The Effects of Guanfacine on Context Processing Abnormalities in Schizotypal Personality Disorder

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Background: The signature of impaired cognition in people with schizotypal personality disorder (SPD) may be centrally related to working memory impairments. Guanfacine, an α_{2A} agonist that acts post-synaptically in the prefrontal cortex (PFC), has shown potential for reducing working memory limitations in other populations. This study examined the potential of guanfacine for improving context processing, a feature of working memory, in SPD.

Methods: 29 individuals with SPD entered into a 4-week, randomized parallel-design, double-blind, placebo-controlled trial of guanfacine treatment, followed by a 4-week open-label extension. A modified version of the AX-Continuous Performance Test (AX-CPT) was administered. On this task, evidence of intact context processing includes few BX errors (false cue, correct probe) and higher levels of AY errors (correct cue, false probe).

Results: At the end of double-blind treatment, participants treated with guanfacine demonstrated a significant reduction in BX errors and a small but significant increase in AY errors, a pattern that was not seen in the participants treated with placebo.

Conclusions: SPD participants improved in their context processing toward a normal response bias, making fewer BX and more AY errors, after being treated with guanfacine.

Key Words: Cognition, guanfacine, pharmacology, Schizophrenia, Schizotypal, working memory

Impaired cognition, one of the most defining symptoms of schizophrenia (Heinrichs 2005), is also found in individuals with schizophrenia spectrum disorders such as schizotypal personality disorder (SPD; Siever *et al.* 1993). SPD patients have impairments in several areas, such as episodic (Cadenhead *et al.* 1999) and working memory (Roitman *et al.* 2000), cognitive inhibition (Moritz and Mass 1997), abstraction (Voglmaier *et al.* 1997), and sustained attention (Roitman *et al.* 1997). In a recent paper (Mitropoulou *et al.* 2005), we argued that the entire signature of cognitive impairments in SPD patients could be explained by deficits in working memory. Thus, the search for pharmacological interventions for these cognitive impairments should logically focus on compounds with promise to reduce working memory abnormalities.

The role of the noradrenergic system in normal cognitive functions has been systematically evaluated in numerous animal studies, and it appears that the prefrontal cortex (PFC) is particularly important for tasks that require working memory and sustained attention (Friedman *et al.* 1999). A recent vein of research, focusing on the role of norepinephrine in the treatment of deficits in these domains, has demonstrated that the activation of α_{2A}-adrenoceptors (for review, see Arnsten 2004) may ameliorate some of these cognitive limitations. Pharmacological agents such as guanfacine, an α_{2a} agonist that acts post-synaptically in the PFC, would thus seem to be promising intervention possibilities. The one published study (Friedman *et al.* 2001) that attempted to use guanfacine to treat cognitive impairments in schizophrenia had encouraging results, in that working memory and vigilance were specifically improved, but findings of an interaction with type of antipsychotic medication patients were taking made the establishment of clear efficacy for guanfacine in schizophrenia challenging. Thus, the examination of guanfacine for cognitive impairment in SPD seems a reasonable step, as SPD patients demonstrate cognitive deficits that are intrinsically related to working memory but are largely free from the potential confounds found in schizophrenia samples, such as psychosis and the effects of antipsychotic medications (Siever *et al.* 1993).

We have also shown that individuals with SPD, like individuals with schizophrenia, experience a substantial deficit in the ability to appropriately represent and maintain contextual information (Barch *et al.* 2004). Context is defined as prior task-relevant information that is represented in such a form that it influences selection of the appropriate behavioral response. Such context representations can include task instructions, a specific prior stimulus, or the result of processing a sequence of prior stimuli. Thus, three cognitive functions that are often treated as independent—attention, active memory, and inhibition—are all influenced by a single mechanism responsible for the processing of context (Cohen *et al.* 1999). Therefore, Cohen and colleagues have argued that disturbances in attention, working memory, and inhibition in schizophrenia can all be understood in terms of a deficit in context-processing (Barch *et al.* 2001; Braver *et al.* 1999; Braver and Cohen 1999; Cohen *et al.* 1999; Cohen and Servan-Schreiber 1992).

This deficit is revealed during performance of the modified AX-Continuous Performance Task (AX-CPT). Participants are presented with cue-probe pairs and are told to respond affirmatively to an "X" (probe), but only when it is preceded by an "A" (cue). The task also includes three types of non-target trials that allow one to selectively assess context processing deficits: AY trials ("A" cue followed by any letter other than "X"); BX trials (non-"A" cue

