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"Effects of dopaminergic treatment in inhibition of saccades in Parkinson disease (PD)."

Msc thesis

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Abstract- Parkinson's disease (PD) is associated with a loss of central dopaminergic pathways in the brain leading to an abnormality of movement, including eye movements like saccades. The pathophysiology of Parkinson's disease (PD) is considered to be the increase in the activities of basal ganglia (BG) output nuclei, which excessively inhibits the thalamus and superior colliculus (SC) and causes preferential impairment of internal over external movements. In PD, analysis of saccadic parameters and saccadic latency distributions, can provide information about how the neural decision process and inhibition are affected by dopaminergic treatment and disease state. Current study's purpose is to examine the effects of dopaminergic treatment in inhibition of saccadic eye movements in advanced state of PD. Executive function was measured through eye movements, reflexive prosaccades and voluntary antisaccades. Ten patients with advanced idiopathic PD, "off" and "on" anti-Parkinsonian medication, were tested on a prosaccade and an antisaccade task. Saccadic eye movements were measured while patients were "off" and "on" anti- Parkinsonian medication, to study how the initiation and inhibitory control of saccades varied with the anti-Parkinsonian medication. To measure the inhibitory control of saccades, we studied the directional errors in the antisaccade task. Dopaminergic treatment was found to prolong reflexive prosaccadic latency and incorrect prosaccadic latency in antisaccade task. However, dopaminergic treatment did not suppress incorrect prosaccades during the antisaccade task. There was no improvement for voluntary cognitive processes in advanced stage PD. The saccadic parameters of reflexive and voluntary saccades showed no correlation with Unified Parkinson's Disease Rating Scale III motor subscores reflecting dopaminergic function. The results suggest that dopaminergic treatment affects both reflexive and voluntary saccades. The impairment in reflexive and voluntary saccades may be caused by the excessive

inhibition of the SC due to the increased BG output and the decreased activity of the frontal cortex-BG circuit. The impaired suppression of reflexive saccades in antisaccade task may be explained of increased SC inhibition and reduced pre-oculomotor drive due to dysfunctional frontal cortex-BG-SC circuit. Changes in saccade parameters suggest that frontal cortex-BG circuit activity decreases with disease progression.

Introduction

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system, affecting approximately 2% of the population over the age of 70 and causing an abnormality of movement, including saccades (Michell et al., 2006).The clinical symptoms of the PD involve asymmetric bradykinesia, muscular rigidity, tremor at rest, postural instability and reduction in cognitive function (Lezak, 2012).

Parkinson’s disease motor manifestations are caused by dopaminergic cell loss within the substantia nigra pars compacta (SNc), resulting in dysfunction of the BG (Briand et al.,1999; Chambers et al., 2010). There is increased inhibitory output from BG, which affects thalamo-cortical circuits and SC, leading to motor symptoms (Briand et al.,1999; Chambers et al., 2010). As a consequence of the general impairment in the motor functions, eye movement impairments have also been reported in these patients (Briand et al.,1999; Chambers et al.,

2010). Abnormal saccadic performance in PD is considered to be due to depletion of dopamine in the caudate nucleus (DeLong et al.,1990; DeLong et al.,2007). There is an overall increase in the inhibitory output to SC and thalamus due to increased activity in the indirect pathway leading to more excitatory activity of STN and a decreased activity in the direct pathway leading to increased inhibition of SNr/GPi (DeLong et al.,1990; DeLong et al.,2007).

The BG have two output pathways implicated in the control of movements: the thalamocortical parallel pathways (Alexander et al., 1986) and the brainstem motor networks (Hikosaka et al., 2000). The oculomotor circuit of the former projects back to the frontal eye field and supplementary eye field, which plays an important role in the suppression process (Perneczky et al., 2011; Connolly et al., 2002; Aron et al., 2005). The role of the supplementary eye field on saccadic eye movement has been demonstrated not only anatomically but also physiologically and pharmacologically (Hikosaka et al., 2000; Fawcett et al., 2005). Through the BG–superior colliculus (SC) pathway and the corticotectal pathways, the SC is the common terminal for controlling saccadic eye movements. Therefore, saccades reflect the output of the BG and could represent a potential indicator of BG function Yugeta et al., 2010).

The interaction between the frontal cortex and the BG in action selection has been described in terms of a set of parallel but mostly segregated cortico-basal ganglia (CBG) loops (Alexander et al., 1986).

Measurement of eye movements permits assessment of both behavior and motor function (Ramat et al.,2007; Macaskill et al., 2012). Neural circuitry of saccades is complicated and involves various cortical (parietal, frontal) and subcortical structures, like basal ganglia (BG),

superior colliculus (SC), thalamus, brainstem and cerebellum (Munoz et al., 2004). Saccadic eye movements have been widely studied in patients with PD using various oculomotor tasks. The prosaccade task is primarily a reflexive task that requires the participant to make a saccade toward a visual target (Saslow, 1967). In prosaccade task, the fixation point was turned on, and the subjects had to fixate on this point. It was turned off after an arbitrary period of 1,500 –2,000 msec, and simultaneously the target point was turned on at 10 degrees to the left or right randomly, and the subjects had to make a saccade quickly to the new position (Figure 1).

