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# Differential benefits of olanzapine on executive function in schizophrenia patients: Preliminary findings

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## Abstract

**Objective:** Schizophrenia patients show executive function (EF) impairments in voluntary orienting as measured by eye-movements. We tested 14 inpatients to investigate the effects of the antipsychotic olanzapine on EF, as measured by antisaccade eye-movement performance.

**Methods:** Patients were tested at baseline (before olanzapine), 3–5 days post-medication, and 12–14 days post-medication. Patients were also assessed on the Positive and Negative Syndrome Scale (PANSS) to measure the severity of schizophrenia-related symptoms, and administered the Stroop task, a test of EF. Nine matched controls were also tested on the antisaccade and Stroop.

**Results:** Both groups showed improvement on Stroop and antisaccade; however, the schizophrenia group improved significantly more on antisaccade, indicating an additional benefit of olanzapine on EF performance. Patients with poorer baseline antisaccade performance (High-Deficit) showed significantly greater improvement on the antisaccade task than patients with better baseline performance (Low-Deficit), suggesting that baseline EF impairment predicts the magnitude of cognitive improvement with olanzapine. These subgroups showed significant and equivalent improvement on PANSS scores, indicating that improvement on the antisaccade task with olanzapine was not a result of differences in magnitude of clinical improvement.

**Conclusions:** This preliminary study provides evidence that olanzapine may be most advantageous for patients with greater baseline EF deficits.

KEYWORDS

antipsychotics, antisaccade task, cognitive heterogeneity, executive function, eye-movements, Stroop task

## 1 | INTRODUCTION

In addition to prominent clinical symptoms (e.g., hallucinations), schizophrenia patients commonly have cognitive impairments, which include deficits in attention, verbal and spatial working memory, and executive function (Hartman, Steketee, Silva, Lanning, & McCann, 2003; Orellana & Slachevsky, 2013). Most schizophrenia patients show such cognitive deficits (Keefe & Fenton, 2007), indicating that cognitive impairment is a core feature of the disorder (Bowie & Harvey, 2006). Cognitive impairments are thought to be present before clinical and psychotic symptoms emerge (Lencz et al., 2006; Vöhringer et al., 2013). Executive function deficits, in particular, can be useful for predicting functional outcome, such as attending work or participating in community activities (Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009), and thus, are important to consider when treating patients (Gold, 2004).

  

Antipsychotic medications have shown variable effects on cognition (for review see Meltzer, 2013). Typical antipsychotics have prominent antagonistic effects on the D2 dopamine receptor, thus alleviating many of the psychotic symptoms associated with schizophrenia. However, their effectiveness in improving cognitive dysfunction in schizophrenia is variable, due in part to dosage and differences in their binding profiles (Mishara & Goldberg, 2004; Woodward, Purdon, Meltzer, & Zald, 2007). The variability in medication effects on cognitive dysfunction may also reflect heterogeneity among patients. For example, we have previously shown that the typical antipsychotic haloperidol improved executive function in cognitively impaired patients, while worsening performance in nonimpaired patients (Babin et al., 2011; Larrison-Faucher, Matorin, & Sereno, 2004). Despite the efficacy of typical antipsychotics in reducing the severity of psychotic symptoms, there are several drawbacks to these medications, including extrapyramidal (i.e., parkinsonian) side effects (Tenback, van Harten, Slooff, & van Os, 2006) and tardive dyskinesia. These motor impairments are one key reason why typical antipsychotics are less commonly prescribed today than atypical antipsychotics, despite their well-established clinical efficacy in alleviating positive schizophrenia symptoms.

Like typical antipsychotics, atypical antipsychotics block transmission at the D2 receptor, and are as effective as typical antipsychotics at alleviating psychotic symptoms, but with much less motor impairment (Leucht et al., 2013). Atypicals also improve various types of cognitive deficits, such as verbal fluency, working memory, and attention (Bilder et al., 2002; O'Grada & Dinan, 2007; Purdon et al., 2000), although the magnitude of the cognitive benefits appear to be modest (Hill, Bishop, Palumbo, & Sweeney, 2010). Unlike typical antipsychotics, atypicals, such as olanzapine, also have a strong affinity for various serotonin receptors; activation of these receptors has been associated with improvement in several domains of cognition (Meltzer & Massey, 2011). These receptor binding profiles have been implicated in their beneficial effects on cognitive processing while reducing motor side effects (Leucht et al., 2013).

The beneficial cognitive effects of atypical medications make them an appealing choice for treating schizophrenia (Wang et al., 2013). However, the increased risk for deleterious metabolic side effects (i.e., weight gain, increased risk for Type II diabetes) of some atypicals such as olanzapine (OLZ; Rummel-Kluge et al., 2010) underscores the importance of clarifying its effects on cognition function. The effect of OLZ on cognition in schizophrenia patients shows mixed results (Hill et al., 2010). Some research demonstrates cognitive advantages of OLZ compared with other typical and atypical drugs (McGurk, Lee, Jayathilake, & Meltzer, 2004), and some studies show similar benefits (Tybura et al., 2013) of OLZ on performance on measures of cognition, including on eye-movement paradigms (Broerse, Crawford, & den Boer, 2002; Trillenberg, Lencer, & Heide, 2004).

A better understanding of the cognitive improvement associated with atypicals is important because executive function performance is the best predictor of long-term outcome in schizophrenia patients (Bowie & Harvey, 2006; Green, 2006; Kahn & Keefe, 2013). Eye-movement tasks are a fast and sensitive technique for assessing sensorimotor and executive function in psychiatric patients compared with controls (Benson et al., 2012). The antisaccade task is used to measure impairments in executive function. Schizophrenia patients consistently have a higher rate of antisaccade errors than controls (Levy, Mendell, & Holzman, 2004; Light et al., 2012; Reuter & Kathmann, 2004). Performance on the antisaccade task depends on several processes, including aspects of executive functioning such as voluntary motor planning and programming and cognitive control (inhibitory control) as well as aspects of cognition such as memory (Amador, Hood, Schiess, Izor, & Sereno, 2006; Everling & Fischer, 1998). However, a recent model suggests that antisaccade performance need not depend on a top-down inhibitory signal suppressing the erroneous response (Cutsuridis, Kumari, & Ettinger, 2014). Cognitive processes such as inhibitory control, planning and programming, and memory are often thought to be independent and dissociable; however, previous work in schizophrenia (Fukushima et al., 1990) and other clinical disorders such as Parkinson's Disease (Briand, Strallow, Hening, Poizner, & Sereno, 1999) and autism (M. C. Goldberg et al., 2002) has shown that the processes of reflexive saccade inhibition and voluntary saccade generation are interdependent. That is, the separation of these two processes in time in the delayed antisaccade task facilitated the successful execution of the antisaccade (decreased antisaccade errors) (see Amador et al., 2006, for additional discussion). Finally, it has been long documented that schizophrenia patients are heterogeneous with respect to eye-movement performance (Levy, Holzman, Matthysse, & Mendell, 1993). Using the antisaccade eye-movement task, we previously showed that cognitively impaired schizophrenia patients benefited from the typical antipsychotic haloperidol, whereas nonimpaired patients showed a decline in cognitive performance with haloperidol (Babin et al., 2011). Given that only about 60% of schizophrenia patients show impaired performance on the antisaccade task (Larrison-Faucher et al., 2004) and that good and poor performing patients show different effects to substances such as nicotine or haloperidol on cognition (Babin et al., 2011; Larrison-Faucher et al., 2004), it is possible that the effects of OLZ on cognition may vary as a function of baseline cognitive performance.

