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In a rush to decide: Deep brain stimulation and dopamine agonist therapy in Parkinson's disease

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Abstract

Background—It has been suggested that all patients with Parkinson's disease (PD) who undergo functional neurosurgery have difficulties in slowing down in high conflict tasks. However, it is unclear whether concomitant dopaminergic medication is responsible for this impairment.

Objective—To assess perceptual decision making in PD patients with bilateral deep brain stimulation.

Methods—We tested 27 PD patients with bilateral deep brain stimulation on a task in which participants had to filter task relevant information from background noise. Thirteen patients were treated with Levodopa monotherapy and 14 patients were treated with Levodopa in combination with a dopamine agonist. Results were compared to healthy matched controls.

Results—We found that all PD patients who were treated with a dopamine agonist made faster decisions than controls and PD patients who were not exposed to a dopamine agonist. Further, all patients made more errors than controls, but there was no difference between the two patient groups.

Conclusions—Our results suggest that dopamine agonist therapy rather than deep brain stimulation is likely responsible for the inability to slow down in high conflict situations in PD. These results further strengthen the need to reduce dopamine agonists in PD patients undergoing functional neurosurgery in order to prevent them making inadvisable decisions.

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Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is commonly used in patients with advanced Parkinson's disease (PD) to improve motor handicap [1]. Whether STN-DBS can cause or improve impulsivity in PD is, however, the subject of ongoing debate. Some neurobehavioural tests have shown that PD patients with STN-DBS have difficulty slowing down in high conflict situations [2], whereas other studies have shown that impairments on information sampling tasks are induced by dopamine agonist therapy and not DBS [3]. Similarly, some clinical studies suggest that STN-DBS can either cause [4] or improve [5] addictive behaviours in PD. Variable electrode placement or differential reduction in dopaminergic medication may contribute to differences in outcome [5, 6]. The STN has been suggested to act as a "brake" influencing cortico-striatal pathways to allow more time to elapse before committing to a decision [7]. Dopamine agonists on the other hand have been shown to reduce prefrontal cortical function, and at the same time increase activity of the mesolimbic dopaminergic neurons during reward processing [8].

To clarify the role of STN-DBS and dopamine agonist therapy in high conflict decisions we tested PD patients on a perceptual decision making task. In perceptual decision making tasks participants are required to select relevant information from a noisy background. For example in the "random dot motion task", participants need to report in which direction the majority of dots are moving. A recent study using this random dot task showed an acute effect of STN-DBS stimulation on task performance. On STN-DBS participants responded faster in high conflict situations compared to off stimulation, demonstrating that the STN plays a key role in decision threshold [9]. However, the effects of STN-DBS stimulation under stable conditions and in combination with dopamine agonist therapy on perceptual decision making tasks are unclear.

Therefore, we recruited two PD groups, both of whom had undergone bilateral STN-DBS. One group was treated with Levodopa with a dopa decarboxylase inhibitor (L-dopa) in combination with a dopamine agonist, whereas the other group was treated with L-dopa monotherapy.

We hypothesized that PD patients with STN-DBS and dopamine agonist therapy would respond quicker than those STN-DBS patients who were just on L-dopa monotherapy. Further, we speculated that those patients who were on L-dopa monotherapy would make fewer errors than those who were treated in addition with a dopamine agonist and that both patient groups would make more errors than healthy control subjects.

Methods

Only participants who scored above 26/30 points on the Mini-Mental state examination were included [10]. All participants provided written informed consent according to the declaration of Helsinki and had full capacity to consent. The study was approved by the UCLH Trust Research Ethics Committee.

All PD patients were recruited from the National Hospital for Neurology and Neurosurgery London, fulfilled the Queen Square Brain Bank criteria for the diagnosis of PD [11] and

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were treated with L-dopa. We recruited 27 PD patients who had previously undergone bilateral STN-DBS. Fourteen of these PD patients were treated with L-dopa in combination with a dopamine agonist and 13 were treated with L-dopa monotherapy having never been exposed to a dopamine agonist previously. None of the PD patients had a history of impulsive or compulsive behaviours. Results were compared to 17 healthy matched controls.