The antisaccade task requires the participant to first inhibit a reflexive saccade to a visual target and then internally generate a saccade in the opposite direction from the target (Hallet, 1978) In antisaccade task, the fixation point and a cue point were turned on and off in the same way as in the prosaccade task, but the subject had to make a saccade toward the opposite location of the cue point (Figure 1). The actual target point for the saccade was a point opposite to where the cue stimuli appeared. Saccades erroneously made toward the cue point were termed prosaccades. Thus, the antisaccade task requires responses based on internal plans rather than sensory cues and requires more cognitive processing than visually guided prosaccades to suddenly appearing targets (Goelz et al., 2016).

Saccadic tasks are objectively quantifiable and are a sensitive way of evaluating aspects of the function of CBG circuits (Leigh et al., 2004). Performance in simple “reflexive” prosaccades (looking toward a visual stimulus) may represent function purely within the oculomotor loop (Antoniades et al., 2015). The more complex antisaccade task (AS) (looking away from a visual stimulus; Hallett, 1978) requires inhibition of the normal reflexive response, which is known to require the dorsolateral prefrontal cortex, part of the prefrontal

loop (DeSouza et al. 2003; Munoz and Everling, 2003; Pierrot-Deseilligny et al., 2004). Prosaccades are natural and easy to perform, but antisaccades impose a higher demand on attentional and cognitive resources (Ettinger et al., 2008). The antisaccadic error rate (AER) quantifies how often a subject erroneously makes prosaccades rather than antisaccades during an antisaccade task and is thus a measure of failure of response inhibition. An elevated AER may, therefore, reflect impairment of information transfer from the prefrontal to the oculomotor loop (Antoniades et al., 2015).

Different saccadic paradigms have been used to understand stages of information processing when subjects perform these tasks and how impaired circuitry manifests itself in behavior in PD. Different results of saccadic performance of PD patients have been observed. One of the most prominent features of eye movement abnormality in PD is saccade hypometria (Terao et al., 2013; White et al., 1983). Hypometria is more severe in voluntary saccades, particularly in memory-guided saccades, where a subject is required to make a saccade to a remembered target location (Crawford et all., 1989; Nakamura et all., 1994; Vermersch et all., 1994). Reflexive saccades, usually preserved in the initial stages of PD, can become hypometric in later stages (Gorges et al., 2014). Reflexive saccade hypometria is thought to result solely from excessive SC inhibition, compared to hypometric voluntary saccades that are supposed to be caused by both increased SC inhibition and reduced pre-oculomotor drive due to dysfunctional frontal cortex-BG-SC circuit (Terao et al., 2011).

Latency of voluntary saccades and error rates of antisaccades (AER) are increased, indicating difficulty in initiating volitional eye movements (Lueck et all., 1990; Kitagawa et all., 1994; Briand et all., 1999; Chan et all., 2005). The AER quantifies how often a subject erroneously makes prosaccades rather than antisaccades during the AS and is thus a measure of failure of

response inhibition. PD patients are shown to have problems in inhibiting reflexive saccades in antisaccade task, suggesting executive control deficits in PD (Terao et al., 2011). Importantly, the AER is also significantly increased (Rivaud-Pe´choux et al., 2007; Terao et al., 2013), even in some newly diagnosed cases (Kitagawa et al., 1994; Antoniades et al., 2015), suggesting that defects in interloop information transfer are present from an early stage.

In PD, latency for prosaccades is prolonged, particularly for large target eccentricities in more advanced stage of disease (Chan et al., 2005; Amador et al., 2006; Hood et al., 2007; Antoniades et al. 2013b). In contrast, reflexive saccades to visual targets such as visually guided saccades are relatively spared (White et all., 1983; Rascol et al., 1989; Vidailhet et al., 1994; Briand et al., 1999). PD patients have difficulty in initiating reflexive saccades suggesting executive control deficits in PD (Terao et all., 2011). The preferential impairment of voluntary saccades as compared with reflexive saccades might explain by the fact that the BG are more involved in voluntary saccades (Briand et al., 1995; Fukushima et al., 1994; Piarrot- Deseillignv et al., 2004). In addition to the difficulty in initiating saccades, patients with PD have difficulty in suppressing incorrect prosaccades to cues in the memory-guided task (Hikosaka et al., 2000). Nevertheless, it remains unclear how the impairment of initiation and inhibition of saccades can coexist.