In this study we examined the effects of OLZ on cognition by measuring executive function before and during treatment using the antisaccade and Stroop tasks. We hypothesize that OLZ will improve executive function deficits, as measured by a decrease in antisaccade error rate and improvement in scores on the Stroop task. We also examine whether the cognitive effects of OLZ vary as a function of baseline cognitive performance.

## 2 | MATERIALS AND METHODS

### 2.1 | Participants

All participants provided written informed consent in accordance with the Declaration of Helsinki and were enrolled into a study approved by the Committee for the Protection of Human Subjects, the Institutional Review Board at the University of Texas Health Science Center

at Houston. Fourteen inpatients with schizophrenia and 14 control participants were recruited for the study. The final sample included 14 inpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a diagnosis of schizophrenia by a board-certified psychiatrist and nine controls between 18 and 60 years old (see Babin et al., 2011 for recruitment and inclusion criteria). Four controls were excluded from statistical analyses due to incomplete data and one control was excluded for exceeding the age range. All schizophrenia patients had been off antipsychotic medications for a minimum of 3 weeks. The following tasks were administered at three different testing sessions: prior to starting daily OLZ medication (Day 0); after short-term (3–5 days) treatment with OLZ (Day S); and after long-term (12–14 days) treatment with OLZ (Day L). Control participants were not given any medication but were tested at the same three time intervals. These timepoints were chosen based on studies that showed significant clinical improvement with antipsychotics (including olanzapine) within 24 hr to 1 week after starting the medication (Mousavi, Rostami, Sharbafchi, Boroujeni, & Mahaki, 2013), and that more improvement occurred over the first two weeks than in any period thereafter (Agid, Seeman, & Kapur, 2006), including up to 1 year of treatment (Leucht, Busch, Hamann, Kissling, & Kane, 2005). Based on baseline performance on the antisaccade task (Day 0), schizophrenia participants were subdivided (median split) into low ($n$ = 7; Low-Deficit) and high ($n$ = 7; High-Deficit) cognitive deficit subgroups.

Demographic data for each group are shown in Table 1. The schizophrenia group had a significantly larger proportion of males than the control group ($X^2$ = 7.08, $df$ = 1, $p$ < .05). Both patient subgroups were also disproportionately male, but differed significantly from controls only for the Low-Deficit subgroup ($X^2$ = 6.35, $df$ = 1, $p$ < .005). There were no other demographic differences between the groups or subgroups. All medications of schizophrenia patients are listed in Table 2.

## 2.2 | Apparatus

An infrared ISCAN RK-826 PCI eye-tracking system (Babin et al., 2011; Patel, Jankovic, Hood, Jeter, & Sereno, 2012) was used to measure and record all saccadic eye-movements during the eye-movement tasks. During testing, participants rested their heads in a chin rest positioned and secured 72 cm away from a 17-inch CRT monitor. The spatial resolution of the eye-tracker was approximately 0.5° of visual angle, and the temporal resolution was 4 ms (240 Hz). Participants were calibrated before beginning the various eye-movement tasks. For the calibration, participants moved their eyes to nine 0.2° × 0.2° white boxes that were positioned on a black screen, and gains and biases were adjusted automatically with the calibration. Each eye-movement task involved fixating a grey fixation point subtending 0.2° of visual angle at the center of the screen, and the target stimuli were 0.2° × 0.2° white boxes that appeared 7° either to the right or left of the fixation point. For saccade initiation, eye velocity had to be above 47.5°/s, and for saccade termination, eye velocity had to be below 12°/s and within 4.4° of the correct target response location.

## 2.3 | Testing procedures

As described in Babin et al. (2011), eye-movement tasks (prosaccade, antisaccade) as well as measures to evaluate clinical symptomology (PANSS; Kay, Fiszbein, & Opler, 1987) and cognitive performance (Stroop test; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999) were completed.

### 2.3.1 | Eye-movement tasks

All schizophrenia participants were administered two eye-movement tasks (prosaccade and antisaccade; each comprised of 48 trials) at the three different testing sessions. Each task was preceded by a 10-trial practice block. Further, to ensure understanding of task instructions, each participant was asked to verbally explain the instructions before each task began. To begin a trial, the participant had to fixate a white spot located in the center of the dark screen for 600 ms. After successful fixation, a white target randomly appeared 7° to the left or right of fixation. The fixation point was extinguished simultaneously with the target presentation. For the saccade task, participants had to look at the peripheral target as quickly as possible, whereas for the antisaccade task, the participant had to look to the opposite side or

**TABLE 1** Demographic and baseline characteristics

| Variable | Schizophrenia ($N$ = 14) | Low-deficit ($N$ = 7) | High-deficit ($N$ = 7) | Control ($N$ = 9) |
|---|---|---|---|---|
| Age (year, SD) | 36.9 (12.5) | 38.3 (12.3) | 35.6 (11.7) | 38.0 (6.3) |
| Education (years, SD) | 11.6 (1.7) | 11.6 (1.0) | 11.6 (2.1) | 12.6 (1.2) |
| Handedness (right, %) | 11 (79%) | 5 (71%) | 6 (86%) | 8 (89%) |
| Smoking (yes, %) | 9 (64%) | 5 (71%) | 4 (57%) | 3 (33%) |
| Gender (male, %) | 11 (79%)* | 6 (86%)* | 5 (71%) | 2 (29%) |
| Age of onset (years, SD) | 29.8 (11.0) | 27.9 (7.6) | 31.7 (12.6) | – |
| Duration of illness (years, SD) | 7.2 (6.9) | 10.7 (7.7) | 3.8 (3.6) | – |

*Note*: Comparison to controls: *$p$ < .05.

**TABLE 2** Medications of schizophrenia patients with all dosages shown per testing session

| Subjects | Age | Medications | | |
|---|---|---|---|---|
| | | Day 0 | Day S | Day L |
| **Patients** | | | | |
| *Low-Deficit* | | | | |
| 1 | 60 | H-5, A, B | O-20, V | Same as Day S |
| 2 | 26 | | O-20 | Same as Day S |
| 3 | 44 | | O-20 | Same as Day S |
| 4 | 20 | H-10, A | O-30 | Same as Day S |
| 5 | 36 | | O-30 | Same as Day S |
| 6 | 36 | | O-20 | Same as Day S |
| 7 | 46 | P, C | O-20 | Same as Day S |
| *High-Deficit* | | | | |
| 1 | 27 | | O-20 | Same as Day S |
| 2 | 53 | | O-20 | Same as Day S |
| 3 | 45 | | O-20 | Same as Day S |
| 4 | 24 | | O-10 | O-20 |
| 5 | 34 | | O-30 | Same as Day S |
| 6 | 46 | | O-20 | Same as Day S |
| 7 | 20 | | O-20 | Same as Day S |

Abbreviations: O-10, 10 mg olanzapine; O-20, 20 mg olanzapine; O-30, 30 mg olanzapine; A, 2 mg Ativan; H-10, 10 mg haloperidol; H-5, 5 mg haloperidol; V, 10 mg Vasotec; P, 5 mg Prolixin; C, 2 mg Cogentin; B, 50 mg Benadryl.

mirror location of the peripheral target as quickly as possible. The peripheral target remained on the screen until the eye-movement was completed. Trials that were interrupted by a blink were aborted and randomly re-presented. Visual feedback on performance was provided only after error trials.

