“Levodopa slows prosaccades and improves antisaccades: An eye movement study in Parkinson’s disease”

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ABSTRACT

Background: The integrity of frontal systems responsible for voluntary control and their interaction with subcortical regions involved in reflexive responses are studied in Parkinson’s disease (PD) patients. Previous studies have shown PD patients have impaired executive function including deficits in attention, motor planning, and decision-making.

Methods: Executive function was measured through eye movements: reflexive (stimulus-driven) prosaccades and voluntary (internally-guided) antisaccades. Patients with advanced idiopathic PD, OFF and ON their optimal levodopa therapy, were tested on a prosaccade and an antisaccade task and compared to matched controls.

Results: Levodopa significantly increased response time for reflexive prosaccades and reduced error rate in voluntary antisaccades.

Conclusions: Consistent with our proposed model, PD patients in the medicated state are better able to plan and execute voluntary eye movements. These findings suggest levodopa improves function of the voluntary fronto-striatal system, which is deficient in PD.

Keywords: Parkinson’s disease, dopamine, saccade, executive function, prefrontal cortex.
Parkinson’s disease (PD) is identified by a series of motor abnormalities caused by dopaminergic disruption in the basal ganglia. And, the basal ganglia have many diverse connections with several brain regions, including frontal cortical areas responsible for executive function and other cognitive processes. Therefore, PD patients can develop a wide range of cognitive difficulties (e.g., dementia, psychosis, depression), and imaging shows PD patients tend to have decreased activity in the prefrontal cortex.[1,2] The most common medical treatment of PD, levodopa/carbidopa, helps replenish the lack of dopamine and reduces tremor, rigidity, and other common motor symptoms, but what effect does levodopa have on cognition? Recent work has shown levodopa to have both deleterious and beneficial effects on cognition of PD patients.[3-7] Some researchers conclude dopaminergic medication may improve certain types of neuropsychological performance and hinder others because the brain regions involved are differentially affected by dopamine.[3] A reasonable hypothesis is brain regions have an optimal dopamine level, and shifts from the norm can impair some tasks/measures while enhancing others. Therefore, the present study measures the effect of levodopa on two saccade tasks with dissociable neural substrates.

The analysis of saccades is increasingly used for studying cognition and memory.[8] Saccade circuitry is clearly understood, and saccades possess dynamic properties that are easily measured noninvasively.[9,10] It is clear from recent imaging studies that the physiological substrates for spatial attention (covert orienting) and saccades (overt orienting) overlap in many brain regions.[11] Moreover, recent work has shown a similar pattern of dysfunction across overt and covert orienting in various clinical populations, suggesting saccades may be a useful tool to evaluate higher cognitive functions.[12,13]

Our Tonic Inhibition Model of orienting proposes there is a voluntary system (prefrontal cortex and basal ganglia) exerting tonic inhibition on a reflexive system (SC and
brainstem); the voluntary system modulates reflexive saccades and attention.[14] Typical paradigms testing this model are the prosaccade (reflexively look at the stimulus) and the antisaccade (inhibit the reflexive response and voluntarily look AWAY from the stimulus).

In the Tonic Inhibition Model, a deficit in the voluntary system would predict both impaired performance in voluntary saccades and decreased inhibition of reflexive saccades (e.g., more errors in an antisaccade task and/or shorter latencies for reflexive saccades). Such a baseline pattern has been found in pathologies that involve frontal dysfunction such as schizophrenia, PD, autism, and ADHD.[e.g., 8,15-20]

Saccades have rarely been used to test the effects of levodopa in PD. Therefore, we test PD patients in a moderately advanced stage of the disease on a voluntary antisaccade task and a reflexive prosaccade task to measure the effects of levodopa on executive function. Further, each task will contain both gap and overlap trials to maximize task sensitivity.[12] The present study has two main hypotheses: 1) levodopa will improve performance on the antisaccade task due to improved frontal lobe function; 2) levodopa will enhance the tonic inhibition of the reflexive system, consequently slowing performance on the reflexive prosaccade task. Finally, a control group is included to evaluate levodopa’s ability to normalize voluntary and reflexive performance.

METHODS

Participants

Parkinson’s disease (PD) patients recruited from the University of Texas Movement Disorders Clinic, had been diagnosed with PD based on the CAPIT Diagnostic Criteria for PD, responded to levodopa, and had reached a steady dosing schedule before testing (Table 1). Patients with atypical parkinsonism or dementia were excluded. Both the Control and PD groups were required to have a Mini Mental State Exam (a general screening for severe dementia) score of at least 26/30, normal or corrected-to-normal
vision, and no history of substance abuse exceeding five years. The controls were recruited from the community via pre-approved advertisements. Each participant gave informed consent before enrollment, and this study was approved by the Committee for the Protection of Human Subjects at our institution in accordance with the Declaration of Helsinki.