Therefore, patients with PD can develop a wide range of cognitive deficits and imaging techniques show that PD patients tend to have decreased activity in the prefrontal cortex (Jahanshahi et al., 1995; Playford et al., 1992). Levodopa, which is consider as the milestone in PD medication replenish the lack of dopamine and reduces tremor, rigidity and other common motor symptoms. However, it is not clear the effect of dopaminergic treatment on

saccadic parameters and inhibition. Various studies have been conducted in order to determine the effect of medication on saccadic eye movements in patients with PD. Recent work has shown that levodopa has both deleterious and beneficial effects on saccadic eye movements in patients with PD (Cools et al., 2001; Gotham et al., 1988; Kulisevsky et al. 2000; Lange et al. 1992; Swainson et al., 2000). Some researchers conclude that dopaminergic medication may improve certain types of neuropsychological performance and hinder others because the brain regions involved are differentially affected by dopamine. A reasonable hypothesis is that brain regions have an optimal dopamine level and shifts from the norm can impair some tasks/measures while benefiting others (Cools et al., 2001).

Some researchers conclude that dopaminergic treatment may improve eye movements in patients with PD (Gibson et al., 1987). This improvement was reflected in increase of saccadic accuracy. Mean latencies of the saccades also reduced. Recent work has shown that dopaminergic treatment improved saccadic amplitude after ninety minutes of medication (Rascol et al., 1989). Saccadic latency improved mildly when tested after dopaminergic treatment, but there was no improvement in peak velocity. Step task saccadic paradigm with conditions of no gap or overlap was administered on twenty two PD patients (Michell et al., 2006) Results suggested increase in saccadic latencies which reflects that medication slowed patients with PD on saccadic tasks. Similar results were reported where prolonged response time was observed when PD patients performed on reflexive saccadic task (Hood et al., 2007). Improvement in saccadic parameters after medication was reflected in reduced error rate when patient performed on voluntary antisaccade task. It was suggested that medication (levodopa) helped patients to plan and execute eye movements better which is a reflection of improved impaired frontal-striatal circuitry involved in voluntary eye movements (Hood et

al., 2007). Patients with PD were recruited on reflexive saccadic eye movement tasks where dopaminergic treatment prolonged latencies and reduced peak saccadic velocity and enhanced hypometria. Authors concluded that oculomotor activity in patients with PD gets worsened after medication (Dec M. et al., 2012).

The results of current literature are conflicting. Most of the studies suggest beneficial effects of dopaminergic treatment on saccades in PD in addition to improvement in general motor movements. However, studies which report no beneficial effect of dopaminergic treatment on saccadic parameters like latency, amplitude and accuracy. Further research is required to identify what aspects of saccadic eye movements are affected by dopaminergic medication.

The current experiment studied the effects of dopaminergic treatment in inhibition of saccadic eye movements in advanced state of PD. Therefore, we tested patients with idiopathic PD in a moderately advanced stage of the disease on a voluntary antisaccade (AS) task and a reflexive prosaccade (PS) task to measure the effects on executive function. We measured saccadic parameters in idiopathic PD patients on prosaccade and antisaccade task while patients were “off” and “on” anti- Parkinsonian medication, to study how the initiation and inhibitory control of saccades varied with the anti- Parkinsonian medication. To measure the inhibitory control of saccades, we studied the directional errors in the antisaccade task.

The present study had two hypotheses: (i) dopaminergic medication would improve performance on the AS task because of improved interaction between the basal ganglia and the frontal lobe function; and (ii) dopaminergic medication would enhance the tonic inhibition of the reflexive system, consequently slowing performance on the reflexive PS

task. Along with the effect of dopaminergic treatment on inhibition of saccades, our findings provide novel insights into the function of the BG and the pathophysiology of PD.

Materials and Methods

Participants

Patients with PD were recruited for this study from the University of Athens Medical School, "Evangelismos" Hospital. They had been diagnosed with idiopathic PD. Patients were examined by a movement disorders neurologist and were included in the study if they met UK Parkinson's disease Society Brain bank diagnostic criteria for PD (Hughes et al. 1992) and exhibited no eyelid opening apraxia or other clinically evident eye movement abnormalities. Patients with atypical parkinsonism or dementia were excluded. With the exception of PD the patients had no other known neurological disorders.

The final group was comprised of 10 idiopathic patients with PD (8 males, 2 females; mean age 68.5 years ± SD 8.56) were selected to participate in the off/on medication study. All patients were right-hand dominant as confirmed by the Edinburgh Handedness Inventory (Oldfield 1971).

Written informed consent was obtained from all participants after the procedures were explained to them and the study was approved by the Committee for the Protection of Human Subjects at our institution in accordance with the Declaration of Helsinki. Demographics and clinical characteristics are shown in table 1.

Table 1: PD patients demographic and clinical measures.