*Latency*

Saccade latency, or response time (RT), was measured by the number of milliseconds it took for the eye to leave fixation after target onset. RTs for incorrect saccades were excluded from the RT analyses. Any RTs below 82 ms (considered nonphysiologically visually dependent and therefore anticipatory) and above 900 ms were excluded. In addition, any latencies that were 2.5 standard deviations outside of the condition mean for each individual participant and task, at each testing session were excluded. These trimming procedures removed 5.2% of trials for schizophrenic patients and 1.8% of trials for the control group. Average RT for each participant, for each eye-movement task, at each testing session was then computed from all remaining trials.

*Error rate*

Error trials were defined as trials in which the participant's first saccade from the fixation did not land within the target location for the prosaccade task or opposite the target location for the antisaccade task (see Larrison et al., 2011 for details regarding saccade initiation and termination). Mean error rate was calculated as the number of errors divided by the total number of trials (48) for each participant, task, and time point. Errors on the prosaccade task are typically nonexistent or very small (see Table 3); therefore, error rates for the prosaccade task were not further analyzed due to the small number of prosaccade errors made in both schizophrenia and control groups. Antisaccade errors are more common and reflect a lack of cognitive control (failure to inhibit the stimulus-driven response and to generate a willful or voluntary response), with increased errors reflecting an executive function deficit.

### 2.3.2 | Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale (PANSS) is a 30-item scale that rates severity of positive and negative symptoms, as well as general psychopathology. Each item was given a score from 1 (absent) to 7 (severe), and then all items (for positive, negative, and general symptoms) were summed to give a total PANSS score, which was used in the analyses. Thus, a higher score indicates more severe symptomology. The test was administered to all of the schizophrenia patients within 24 hr of each of the three testing sessions.

### 2.3.3 | Stroop test

The Stroop test, a common neuropsychological test of frontal and selective attentional function, was also administered to all participants. To minimize known repetition effects (Davidson, Zacks, & Williams, 2003), it was given only on the Day 0 and Day L testing sessions. For this study, the "Naming Colored Words" variant of the test was used, and the performance on the Color-Word Interference task was specifically examined. In the Color-Word Interference task, the participant was required to name the color of the ink of as many items as possible in 45 s from a list of color words. The color words in the list were typed in a color different from the word that was printed (i.e., the word "blue" typed in red ink). The number of items named correctly was the reported score for each participant, and these scores were used in the analyses.

## 2.4 | Statistical analyses

### 2.4.1 | Comparison of schizophrenia and control groups

A mixed effect model was used to compare total PANSS scores across sessions (Day 0, Day S, and Day L) in the schizophrenia group. Planned comparisons were conducted to evaluate changes after short and long exposure to OLZ (Day 0 to Day S and Day 0 to Day L). Additionally, Color-Word Stroop Interference Scores were compared between Group (Schizophrenia and Control) and Session (Day 0 and Day L), and their interaction was analyzed using a mixed effect model.

**TABLE 3** Unadjusted eye-movement measures and clinical subscale scores

| | SZ (*n* = 14) | HD (*n* = 7) | LD (*n* = 7) | C (*n* = 9) |
|---|---|---|---|---|
| **Mean (SD) Latency (ms)** | | | | |
| *Prosaccade* | | | | |
| Day 0 | 226.9 (45.8) | 231.5 (54.3) | 222.4 (39.3) | 234.7 (31.1) |
| Day S | 228.9 (45.6) | 222.7 (53.7) | 235.2 (39.5) | 227.4 (25.8) |
| Day L | 236.2 (51.9) | 248.7 (53.5) | 223.7 (40.1) | 234.1 (25.8) |
| *Antisaccade* | | | | |
| Day 0 | 400.1 (81.6) | 374.1 (81.4) | 426.1 (78.9) | 358.9 (57.7) |
| Day S | 414.2 (106.2) | 385.8 (114.8) | 442.5 (96.7) | 333.6 (46.2) |
| Day L | 402.3 (61.6) | 392.9 (77.3) | 411.7 (45.3) | 356.5 (71.9) |
| **Error rate (%)** | | | | |
| *Prosaccade* | | | | |
| Day 0 | 3.1 (3.6) | 4.5 (3.7) | 1.8 (3.3) | 2.1 (2.6) |
| Day S | 2.8 (2.8) | 4.2 (3.2) | 1.2 (1.1) | 1.4 (2.9) |
| Day L | 1.8 (1.6) | 2.4 (1.9) | 1.2 (1.1) | 1.9 (3.4) |
| *Antisaccade* | | | | |
| Day 0 | 49.7 (17.8) | 64.6 (5.5) | 34.8 (11.8) | 14.8 (8.2) |
| Day S | 34.8 (11.2) | 37.8 (14.8) | 31.8 (5.9) | 11.1 (5.2) |
| Day L | 27.2 (13.5) | 32.7 (15.0) | 21.7 (9.9) | 5.1 (4.0) |
| **Stroop test** | | | | |
| *Word* | | | | |
| Day 0 | 69.3 (22.6) | 63.7 (22.1) | 74.9 (23.4) | 88.3 (9.9) |
| Day S | – | – | – | – |
| Day L | 70.4 (20.5) | 66.6 (18.2) | 74.3 (23.3) | 91.1 (13.5) |
| *Color* | | | | |
| Day 0 | 51.6 (12.2) | 47.7 (13.5) | 55.4 (10.2) | 62.8 (10.1) |
| Day S | – | – | – | – |
| Day L | 55.1 (9.8) | 52.9 (9.1) | 57.3 (10.8) | 68.3 (11.4) |
| *Color-Word* | | | | |
| Day 0 | 30.1 (7.0) | 26.9 (4.5) | 33.3 (7.9) | 35.7 (6.7) |
| Day S | – | – | – | – |
| Day L | 33.2 (7.2) | 32.6 (7.6) | 33.9 (7.3) | 41.0 (9.8) |
| **PANSS** | | | | |
| *Positive* | | | | |
| Day 0 | 24.8 (3.8) | 26.3 (2.2) | 23.3 (4.6) | – |
| Day S | 21.1 (3.2) | 21.0 (2.8) | 21.1 (3.8) | – |
| Day L | 16.4 (5.6) | 19.4 (3.6) | 13.3 (5.7) | – |
| *Negative* | | | | |
| Day 0 | 28.0 (6.5) | 29.0 (3.7) | 27.0 (8.7) | – |
| Day S | 24.4 (6.9) | 23.9 (3.0) | 25.0 (9.7) | – |
| Day L | 20.3 (7.5) | 23.3 (7.3) | 17.3 (6.8) | – |
| *General* | | | | |
| Day 0 | 48.0 (8.2) | 51.7 (4.1) | 44.3 (9.8) | – |
| Day S | 37.4 (8.9) | 38.9 (8.8) | 35.9 (9.5) | – |
| Day L | 33.1 (12.1) | 39.3 (12.1) | 27.0 (9.2) | – |

(Continues)

**TABLE 3** (Continued)

| | SZ (*n* = 14) | HD (*n* = 7) | LD (*n* = 7) | C (*n* = 9) |
|---|---|---|---|---|
| *Total* | | | | |
| Day 0 | 100.8 (15.8) | 107.0 (8.2) | 94.6 (19.6) | – |
| Day S | 83.6 (16.1) | 83.7 (13.3) | 82.0 (20.7) | – |
| Day L | 69.6 (23.5) | 82.0 (20.6) | 57.6 (20.5) | – |

Planned comparisons included the following: (a) between sessions (Day 0 to Day L) within group, and (b) changes in session (Day 0 to Day L) between groups (Schizophrenia and Control). The effect sizes were based on Cohen's *d*, which was calculated using estimated contrast/se*sqrt(*df* + 1) obtained from the mixed effect model.

