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Effects of adjunct valproic acid on clinical symptoms and saccadic eye movements in schizophrenia

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Objective Valproic acid (VPA) has been suggested as a potential adjunct therapy in schizophrenia for the treatment of clinical symptoms and cognitive deficits. Here, we investigate the effects of VPA on clinical symptoms and saccadic eye movements while controlling for multiple medication effects.
Methods Remitted and first-episode schizophrenia patients taking haloperidol were given adjunct VPA for approximately 2 weeks and tested using a measure of clinical symptoms (Positive and Negative Syndrome Scale) and saccadic eye movement tasks over three testing periods. The effects of VPA were compared with schizophrenia patients medicated with equivalent doses of haloperidol alone (HAL group) and normal controls.
Results Schizophrenia patients had higher error rates on the antisaccade task (AS task) compared with normal controls. Adjunct VPA did not affect AS task error rates but was associated with an increase in response times for both saccade and AS tasks, with a significantly greater and dose-dependent increase in response times for the AS task. There were no differences in clinical improvement between VPA and HAL schizophrenia patient groups when controlling for haloperidol medication state.
Conclusions These results suggest that adjuvant VPA therapy results in both sensorimotor and cognitive slowing but does not either help or further impair inhibitory control in schizophrenia, as measured by the elevated AS task errors.

KEY WORDS—saccade; antisaccade; valproic acid; schizophrenia; haloperidol

INTRODUCTION

Valproic acid (VPA) in various forms has been used successfully in the treatment of bipolar disorder for more than two decades and has been shown to be well tolerated and effective in the treatment of clinical symptoms (Macritchie *et al*., 2009). VPA is also, albeit less commonly, used as an adjunct therapy in schizophrenia and has been suggested as a potential treatment for negative symptoms and cognitive deficits associated with the disorder (Ichikawa *et al.*, 2005).

Cognitive impairment in schizophrenia is a considerable factor in the personal well-being and functional outcome of affected individuals (Green, 1996; Harvey *et al*., 1998; Hogarty and Ulrich, 1998; Meltzer and McGurk, 1999; Velligan *et al*., 2002). Traditional neuroleptic treatments are successful in reducing psychotic symptoms, but there are fewer studies demonstrating efficacies in ameliorating cognitive dysfunction (Babin *et al*., 2011). Although there is great interest in developing effective therapies for cognitive dysfunctions associated with schizophrenia and theoretical research on the subject is supportive of this interest, there is a dearth of clinical trials and controlled experimental studies examining these potential cognitive therapeutics in schizophrenia patients (see Hyman and Fenton, 2003, for a discussion of this issue).

Valproic acid has been suggested as a potential adjunct therapy in schizophrenia with the potential to effectively treat clinical and cognitive symptoms (but see, Schwarz et al., 2010, for review). There have been studies demonstrating early clinical efficacy of adjunct VPA, in particular, in schizophrenia patients experiencing hostility or acute exacerbation of the illness (Wassef *et al*., 2000; Citrome *et al*., 2004). In addition, there are numerous studies examining the effects of VPA on cognitive function in epilepsy (see Vermeulen and Aldenkamp, 1995); however, there are no published studies to date examining the effectiveness of VPA on attentional function in schizophrenia using measures of saccadic eye movements.

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In patient populations other than those with schizophrenia, VPA has been shown to impact cognitive deficits associated with attention and learning. Torrioli *et al*. (2010) showed that VPA therapy resulted in an improvement in the symptoms of ADHD in 10 subjects with comorbid Fragile X syndrome. Barzman *et al*. (2006) found that VPA reduced impulsivity in adolescents with bipolar and comorbid behavioral problems. VPA was further shown to reduce reversal learning deficits induced by phencyclidine or amphetamine in an animal model of psychosis (Idris *et al*., 2009). In addition, VPA has been shown to increase frontal cortical dopamine levels, an effect that theoretically could result in improved cognitive functioning in schizophrenia patients (Ichikawa and Meltzer, 1999).