Pixel task

In the perceptual inference task [12] participants were shown a circle in which a proportion of the pixels were red and the rest were blue. Participants then had to guess whether there were more blue or more red pixels presented on the screen. Sixty trials were performed in total, 20 of which contained a high conflict 60/40 distribution of red and blue pixels, 20 an easier 70/30 distribution and a further 20 trials starting with a 60/40 condition gradually changing to an 80/20 distribution of coloured pixels after 2.5 seconds.

Participants were told to press the labelled keys whenever they thought they knew the answer.

Feedback (“correct”/ “wrong”) was given instantly. Correct choices were rewarded with 0.25 units, incorrect choices were unrewarded. Participants were told that faster responses did not lead to higher rewards.

The majority of these patients- (7 DBS+DA, 10 DBS-DA) and all controls also performed a baseline reaction time (RT) task, in which they were presented with a solid blue or red circle and had to respond as quickly as they could. At the end of the task participants received a modest amount of money depending on their final score, usually around £10–£15.

Statistics

Data analyses were performed using SPSS 21 using a mixed model Anova. Demographic variables were analysed using ANOVA, or $\chi 2$ tests. RTs and baseline RTs were log transformed and residuals were normally distributed. Condition (60/40, 70/30/, morphing to 80/20) and group were modelled as fixed factors. Errors were analyzed using a non-parametric Kruskal Wallis ANOVA.

Results

Demographic characteristics

There were no significant differences on any demographic characteristics between the groups (Table 1).

Baseline reaction time

We first analysed baseline RT and found a significant group difference ($F_{2,23}$=4.1, p=0.027). Post hoc comparison showed that both DBS groups were significantly slower than controls (p<0.001). There was no difference between the two patient groups (p=0.67) (see Figure 3-supplementary material).

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Next we analysed errors on the baseline RT task and found a significant group difference ($F_{2,132}$=5.2, p=0.01). Pairwise comparison showed that controls made significantly less errors than both patient groups (p<0.001). Furthermore, DBS-DA made less errors than DBS +DA (p<0.001) (See Figure 4-supplementary material).

Pixel task

A three (control, DBS-DA, DBS+DA) by three (condition 1(60/40), condition 2(70/30), condition 3(80/20) mixed ANOVA (Greenhouse-Geisser corrected) revealed a significant group difference in RT ($F_{2,153}$=15.0, p<0.001). Post hoc comparison showed that DBS+DA were significantly faster than controls (p=0.001) and DBS-DA (p<0.001). There was, however, no difference between controls and DBS-DA (p=0.14) (Figure 1). There was also a significant effect of condition (p<0.0001) but no interaction of group and condition (p>0.7).

We then examined the total amount of errors and found a significant group effect ($F_{2,60}$=15.4, p<0.001). Pairwise comparison showed that controls made less errors than DBS-DA (p=0.002) and DBS+DA (p<0.001). There was no difference between the two PD groups (p=0.2) (Figure 2). There was also a significant effect of condition ($F_{2,87}$=10.9, p<0.001) but no group by condition interaction.

Discussion

We found that all participants were faster and made fewer errors in the easier 70/30 condition. Further, PD patients who underwent bilateral STN-DBS and who were treated with L-dopa in combination with dopamine agonists made significantly faster decisions than STN-DBS patients who were on L-dopa monotherapy and matched volunteers.

Previous reports in PD patients treated with bilateral DBS suggested that STN-DBS in general impairs the ability to slow down during high conflict tasks [2, 13] leading to impulsive choice [7].However, in these studies it is not clear whether PD patients were treated with dopamine agonists. Our findings expand these results as they suggest that dopamine agonist therapy and not STN-DBS is likely responsible for the inability to slow down in high conflict situations.