Saccade latencies and antisaccade error rates were analyzed using mixed effect models with Group (Schizophrenia and Control), Session (Day 0, Day S, and Day L), and their interaction for each task. Planned comparisons were conducted when the interaction term was significantly different to compare (a) between sessions (Day 0 to Day S and Day 0 to Day L) for each group, and (b) changes in session (Day 0 to Day L) between groups (Schizophrenia and Control). All variables were adjusted by gender, if needed.

### 2.4.2 | Antisaccade error rate, Stroop, and PANSS score change across sessions versus baseline error rate

In order to test how baseline error rate was affected by medication regimen, we analyzed antisaccade error rates, Stroop, and PANSS scores using linear regression with the participants' baseline error rate as the independent variable, and the change in error rate, Stroop score, and PANSS score across testing sessions (Day 0 to Day L) as the dependent variable.

### 2.4.3 | Comparison of Low-Deficit versus High-Deficit schizophrenia subgroups

Given the known heterogeneity in the severity of cognitive deficits in the schizophrenia population, and our previous results indicating differential effects of haloperidol on antisaccade performance as a function of baseline cognitive performance (Babin et al., 2011), we divided the schizophrenia group (median split of baseline antisaccade performance) into two subgroups, Low-Deficit and High-Deficit, for further analyses. Patients with antisaccade error rates below the median Day 0 antisaccade error rate (56.25%; SD = 17.8), were considered Low-Deficit (*n* = 7; average 34.8% error rate, SD = 5.5), and patients with error rates above 56.25% were considered High-Deficit (*n* = 7; average 64.6% error rate, SD = 11.8).

Statistical analyses were performed similar to those described above with minor modifications. Namely, for the PANSS, a mixed effects model was run with Subgroup (High-Deficit subgroup, Low-Deficit subgroup) and Session (Day 0 and Day L). Planned comparisons were conducted if the corresponding main effect or interaction was statistically significant. The following planned comparisons were considered: (a) across testing sessions (Day 0 to Day L) for each subgroup, and (b) between subgroups across testing sessions (Day 0 to Day L). For the Stroop and eye-movement tasks, similar analyses and planned comparisons as described above for the PANSS and eye-movement tasks were conducted.

### 2.4.4 | Effect size and power

The primary analyses in this study are (a) to investigate treatment effect (between Day 0 and Day L) on antisaccade error rate in the schizophrenia group, and (b) to compare changes in antisaccade error rate from Day 0 to Day L between groups (Schizophrenia and Control). A previous report showed that mean antisaccade error rates at baseline (Day 0) in the schizophrenia and control groups were 52% (SD = 26%) and 15% (SD = 8%), respectively (Babin et al., 2011). In controls, antisaccade practice effects (test–retest) depend modestly on spacing and duration of the testing sessions, and were estimated to be a 5% reduction (from 21% reduced to 16%) when tested twice over a two month span (Ettinger et al., 2003), and a 6.3% reduction when tested twice over a two week span after daily practice (Dyckman & McDowell, 2005). Although the practice effect has not been studied in a schizophrenia group, it is reasonable to assume that the effect is around 10%, due to higher baseline error rate. A 26% (=50% of baseline) error rate reduction from the baseline due to the treatment, with an additional 10% practice effect, for a total of 36% (10% + 26%) reduction, in schizophrenia was considered a substantial (and effective) treatment effect within group. Assuming the SD of changes in error rates between two sessions is similar to the SD for the baseline, 26% in schizophrenia (Babin et al., 2011), seven schizophrenia participants were required for the primary analysis (1, above) at 80% power and 5% significance level. For primary analysis (2, above) a 25% difference in changes of error rates from Day 0 to Day L between groups was considered a substantial (and effective) treatment effect between groups. Assuming SD of changes are 26% and 8% for schizophrenia and control, respectively, 14 schizophrenia participants and 5 controls are required.

## 3 | RESULTS

Data were first summarized and reported as unadjusted means (Table 3; see also figures). There were small but significant differences in gender for some specific group comparisons. The statistical effects and interactions reported below are adjusted for gender.

### 3.1 | Schizophrenia and control group comparisons

#### 3.1.1 | PANSS

Raw PANSS scores averaged across all the schizophrenia patients and their standard deviations (SDs, in parentheses for all cells in the table) are reported in Table 3. The mixed effect model for PANSS score in the patient group revealed a significant main effect of Session ($F_{2,26}$ = 21.39, $p$ < .01), such that patients had the highest scores at the baseline time point (100.8), followed by the short time point (82.9), and then long time point (69.8) (Figure 1a). PANSS scores decreased significantly from Day 0 to Day S (17.9, Cohen's $d$ = 0.75; $t$(26) = 3.77, $p$ < .001) and from Day 0 to Day L (31.0, Cohen's $d$ = 1.3; $t$(26) = 6.51, $p$ < .001). These results show that severity of clinical symptomology improved significantly with both short term and longer-term olanzapine administration.

#### 3.1.2 | Stroop

Raw Stroop scores averaged across all the schizophrenia patients and their SDs are reported in Table 3. As illustrated in Figure 1b, the mixed effect model for Color-Word Stroop Interference scores revealed significant main effects for both Session ($F_{1,21}$ = 8.74, $p$ < .01) and Group ($F_{1,21}$ = 5.24, $p$ = .03; shown in figure) but no interaction effect between Session and Group ($F_{1,21}$ = 0.58, $p$ = .45). The control group