Perhaps one of the most precise measurements of cognitive performance and treatment effects on cognitive performance is the use of saccadic eye movement tasks (Larrison-Faucher *et al*., 2004; Hood *et al*., 2007; Hutton, 2008). There is extensive research showing impaired performance by schizophrenia patients on a common variation of the saccadic eye movement task known as the antisaccade task (AS task) (Fukushima *et al*., 1988, 1990a, 1990b; Sereno and Holzman, 1995; Karoumi *et al*., 1998; Levy *et al*., 1998). In the AS task, subjects must respond to a visual target by making a saccade to the location directly opposite the target location. Performance on this task is typically compared with that of the prosaccade task, in which the subject instead looks directly at the target when it appears. Schizophrenia patients have shown both increased error rates and longer response times (RTs) in the AS task, whereas they show normal RTs and no differences in error rates when performing the prosaccade task. Because the tasks are identical with respect to the target presentation and eye movement response and only the cognitive response demands differ (low, looking toward, or high, away from the target), the comparisons of performance across these tasks have been used to look at differences in the underlying cognitive demands of the tasks (Hutton and Ettinger, 2006). Converging evidence suggests that the impairment in antisaccades relative to saccades in this population may be related to the deficits in the prefrontal cortical circuitry (Fukumoto-Motoshita, *et al.* 2009). This distinction between AS task and saccade task (S task) performance is important as it specifically implicates frontal cognitive control systems as opposed to a more general sensorimotor deficit (Guitton *et al*., 1985; Munoz and Everling, 2004).

Given the relationship between AS task performance and prefrontal function, pharmacological interventions aimed at enhancing prefrontal function might be expected to correspondingly improve AS task performance (see, e.g., Hood *et al*., 2007). Both traditional and atypical antipsychotics, however, have shown inconsistent effects on performance on the AS task (Cassady *et al*., 1993; Crawford *et al*., 1995; Hutton *et al*., 1998; Muller *et al*., 1999; Harris *et al*., 2006; Babin *et al*., 2011). Here, we measure the effects of adjunct VPA on the performance of the saccade task (S task) and AS task in participants who have schizophrenia taking the typical neuroleptic haloperidol over an approximately 2-week period. The Positive and Negative Syndrome Scale (PANSS) is used to measure clinical improvement, whereas changes in antisaccade response latencies and error rates are used to measure cognitive effects of adjunct VPA.

METHODS

Subject recruitment

Schizophrenia patients were recruited from the University of Texas Harris County Psychiatric Hospital, Houston, Texas. All the testing on schizophrenia patients was performed while they were inpatients in the hospital. Patients were recruited as part of ongoing studies on attention and eye movement in our lab.

The diagnosis of schizophrenia was made by a board certified psychiatrist using the Diagnostic and Statistic Manual of Mental Disorders, fourth edition (DSM-IV). Patients and controls were excluded from our study if they had a history of Parkinson's disease, epilepsy, autism, severe head trauma, or any current substance abuse/dependence. In addition to these exclusion criteria, controls had no previous history of psychosis and had no first-degree relatives with a diagnosis of schizophrenia, bipolar disorder, or autism. All schizophrenia patients were off psychotropic medications for at least 3 weeks prior to enrollment in this study with one exception. A single dose of haloperidol (10 mg) was administered to one remitted patient in our haloperidol control group before baseline testing. No differences were noted in performance on any of the measured eye movement tasks for this subject compared with the haloperidol control group, and therefore, he was included in the analyses. All study participants gave informed consent at the start of each testing session. This study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston and Harris Country Psychiatric Center and in accordance with the Declaration of Helsinki.

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Apparatus

Saccadic eye movements were recorded using an infrared ISCAN RK-826 PCI (ISCAN Inc., Woburn, MA, USA) eye tracking system. Subjects were seated in front of a 17-inch CRT monitor with their heads placed in a stable chin rest that was positioned 72 cm from the screen. The spatial and temporal resolutions of the eye tracker were approximately 0.5° visual angle and 4 ms (240 Hz), respectively. Before the start of an eye movement recording session, the subject was calibrated by moving their eyes to nine positions on the screen indicated by 0.2° × 0.2° white boxes on a black background. For the eye movement tasks, a gray fixation point of 0.2° was illuminated in the center of the black screen. Target stimuli were 0.2° × 0.2° white boxes that appeared 7° to the right and left of the fixation point. Saccade initiation and termination were defined by areal and velocity criteria. Specifically, for saccade initiation, eye velocity had to be above 47.5°/s, and for saccade termination, eye velocity had to be both below 12°/s and within 4.4° of the target.