Patients	Age (y)	Sex	Disease diagnosis (years)	LED	H &Y OFF MED	H & Y ON MED	S &E OFF	S &E ON	UPDRS III OFF MED	UPDRS III ON MED	% Change
1	69	M	6	510	2	2	100	100	24	19	20.8
2	80	M	8	1020	2	2	70	90	38	19	51.3
3	64	M	11	800	4	4	40	60	48	38	20.8
4	55	M	10	1127.5	2	2	70	100	22	8	63.6
5	83	M	7	640	2	2	100	100	25	15	40
6	74	M	15	810	2	2	90	100	34	24	29.4
7	60	F	23	1050	2.5	2.5	70	100	44	10	77.3
8	66	M	16	1547.5	2.5	2.5	80	100	38	15	60.5
9	66	F	1	700	2	2	80	100	27	16	40.7
10	68	M	6	510	2	2	90	100	21	11	47.62
Mean (n=10)	68.5~8.56	8M; 2F	10.3	871.5	2.3	2.3	**79/95****		**32.1/ 17.5*****		

LED, L-Dopa–equivalent daily dose; H&Y, Hoehn and Yahr Scale; S&E, Schwab and England Scale; UPDRS, Unified Parkinson Disease's Rating Scale part III scores off/ on medication state (**Bold % Change =** clinically significant improvement (>20%)).
**p< 0.01; ***p< 0.001 PD on medication state is significant better than PD Off medication state.

Procedure

Each participant was tested twice on one day on two separate occasions. The PD patients were first tested in the "off" medication state, at least 12 h after the last antiparkinsonian medication (Langston et al., 1992) and then in the "on" medication state when patient and neurologist agreed the medication was in full effect 0.5–2 h after the dose (Schiess et al., 2000). The dopaminergic treatment regimen was recorded as L-Dopa–equivalent daily dose (LED) and is calculated according to recognized standard conversions.

A movement disorders specialist administered a battery of clinical measures, including the Hoehn and Yahr Rating Scale (Hoehn and Yahr 1967), Schwab and England Activities of Daily Living Scale and the Unified Parkinson's Disease Rating Scale version III (Fahn et al. 1987) to evaluate disease severity, functional capacity and disease state, respectively. The prosaccade (PS) and antisaccade task (AS) followed the clinical evaluation. The order of the two saccade tasks was randomized. Each saccade task lasted approximately 20 min (Antoniades et al. 2013a). Breaks were provided as needed between and within tasks. Each session occurred between 9 am and 11 am.

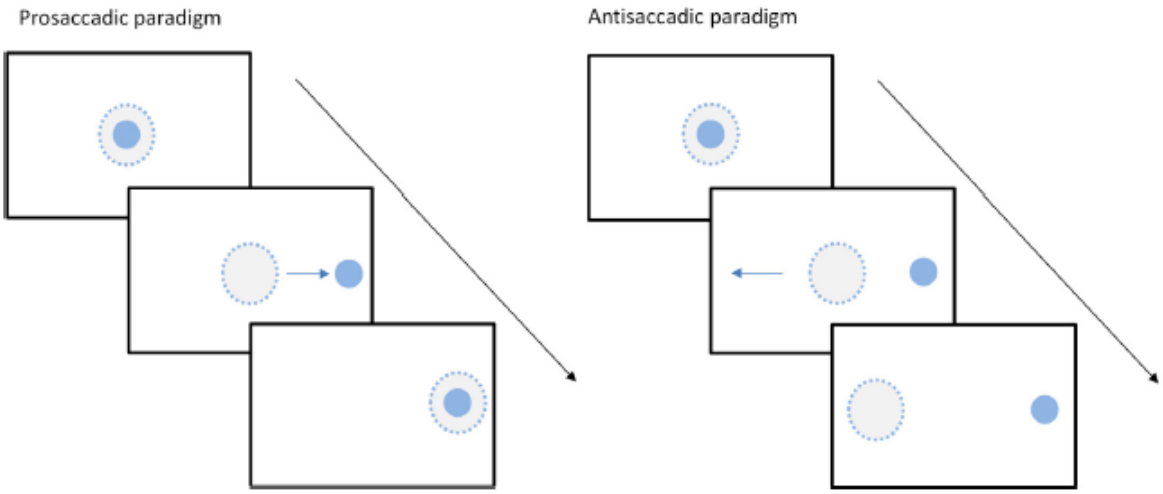


Figure 1. Oculomotor task. The filled circle represents the stimulus, and the dashed circle represents gaze location. Left, Prosaccadic paradigm. Participants were instructed to move their eyes to the new target position that was randomly either to the left or to the right. Right, Antisaccadic paradigm. Participants were instructed to move their eyes in the opposite direction to the movement of the stimulus.

Oculomotor tasks.

Visually guided horizontal saccadic eye movements were recorded using an infrared head-mounted oculometer, with three built-in lasers projecting red spots in a horizontal line in the midline and at ± 10° (Antoniades et al. 2012). We used the antisaccadic protocol (Antoniades et al., 2013a; Figure 1). In Prosaccadic task, participants were instructed to move their eyes to the new target position that was randomly either to the left or to the right. In antisaccadic task, participants were instructed to move their eyes in the opposite direction to the movement of the stimulus. After an initial calibration set consisting of 20 prosaccades (10 to the right and 10 to the left), this protocol consisted of five blocks as follows: a block of 60 prosaccades, three blocks of 40 antisaccades, and a final block of 60 prosaccades, with a break of 1 min between blocks.