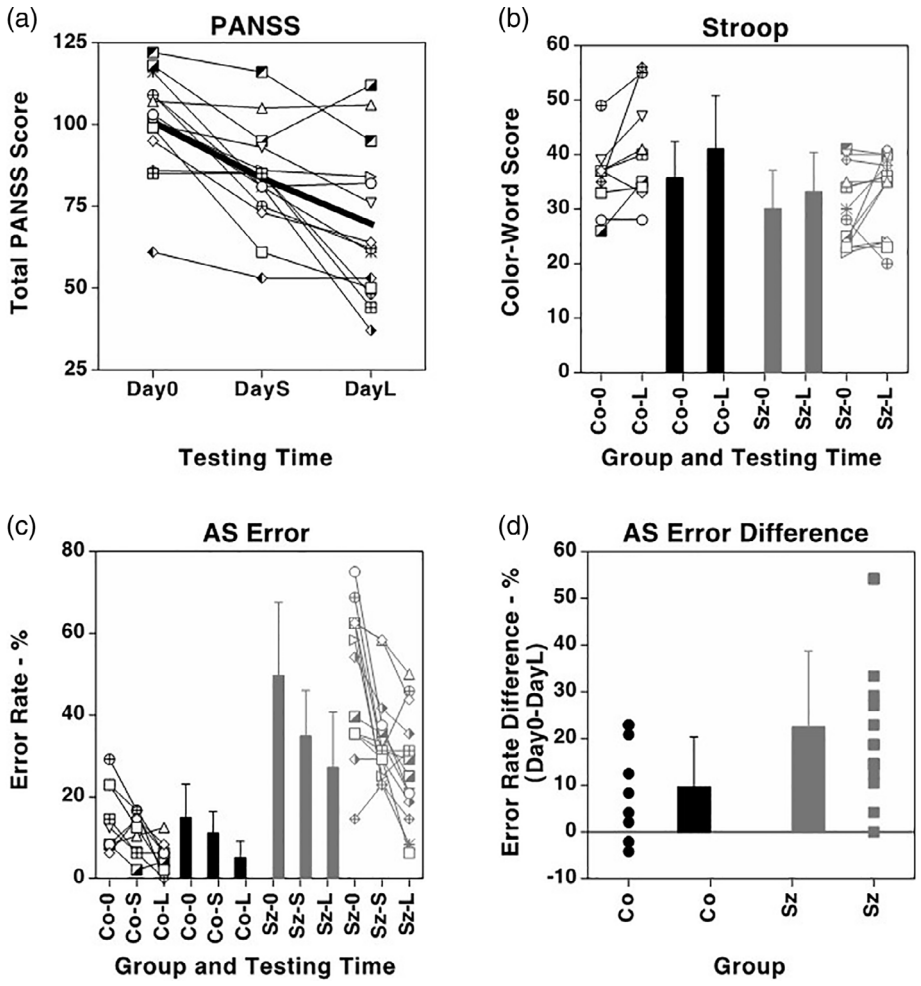


**FIGURE 1** Performance across session for schizophrenia and control groups. (a) PANSS total scores for individual subjects, schizophrenia group only, unadjusted. In this and other subpanels, each plot symbol represents the subject's identity. Clinical symptom severity as measured by the PANSS improved over both the short (Day 0–Day S) and longer (Day 0–Day L) time interval with administration of olanzapine. The thick black line represents the average data. (b) Color-Word Stroop scores, unadjusted. In this and other subpanels, each filled bar represents data averaged across subjects. Error bars in bar plots represent 1 standard deviation. Color-Word Stroop scores for control (dark symbols, lines and bars) and schizophrenia groups (light symbols, lines and bars) at baseline (Day 0) and long (Day L) testing sessions, showing a significant group main effect, with the session main effect not shown. (c) Antisaccade (AS) unadjusted error rates for control and schizophrenia groups and for different testing times. Mean AS error rate showing the main effect of session for the control and schizophrenia groups at baseline (Day 0), short (Day S), and long (Day L) testing sessions. (d) AS error rate difference from Day 0 to Day L for the control (dark symbols, bars) and schizophrenia (light symbols, bars) groups, indicating a significant difference between groups across sessions. Statistical convention: $^{\dagger}p$ < .10; $^{*}p$ < .05; $^{**}p$ < .01

scored an average of 6.7 (Cohen's $d$ = 0.53) points higher than patients. All participants scored higher at Day L (37.1) than at Day 0 (32.9, Cohen's $d$ for difference = 0.53).

Each group tended to improve their Color-Word scores from Day 0 to Day L ($t(13) = -1.83$, $p = .09$, 30.1–33.2 for the schizophrenia group—Cohen's $d$ for difference = 0.53; and $t(8) = -2.24$, $p < .06$, 35.7–41.0 for the controls—Cohen's $d$ for difference = 0.85). Controls (mean = 35.7) had slightly better performance than the patients (mean = 30.1; $t(21) = 3.64$, $p = .07$) on Day 0 whereas on Day L, they were significantly better than the patients (control mean = 41.0 and schizophrenia mean = 33.2; $t(21) = 4.81$, $p = .04$), Cohen's $d$ for difference = 0.49. These results suggest that improvement on Stroop was not due to olanzapine administration per se, as controls showed comparable improvement to patients.

### 3.1.3 | Eye-movement tasks: Latency

*Prosaccade latency*

Unadjusted prosaccade latencies averaged across all the schizophrenia patients and their SDs are reported in Table 3. The mixed effect model revealed no main effects of Session ($F_{2,42} = 0.36$, $p = .70$), or Group ($F_{1,21} = 0.01$, $p = .93$), and no significant interaction ($F_{2,42} = 0.22$, $p = .81$), suggesting that olanzapine had no effects on sensorimotor function.

*Antisaccade latency*

Unadjusted antisaccade latencies averaged across all the schizophrenia patients and their SDs are reported in Table 3. The mixed effect model revealed no main effect of Session ($F_{2,42} = 0.06$, $p = .94$). However, a main effect of Group was observed ($F_{1,21} = 5.14$, $p = .03$), indicating that the patients were significantly slowed (45.8 ms; Cohen's $d$ = 0.31) compared to controls when making a correct antisaccade. No interaction between Group and Session was observed ($F_{2,42} = 0.68$, $p = .51$).

### 3.1.4 | Eye-movement tasks: Antisaccade error rate

Unadjusted antisaccade error rates averaged across all the schizophrenia patients and their SDs are reported in Table 3. As shown in Figure 1c, the mixed effect model for antisaccade error rates revealed a main effect of Session ($F_{2,42} = 17.97$, $p < .0001$); specifically, that there was a significant decrease in error rate from Day 0 (mean of 36.1%) to Day L (mean of 18.6%, Cohen's $d$ for difference = 0.36). Additionally, there was a main effect of Group ($F_{1,21} = 44.1$, $p < .0001$), indicating that the patients had a significantly higher antisaccade error rate (mean of 37.3%) than the controls (10.4%, Cohen's $d$ for difference = 0.68). There was also a significant Group by Session interaction ($F_{2,42} = 3.32$, $p = .05$), indicating that the patient group (treated with olanzapine) had a greater reduction in antisaccade error rate over time than did the control group.

With respect to within-group change across sessions (see Figure 1c), for the patients there were significant reductions in the antisaccade error rates from Day 0 (mean of 49.7%) to Day S (mean of 34.8%; $t(42) = -4.41$, $p < .0001$, Cohen's $d$ for difference = 0.69), and between Day 0 and Day L (mean of 27.2%, Cohen's $d$ for difference = 1.04; $t(42) = -6.6$, $p < .0001$). The controls also showed a significant decrease in antisaccade error rates from Day 0 to Day L ($t(42) = -2.31$, $p = .03$, Cohen's $d$ for difference = 0.36) but not from Day 0 to Day S ($t(42) = -0.88$, $p = .38$; 14.8%, 11.1%, and 5.1% for Day 0, Day S, and Day L, respectively). No demographic variables were significantly correlated with antisaccade error rate.

Finally, the contrasts between groups across sessions, illustrated in Figure 1d, showed a significant difference between groups across sessions (Day 0 to Day L), $t(42) = 2.36$, $p = .02$ reflecting a significantly greater error rate reduction in patients treated with olanzapine (22.5%) than in controls (9.7%, Cohen's $d$ for difference = 0.37).

## 3.2 | Baseline-dependent antisaccade error rate, Stroop, and PANSS score changes

The linear regression (see Figure 2) looking at and making explicit the relationship between the patients' Day 0 antisaccade error rate and their antisaccade error rate improvement (Day 0–Day L) showed that about 48% of the variability in the error rate improvement with OLZ is predictable from patients' baseline (Day 0) error rates. The regression also revealed a positive correlation ($r = .69$, $p < .01$) between the patients' baseline error rate and their error rate improvement (see Figure 2). In contrast to data shown in Figure 2, no correlation was found between Day 0 antisaccade error rate and Stroop score improvement (Day 0–Day L; $r = -.44$, $p = .11$) nor between Day

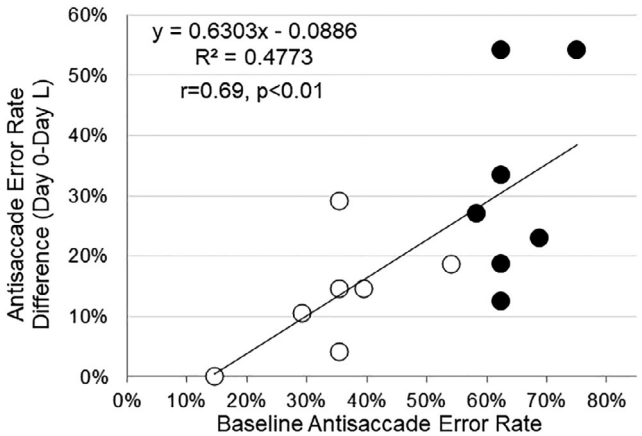


**FIGURE 2** Schizophrenia group antisaccade (AS) error rate change as a function of baseline performance. Mean change in unadjusted antisaccade error rate with olanzapine treatment as a function of the baseline performance (before treatment), with the Low-Deficit patients represented by the white circles and High-Deficit patients represented by the black circles. Higher baseline error rates predicted greater error rate improvement over session

0 antisaccade error rate and PANSS score improvement (Day 0–Day L; $r = -.07$, $p = .82$).