Procedure

Prosaccade and AS tasks were administered to all schizophrenia patients and controls at three different time points: baseline (BL), time 1 (T1; 3–5 days after initial testing), and time 2 (T2; 12 –15 days after initial testing). The prosaccade and AS tasks were administered in two blocks of 48 trials, with the S task always preceding the AS task. Trials interrupted by a blink were aborted and randomly re-presented. Each task was preceded by a 10-trial practice block, and instructions were verbally repeated by each subject before each task began. Target position was balanced for presentation in the left or right visual field. To begin a trial, the subject had to fixate a point located straight ahead for 600 ms. After this fixation period, the target randomly appeared 7° to the left or right of the fixation point. For the prosaccade task, the subject had to look at the peripheral target, whereas for the AS task, the subject had to look to the opposite side or mirror image location of the peripheral target. There were no auditory cues that accompanied target onset or that provided feedback to the subjects. Visual feedback was provided to the subjects if the eye movement was incorrect.

RESULTS

Participant population

Nine participants in each of three groups (VPA, HAL, and normal control) were matched for age, education, and smoking (see Table 1). Ages ranged from 20 to 40 years old for our patient and control groups. Overall, there were no significant differences on any of our matched variables; however, there was a trend toward more female participants in the control group than in the patient groups ($\chi^2 = 4.6$, $p = 0.10$). There were no correlations between gender and any of the eye movement measurements in the schizophrenia and control groups; therefore, in our analyses, data from both genders were combined.

Table 1. Group demographics

$N = 9$/group	Age	Years of education	Gender (F/M)	Smoker (smoke/month, #cigs/day)
VPA	27.6	12.1	2F/7M	7/2, 9/day
HAL	27.3	11.8	1F/8M	6/3, 8.2/day
Control	30.8	12.6	5F/4M	6/3, 7/day

Groups were matched for age, education and smoking status.

Patient population

The majority of our patient population was diagnosed with the paranoid subtype of schizophrenia. Eight out of nine participants in the VPA group and seven of nine participants in the haloperidol group were of the paranoid subtype. The remaining three patient participants were diagnosed as follows: for VPA, one disorganized participant and, for haloperidol, two undifferentiated participants. Patients were additionally matched for illness duration and episode status. Four of nine patients in each group were first episode, and the remainders were remitted.

Medication protocol

Patient populations were administered either haloperidol alone (HAL) or haloperidol and VPA (VPA) in order to control for medication effects of haloperidol. However, the time course of medication administration differed between our two groups. For our patient control group (HAL or haloperidol alone), all data measures at the baseline (BL) session were administered in an unmedicated or drug-free state. Following the BL session, the HAL group began a daily regimen of therapeutic doses of haloperidol. For the VPA group, haloperidol treatment began 3 days prior to the BL testing session. Haloperidol was continued throughout the study with the addition of daily VPA therapy in this group, which began just following the BL session (see Table 2). By the T2 testing session (11–15 days post BL testing session), both HAL and VPA groups had received approximately 2 weeks of treatment.

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Table 2. Testing and treatment time course for patents and patient controls

GROUP	BL session	T1, 3–5 days	T2, 11–15 days
VPA	3 days HAL	6-8 days HAL + 3–5 days VPA	~2 weeks HAL + VPA
HAL	Unmedicated	3–5 days HAL	~2 weeks HAL

HAL, haloperidol.