For both prosaccades and antisaccades, a central fixation target was displayed for a random foreperiod of 1.0 –2.0 s. Then one of the peripheral targets chosen randomly either to the left or right was presented, and the central stimulus was simultaneously removed. The peripheral target remained illuminated until 200 ms after the end of the ensuing saccade. For prosaccades, participants were instructed to make a saccade quickly to the new target position. For the antisaccades, participants were instructed to make a saccade in the opposite direction. The antisaccades required considerably more cognitive load than the prosaccades because the participant was required to inhibit the reflexive draw to look at the stimulus and generate a voluntary saccade away from the stimulus to blank space (Ettinger et al., 2008).

Data and statistical analysis.

For each subject, saccadic data were analyzed using Latency Meter (version 4.14; Ober Consulting). This software determines the saccadic latency using a saccade-detection algorithm based on velocity and acceleration. For each participant, we calculated correct and incorrect mean prosaccadic and antisaccadic gain (ratio of actual amplitude to correct amplitude), amplitude, peak velocity, latency for prosaccades, correct antisaccades and error prosaccades in the antisaccade task (AER). The AER was defined as the percentage of directional errors, i.e., saccades triggered toward the lateral target. Saccades with latencies < 90 ms or over 1000 ms were excluded from the analysis.

Descriptive values were extracted for all variables of interest, including demographic, clinical and oculomotor measures. Normality assumptions were initially tested and further parametric statistics were applied for the purpose of the present study. To assess the effect of medication in Unified Parkinson Disease's Rating Scale part III, motor scores were compared using a two- tailed paired sample dependent *t* test. To compare paired data (the value of a certain saccadic parameters "off" medication and "on" medication state), was used a one way, within subject repeated measures analysis of variance (ANOVA) with task (PS, AS) and medication state (off, on) for patients with idiopathic PD to measure within subject medication effect. To examine the effect of medication state (off, on) on AER, was used a one way, within subject repeated measures analysis of variance (ANOVA). Statistical tests were considered significant at $p<0.05$ level and *p* values associated with pairwise comparisons were corrected

using the Bonferroni method. SPSS for Window (25.0; SPSS Inc., Chicago, IL) was used for all statistical analyses.

Table 2: PD patients means for PS and AS task.

	PD patients	
	Off Med.	On Med.
AER (%)		
Antisaccade incorrect	52.6	50.8
Latency (ms)		
Prosaccade correct	**256.85**	**303.64****
Antisaccade correct	350.37	389.02
Antisaccade incorrect	**267.9**	**312.01***
Gain (deg)		
Prosaccade correct	1.05	1.23
Antisaccade correct	1.14	1.09
Antisaccade incorrect	1.03	0.98
Amplitude (deg)		
Prosaccade correct	10.46	12.33
Antisaccade correct	11.39	9.86
Antisaccade incorrect	10.3	9.86
Peak velocity (deg/s)		
Prosaccade correct	424.75	490.75
Antisaccade correct	391.1	420.2
Antisaccade incorrect	441.33	430.4

Means of correct and incorrect prosaccade and antisaccade parameters in the “off” medication and “on” medication state.

Results

Clinical measures

The seemingly variable Unified Parkinson Disease’s Rating Scale part III (UPDRS III) motor scores did not contain outliers, and these scores improved significantly with medication ($t(9) = 5.406$, $p < 0.001$). Also, there was a significant improvement in Schwab and England

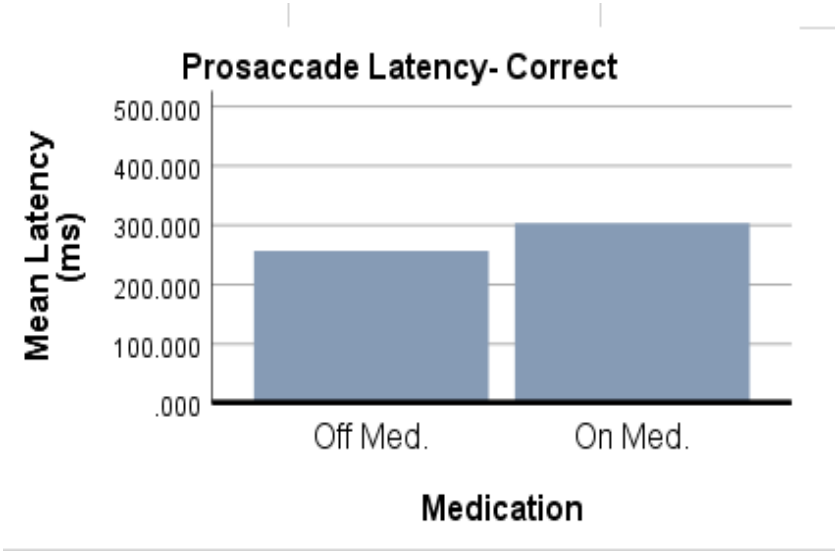
Activities of Daily Living Scale scores in the “on” medication compared to “off” medication state ($t(9) = -4.707$, $p<0.01$). The demographic, clinical details, UPDRS III and Schwab and England Activities of Daily Living Scale scores of the “off” medication and “on” medication PD patients are shown in table 1.