It is possible that the correlation between Day 0 antisaccade error rate and antisaccade error rate improvement with OLZ occurs because there is more room for improvement in the poor performing subjects. Such an explanation would suggest that antisaccade error rate on Day L is more or less constant (i.e., there is an upper limit or ceiling to improvement for all patients) for all values of Day 0 antisaccade error rates (thus no correlation between Day 0 and Day L). In other words, there is only so much room for improvement in the patients. We checked the correlation between Day 0 and Day L antisaccade error rates and found a marginally significant positive correlation ($r = .49$, $p = .076$) suggesting that antisaccade performance at Day L was not constant for all Day 0 antisaccade error rates.

### 3.3 | Low-Deficit versus High-Deficit subgroup (median split) comparisons

The PANSS score was used as a covariate in the analyses of prosaccade, antisaccade, and Stroop variables.

#### 3.3.1 | PANSS subgroup comparisons

Unadjusted PANSS scores for Low-Deficit and High-Deficit subgroups at Day 0 and Day L are illustrated in Figure 3a and Table 3. The mixed effect model for the schizophrenia subgroups (Low-Deficit and High-Deficit) revealed a main effect of Session ($F_{2,24} = 25.29$, $p < .01$), but mean PANSS scores did not differ in the patient subgroups

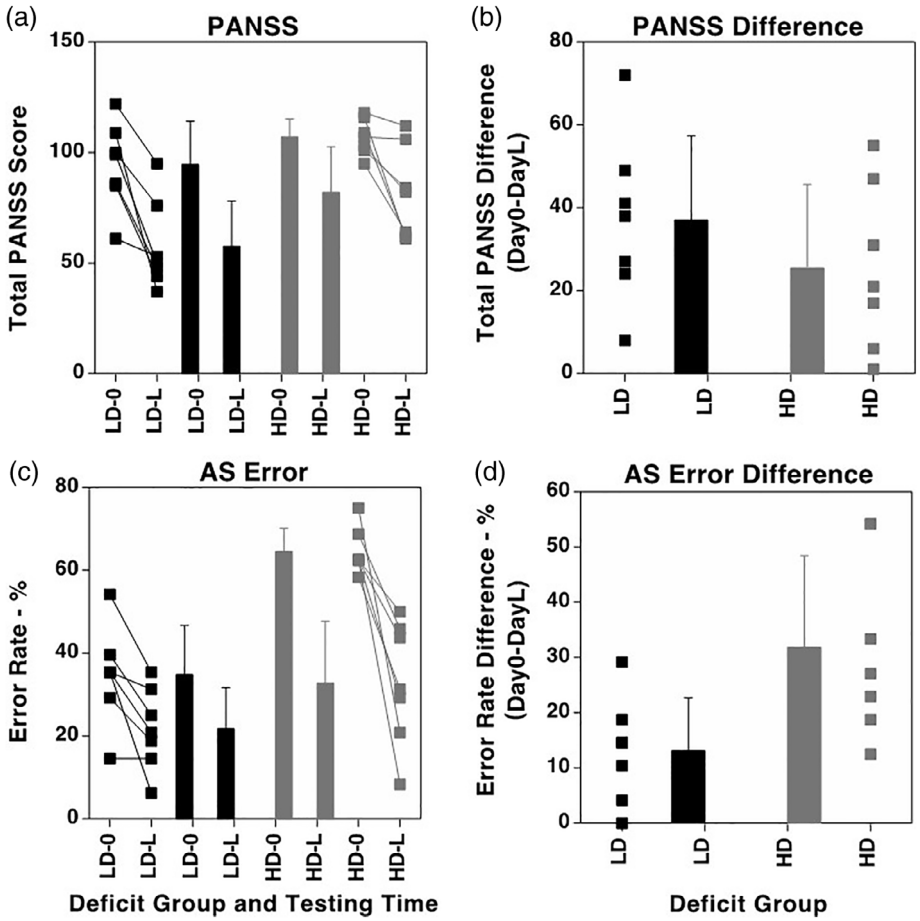


**FIGURE 3** Performance across session for schizophrenia subgroups. (a) Unadjusted PANSS total scores by subgroup. In this and other subpanels, each plot symbol represents the subject's identity and each filled bar represents data averaged across subjects. Error bars in bar plots represent 1 standard deviation. Both schizophrenia subgroups (Low-Deficit (LD), High-Deficit (HD)) show significant improvement on PANSS across testing sessions (Day 0 and Day L). (b) Unadjusted PANSS difference (Day 0–Day L) by subgroup. There is no difference in the reduction of clinical symptom severity with olanzapine treatment between patients with lower baseline cognitive deficits (LD subgroup) and those with higher baseline cognitive benefits (HD subgroup). (c) Unadjusted antisaccade (AS) error rates by subgroup and testing times. Both schizophrenia subgroups show significant improvement in antisaccade error rates across testing sessions. (d) AS error difference by subgroup. There is a greater change in antisaccade error rate (% improvement) across session (Day 0–Day L) for High-Deficit (HD) schizophrenia patients than Low-Deficit (LD) patients, indicating a greater benefit of olanzapine treatment for patients with higher baseline cognitive deficits. The figure follows the same statistical conventions as Figure 1

($F_{1,12}$ = 2.54, $p$ = .14). The interaction between subgroups and sessions was not statistically significant ($F_{2,24}$ = 3.37, $p$ < .10).

The planned contrasts for Session (Figure 3a) showed a significant reduction in symptom severity across sessions for each subgroup (change from Day 0 to Day L: −37 for Low-Deficit, $t$(24) = −5.98, $p$ < .0001, Cohen's $d$ = 2.07 and −25 for High-Deficit, $t$(24) = −4.04, $p$ < .001, Cohen's $d$ = 1.4). The subgroups did not differ significantly in these changes across testing session ($t$(24) = 1.37, $p$ = .18) indicating that the magnitude of clinical improvement over time was independent of baseline AS performance (Figure 3b). This finding is consistent with the lack of significant correlation between baseline antisaccade error rate and PANSS score change across sessions.

#### 3.3.2 | Stroop subgroup comparisons

Unadjusted average Stroop scores and their SDs for Low-Deficit and High-Deficit subgroups at Day 0 and Day L testing sessions are reported in Table 3. The mixed effect model on the Stroop scores for the Low-Deficit and High-Deficit groups revealed a marginal effect for Session ($F_{1,12}$ = 3.73, $p$ < .10), but no significant Subgroup effect ($F_{1,12}$ = 1.34, $p$ = .27) or Subgroup by Session (Day 0 to Day L) interaction ($F_{1,12}$ = 2.5, $p$ = .14). This finding is consistent with the lack of significant correlation between baseline antisaccade error rate and Stroop score change across sessions.