Clinical effects of VPA on the Positive and Negative Syndrome Scale

Separate 2×3 mixed analyses of variance (ANOVAs) were performed to examine the change in Positive, Negative, and General scales of the PANSS. The between factor represented the two patient groups, GROUP (VPA and HAL), and the within factor represented the three testing points, TIME (BL, T1, and T2). There was a significant main effect for TIME for the Positive, Negative, and General subscales ($F_{(2,32)} = 50.8$, $F_{(2,32)} = 26.9$, and $F_{(2,32)} = 39.9$, respectively, all p-values <0.001). However, there were no main effects for GROUP on any of the PANSS subscales. There was, however, a significant interaction between GROUP and TIME for the Positive and General subscales ($F_{(1,16)} = 4.26$, $p < 0.05$, and $F_{(1,16)} = 3.48$, $p = 0.05$; see Figure 1). Although both groups responded significantly to treatment as measured on the PANSS, there was an apparently greater reduction in PANSS in patients receiving haloperidol (HAL). This finding may have been due to the participants in the HAL group being unmedicated at the BL (baseline) testing point, whereas the VPA group had already received 3 days of haloperidol medication prior to their first BL testing day.

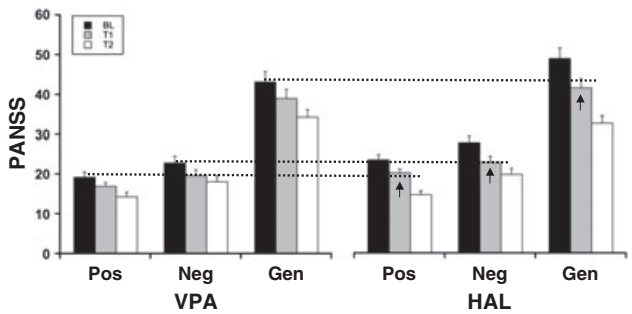

Figure 1. Positive and Negative Syndrome Scale scores in patients receiving either haloperidol and valproic acid (VPA) or haloperidol alone (HAL). Both patient groups significantly improved on all clinical measures (POS, NEG, and GEN) over the course of treatment. Patient controls (HAL) were unmedicated at BL and also were significantly more clinically impaired than the VPA group at BL (no VPA, but 3 days of haloperidol; level marked by dotted lines). After 3 days of haloperidol treatment, note that the HAL group at T1 (bars with arrows) were clinically identical to the VPA patients at BL (3 days of haloperidol before treatment with VPA; compare bars with arrows to respective dotted line), and by 2 weeks of treatment (T2; open bars), there were also no clinical differences between our groups. The error bars represent ± 1 SEM

Post hoc analyses

Individual t-tests were performed to investigate the possible relationship between PANSS scores and drug treatment. At BL, there was a significant difference between our patient groups for both the Positive ($t = -2.28$, $p < 0.05$) and Negative ($t = -2.19$, $p < 0.05$) syndrome subscale scores, but no difference for the General subscale. This was likely due to a difference in medication state at the BL testing session. That is, the BL PANSS scores for our HAL group were assessed in an unmedicated state, whereas the BL scores in the VPA group were assessed in patients who had been receiving haloperidol for 3 days prior to this BL testing session. Therefore, a more equivalent measurement to assess if there were any clinical differences between our patient groups at baseline with 3 days of haloperidol treatment (i.e., before treatment with VPA) would be to compare the VPA BL test scores (which corresponded to 3 days on haloperidol; marked with dashed lines, separately for Positive, Negative, and General subscales in Figure 1) to the HAL T1 test scores (which likewise corresponded to 3 days on haloperidol; right-hand side, light grey bars). Using the same post hoc t-tests and comparing VPA BL with haloperidol T1, there were no significant differences between our groups on any of the PANSS measures, supporting the idea that our patient groups were clinically matched for symptom severity with 3 days of haloperidol treatment and before treatment with VPA.

To assess if there were any clinical differences between our patient groups after approximately 2 weeks of treatment with VPA, T2 PANSS measurements provided the best comparison. Note that the rate of clinical improvement decreases with the duration of antipsychotic treatments; thus, the three additional days of haloperidol treatment in the VPA group would have a negligible effect on the clinical comparison between the VPA and HAL groups after approximately 2 weeks of treatment (T2). Looking at T2 data separately, there were no significant differences for Positive, Negative, or General syndrome subtests (see Figure 1).

Saccade and antisaccade latency and error rates

All trials were used for analyses of error rates. Only correct and trimmed trials (prosaccade task: [<90 and >600]; AS task: [<90 and >800]) were included for analyses of saccade RTs. Separate 3×3 mixed ANOVAs (between groups and within repeated measures) were performed for S and AS tasks performance for RT and error rate. The between factor represented GROUP (VPA, HAL, and CONT) and the within factor represented TIME (BL, T1, and T2). Planned comparisons (between

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groups or between BL and T2) were performed using the mean square error term from the ANOVA.