The final groups contained 14 PD patients and 14 Controls; there were no statistical differences between the groups in terms of gender, age, or education (Table 1).

**Table 1. Participant Demographics and Clinical Measures**

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Education (years)</th>
<th>MMSE Average</th>
<th>Disease length</th>
<th>H&amp;Y</th>
<th>S&amp;E</th>
<th>UPDRS (motor) Off / On</th>
<th>Medications</th>
</tr>
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<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>61</td>
<td>15</td>
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<td>40</td>
<td>76/70</td>
<td>7.9 L, E, R</td>
</tr>
<tr>
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<td>16</td>
<td>27</td>
<td>20</td>
<td>3.5</td>
<td>60</td>
<td>32/29</td>
<td>9.4 L, E, P</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>61</td>
<td>4</td>
<td>29.5</td>
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</tr>
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<td>83.3 L, P</td>
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<td>70</td>
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<td>60.0 L, P</td>
</tr>
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<td>29.5</td>
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<td>63/34</td>
<td>46.0 L, P</td>
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<td>49.2 A, L, P</td>
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<td>3.5</td>
<td>60</td>
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<td>4</td>
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<td>70</td>
<td>54/41</td>
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<td>26</td>
<td>16</td>
<td>3.0</td>
<td>80</td>
<td>29/25</td>
<td>13.8 L</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>66</td>
<td>17</td>
<td>27</td>
<td>25</td>
<td>2.5</td>
<td>80</td>
<td>54/35</td>
<td>35.2 L, E, R</td>
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<td>Avg.</td>
<td></td>
<td>59.93</td>
<td>11.57</td>
<td>27.89</td>
<td>14.71</td>
<td>3.6</td>
<td>61.54</td>
<td>56/31* 41.0</td>
<td></td>
</tr>
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</table>

* p < .01 PD-ON is better than PD-OFF

<table>
<thead>
<tr>
<th>Controls</th>
<th>Avg.</th>
<th>Avg.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=14</td>
<td>57.79</td>
<td>14.21</td>
<td></td>
</tr>
</tbody>
</table>

MMSE: Mini Mental State Exam  H&Y: Hoehn and Yahr  S&E: Schwab and England  UPDRS: Unified Parkinson Disease Rating Scale => **Bold % Change** = clinically significant improvement (>20%).  A = Amantadine HCl  E = Entacapone  L = Carbidopa/Levodopa  P = Paramipexole dihydrochloride  Pe = Pergolide  R = Ropinirole HCl

**Procedure**

Each participant was tested on one day; the controls were tested once, and the patients twice. Previous work in our lab shows re-test on these tasks does not affect performance.[21] The PD group was first tested in the OFF state (at least 12 hours after...
the last levodopa dose [22]) and then in the ON state (when patient and neurologist agreed the medication was in full effect [23]; 0.5 to 2 hours after dose). Because many patients came from long distances, it proved difficult to bring them back in a timely fashion for a second testing session, so medication states were not randomized.

The behavioral testing took 30 to 45 min for each session, and the PD patients had a break between sessions to take medication. Also, a neurologist conducted a battery of clinical measures, including the Hoehn & Yahr Rating Scale, Schwab & England Activities of Daily Living Scale, and Unified Parkinson Disease Rating Scale version 3.0 to evaluate disease severity, functional capacity, and disease state, respectively. Table 1 shows the individual scores.

**Apparatus & Tasks**

Eye movements were recorded using an ISCAN RK-426 with an infrared-sensitive camera, which has a spatial resolution of 0.5° visual angle and a temporal resolution of 6 ms. The participant placed his/her head on a chin rest, and the apparatus was calibrated for each participant. The display was black with a gray fixation point in the center, and the targets were presented at 7° eccentricity. Variable fixation intervals (400 or 800 ms) before target onset helped prevent anticipations.

Each task contained 96 trials that balanced overlap and gap trials and left and right targets. During overlap trials, the fixation point remained visible for the entire trial. During gap trials, the fixation point was removed 183 ms before target onset (Figure 1). The task sessions were counterbalanced such that half the participants performed the Prosaccade task first, and each PD patient retained his/her same order for both sessions. There was no statistical difference between counterbalance orders.