Further, our results are in line with previous studies showing that PD patients who are treated with dopamine agonists make faster decisions [14] and sample less information, regardless of whether they were treated with bilateral STN-DBS or not [3]. It is possible that dopamine agonists in combination with STN-DBS sensitize brain areas that are involved in reward processing [15] such as the ventral striatum. These higher mesolimbic dopamine levels then cause incentive salience, where previously neutral stimuli trigger motivational value and can lead to faster responses [16, 17].

An alternative explanation is that here we tested PD patients under stable conditions, to more closely resemble their real-life clinical situations, whereas previous tests were done in acute “on/off” changes. Acute changes of STN-DBS increase impulsivity and reduce the ability of slowing down in high conflict situations whereas under stable conditions STN-DBS reduces impulsive action [18].

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Further, we found that both PD groups made more errors than controls, but there was no group difference between patients. Preliminary results in a small cohort of DBS patients on the baseline RT task showed that those treated with dopamine agonists made significantly more errors than those not using dopamine agonists, which is generally consistent with our previous study demonstrating poorer task performance in STN-DBS patients on dopamine agonist therapy [3]. It is, however, important to acknowledge that the sample size for the baseline reaction time was too small to draw any definite conclusions.

Whether dopamine agonists reduce accuracy in STN-DBS patients in a simple reaction time tasks needs to be explored in a larger cohort of patients. Accuracy is reduced in PD patients “on” STN-DBS compared to “off” STN-DBS [9] and thus, “off” stimulation testing may have reduced error rates. However, “off medication” testing can cause dysphoria and anxiety [19] which can interfere with task performance.