For the S task RT data, there was no significant main effect of GROUP; however, there was a significant main effect of TIME, $F_{(2,48)} = 3.7$, $p < 0.05$. There was a marginally significant GROUP × TIME interaction, $F_{(4,48)} = 2.2$, $p = 0.08$. Planned comparisons showed that there was a significant increase in RTs from baseline to T2 in the patient population taking VPA ($t(47) = 3.1$, $p < 0.005$, see Figure 2(A)). Further, RTs in the VPA group were significantly higher than those in the HAL group ($t(47) = 3.2$, $p < 0.01$). Collapsed across TIME, neither VPA nor HAL groups had different saccade RTs compared with the CONT group.

For the S task error rates, the same 3×3 factor ANOVA showed no significant main effect of GROUP, $F_{(2,24)} = 2.7$; however, there was a significant effect of TIME, $F_{(2,48)} = 3.25$, $p < 0.05$ (Figure 2(B)), but it did not further interact with GROUP. Planned comparisons showed small but significantly higher error rates in VPA and HAL groups compared with CONT group (VPA: $t(36) = 2.5$, $p < 0.05$; HAL: $t(36) = 2.9$, $p < 0.01$).

For the AS task RT data, there were no significant main effects for either GROUP, $F_{(2,48)} = 0.67$, or TIME $F_{(2,48)} = 0.54$. However, there was a significant interaction of GROUP × TIME, $F_{(4,48)} = 4.38$, $p < 0.005$. Planned comparison showed an increase in RT from BL to T2 testing period (as was seen in the S task data) in the patient population taking VPA ($t(43) = 3.5$, $p = 0.001$, Figure 2(C)). Further, as was seen in the S task data, RTs in the VPA group were significantly higher than those in the HAL group ($t(43) = 2.5$, $p < 0.05$). As was the case with the S task data, neither VPA nor HAL groups had different RTs than the CONT group.

For the AS task error rates, there was a significant main effect of GROUP, $F_{(2,24)} = 7.88$, $p < 0.005$, showing increased errors on AS task in schizophrenia patients. There was also a main effect for TIME, $F_{(2,48)} = 3.85$, $p < 0.05$; however, no significant interaction between GROUP and TIME (Figure 2(D)). Planned comparison showed that AS task errors were significantly higher in VPA and HAL groups compared with CONT group (VPA: $t(42) = 9.7$, $p < 0.001$; HAL: $t(42) = 9.5$, $p < 0.001$).