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followed by an "X" probe); and BY trials (non-"A" cue followed by a non-"X" probe). The target, or AX, trials occur with high frequency (70%), creating two important response biases. First, this high AX frequency creates a bias to make a target response to any stimulus following an A cue (as a probe "X" occurrence is highly likely following an "A" cue). In healthy individuals, maintenance of context is demonstrated by the tendency to make a false alarm after occurrence of the A cue (leading to increased AY errors), or a slowing of reaction times on correct AY responses (as the prepotent bias to make a target response needs to be overcome). The second bias created by the high AX frequency is the tendency to make a target response to the "X" probe, as this is the correct response the majority of the time. On BX trials, maintenance of the context provided by the cue (non-A) is needed to prevent BX false alarms. Therefore, on the AX-CPT, deficits in context processing are not indicated by an overall increase in any type of false alarm, but rather a specific pattern (decreased AY errors and increased BX errors). Thus, successful performance on the AX-CPT depends upon an individual's ability to attend to the stimuli, maintain stimuli in working memory, and effectively use the prior information of the cue when deciding whether or not to respond to the probe. In our previous study, patients with SPD made fewer AY than BX errors (Barch *et al.* 2004), in contrast to healthy individuals where these error tendencies were reversed. Such a pattern in SPD individuals is consistent with a specific deficit in context processing and in working memory, similar to that found in individuals with schizophrenia (Barch *et al.* 2001; Braver *et al.* 1999; Braver and Cohen 1999; Cohen *et al.* 1999; Cohen and Servan-Schreiber 1992), as maintenance of the cue in working memory would result in a higher rate of AY errors and a lower rate of BX errors.

The goal of the present study was to evaluate the ability of guanfacine to improve context processing in individuals with SPD, indexed by more "normal" performance on the AX-CPT, in a double-blind, placebo controlled study. We hypothesized that guanfacine would lead to a reduction in the BX errors and an increase in the AY errors made by individuals in the SPD group, so that their post-treatment performance would be more similar to the way that healthy controls have performed in prior studies.

Methods and Materials

Participants

Participants were 29 individuals with DSM-IV SPD. Recruitment, diagnosis, and exclusion criteria have been presented in previous publications (for a full description, please see Mitropolou *et al.* 2005). Consensus diagnoses were reached in a meeting of all raters with an expert diagnostician (k = .73 for SPD). Demographic characteristics are shown in Table 1. All participants signed informed consent forms in accordance with the IRB approvals of this study at both the James J. Peters VAMC and Mt. Sinai School of Medicine.

Table 1. Sample Characteristics

	Guanfacine Group $N = 20$	Placebo Group $N = 9$
	M (SD)	M (SD)
Age (in years)	38.6 (11.2)	40.3 (8.2)
Sex (% male)	65.0	88.9
Education (in years)	14.9 (2.2)	14.2 (4.1)
Vocabulary Score	10.3 (2.8)	10.2 (2.9)
Block Design Score	9.9 (2.7)	10.2 (3.7)

AX-CPT Task. Participants performed three conditions of the AX-CPT: standard, degraded and interference; due to space limitations, only the standard version will be considered. Sequences of letters were visually presented one at a time in a continuous fashion on a computer display. Participants were instructed to make an affirmative response on target trials and a negative response otherwise (for a full description, please see Barch *et al.* 2004). The delay between cue and probe was manipulated so that half of the trials had a short delay and half had a long delay. On short delay trials, the cue-probe interval was 1 sec, and the inter-trial interval was 4900 msec. On long delay trials, the cue-probe interval was 5 sec and the inter-trial interval was 1 sec. Thus, the total trial duration was equivalent across conditions, providing a means of controlling for general factors that might affect performance (e.g., pace of the task, response frequency, total time on task). The task was presented in 4 blocks of 50 trials, all of which were either short (2 blocks) or long (2 blocks) delay trials, with the order of short and long delay blocks counterbalanced across subjects. Participants were asked to respond as quickly as possible to each stimulus while maintaining accuracy.

Procedure

Following a baseline assessment, participants entered into a 4-week, double-blind, parallel design treatment phase during which they were randomly assigned to receive either guanfacine or placebo, followed by an open-label extension. Participants were assigned at a 2:1 ratio for guanfacine as compared to placebo. Participants on active drug were titrated to 2.0 mg daily over the first two weeks and remained on 2.0 mg for the duration of the study. The AX-CPT was administered at baseline and repeated biweekly.

Data Analysis

Data were analyzed using error rates (misses on AX trials and false alarms on all other trials) and reaction times (medians for correct trials) following double-blind treatment, with a last observation carried forward (LOCF) plan. We focused on the two error types that have been shown to be most sensitive to the integrity of context processing performance (BX and AY) at the two delay conditions (short and long), across the two treatment conditions (active and placebo) within each subject group. We used an ANCOVA with trial type (AY, BX), delay (short, long), and session (baseline, post-treatment) as within-subject factors and treatment (placebo, active) as the between-subjects factor. WAIS-R Vocabulary and Block Design Scores were included as covariates, to adjust for individual differences in IQ.

Results

The ANCOVA revealed a main effect of trial type, $F(1,24) = 4.58$, $p<.05$, with overall more BX than AY errors. There was also a session by trial type by treatment interaction, $F(1,24) = 7.6$, $p<.05$. To understand the source of the session by trial type by treatment interaction, we computed separate trial type by treatment ANCOVAs for the baseline and post-treatment sessions. There was a significant trial type by treatment interaction for the post-treatment scores, $F(1,24) = 5.07$, $p<.05$, but not for baseline scores, $F(1,24) = .03$, $p>.8$.

As illustrated in Figure 1, planned contrasts indicated that BX errors showed the predicted decrease from baseline to post-treatment with guanfacine ($p<.05$), consistent with an improvement in context processing. In contrast, BX errors actually showed a significant increase from baseline to post-treatment with placebo ($p<.05$). Also as predicted, there was a small but significant increase in AY errors from baseline to post-treatment with guanfacine ($p<.05$), a