In summary we have shown distinct differences in perceptual decision making in PD patients treated with STN-DBS depending on whether they were exposed to dopamine agonist therapy or not. It is possible that dopamine agonists in combination with STN-DBS cause sensitization of the mesolimbic dopamine levels resulting in reduced decision threshold in perceptual decision making tasks. As was the case in our cohort, a significant proportion of people with PD undergoing DBS have a younger age of PD onset, which in itself is a risk factor for the development of impulsive-compulsive behaviours (ICBs)[20]. Additionally, younger PD patients are often prescribed dopamine agonists more frequently than L-dopa, and dopamine agonists are generally accepted to be more strongly associated than levodopa with the development of most ICBs. Whether STN-DBS itself is a risk factor or protective factor in the development of ICBs is still unclear. It is, however, important for treating clinicians to be aware of the effects of dopamine agonists on decision-making in PD patients with DBS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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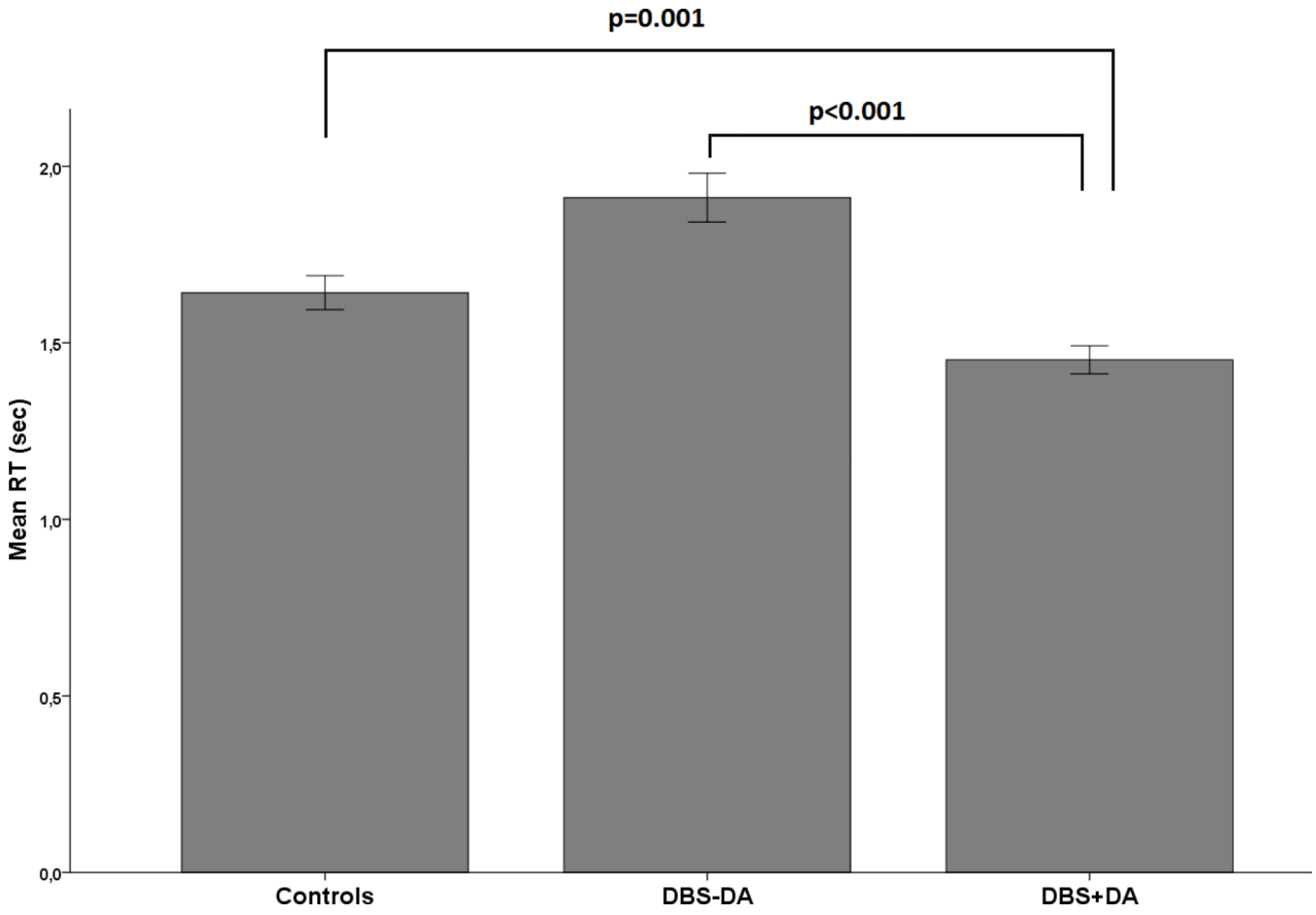

Figure 1.

Mean reaction time across all trials. Controls, Parkinson's disease patients, who underwent deep brain stimulation without (DBS-DA) and with dopamine agonist therapy (DBS+DA). All error bars are +/− 1 standard error.