#### 3.3.3 | Pro- and antisaccade latency subgroup comparisons

Unadjusted average pro- and antisaccade latencies and their SDs for Low-Deficit and High-Deficit subgroups at Day 0 and Day L testing sessions are reported in Table 3. There were no significant Session, Subgroup, or Subgroup by Session effects or interactions for prosaccade or antisaccade latency in the Low-Deficit and High-Deficit subgroups (all $p$'s > .20).

#### 3.3.4 | Antisaccade error rate subgroup comparisons

Unadjusted average antisaccade error rates and their SDs for Low-Deficit and High-Deficit subgroups at Day 0 and Day L testing sessions are reported in Table 3. Main effects of Subgroup ($F_{1,12}$ = 10.97, $p$ < .01), Session ($F_{2,24}$ = 26.02, $p$ < .0001), and their interaction ($F_{2,24}$ = 7.83, $p$ < .01) on antisaccade error rate were statistically significant (Figure 3c). Planned comparisons indicated that both subgroups showed significant improvements in antisaccade errors across sessions (Day 0 to Day L; $t$(24) = −2.92, $p$ < .01, Cohen's $d$ = 0.61 and $t$(24) = −7.11, $p$ < .0001, Cohen's $d$ = 1.48 for Low-Deficit and High-Deficit subgroups respectively). There was also a significant difference between subgroups across sessions, with the Low-Deficit subgroup showing a significantly smaller reduction in antisaccade error rate (mean improvement of 6.8) from Day 0 to Day L than the High-Deficit subgroup (mean improvement of 17.0) ($t$(24) = 2.96, $p$ < .01, Cohen's $d$ for difference = 0.62) (Figure 3d). This finding is consistent with the significant correlation between baseline antisaccade error rate and antisaccade error rate change across sessions.

## 4 | DISCUSSION

### 4.1 | Summary of eye-movement and clinical results

Treatment with OLZ resulted in significant improvements in executive function as measured by performance on an eye-movement task (antisaccade), while showing no effects on sensorimotor performance (prosaccade task). The magnitude of the improvement on antisaccade errors was significantly correlated with the magnitude of the baseline deficit on the antisaccade task. In contrast, changes in Stroop and PANSS scores did not significantly correlate with baseline deficit on antisaccade task. Further, on the antisaccade task, the High-Deficit patient subgroup improved more (greater reduction in antisaccade errors) across sessions than the Low-Deficit subgroup, indicating that treatment with OLZ resulted in significantly greater improvement in patients who were most impaired at baseline. In contrast, there was no significant difference across sessions in the Stroop task for the Low-Deficit and High-Deficit subgroups. These results suggest that antisaccade task performance may be a more sensitive measure of executive function change than the neuropsychological Stroop task. The High- and Low-Deficit patient subgroups also did not differ in magnitude of clinical improvement (as measured by the PANSS) during treatment with OLZ, indicating that the improvement in executive function was not dependent on the magnitude of improvement in severity of clinical symptoms.

### 4.2 | Measuring executive function

Both the antisaccade task and Stroop task are considered measures of executive function (Diamond, 2013; Everling & Fischer, 1998) that require inhibition of a prepotent or reflexive response and the generation of another action, although the exact processes involved remain debatable (Cutsuridis et al., 2014). One possible explanation for the differences in sensitivity of the two tasks is that the Stroop task involves more complex visual stimuli, involvement of word processing, and longer response durations than simple eye-movement tasks, increasing variability and introducing additional sources of heterogeneity. Recent modeling of spatial attention and memory (Patel, Red, Lin, & Sereno, 2015) has demonstrated that even when both processes share a common neural substrate, a simple (single) disruption of the network resulted in the appearance of a dissociation between memory and attentional processes. Without additional physiological or behavioral evidence that can specify involvement of precise neural substrates or separable cognitive processes, it is reasonable to

interpret poor performance on the antisaccade and Stroop to indicate a deficit in cognition or executive function, more specifically. Nevertheless, our findings do suggest that the antisaccade task may be a more robust or sensitive measure of executive function changes than the Stroop task.

### 4.3 | Concerns about practice effects

Other studies assessing cognitive improvements on neuropsychological tests during treatment with atypical psychotics have reported significant practice effects of repeated neuropsychological assessments (T. E. Goldberg et al., 2007), which complicates the interpretation of whether these drugs truly improve executive function per se, or reflect practice effects. On the antisaccade task only, we demonstrate that the schizophrenia patients show greater improvement than control participants (Figure 1d), consistent with improvement beyond practice or ceiling effects.

### 4.4 | Olanzapine versus typical antipsychotics

Previous work has demonstrated that treatment with OLZ results in greater overall improvement in executive function than haloperidol does (Leucht, Pitschel-Walz, Abraham, & Kissling, 1999). Our findings that treatment with OLZ improves executive function in both High-Deficit and Low-Deficit subgroups are in agreement. All schizophrenia patients showed a reduction in antisaccade errors regardless of the magnitude of their baseline impairment. This finding contrasts with a previous report examining the effects of the typical neuroleptic haloperidol (Babin et al., 2011), which showed that haloperidol improved antisaccade task performance only in schizophrenia patients who were more impaired before treatment but worsened performance in patients who were less impaired before treatment, resulting in a U-shaped effect of haloperidol on antisaccade error rates. Similar effects in patient subgroups were only partially reflected in performance on the Stroop task (i.e., no change for the overall patient group; marginally significant worsened performance for low-deficit patients; and non-significant improvement for high-deficit patients).

A sigmoid function is common in drug response profiles (McKim, 2002). We have previously shown that if one assumes that the sigmoidal drug response profiles are different for participants who have different baseline responses, then a simple model can explain the differential inverted-U shaped effect of haloperidol on antisaccade error rates in schizophrenia patients (Babin et al., 2011). In that model, we assumed that increasing haloperidol dose would *increase* or overall negatively impact antisaccade error rates (or executive function) and that more cognitively intact patients may be more resilient to the cognitive effects of the drug. In the model here, we assume that increasing olanzapine dose will *reduce* antisaccade error rates and that the normalizing effect of olanzapine on error rate starts at a lower dose. Similar to haloperidol, we assume that the magnitude of the drug effect increases with dose in those subjects whose baseline cognitive deficit (i.e., antisaccade error rate) is worse (see Figure 4a). Figure 4b illustrates an example relationship between baseline error rate and change in response from baseline for administered dose illustrated in