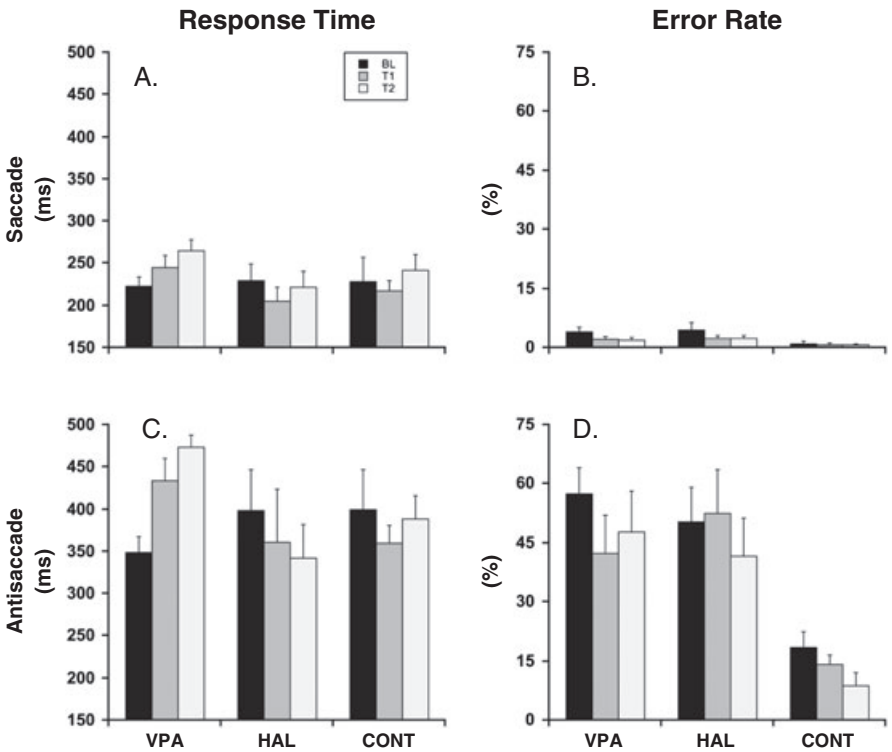

Figure 2. Effects of adjuvant valproic acid (VPA) on eye movement measures. VPA adjuvant to haloperidol significantly slowed saccade RTs (A) and antisaccade RTs (C) across the time points BL and T2, with a significantly greater increase in antisaccade RTs (also see Figure 3). There were no significant effects of VPA on saccade or antisaccade error rates ((B) and (D), respectively). Overall, schizophrenia patients (VPA and HAL groups) showed significantly greater numbers of errors on the antisaccade compared with normal controls (CONT group). The error bars represent ±1 SEM

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Valproic acid task effects: difference scores and percent change

This analysis examined whether S and AS tasks differed significantly in regards to effects of VPA. Our initial and separate ANOVAs showed that both S and AS RTs were increased following VPA treatment; however, in the S task, this GROUP × TIME interaction was only marginally significant. In order to determine whether the AS task showed a differential effect of VPA as compared with the S task, we applied a mixed model analysis technique. Because S and AS RT data have significantly different variances, we used an alternative to the repeated measures ANOVA, the mixed model repeated measures analysis with an autoregressive covariance structure. Unlike ANOVA, mixed model analysis does not assume (i) equal variance for the two tasks and (ii) independence between the two tasks. In case the variances are equal and the two tasks are independent, mixed model analysis would yield similar results as ANOVA. Thus, a mixed model approach was deemed appropriate given the ability for this approach to implicitly account for different task variances as well as any possible correlations between tasks. Because S and AS tasks involve overlapping distinct systems in the brain, this analysis was applied to address whether VPA resulted in a general sensorimotor slowing (S task and AS task), or whether there was additional slowing in the AS task that related to a frontal cognitive control deficit. Using the mixed model approach, we compared S and AS RT (i) differences from BL as well as (ii) percent change from BL, at each of our testing sessions.

Fixed factors for our model included TASK (S and AS), TIME (T1 and T2) and the TASK × TIME interaction. The dependent variables were difference score (e.g., T2 RT − BL RT) and percentage difference score (e.g., [T2 RT − BL RT]/BL RT). Our initial analysis indicated no significant interaction effects for TASK * TIME, so it was subsequently removed from the model and F scores for the two fixed factors model are presented here. For difference scores (e.g., T2 RT − BL RT), there was a significant effect of TASK, $F_{(1,11)} = 14.05$, $p < 0.005$, but only a trend toward significance for TIME, $F_{(1,26)} = 3.8$, $p = 0.06$. For percent change scores (e.g., [T2 RT − BL RT]/BL RT), there was both a significant effect of TASK, $F_{(1,11)} = 5.73$, $p < 0.05$, and TIME, $F_{(1,25)} = 5.3$, $p < 0.05$. These effects are consistent with a significantly greater effect of VPA in increasing AS compared with S RTs (see Figure 3).

Dose-dependent effects of valproic acid

Measures of free plasma VPA were correlated with changes in saccade performance as measured by difference scores (T2 − BL). Differences were calculated for RT and error rates on both the S and AS tasks. There were no significant correlations for the S task and levels of VPA; however, there was a highly significant correlation between free plasma VPA and change in RT for the AS task, Pearson's $r = 0.84$, $p < 0.01$ (see Figure 4). Although a small sample size, the findings suggest that free plasma VPA levels above 25 μg/mL result in cognitive slowing. The fact that AS RTs, as opposed to S RTs, were more prominently affected by VPA agrees with previous reports suggesting that a key target of VPA effects is on frontal cortical regions (Ichikawa and Meltzer, 1999).