Latency

Table 2 shows the means of correct prosaccade and incorrect antisaccade latency in the “off” medication and “on” medication state. For the correct answers in PS task, there was a significant main effect of medication state ($F(1,9) = 22.382$, $p< 0.001$, $\eta^2= 0.713$) such that medication prolonged correct prosaccade latency. PD patients were significantly slower to respond when “on” medication state (vs off) (Figure 2A).

In contrast, there was no significant main effect of medication state ($F(1,9) = 2.826$, $p= 0.127$, $\eta^2= 0.239$) for the correct AS answers but there was a significant main effect of medication state ($F(1,9) = 9.889$, $p= 0.012$, $\eta^2= 0.524$) for the incorrect answers. The latency of correct antisaccades was not affected by medication but medication prolonged incorrect antisaccade latency. PD patients were significantly slower to respond when “on” medication state (vs “off) as it seems in table 2 and figure 2B.

A)



B)

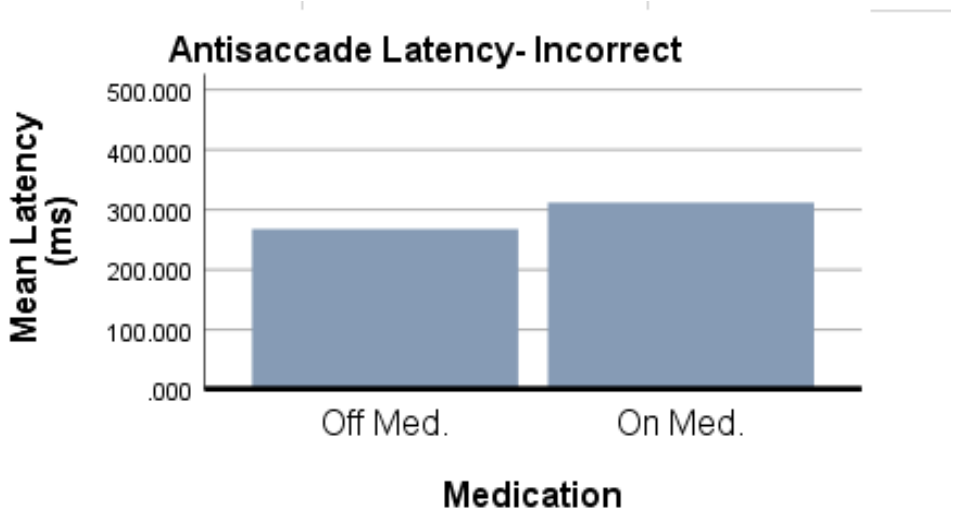


Figure 2: Mean latencies (ms) of correct prosaccades and incorrect antisacades answers. (A) $^{***}p< 0.001$ PD patients were significant slower in the "on" medication than "off" medication state on prosaccade task. (B) $^{*}p< 0.012$, PD patients were significant slower in the "on" medication than "off" medication state on antisaccade task.

Antisaccade error rate (AER)

There was no significant main effect of medication state (F (1,9) = 0.284, p= 0.607, n^2= 0.031), such that PD patients did not improve (fewer errors) when "on" medication state (vs "off") on the AS task (Table 2).

Gain

There were no significant main effects of medication for the correct prosaccade (F (1,9) =3.758, p= 0.084, η^2= 0.295) and correct antisaccade answers (F (1, 9) = 0.285, p= 0.607, η^2=0.031), same there was no significant main effect of medication for the incorrect antisaccade answers (F (1,9) =0.321, p= 0.585, η^2 = 0.034). Antisaccadic correct and incorrect mean gain reduced and prosaccadic correct mean gain increased but it did not reach significance level. (Table 2).

Amplitude

There was no significant main effect of medication for the correct prosaccades (F (1,9) = 3.758, p= 0.084, η^2 =0.295). Also, there was no significant main effect of medication for the correct (F (1,9) = 0.004, p= 0.951, η^2= 0.001) and incorrect antisaccades answers (F (1,9) = 0.321, p= 0.585, η^2= 0.034). Patients with PD had abnormally short saccades that undershot the target, and medication did not improve amplitude further on the PS and AS trials (Table 2).