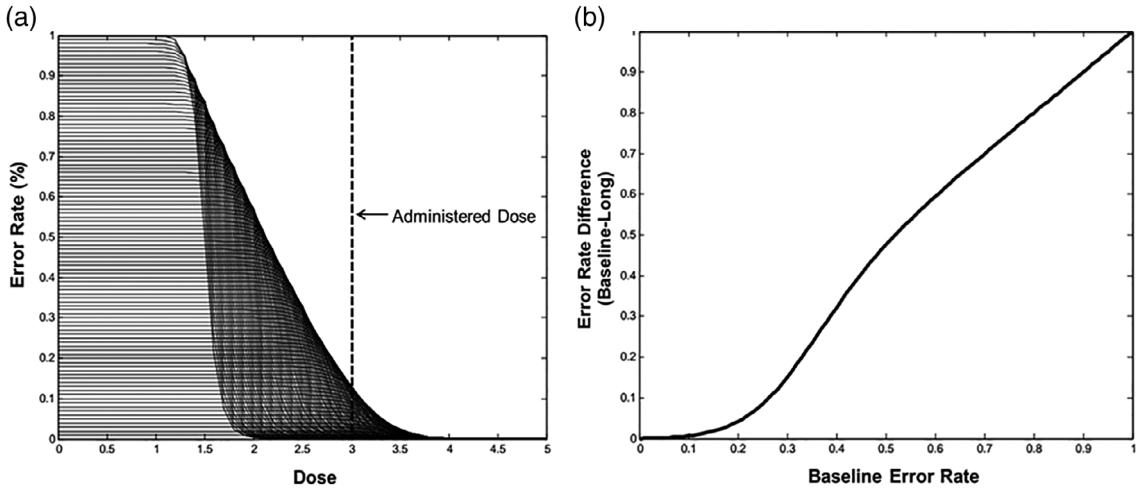


**FIGURE 4** Hypothetical sigmoidal dose–response curves for numerous participants that differ in their initial baseline performance on the antisaccade task. (a) Each curve represents the hypothetical change in per cent error for a participant on the antisaccade task as a function of a drug dose, such as olanzapine. The vertical dotted line represents the actual dose that may be administered to all participants. It is clearly seen that the change in per cent error from no dose (0) to administered dose depends on the participant's initial baseline performance. The change in per cent error increases as we move from the bottom curves to the top curves. To obtain all of the sigmoidal curves, we systematically varied two parameters: (1) The baseline response curve and (2) the dose at which the performance changes, with the assumption here being that the more cognitively intact patients (represented by curves near the bottom) may be more resilient to the cognitive effects of the drug. (b) Example relationship between baseline (Day 0) response and change in response from the baseline obtained from the hypothetical dose–response curves and the administered dose illustrated in Figure 4a

Figure 4a—the larger the baseline error rate, the greater the difference between baseline and Day L performance. In other words, Figure 4b illustrates that the magnitude of the improvement is significantly greater in the high deficit subgroup than the low deficit subgroup. Notably, in contrast to the haloperidol model, neither subgroup shows worsened performance. Our data shown in Figure 2 are consistent with this model.

The difference in binding mechanisms between haloperidol and olanzapine may also play a role in the contrasting results of haloperidol and olanzapine on antisaccade performance. Although both medications block dopamine transmission at the D2 receptor, olanzapine's strong affinity for and activation of serotonin receptors may contribute to its beneficial effect on cognitive performance even in the lower deficit subgroup (Meltzer & Massey, 2011). Serotonergic mechanisms may be involved in improved antisaccade performance in patients regardless of severity of cognitive impairment. That is, serotonergic mechanisms may compensate for the deleterious effects of dopaminergic blocking in the low deficit subgroup whereas in the high deficit subgroup, serotonergic mechanisms may add further benefit to the beneficial effects of dopaminergic blocking in these more cognitively impaired patients. Therefore, these findings suggest that olanzapine, unlike haloperidol, may be beneficial even for schizophrenia patients who are less impaired.

### 4.5 | Regression toward the mean

We find that the change in antisaccade error rate with OLZ treatment is dependent on baseline error rate, that is, during treatment with OLZ the High-Deficit subgroup had a larger reduction than the Low-Deficit subgroup. An alternative explanation is that there is no effect of medication and that improvement over time is merely regression to the mean. Taking these findings by themselves, such an interpretation is possible. However, we think this interpretation unlikely for several reasons. First, we observed a significantly greater reduction in error rate in the schizophrenia group as a whole compared to the controls across sessions. Although one might argue this is a "regression-toward-the-mean" group effect, this group effect across session did not occur in a prior study using the exact same tests, apparatus, and conditions (e.g., in the same inpatient ward) examining treatment with haloperidol in schizophrenia patients (Babin et al., 2011). Further, in the Babin et al. study, the low deficit schizophrenia subgroup actually became more impaired during treatment with haloperidol than at baseline, whereas the high deficit group showed a reduction in errors. Treatment with OLZ, in contrast, resulted in significant greater improvement in antisaccade performance in both patient subgroups. Hence, there are differential treatment effects across sessions and sessions by subgroups in these studies. Demonstrating that baseline antisaccade error rates (i.e., the measure defining low and high deficit patients) result in different antisaccade error rate changes, depending on medication treatments, in these subgroups, suggests that changes with treatment cannot simply be explained by regression to the mean. That is, low-deficit patients show improvement with olanzapine treatment but greater impairment with haloperidol. Finally, the baseline performance model that we have proposed is simple and can explain both haloperidol and olanzapine findings without assuming there is regression to the mean in one but not the other study. The only thing we alter in the model is that one drug is beneficial and the other is not beneficial with respect to executive function. Additional work with more patients, perhaps in a cross-over design, directly comparing medications such as haloperidol and OLZ in the same populations of low and high deficit patients would help to tease apart how medications are influencing the findings and test whether baseline cognitive performance can predict medication efficacy in improving executive function.

### 4.6 | Future directions and limitations

Although OLZ treatment results in beneficial effects on executive function, some caution is warranted, given the metabolic side effects of OLZ. In addition, it would be interesting to examine whether the short-term effects of OLZ we observed on cognition are lasting and stable. Although our sample sizes are small, as clinical practice moves toward individualized treatment plans, it is critical that biobehavioral measures are sensitive and reliable *at an individual level*. Further, small sample sizes have long been used when measuring eye-movements in schizophrenia patients (for recent work see: Meyhofer et al., 2017; Seymour et al., 2017; Thakkar et al., 2018). We use eye-movement measures in the present study to examine the effect of a drug treatment and demonstrate robust preliminary findings that significant differences can be observed using the antisaccade task. In addition to having a small sample, our sample, on average, had relatively late age of onset (29.8 years) and short duration of illness (7.2 years). Additional work with larger samples, that vary systematically in relevant clinical dimensions (e.g., positive vs. negative symptomology, age of onset, and duration of illness) will be needed to see to how these changes in antisaccade performance relate to other variables (e.g., clinical measures, drug response, pharmacological profile) and to what extent the findings are generalizable.

Though previous work has divided schizophrenia patients into at least three cognitive subgroups (Hall et al., 2012; Lewandowski, Sperry, Cohen, & Ongur, 2014; Ohi et al., 2017), based on performance on the antisaccade task, we selected a median split of schizophrenia patients into High-Deficit and Low-Deficit subgroups due to the small sample size. It is possible that some other method of generating meaningful subgroups in a larger sample may be informative.

## 5 | CONCLUSIONS

We show that olanzapine, unlike haloperidol, improves the executive function component of cognition in all schizophrenia patients, as measured by the antisaccade task. Patients with greater cognitive deficits before treatment showed greater cognitive improvements than those with lesser deficits. Given that cognition is one of the strongest

predictors of long-term prognosis in schizophrenia patients, these findings suggest that olanzapine may have certain advantages especially in patients with more severe cognitive deficits. Additional studies with larger samples would clarify the robustness of the preliminary findings reported here.

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## AUTHOR CONTRIBUTIONS

N.M. worked on data collection, data analysis, and manuscript preparation and review. M.W. was involved in manuscript preparation and review. S.B. contributed to the study design, data collection, and initial analysis. S.P. was involved in data analysis and manuscript review. A.W. contributed to subject recruitment, clinical testing, evaluation and diagnosis. A.C. worked on data analysis and manuscript preparation and review. A.S. contributed to study formulation, design, data collection and analysis, and manuscript preparation. All authors contributed by drafting parts of the work, have approved the final version, and agreed to be accountable for all aspects of the work.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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