DISCUSSION

There were no significant clinical effects of VPA above and beyond what was seen in therapeutic

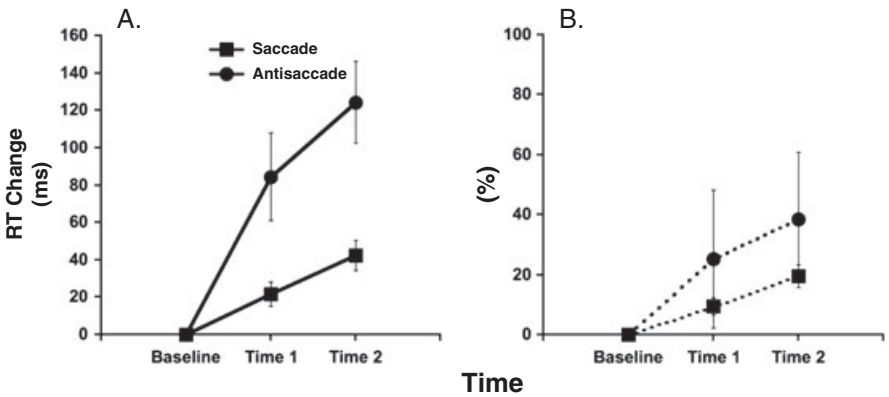

Figure 3. Simple difference (A) or percent difference (B) in saccade and antisaccade RTs from BL. Valproic acid adjuvant to haloperidol showed a significant greater effect on RT changes over time for the antisaccade task. This was true for both difference score measures (A) as well as for scores adjusted for baseline difference in RT, that is, percent difference measures (B). The error bars represent ±1 SEM

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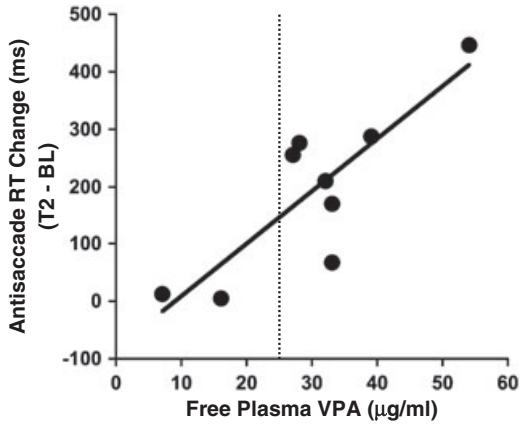

Figure 4. Scatter plot showing a significant relationship between free valproic acid blood level measures and change in AS RT from BL to T2 ($r = 0.84$)

haloperidol treatment alone. This is consistent with some reports (Glick *et al*., 2009) but inconsistent with others (Wassef *et al*., 2000) that suggested a more rapid and effective reduction in PANSS scores with adjunct VPA. In addition, we did not find a unique benefit of VPA on Negative Syndrome scores as has been predicted in modeling the therapeutic effects of the drug (Ichikawa and Meltzer, 1999). It is possible that VPA may still provide a superior benefit in relieving schizophrenia symptoms in cases that are treatment resistant (see Lopez *et al*., 2004).

Findings from our patient population on the saccadic eye movement tasks indicate a marginally significant slowing of RTs on the prosaccade task following less than 2 weeks of VPA therapy. This finding is consistent with the reports in various other populations showing psychomotor slowing and increased RTs following VPA (Thompson and Trimble, 1981, 1982; Brodie *et al*., 1987; Craig and Tallis, 1994; Aldenkamp *et al.*, 1993; Gualtieri and Johnson, 2006). The profile of this sensorimotor slowing is consistent with a slowed processing of the visual target and subcortical motor processing circuitry necessary to generate a prosaccade. It is important to recognize that this slowing of prosaccadic responses should not be equated with cognitive impairment.

