administered. In every task, the presentation of an unwarned imperative visual stimulus in the centre of a computer screen signalled the need for a speeded response. RTs were recorded via a two-button (yes/no) response box. At the start of every task, the right index finger rested upon the right 'Yes' button and left index finger upon the left 'No' button. The block of three tasks required approximately 7 min for completion. The three RT tasks were as follows:

1. Simple Reaction Time Task: serial presentation of 50 imperative stimuli consisting of the word 'Yes' occurring with a variable interstimulus interval (range 1–3.5 s). Subjects were instructed to respond only with the right 'Yes' button. Minimum response time=0.1 s. Measured variable: SRT=simple reaction time.
2. Digit Vigilance Task: a continuous performance task. Serial presentation of 450 stimuli (random digits from 1 to 9) in the centre of the screen at a rate of 150 per min. One digit (any from 1–9) was assigned as the imperative stimulus requiring a speeded response with the right-hand 'Yes' button. The imperative stimulus occurred randomly 45 times per task. As a reminder, the identity of the imperative stimulus was displayed constantly on the right side of the screen. Measured variables: VIGRT=vigilance reaction time, VIGACC=accuracy (percentage of imperative stimuli detected), VIGFA=false alarms (absolute number of false alarms).
3. Choice Reaction Time Task: serial presentation of 50 imperative stimuli consisting of either the word 'Yes' or 'No' (occurring randomly; each with a 50% chance of occurrence). Interstimulus interval was variable (range 1–3.5 s). Subjects were instructed to respond with the relevant 'Yes' or 'No' button. Minimum response time=0.15 s. Measured variables: CRT=choice reaction time, CRT accuracy (percentage correct responses).

Experiments

Experiments were conducted after overnight withdrawal of dopaminergic medication. Stimulation of ZI was switched off, if present. A block of RT tasks was performed for each of the following four conditions: no stimulation, 5 Hz, 10 Hz and usual therapeutic frequency stimulation (20–35 Hz). The optimal frequency of PPN stimulation in PD is uncertain. In contrast to the high frequencies (usually about 130 Hz) delivered to the subthalamic nucleus (STN) and globus pallidus interna (GPi), low-frequency stimulation is employed for the PPN. In the MPTP treated non-human primate, 5–10 Hz PPN stimulation was effective at improving movement counts.[30] However, in clinical reports of stimulation of the PPN area in patients with PD and FOG/PI, the choice of stimulation frequency has been

20–35 Hz for bilateral PPN stimulation and up to 70 Hz for unilateral PPN stimulation.[1 2 19] Thus, a range of low frequencies were tested to establish any frequency selectivity for stimulation effects on RT performance.

Across conditions, pulse width and voltage remained constant (at their usual therapeutic levels). Stimulation was delivered bilaterally (except in one case with a unilateral deep brain stimulation electrode) through the usual contacts employed for therapy. There was a minimum 30 min 'washout period' between the changing of stimulation frequency and RT testing. Patients were blinded to the parameters of stimulation. Transient paraesthesia occurred occasionally when stimulation was adjusted. However, persistent symptoms allowing identification of the presence or type of stimulation did not occur. The ordering of conditions was pseudo-randomised across patients.

To minimise learning effects, two blocks ('practice blocks') were performed on the day prior to the experiment. These practice blocks were administered in the on medication state and while both on and then off therapeutic PPN stimulation. In addition, prior to every block, an abbreviated practice CRT task was performed. Within each block, the three tasks were presented in a fixed order (SRT task, Digit vigilance task then CRT task).

Data analysis

Surgery in the PPN area is in its infancy, and we were only able to recruit 12 patients, despite including three surgical centres. Thus, to limit multiple testing which, after correction, would have demanded prohibitive p values from our small sample, we used two composite RT scores as our primary endpoints:

1. Speed of Reaction=mean SRT+mean vigilance reaction time (VIGRT)+mean CRT;
2. Accuracy of Reaction=(VIGRT accuracy×0.45)+(CRT accuracy×0.5)−VIGRT false alarms.