Peak velocity

There was no significant main effect of medication for the correct prosaccade ($F(1,9) = 3.012$, $p = 0.117$, $\eta^2 = 0.251$) and antisaccade answers ($F(1,9) = 1.621$, $p = 0.235$, $\eta^2 = 0.153$), saccade peak velocity on AS task increased block to block but it did not reach significance level. Also, there was no significant main effect of medication for the incorrect antisaccade answers ($F(1,9) = 0.100$, $p = 0.759$, $\eta^2 = 0.011$).

Correlations

We did not find any significant correlations between behavioural and clinical variables for the patients with PD, whereas correct antisaccade peak velocity was significantly correlated with UPDRS part III ($r(8) = 0.549$, $p = 0.05$).

Discussion

In this study, we examined the effects of dopaminergic treatment in inhibition of saccadic eye movements in advanced state of PD. Therefore, we tested patients with idiopathic PD in a moderately advanced stage of the disease on a voluntary antisaccade (AS) task and a reflexive prosaccade (PS) task to measure the effects on executive function. We measured saccadic parameters in idiopathic PD patients on prosaccade and antisaccade task while patients were “off” and “on” anti- Parkinsonian medication, to study how the initiation and inhibitory control of saccades varied with the anti- Parkinsonian medication. To measure the inhibitory control of saccades, we studied the directional errors in the antisaccade task.

The main findings of this study are that the distribution of saccadic latency significantly affected by dopaminergic treatment, which tends to slow latency, with important implications for the role of dopamine in the neural decision process. Dopaminergic treatment was found to prolong reflexive prosaccadic latency and incorrect prosaccadic latency in antisaccade task. However, dopaminergic treatment did not suppress incorrect prosaccades during the antisaccade task. PD patients exhibited impaired ability to suppress incorrect prosaccades. Both the initiation of reflexive prosaccades and the inhibitory control of reflexive prosaccades in antisaccade task (saccades to cue and saccades to target) deteriorated with the dopaminergic treatment and the advanced state of the disease. The saccadic parameters of reflexive and voluntary saccades showed no correlation with Unified Parkinson's Disease Rating Scale III motor subscores reflecting dopaminergic function.

The basal ganglia (BG) play an important role in controlling saccades (Hikosaka et al., 1983). In PD, both the initiation and the inhibition of incorrect reflexive prosaccades are impaired (Yugeta et al., 2010). At "off" anti- Parkinsonian medication, the PD patients were impaired on the voluntary AS task and slow on the reflexive PS task. After taking levodopa reflexive performance slowed further. In our study there was no improvement in error rate. And participants showed voluntary performance compared to the correct antisaccade answers. In "on" anti- Parkinsonia medication state participants showed increase latency for the incorrect prosaccades in AS task. It could be evidence of levodopa cannot strengthen voluntary cognitive processes in advanced stage disease (Hood et al., 2007). In a previous study, the latency of incorrect prosaccades to cue in memory guided saccades was found to be increased in patients with PD, suggesting impaired inhibitory control of incorrect prosaccades

(Hikosaka et al., 2000). Excessive inhibition of the SC, as postulated in the rate model of the BG circuit, would actually prevent direct visuomotor execution in response to the cue stimulus (Yugeta et al., 2010). Additionally, patients undershot the targets (low gain) on voluntary AS task, and levodopa did not improve this deficit. In contrast, gain on reflexive PS task improved mildly (increased) when tasted after levodopa but no significant level. There was increase in peak velocity for correct reflexive and voluntary saccades.

The finding of this study is that the distribution of saccadic latencies can be significantly affected by dopaminergic treatment, which tends to slow reflexive prosaccade and voluntary antisaccade latency. When the patients received medication, they showed increased reflexive prosaccade latency compared to the condition of not receiving medication. Our observation that medication prolongs prosaccade latency is inconsistent with findings from other studies were latency has been reported to be shortened by dopaminergic treatment (Gauntlett-Gilbert and Brown 1998). In previous studies, PD patients were tasted on reflexive saccadic eye movement tasks where dopaminergic treatment prolonged reflexive prosaccade latency in advanced state PD (Hood et al., 2007; Dec et al., 2012). The increase in prosaccade latency of prosaccade task may be caused by the heightened level of the SNr–SC inhibition. In addition to SC inhibition, the pre-oculomotor drive decreases as the disease progresses, which increases the latency of memory guides saccades more prominently than that of prosaccades (Terao et al., 2011).

