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Effects of the D₁ dopamine receptor agonist dihydroxidine (DAR-0100A) on working memory in
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ABSTRACT

Pharmacological enhancement of prefrontal D₁ dopamine receptor function remains a promising therapeutic approach to ameliorate schizophrenia-spectrum working memory deficits, but has yet to be rigorously evaluated clinically. This proof-of-principle study sought to determine whether the active enantiomer of the selective and full D₁ receptor agonist dihydrexidine (DAR-0100A) could attenuate working memory impairments in unmedicated patients with schizotypal personality disorder (SPD). We performed a randomized, double-blind, placebo-controlled trial of DAR-0100A (15 mg/150 mL of normal saline administered intravenously over 30 minutes) in medication-free patients with SPD (n=16) who met criteria for cognitive impairment (i.e., scoring below the 25th percentile on tests of working memory). We employed two measures of verbal working memory that are salient to schizophrenia-spectrum cognitive deficits, and clinical data implicate as being associated with prefrontal D₁ availability: 1) the Paced Auditory Serial Addition Test (PASAT); and 2) the N-back test (ratio of 2-back:0-back scores). Study procedures occurred over four consecutive days with working memory testing on Days 1 and 4, and DAR-0100A/placebo administration on Days 2-4. Treatment with DAR-0100A was associated with significantly improved PASAT performance relative to placebo, with a very large effect size (Cohen's $d = 1.14$ for both tests). Performance on the N-back ratio was also significantly improved, however, this effect rested on both a non-significant enhancement and diminution of 2-back and 0-back performance, respectively; therefore interpretation of this finding is more complicated. DAR-0100A was generally well tolerated, with no serious medical or psychiatric adverse events; common side-effects were mild-to-moderate and transient, consisting mainly of sedation, lightheadedness, tachycardia, and hypotension; however, we were able to minimize these effects, without altering the dose, with supportive measures, e.g., co-administered normal saline. Although preliminary, these findings lend further clinical support to the potential of D₁ receptor agonists to treat schizophrenia-spectrum working memory impairments. These data

suggest a need for further studies with larger group sizes, serum DAR-0100A levels, and a more comprehensive neuropsychological battery.

KEYWORDS:

schizophrenia; cognition; working memory; dopamine; schizotypal personality disorder

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INTRODUCTION

Cognitive deficits are a critical determinant of functional outcomes in schizophrenia and related psychiatric conditions (Green 2006), yet they remain relatively resistant to standard treatment (Keefe 2007) approaches. A number of experimental agents with preclinical promise have, unfortunately, yielded disappointing results in clinical trials (Buchanan et al. 2011; Egan et al. 2013; Harvey 2009; Velligan et al. 2012). Numerous studies have established that compromised working memory function is a central component of schizophrenia-spectrum cognitive deficits (Goldman-Rakic 1994). Therefore, targeting mediators of working memory, particularly those with pathophysiological significance, is an essential approach to developing effective therapeutics for the cognitive impairments of the schizophrenia spectrum.

There is an abundant experimental literature demonstrating the critical role of the D₁ dopamine receptor in the modulation of working memory in the dorsolateral prefrontal cortex (DLPFC) (Goldman-Rakic et al. 2004). Furthermore, frontocortical D₁ receptor availability has been shown to be relatively increased in antipsychotic-naïve patients with schizophrenia; and this has been proposed to reflect compensatory, albeit insufficient, D₁ up-regulation in response to possible cortical hypodopaminergia in the schizophrenia-spectrum (Abi-Dargham 2003). Therefore, pharmacological enhancement of D₁ receptor activity is a highly promising therapeutic mechanism for the amelioration of schizophrenia-spectrum cognitive deficits. Importantly, however, there have been barriers to the development of pharmacological agents with D₁ agonist activity (Mailman et al. 2001; Zhang et al. 2009), and therefore, enhancement of working memory in the schizophrenia-spectrum via direct D₁ stimulation has yet to be studied definitively in the clinical setting.

Although it was recognized by the late 1970's that there were two major populations of dopamine receptors (Garau et al. 1978; Keabian and Calne 1979), the prototypical D₁ agonist SKF38393 (Setler et al. 1978) was of limited experimental utility largely due to the fact that it

had low intrinsic activity (Gilmore et al. 1995; Watts et al. 1993; Watts et al. 1995). It was a decade before dihydrexidine (DHX), the first selective and full D₁ agonist, was described (Lovenberg et al. 1989). DHX exhibits more than ten-fold higher affinity and potency at the D₁ receptor than dopamine; and, exhibits full intrinsic activity in every system in which it has been tested to date (Brewster et al. 1990; Mottola et al. 1992; Salmi et al. 2004; Watts et al. 1995). DHX has about ten-fold selectivity for the D₁ versus the D₂ receptor (Mottola et al. 1992), and, at the D₂ receptor it is functionally selective with high bias for regulation of adenylate cyclase versus potassium channels (Gay et al. 2004; Kilts et al. 2002; Mailman 2007; Mottola et al. 2002). When DHX entered development in 2002, it was assigned the label DAR-0100, and the active (both at D₁ and D₂) diastereomer (Knoerzer et al. 1994; Mottola et al. 1996) assigned the label, DAR-0100A.