In the AS task, we found a significantly larger and dose-dependent slowing in RTs for free plasma VPA levels over 25 μg/mL, indicating cognitive slowing and cognitive impairment. Interestingly, this cognitive slowing and impairment with higher levels of free plasma VPA was specific to generating a voluntary movement (i.e., AS RT and not AS task error rate). That is, although AS task error rates were elevated in our schizophrenia patient population, an impairment frequently reported in prior work (Fukushima *et al*., 1988, 1990a, 1990b; Sereno and Holzman, 1995; Karoumi *et al*., 1998; see also Levy *et al*., 1998 for review), there were no significant changes in AS task error rates in our VPA group. AS task errors are typically recognized as a measure of cognitive control or inhibition (see, e.g., Amador *et al*., 2006) and require intact frontal cortical functioning (Guitton *et al*., 1985). These findings indicate that adjuvant VPA therapy neither improved inhibitory control (i.e., reducing impulsive prosaccades to the target) nor further degraded inhibitory control via basal ganglia circuits. Although impaired AS task performance in both latency and errors has been associated with schizophrenia, increased AS task errors are the more reliable and consistent deficit (Broerse *et al*., 2001). Some models have suggested a possible relationship between voluntary control and the ability to inhibit prepotent responses (e.g., Goldman-Rakic, 1987; Reuter *et al*., 2005; Amador *et al*., 2006). These findings suggest instead that the effects of VPA dissociate voluntary control and inhibitory control and provide insight into separable mechanisms and separable treatments.

Studies examining the effects of VPA on cognitive measures have produced quite variable results. Vermeulen and Aldenkamp (1995) reviewed the literature on the cognitive side effects of anti-epileptics and found that the existing literature was inconclusive as to the effects of VPA on cognitive functioning. More recent reports are also varied with some groups reporting no significant cognitive effects of VPA (Prevey *et al*., 1996; Donati *et al*., 2007) and others finding significant benefits of VPA on impulsivity and attention (Torrioli *et al*., 2010) and learning deficits (Idris *et al*., 2009) as well as on mood (Prevey *et al*., 1989). There have been a considerable number of studies indicating negative cognitive effects of VPA. VPA therapy has been shown to worsen performance on working memory tasks (Higgens *et al*., 2009; Umka *et al*., 2010) and verbal measures of IQ (Nadebaum *et al*., 2011). Further, Gallassi *et al.* (1990, 1992) examined the cognitive benefits of withdrawal from VPA. Before withdrawal, patients medicated with VPA showed impairments in attention, visuomotor function, verbal span, and sensory discrimination. Following 1 year of withdrawal, patients' performance was at control levels.

Our findings are consistent with previous reports of psychomotor slowing following VPA. Given that there appears to be a dose-dependent response of VPA (as indicated by a significant correlation between AS latency and free plasma VPA levels), it is possible that some discrepancies in the literature may be due to differences in dose. Our findings suggest that free plasma VPA levels approximately below 20 μg/mL may not produce any cognitive slowing.

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The vast majority of research on the cognitive effects of VPA has been performed in relation to epilepsy, a population with known disorder-associated neurocognitive deficits (see Nichols *et al*., 1993). It is important, therefore, to be cognizant of the extent to which these findings can and should be generalized to schizophrenia. Our findings indicate that adjunct VPA therapy in schizophrenia causes impairment in voluntary control but no effect on inhibitory control using a sensitive measure of cognition and frontal function, the AS task. Given that VPA is still a recognized drug therapy option for schizophrenia, it is important that we understand its actions specifically in this population. Further, given the importance of cognitive function in outcome of affected individuals in schizophrenia, further research is necessary to determine whether there is a critical free plasma threshold for VPA therapy in schizophrenia patients that will be clinically relevant to avoid inducing cognitive impairment (see Drane and Meador, 2002, for a discussion of this issue).

The initial therapeutic action of VPA in psychiatric disorders was attributed to its ability to enhance GABAergic transmission. However, VPA is known to affect multiple signaling pathways as well as some specific targets (see Loscher, 2002; Terbach and Williams, 2009), and it is likely that several of these effects may be relevant to the therapeutic action of VPA. However, the numerous theoretical explanations for how VPA could ameliorate cognitive deficits are not supported by the literature or our findings. The findings reported here do not provide evidence for a cognitive benefit of VPA in either antisaccade latency or error rates and instead suggest cognitive motor slowing at free plasma levels approximately above 25 μg/mL.

CONFLICT OF INTEREST

No conflict of interest declared.

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