These composite scores have been widely used as measures of reaction task performance in patients with parkinsonism and have also been termed 'Power of Attention' and 'Continuity of Attention,' respectively.[24 26 29] The rationale for calculation of these endpoints is based on principal components and Varimax factor analysis of the various RT measures, as described previously.[31] The two primary endpoints were compared between conditions using the Friedman test, as the Shapiro–Wilks test indicated that both primary outcome measures were very unlikely to be normally distributed ('Speed of Reaction' p=0.004 and 'Accuracy of Reaction' p<0.001). Where appropriate, posthoc Wilcoxon signed ranks tests were conducted to determine differences on task performance between conditions. Task performance was compared with age- and sex-matched healthy controls using the Mann–Whitney U test. Each healthy control data set represented the mean results of >80 healthy subjects within a 5-year range of the patient's age (available from the CDR database). p Values <0.05 were considered to be significant after Bonferroni correction for multiple comparisons.

RT distribution analysis was performed to assess the impact of PPN stimulation on the entire population of reaction times. RT distribution curves were obtained using the 'Vincentisation' method.[32 33] This involves ranking RTs for individual patients in order of duration, from fastest to slowest, and computing the percentiles. The mean RTs across patients are calculated for each quantile and plotted against cumulative percentile. This yields the cumulative distribution of the grouped mean RTs. Using this method, an average of all the patients' RT distributions is produced that retains characteristics of an individual RT distribution curve. A Wilcoxon signed ranks test was used to determine differences in the grouped mean RTs for each quantile between different conditions.

RT distribution curves have well-described properties.[32 34] The curves have an 'ex-Gaussian' appearance, which results from the convolution of a Gaussian and an exponential distribution. 'μ' refers to the mean of the Gaussian component. 'τ' refers to the mean of the exponential component. The τ component contains the slowest outliers that are likely to represent attentional lapses.[35] μ and τ in this study were calculated using a validated ex-Gaussian curve fitting function of a toolbox available for Matlab (The Mathworks).[36]

Individual RT distribution curves were also assessed by calculating 'skew.' Skew measures the degree of asymmetry around the mean. After 'Vincentisation' of an individual's RTs, skew was assessed using a function of the SPSS statistical package, version 17.0 (SPSS, Chicago, Illinois). Skew of individual RT distributions was compared between conditions using the Wilcoxon signed ranks test.

Clinical scores at different timepoints were compared using the Wilcoxon signed ranks test. Correlations between clinical scores and RT results were assessed using the Spearman rank test.

RESULTS

The acute and chronic clinical motor responses to stimulation of the PPN region are summarised in table 2. After a 30 min washout period, switching on therapeutic stimulation significantly improved IT27–30 (8.2±1.3 off vs 7.2±1.3 on, Z=−2.460, p=0.04). However, the residual UPDRS did not change with acute therapeutic stimulation (38.3±3.7 off vs 37.7±3.9 on, Z=−1.532, p=0.38). Chronic stimulation of the PPN region reduced the frequency of falls (fall scores of 2.7±0.2 off vs 1.3±0.2 on, Z=−2.873, p=0.01).

Baseline (no stimulation) reaction times from the study participants were compared with age- and sex-matched healthy control data. 'Speed of Reaction' was significantly worse in study participants (1691.8±189.7) than in healthy controls (1193.1±8.0, p<0.001). However, there was no deficit in 'Accuracy of Reaction' in patients (82.2±5.2) compared with controls (90.6±0.1, p=0.56). The mean baseline reaction times of all three individual tasks were worse in study participants than in controls (SRT; 415.9±35.9 vs 282.8±2.9, p<0.001, VIGRT; 531.5±20.7 vs 428.3±1.50, p=0.001, CRT; 744.4±149.0 vs 481.6±3.7, p=0.002).

Among stimulation conditions, analysis of the primary endpoints revealed a significant difference for 'Speed of Reaction' (χ^2=9.66, p=0.02; figure 1A) but not 'Accuracy of Reaction' (χ^2=2.27, p=0.52; figure 1B). Post-hoc analysis revealed that only the therapeutic frequency condition significantly improved 'Speed of Reaction' compared with baseline (Z=−2.756, p=0.02; figure 1A). Analysis of the subscores contributing to the 'Speed of Reaction' revealed a significant improvement for only SRT during therapeutic stimulation (SRT; Z=−2.401, p=0.048, VIGRT; Z=0.00, p=1.0, CRT; Z=−2.045, p=0.12, figure 2). There was a trend suggesting a greater percentage improvement of SRT compared with VIGRT (Z=−2.134, p=0.07). However, the percentage improvements of SRT and CRT were not significantly different (Z=−0.622, p=0.53).