There is one other report of step task saccadic paradigm with conditions on saccadic eye movements which suggested increase in prosaccadic latency. Anti- Parkinsonian medication slowed latency on saccadic tasks in early stage disease (Michell et al., 2006). Authors discussed their results in terms of neural decision making process considering Later model

(Reddi and Carpenter, 2000; Reddi et al., 2003) for saccadic eye movements. It was suggested that increased saccadic latencies are due to increased threshold criterion level which is required before making a decision. Levodopa tends to render a subject less impulsive such that they require a higher degree of certainty before making a decision (Reddi and Carpenter, 2000; Reddi et al., 2003; Michell et al., 2006). Given this it might be expected that patients should make fewer prosaccadic errors in AS task 'on' anti- Parkinsonian medication state but the analysis of AER did not show a significant difference as a result of anti- Parkinsonian medication. The incorrect prosaccades in the AS task has been explained by the failure of the prefrontal cortex to inhibit the SC directly via the descending pathway (Fukushimaet al., 1994; Pierrot-Deseilligny et al., 2004; Condy et al., 2004) although some involvement of the BG (i.e., the caudate nucleus) has also been suggested for AS task (Lasker et al 1987; Peltsch et al., 2008). Also, some previous PD studies reported patients with hyperreflexive baseline orienting (Briand et al., 1999; Armstrong et al., 2002). The inhibitory control of saccades impaired in PD because of the excessive inhibition from BG and apart from the excessive inhibition from BG and decreased frontal cortex-BG activity (Terao et al., 2011).

Also, previous studies of reaction time in PD suggest that the effect of levodopa depends on the basal reaction time. If this is slow, the addition of levodopa has a greater beneficial effect (Gauntlett-Gilbert and Brown 1998; Robbins and Brown 1990). It has been suggested that as the supply of dopamine becomes limited it affects fast latencies first, then as the levels fall further slower reaction time become affected (Robbins and Brown 1990). In our study, it is possible that the anti- Parkinsonian medication taken by patients with PD may overdose some

dopaminergic networks in the brain, exceeding an optimal threshold and resulting in slower performance.

In addition, the slowed reflexive baseline performance found in our study may be related to current medication practices. Specifically, dopamine agonists are becoming a more popular and common treatment in PD. Dopamine agonists achieve peak plasma levels rapidly (1–4 h) with complete clearance taking 2–5 days (Deleu et al., 2002). Therefore, it is possible that residual dopamine agonists are responsible for the slowed reflexive baseline responding in our PD group, as three PD patient were taking a dopamine agonist (Briand et al., 2001; Hood et al., 2007; Briand et al., 2012). Previous study suggested that addition of an agonist did not further change the effect of levodopa on an antisaccade task (Clerits et al., 2000). Therefore, even if our patients had a novel baseline performance due to residual agonists, the medication effects we report are likely attributable to LED alone (Hood et al., 2007).

Since the 1980s it has been appreciated that dopamine can worsen some cognitive functions while improving others (Gotham et al. 1988), and there is evidence for a number of frontostriatal circuits that can be differentially affected by dopamine. In particular, it seems that tests of neuropsychological function related to the dorsolateral prefrontal cortex improve with dopamine, whereas ventrolateral and orbitofrontal functions deteriorate (Cools et al. 2001, 2003; Swainson et al. 2000).

In summary, we have shown in this study that dopaminergic treatment affects the distribution of saccadic latencies in patients with advanced Parkinson's disease. Anti- Parkinsonian medication increased mean latency of reflexive prosaccades and incorrect prosaccades in

antisaccade task. This finding could indicate that the increase of latency occurs because it increases the threshold criterion level of evidence required before a decision to move is made. In addition, dopaminergic treatment did not suppress incorrect prosaccades during the antisaccade task. There was no improvement for voluntary cognitive processes in advanced stage PD. The impaired suppression of reflexive saccades in antisaccade task may be explained of increased SC inhibition and reduced pre-oculomotor drive due to dysfunctional frontal cortex-BG-SC circuit. However, the exact site of action of dopaminergic treatment in the control of saccadic eye movements is not clear and requires further research. Dopamine can have diverse effects on different functions of the brain that may or may not be anatomically distinct. Future research, with greater sample may point out what aspects of saccadic eye movements (reflexive, voluntary) are affected by dopaminergic treatment. The effect on latency seems to be dependent on the testing paradigm (simple 'reflexive' latency vs 'voluntary' latency), the dopaminergic tone, which in turn depends on the severity of PD and age of onset of the disease and the dose of replacement therapy.

Conclusion

The aim of this study was to examine the effects of dopaminergic treatment in inhibition of saccadic eye movements in advanced state of idiopathic PD. Executive function was measured through eye movements, reflexive prosaccades and voluntary antisaccades. Dopaminergic treatment was found to prolong reflexive prosaccadic latency and incorrect prosaccadic latency in antisaccade task. However, dopaminergic treatment did not suppress incorrect prosaccades during the antisaccade task. There was no improvement for voluntary cognitive processes in advanced stage PD. The results suggest that dopaminergic treatment

affects both reflexive and voluntary saccades. The impairment in reflexive and voluntary saccades may be caused by the excessive inhibition of the SC due to the increased BG output and the decreased activity of the frontal cortex-BG circuit. The impaired suppression of reflexive saccades in antisaccade task may be explained of increased SC inhibition and reduced pre-oculomotor drive due to dysfunctional frontal cortex-BG-SC circuit. Changes in saccade parameters suggest that frontal cortex-BG circuit activity decreases with disease progression.

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