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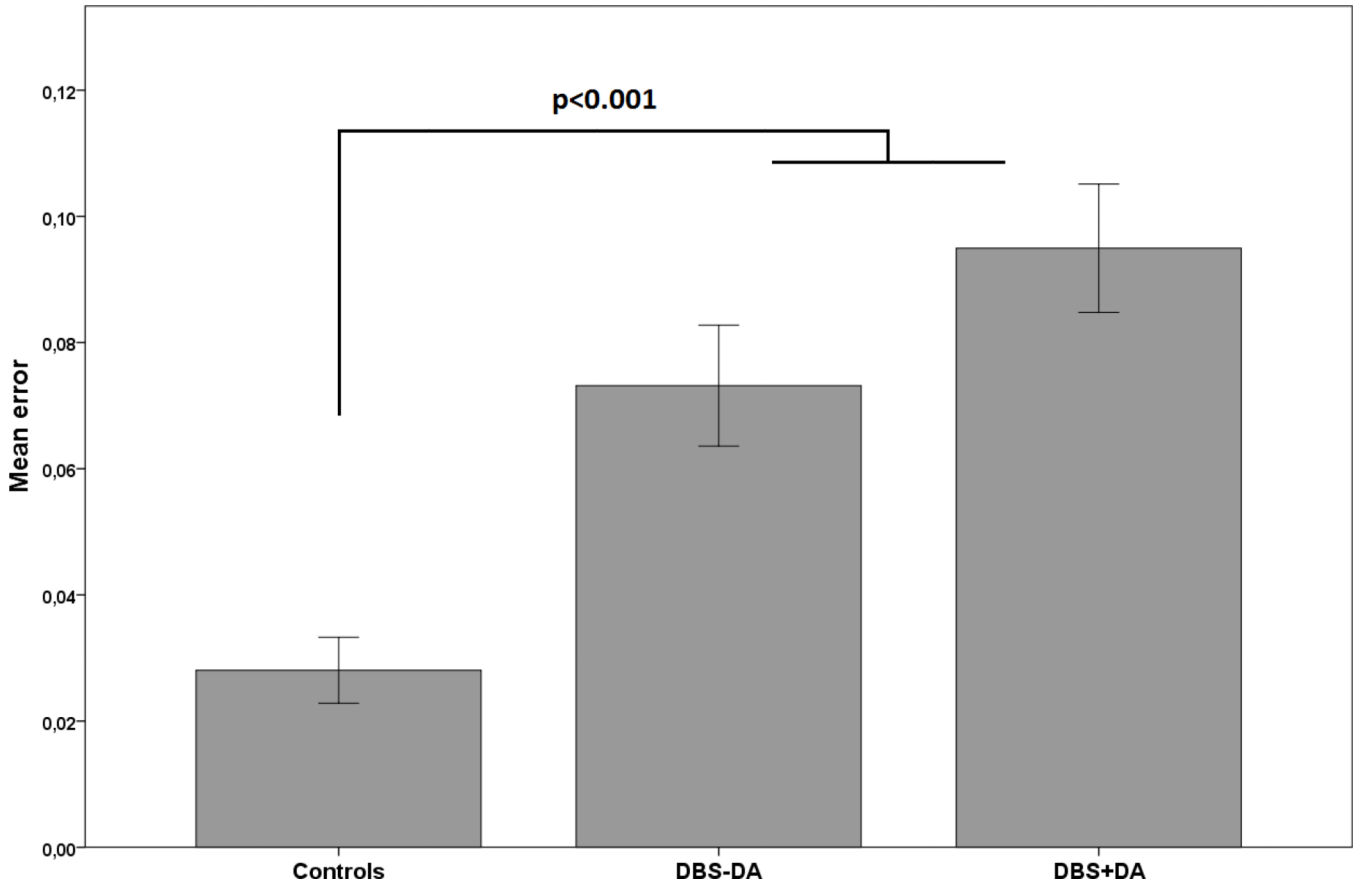

Figure 2.
Mean errors across all trials. All error bars are +/− 1 standard error.

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Table 1

Demographic characteristics

	Controls	DBS-DA	DBS+DA	t statistic χ^2 or F-statistic	p-value
Participants (no.)	17	13	14		
Gender (male)	14	12	11	χ^2 =1.0	0.6
Age (years)	59.9±10.4	60.0±7.2	55.9±10.0	F=0.8	0.4
Age PD of diagnosis		46.1±7.5	40.1±8.1	t=1.8	0.08
PD Disease duration (years)		13.3±4.8	15.0±4.9	t=0.9	0.37
DBS (years)		3.6±2.4	3.9±2.3	t=0.3	0.7
LEU dose(mg/day) **L-dopa (mg/day)**		613.3±379.0 558.6±308.4	794.3±292.2 600.0±327.5	t=1.8 t=0.3	0.085 0.7
UPDRS on		16.5±1.2	15.2±1.2	t=1.1	0.2

UPDRS = Unified Parkinson's Disease Rating Scale; LEU = L-dopa equivalent units;

All values are mean ± SD.

Parkinson's disease patients who underwent deep brain stimulation and were treated with (DBS+DA) and without a dopamine agonist (DBS-DA).