We therefore analysed the RT distributions of the SRT task for the therapeutic frequency and baseline conditions. There was a significant difference in the per-quantile grouped mean RTs between conditions (Z=−5.671, p<0.001). For every quantile, the mean grouped RT for the therapeutic frequency condition

Table 2 Acute and chronic clinical motor outcomes of stimulation of the pedunculopontine nucleus (PPN) region using clinically selected frequencies (20–35 Hz)

Subject no	Total Motor Unified Parkinson's Disease Rating Scale Off/On PPN stimulation (off medication)	IT27–30 Off/On PPN stimulation (off medication)	Residual Unified Parkinson's Disease Rating Scale Off/On PPN stimulation (off medication)	Falls frequency preoperative	Falls frequency postoperative
1	26/26	6/6	20/20	Daily	Never
2	37/32	9/6	28/26	Weekly	Monthly
3	42/42	13/12	29/30	Daily	Monthly
4	56/59	10/10	46/49	Daily	Weekly
5	37/37	2/2	35/35	Daily	Weekly
6	46/36	10/7	36/29	Daily	Weekly
7	75/74	15/15	60/59	Monthly	Monthly
8	53/52	4/3	49/49	Daily	Weekly
9	56/54	12/11	44/43	Daily	Weekly
10	29/28	4/3	25/25	Daily	Monthly
11	54/54	5/4	49/50	Daily	Never

was faster than for the baseline condition. This is evident as a shift of the entire SRT distribution curve to the left (figure 3). The μ and τ components of the SRT distribution curve were similarly reduced by therapeutic stimulation (by 9.3% and 9.0%, respectively). There was also no significant difference in skewness of SRT distributions of individual patients between 0 Hz and therapeutic stimulation conditions ($Z=-0.889$, $p=0.374$).

Further exploratory analysis revealed that the improvement in fall scores significantly correlated with percentage improvement in SRT (Spearman $\rho=0.638$, $p=0.035$) and trended towards correlation with percentage improvement in 'Speed of Reaction' (Spearman $\rho=0.558$, $p=0.074$) with therapeutic stimulation. Changes in IT27–30 did not correlate significantly with changes in SRT or 'Speed of Reaction' with therapeutic stimulation.

DISCUSSION

The major findings of this study may be summarised as follows. Stimulation of the PPN region at therapeutic frequencies improved 'Speed of Reaction.' 'Accuracy of Reaction' did not improve, but subjects did not have a deficit in this measure at baseline compared with healthy controls. Therapeutic frequency stimulation yielded a significant improvement in SRT but not CRT or VIGRT. SRT reaction time distribution analysis revealed a general quickening of all SRTs rather than a selective effect on outliers. Therapeutic frequency stimulation acutely improved the IT27–30 subscore of the UPDRS (assessing gait and balance) but not the residual motor UPDRS (assessing akinesia, rigidity and tremor).Chronic PPN stimulation significantly improved the frequency of falls. Improvement in SRT with therapeutic stimulation significantly correlated with improvement in fall scores.

We acknowledge several limitations of this study. The available cohort was small. However, the non-parametric analysis limited the impact of any single subject on results. Neurosurgical targeting of the PPN is controversial and was not the focus of this study. We consequently take the position that stimulation was delivered within the PPN region and not necessarily directly into the PPN itself. This also respects the fact that volume conduction can occur to neighbouring structures.[37] Patients were blinded to the stimulation condition in RT experiments, but the clinical data were collected by an unblinded researcher. RT assessments were performed in only the off medication state to limit variance from dopaminergic fluctuation. Although the order of conditions was pseudorandomised, the order of tasks within each condition was fixed. We addressed practice effects by rehearsal on the day prior to experiments and before every block. However, it remains conceivable that order effects may have contributed to the differential results across tasks.

Low-frequency stimulation of the PPN region improved SRT in patients with parkinsonism and FOG/PI, but only at therapeutic frequencies (20–35 Hz). Ten Hertz stimulation, which might have mimicked the α activity found in the PPN region following dopaminergic therapy,[11] was not beneficial.