In the Prosaccade (PS) task, the fixation point was presented at the beginning of the trial, the participant was required to maintain fixation and make a speeded saccade toward
the target when it appeared. The Antisaccade (AS) task was identical to the PS task in stimulus presentation; however, the participant had to make a saccade to the visual field opposite the target. The AS requires considerably more cognitive load than the PS because the participant is required to 1) inhibit the reflexive draw to look at the stimulus, and 2) generate a voluntary saccade away from the stimulus to blank space (Figure 1).

**Insert Figure 1 here.**

**Dependent Measures & Analyses**

Error rate is the proportion of incorrect trials. A saccade was correct if the eye position fell within 4.4° of the correct spatial location. When an error occurred, visual feedback (“Wrong Location”) was displayed for 500 ms.

Response time is the latency to initiate a saccade (above 120°/s) after target onset. If no eye movement was made within 1000 ms, visual feedback (“Too Slow”) was presented, and that trial was aborted and randomly presented again. Only response times for correct saccades were included in the analyses.

Gain (amplitude) is the ratio of saccade size (distance to the first saccade endpoint) to distance of the target from the fixation point. Gain below and above 100% reflects an undershot and overshoot target, respectively.

Only trials with latencies between 100 ms and 900 ms were included for analysis. This removed anticipations and akinetic responses (only 8% of the data). Secondly, we checked group data for outliers (in a pair-wise fashion) and instead of complete removal, we replaced any (only 1.6%; within random variation) with the group mean for our analyses. Statistical tests were considered significant at $\alpha = .05$. Group means are listed in Table 2.

**PD Medication Effects Analyses**

We used a three-way within-subject repeated measures analysis of variance (ANOVA) with Task (PS, AS), Fixation Procedure (overlap, gap), and Medication State (OFF, ON) for
the PD patients to measure within-subject medication effects. To test specific hypotheses comparing OFF and ON medication results, we ran planned two-tailed $t$-tests using the mean square error (MSE) of the three-way interaction from this within-subject ANOVA. The within-subject MSE for each dependent measure is listed in Table 2.

Control versus PD Analyses

To analyze the baseline PD deficit and the normalizing properties of levodopa, we used a three-way between-subject repeated measures ANOVA using Task (PS, AS) and Fixation Procedure (overlap, gap) as within factors and Condition (PD-OFF, PD-ON, Control) as the between factor. To test specific hypotheses comparing the Conditions, we ran planned two-tailed $t$-tests using the MSE of the three-way interaction from the between-subject ANOVA. The between-subject MSE for each dependent measure is listed in Table 2.

### Table 2. Group Means for Tasks and Dependent Measures

<table>
<thead>
<tr>
<th>Error Rate (%)</th>
<th>PD Patients</th>
<th>Controls</th>
<th>within-subject MSE</th>
<th>between-subject MSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosaccade –</td>
<td>Overlap</td>
<td>2.8</td>
<td>2.0</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Gap</td>
<td>1.9</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Antisaccade –</td>
<td>Overlap</td>
<td>35</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Gap</td>
<td>50</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>Response Time (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosaccade –</td>
<td>Overlap</td>
<td>314</td>
<td>357</td>
<td>287</td>
</tr>
<tr>
<td></td>
<td>Gap</td>
<td>274</td>
<td>300</td>
<td>234</td>
</tr>
<tr>
<td>Antisaccade –</td>
<td>Overlap</td>
<td>579</td>
<td>571</td>
<td>426</td>
</tr>
<tr>
<td></td>
<td>Gap</td>
<td>497</td>
<td>529</td>
<td>364</td>
</tr>
<tr>
<td>Gain (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosaccade –</td>
<td>Overlap</td>
<td>89</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Gap</td>
<td>88</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>Antisaccade –</td>
<td>Overlap</td>
<td>79</td>
<td>73</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>Gap</td>
<td>80</td>
<td>72</td>
<td>105</td>
</tr>
</tbody>
</table>

**RESULTS**

**Clinical Measures**

The seemingly variable UPDRS scores did not contain outliers, and the UPDRS-motor scores improved significantly with medication (Table 1).
Error Rate

PD Medication Effects

*Within-subject ANOVA*: There was a significant main effect of Medication State, and a significant interaction of Medication State x Task such that PD patients made fewer errors ON medication (versus OFF) on the AS task (with no effect for the PS).

*Planned t-Tests*: For the PS task, there were no significant effects of medication on error rate (Figures 2A, 2B). However, for the AS task, patients were significantly improved (fewer errors) when ON medication (Figures 2C, 2D).