Although discovered more than 20 years ago, DHX remains the prototypical full, selective D₁ agonist. DHX has been shown to enhance working memory in animal models in normal and pathological states (Arnsten et al. 1994; Schneider et al. 1994), yet clinical testing of DHX has been limited for at least two reasons: First, the drug has a very short duration of action, and can only be given parenterally in currently available formulations. Secondly, an initial Phase I/IIa study in Parkinson's disease subjects showed some efficacy, but also resulted in profound hypotension (Blanchet et al. 1998). Later developmental work, however, demonstrated that the drug could be used safely (George et al. 2007), and this provided the foundation for an NIMH-sponsored Cooperative Drug Development Group project (awarded to our Columbia University collaborators) that synthesized the active enantiomer, DAR-0100A, and obtained an *Investigational New Drug* (IND) application to optimize clinical infusion parameters, and examine the effects of DAR-0100A on cognitive function in schizophrenia and related conditions. Our group subsequently obtained an IND to examine DAR-0100A in the schizophrenia-spectrum, as well.

Evaluating the efficacy of novel agents (e.g., DAR-0100A) to attenuate cognitive

impairment in schizophrenia is made difficult by factors such as concurrent/past medication, stage of illness and prior psychotic episodes, relatively global cognitive deficits, and chronic psychosocial stress related to profound functional impairment. One approach to addressing these confounds is to study patients with schizotypal personality disorder (SPD), a schizophrenia-spectrum condition that manifests qualitatively similar working memory deficits that are narrower in scope and severity (Mitropoulou et al. 2002; Mitropoulou et al. 2005). Our prior studies of patients with SPD have shown dopaminergically-mediated improvement of schizophrenia-spectrum cognitive deficits. This effect was first demonstrated with amphetamine (Siegel, Jr. et al. 1996; Kirrane et al. 2000) that increases catecholaminergic activity globally, and more recently with pergolide (McClure et al. 2010), a mixed D_2/D_1 agonist with partial D_1 agonist activity. No published clinical studies to date have demonstrated the efficacy of selective D_1 agonists to mitigate schizophrenia-spectrum cognitive impairments.

Therefore, we have examined whether treatment with DAR-0100A could ameliorate the schizophrenia-spectrum cognitive deficits of unmedicated patients with SPD using two tests of verbal working memory: the PASAT and N-back tests. We specifically selected these two tests of working memory because they consistently reveal cognitive impairments of patients with SPD (Mitropoulou et al. 2002; McClure et al. 2008), and because of the relationship between greater frontocortical D_1 availability (which may reflect D_1 under-stimulation) and degree of impairment of PASAT (Thompson et al. 2014) and N-back performance (Abi-Dargham et al. 2002) in the schizophrenia-spectrum. Furthermore, among a broad array of cognitive function tests, we have shown that PASAT performance accounts for a substantial component of the variance between SPD patients and healthy controls, implicating the salience of this test for assessing cognitive impairment in SPD (Mitropoulou et al. 2005).

METHODS

Participants

The study was approved by the Institutional Review Boards of the Mount Sinai Medical

Center and the James J. Peters Bronx Veterans Affairs Medical Center. Participants provided written informed consent after explanation of study procedures. Participants were recruited from the local population through newspaper advertisements and the internet. All participants underwent a medical clearance, consisting of a medical history by a study physician, physical exam, basic blood and urine tests, and electrocardiogram. All participants were free of significant medical/neurological problems, and were not pregnant or nursing. Sixteen participants (11 male [M] 5 female [F]; mean age = 35.9 years [SD = 12.2, range = 20-55) met criteria for schizotypal personality disorder (SPD). The Structured Clinical Interview for DSM-IV Axis I Disorder was used for Axis I diagnoses, and the Structured Interview for DSM-IV Personality Disorders (SIDP-IV) was used for Axis II diagnoses.