Bilateral PPN lesions in rats and the microinjection of a GABA agonist into the PPN in monkeys cause slowing of RTs.[38–40] Improved RTs with PPN stimulation therefore are consistent with the proposition that the PPN in parkinsonism is underactive and that low-frequency stimulation may somehow enhance or mimic normal PPN activity.[30 41] This does not necessarily imply activation of the nucleus per se but may, for example, arise from modulation of surrounding structures including afferent pathways.[42]

Might the selective improvement of SRT reflect augmentation of attention or improved motor control? All reaction tasks in this study comprised multiple processing stages including, at a minimum, alertness and attention, perception, motor preparation and the final movement itself. A general alerting effect is unlikely to account for our results, as it should have applied similarly across all tasks. In particular, tasks of continuous performance (such as the Digit Vigilance task) are sensitive to alterations in alertness such as due to sleep deprivation,[43–45] and yet did not change. Slow outliers in RT tests (lying in the τ segment of the RT distribution curve) are likely to represent lapses in attention.[46–48] However, with therapeutic stimulation, there was a shift in the entire SRT distribution curve, without a specific effect on τ. Correspondingly, the degree of skew for individual SRT distributions also did not change. These observations suggest improved motor performance rather than augmentation of alertness or general attention.

The question then arises as to whether any improvement in motor performance involved 'central' motor processing prior to movement initiation or a speeding of the movement once initiated. Although we did not record EMG, there is one helpful observation; the SRT and VIGRT tasks required identical movements, and yet only the SRT improved. The implication is that it must have been some element of 'central' motor processing that differed between tasks and sped up in the SRT during stimulation. One notable difference between tasks is the degree of motor preparation that could occur before the imperative stimulus. In the VRT, only one in 10 stimuli was salient so that responses were under tonic inhibition (a Go/NoGo paradigm).[49] Only in the SRT task could the motor response be fully

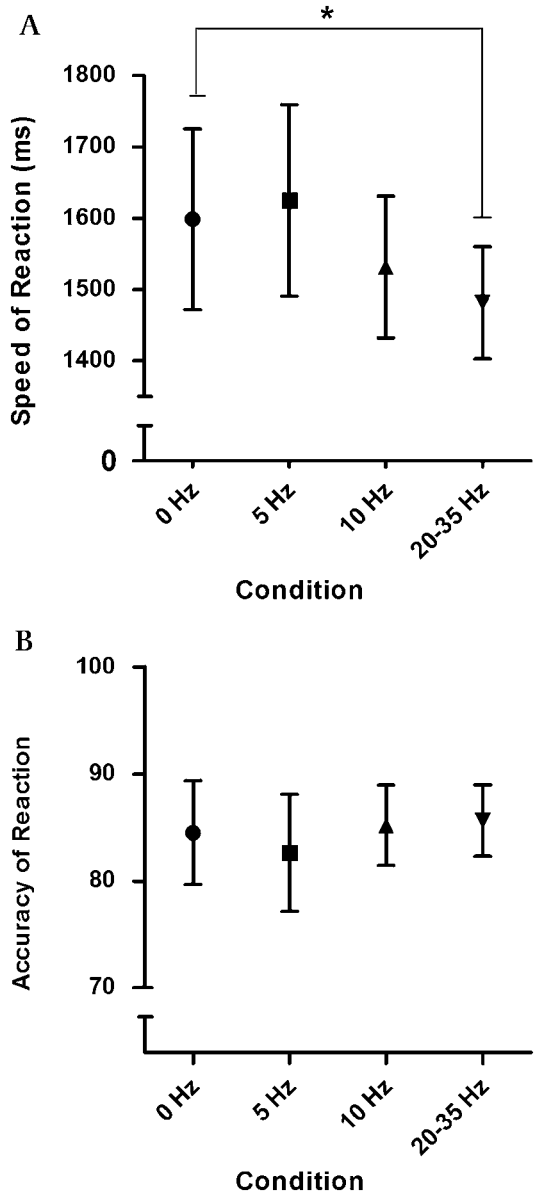

Figure 1 Mean±SEM of (A) 'Speed of Reaction' and (B) 'Accuracy of Reaction' under different conditions. *Significant difference between 0 Hz and 20–35 Hz (p=0.02).