**Insert Figure 2 here.**

Control versus PD

*Between-subject ANOVA*: There were significant main effects of both Task and Fixation Procedure, indicating all participants made more errors on the AS task (versus the PS) and gap trials (versus overlap), respectively. There was also a significant interaction of Task x Fixation Procedure such that participants had the most errors on the AS gap trials. Further, there was a significant interaction of Task x Condition with Controls having fewer errors than PD-ON, and PD-ON having fewer errors than PD-OFF on the AS task (no group differences for the PS).

*Planned t-Tests*: The PD patients (OFF and ON medication) were statistically unimpaired on the PS task (Figures 2A, 2B). In contrast, the PD patients (OFF and ON medication) made significantly more errors than Controls on the AS task (Figures 2C, 2D).

Error Rate Summary

PD patients were impaired (more errors than Controls) on only the AS task, and levodopa medication improved (but did not normalize) their performance.
Response Time

PD Medication Effects

*Within-subject ANOVA*: There was a significant interaction of Task x Fixation Procedure x Medication State, indicating levodopa slowed PD patient responding on each task except AS overlap.

*Planned t-Tests*: For the PS task, patients were significantly slower to respond when ON medication (versus OFF; Figures 3A, 3B). For the AS task, medication slowed response time for only the gap trials (no effect for AS overlap; Figures 3C, 3D).

Insert Figure 3 here.

Control versus PD

*Between-subject ANOVA*: There were significant main effects for both Task and Fixation Procedure, indicating all participants were slower to respond on the AS task (versus the PS) and overlap trials (versus gap), respectively. There was also a significant interaction of Task x Condition indicating there was a larger response time difference between the Control and PD groups on the AS task (versus the PS).

*Planned t-Tests*: Compared to Controls, PD patients OFF medication were normal for the PS overlap, but they became significantly slower ON medication (Figure 3A). However, PD patients (in both medication sates) were significantly slower than Controls on PS gap, AS overlap, and AS gap (Figures 3B – 3D).

Response Time Summary

Compared to Controls, PD patients OFF levodopa were slower to respond (except on PS overlap), and levodopa slowed them further (except on AS overlap).

Gain

PD Medication Effects

*Within-subject ANOVA*: There were no significant main effects or interactions.
**Planned t-Tests**: There was only a significant medication effect for AS gap (Figure 4D), such that levodopa shortened saccade amplitude on this task.

**Insert Figure 4 here.**

Control versus PD

**Between-subjects ANOVA**: There was a significant main effect of Task such that all participants were more accurate on the PS task (versus the AS). In addition, there was a significant interaction of Task x Condition indicating there was a larger difference in gain between the Control group and the PD group on the AS task (versus the PS).

**Planned t-Tests**: The PD patients (OFF and ON medication) had significantly lower gain than Controls on all tasks (Figure 4).

**Gain Summary**

PD patients had abnormally short saccades that undershot the target, and levodopa reduced gain amplitude further on the AS gap trials.

**Correlations**

We did not find any significant correlations between behavioral and clinical variables for the PD patients.

**Additional Analysis**

We performed a sign test to investigate whether the main medication effects reported in this paper – increased response time for prosaccades and decreased error rate for antisaccades in the ON state – truly predicted each patient’s behavior. Ten patients showed this pattern of results and four did not; when compared, the result was highly significant ($\chi^2 = 13.71, p < .001$). Thus, in most PD patients, levodopa slowed prosaccades and reduced antisaccade errors concurrently.
DISCUSSION

Summary

We examine the effects of levodopa on cognition (specifically, executive function) by measuring eye movements in Parkinson’s disease patients. Briefly, at OFF-levodopa baseline, the PD group was significantly impaired (high error rate) on the voluntary task and normal or slow on the reflexive task. Upon taking levodopa, voluntary performance improved (decreased error rate), and reflexive performance slowed further. This concurrent change in error rate and response time could be evidence of levodopa strengthening voluntary cognitive processes. Additionally, patients undershot the targets (low gain) on both voluntary and reflexive tasks, and levodopa did not improve this deficit.

Levodopa Improves Voluntary Saccades

To our knowledge, this is the first study to report antisaccade improvement in PD with levodopa, and it is consistent with a previous study of improved voluntary memory saccades in PD.[24] The Tonic Inhibition Model suggests the improvement in voluntary performance (executive function) we report could be due to improved generation of a voluntary response and/or improved voluntary inhibition of inappropriate reflexive responses.[14] Some researchers suggest these two processes can be anatomically dissociated, and levodopa could primarily affect only one of these processes.[e.g., 3,8,10] Thus, a decrease in antisaccade errors with medication might be a direct measure of improvement in response generation. On the contrary, based on the fact that we see only reduced errors (without benefit for latency or gain), one might conclude levodopa is likely strengthening inhibition of reflexive behaviors.