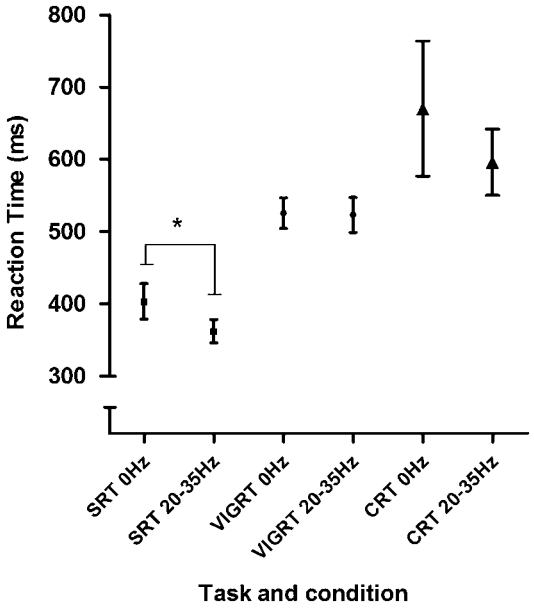

Figure 2 Mean±SEM of simple reaction time (SRT), vigilance reaction time (VIGRT) and choice reaction time (CRT) off stimulation and during clinically effective (20–35 Hz) stimulation of pedunculopontine nucleus. *p=0.048.

anticipated and therefore 'preprogrammed' and stored for release.[50] PPN stimulation could therefore act by improving anticipatory motor preparation or by facilitating the release of the pre-prepared response as is believed to occur in the startle–react phenomenon.[51] Our RT results do not necessarily reflect the underlying therapeutic mechanism of PPN stimulation. However, it is notable that poorer 'Speed of Reaction' assessed with the same computerised tool used in this study, has been found to correlate with a higher frequency of falls.[25] Correspondingly, we found that with therapeutic PPN stimulation, improved falls scores correlated significantly with percentage improvements to SRT. Moreover, adjustments to locomotion (eg, obstacle avoidance) can be facilitated by startle, raising the possibility that some aspects of gait may be 'preprogrammed' and potentially subject to the same facilitatory effects of stimulation of the PPN area as the SRT.[7 50]

Finally, the effects of PPN stimulation appear to differ from those of dopaminergic medication and subthalamic nucleus (STN) stimulation. In a study using the same computerised tasks, acute and chronic dopaminergic therapy did not improve RTs in non-demented PD patients.[28] In studies using different computerised tasks, STN stimulation significantly improved not just SRT but also CRT and Go/NoGo RT.[52 53] Furthermore, unlike dopaminergic medication and STN stimulation, we found a clinical benefit of PPN stimulation for only gait and balance. PPN stimulation did not improve akinesia as had been suggested by the MPTP primate model and early reports in humans.[1 30] The lack of effect on akinesia has recently been corroborated by others.[2] It is also notable that acute on/off stimulation assessments of posture and gait (with IT27–30) revealed only modest effects compared with the substantial chronic impact on falls. This suggests that longer-term outcome measures (such as questionnaires and ambulatory monitoring) may be more appropriate assessments for this target.

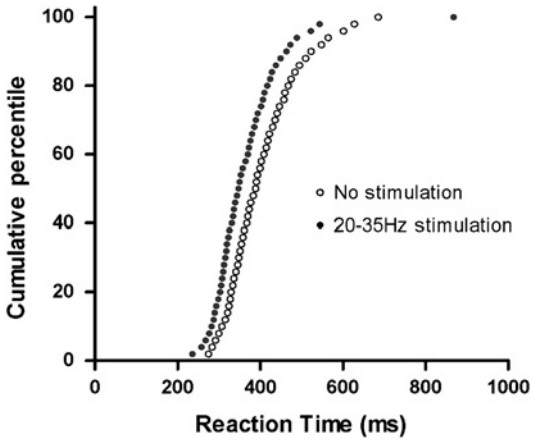

Figure 3 Simple reaction time distribution curves for 0 Hz and therapeutic frequency (20–35 Hz) conditions.

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