Levodopa Slows Reflexive Saccades

When given levodopa, the normal or slow prosaccade response time of our patients increased significantly. There is no previous report of slowed reflexive saccades with
medication in PD. Some previous PD studies reported patients with hyper-reflexive (faster than Controls) baseline orienting.[e.g., 12,15,25] So, in those studies, a levodopa-slowing effect might have been beneficial for patients’ reflexive responding.

**Influence of Dopamine Agonists?**

The present study’s slowed reflexive baseline performance (which contrasts with some previous findings) may be related to current medication practices. Specifically, dopamine agonists are becoming a more popular and common treatment in the United States. Dopamine agonists achieve peak plasma levels rapidly (one to four hours) with complete clearance taking two to five days.[26] Therefore, it is possible residual dopamine agonists are responsible for the hypo-reflexive baseline responding in our PD group, as all but one PD patient were taking a dopamine agonist.[12,15] One previous study suggested that addition of an agonist did not further alter the effect of levodopa on an antisaccade task.[27] Therefore, even if our patients had a novel baseline performance due to residual agonists, the medication effects we report are likely attributable to levodopa alone.

**Levodopa & Prefrontal Cortex**

Decreased voluntary eye movement control has been reported in several pathologies involving prefrontal cortex dysfunction (e.g., schizophrenia, autism, ADHD, PD [e.g., 8,15-20]). In our study we find evidence for improved prefrontal executive function shown by both improved voluntary antisaccades and slowed reflexive saccades after levodopa administration. Therefore, our results may have ramifications for other patient populations with executive dysfunction who are treated with dopamine antagonists (e.g., schizophrenia).

**Gap & Overlap Conditions**

Our previous work has shown that PD saccade latency (compared to Controls) was significantly reduced in a reflexive saccade task with fixation overlap.[12] Here, we only
found significant differences in medication effects between fixation conditions for the AS task. Specifically, on the AS task with gap we observed error rate improvement with levodopa, but worse (slower) response time. Although it is possible that levodopa is independently and oppositely affecting error rate (voluntary inhibition) and response time (voluntary generation) on the AS gap trials, we cannot rule out a simple speed-accuracy trade-off. The AS overlap had no such trade-off; levodopa unambiguously improved voluntary performance on AS overlap trials. Future studies are needed to better understand these differences in medication effects across fixation conditions.

**CONCLUSION**

We demonstrate for the first time in advanced PD patients that levodopa can improve voluntary cognitive performance while concurrently slowing reflexive performance. Our results suggest levodopa may have significant impact on neural substrates of executive function involved in planning and executing voluntary behaviors.
ACKNOWLEDGEMENTS

The authors would like to thank Dr. Stanley Fisher, Dr. Robert Izor, and the staff associated with the University of Texas Movement Disorders Clinic for their help recruiting patients.

COMPETING INTERESTS

The authors report no competing interests.

FUNDING

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REFERENCES


FIGURE LEGENDS

Figure 1. Schematic representation of the stimulus sequences used in the two tasks (Prosaccade and Antisaccade) with two fixation trial-types (overlap and gap). Total fixation time was 400 or 800 ms; in the gap trials the fixation point was removed 183 ms before target presentation.

Figure 2. Error Rate Group Means. A & B: PD-OFF and PD-ON are equal, and both PD conditions are as accurate as Controls on Prosaccade overlap and gap. C & D: PD-ON makes fewer errors than PD-OFF, and Controls make fewer errors than both PD conditions on Antisaccade overlap and gap. ***, $p < .001$; error bars, SEM.

Figure 3. Response Time Group Means. A & B: PD-OFF is slower than Controls on Prosaccade gap. PD-ON is slower than PD-OFF and Controls on Prosaccade overlap and gap. C & D: PD-ON is slower than PD-OFF on Antisaccade gap. Both PD conditions are slower than Controls on Antisaccade overlap and gap. *, $p < .05$; ***, $p < .001$; error bars, SEM.

Figure 4. Gain Group Means. A & B: PD-OFF and PD-ON are equal, and both PD conditions make smaller amplitude saccades than Controls on Prosaccade overlap and gap. C & D: PD-ON has smaller gain than PD-OFF on Antisaccade gap. Both PD conditions make smaller amplitude saccades than Controls on Antisaccade overlap and gap. *, $p < .05$; **, $p < .01$; ***, $p < .001$; error bars, SEM.