Participants with active suicidal ideation, as well as participants who met criteria for major psychotic disorders (such as bipolar I or schizophrenia), or participants who currently met DSM-IV-TR criteria for a Major Depressive Episode were excluded from participation and referred for appropriate treatment. Participants had neither abused illicit substances nor alcohol within the past six months, nor had a past history of substance dependence. All patients were negative on a urine toxicology screen to rule out current use of common substances of abuse. Participants were excluded if they did not exhibit cognitive impairment, as defined by scoring at or below the 25th percentile of published scores for healthy participants on at least one test of working memory battery that included the PASAT, N-back test, and Dot test. Of note, the Dot test -- a measure of visuospatial working memory -- was originally included as a secondary measure; however, too few patients completed the Dot test, and therefore, it was ultimately not included in our final analyses.

Treatment Design

The protocol occurred over four consecutive days that included baseline cognitive testing (see *Cognitive Assessments*, below), and urine drug (and pregnancy, for women of child bearing age) screening on Day 1. On days 2-4, an intravenous (i.v.) catheter was placed by a

qualified nursing staff member of the Clinical Research Unit (CRU) of the Mount Sinai Medical Center; and either DAR-0100A (15 mg/150 mL of normal saline [NS]) or placebo (150 mL of NS) was intravenously infused at a rate of 300 mL/hour. Additionally, 133 mL of i.v. NS was co-infused (beginning five minutes prior to and ending five minutes after DAR-0100A/placebo infusion) at a rate of 200 mL/hour. Repeat cognitive testing (beginning approximately 20 minutes after the start of DAR-0100A/placebo infusion) was performed on Days 2 and 4. Serial liver function testing (LFT) was also performed because transient, clinically insignificant transaminase increases had been seen in three subjects in early studies at Columbia.

Participants were randomized in a double-blind manner to receive either DAR-0100A or placebo throughout the three days of infusion. Day 1 procedures (other than baseline LFT) took place in the research office of the Mood and Personality Disorders Group. Procedures for Days 2-4 occurred in the Clinical Research Unit (CRU) of the Mount Sinai Medical Center. On days 2-4, participants were semi-recumbent in a standard hospital bed with the upper body raised to approximately 45 degrees during cognitive testing. Participants were monitored by a study physician and the CRU nursing staff; and vital signs were obtained every five minutes during DAR-0100A/placebo infusion, and every 15 minutes for one hour after completion of the infusion.

Cognitive Assessments

Rationale for choice of cognitive assessments. Based on our prior studies in SPD and schizophrenia, we selected two tests of verbal working memory that we have demonstrated are impaired in SPD (McClure et al. 2008; Mitropoulou et al. 2002; Mitropoulou et al. 2005), and that evidence suggests are related to frontocortical D₁ availability (Abi-Dargham et al. 2002; Thompson et al. 2014): 1) the PASAT (Paced Auditory Serial Addition Test); and, 2) the N-back test. (As indicated above, the Dot test -- a measure of visuospatial working memory -- was originally included, however, data were available for too few participants.) Of note, we did not include neuropsychological tests that formally assess cognitive processes other than working

memory (e.g., attention, executive function, declarative memory, processing speed) given the short half-life of DAR-0100A, and the anticipated narrow window of opportunity for identifying a therapeutic effect.

PASAT: The PASAT is a test of auditory/verbal working memory. Participants are presented with a series of numbers (50 numbers at a rate of one digit per two seconds) by audiotape, and are asked to add each adjacent pair of numbers and report the sum. The total number of correct responses (range 0-49) was computed. We then calculated ratio scores (post-treatment minus baseline / baseline) in order to control for baseline differences in performance. This ratio score was the dependent variable in this study.

N-back test: The N-back test is an assessment of visual/verbal working memory. We employed two conditions: a) The 0-back -- a control condition which primarily assesses sustained attention -- in which participants are instructed to press a target button when presented with the letter "X"; and, b) The 2-back -- which requires working memory as well as sustained attention -- in which participants are instructed to press a target button when the letter appearing is the same as the letter that appeared two previous screens back. In order to account for individual differences in attentional functioning, N-back test scores are represented in terms of a 2-back:0-back ratio. We again calculated ratio scores (post-treatment minus baseline / baseline), in order to control for baseline differences in performance. This ratio score was the dependent variable.

Data Analysis

Between-group t-tests were used to examine potential group (DAR-0100A and placebo) differences of baseline scores and percent change scores (post-treatment minus pre-treatment). A two group Chi square test was used to examine potential group differences of baseline gender ratios.

RESULTS

The average age of the 16 participants (11 M, 5 F) who were diagnosed with SPD and completed the study was 35.9 years (SD=12.2, range=20-55) (Table 1). The DAR-0100A (n=8) and placebo (n=8) groups were comparable with respect to age and gender (Table 1). The two groups did not differ significantly on baseline cognitive scores (Table 2).

Comparisons of change scores of our tests of verbal working memory between the two groups are illustrated in Table 2 (note that one of the participant's N-back data in the DAR-0100A group was lost due to computer error, and therefore could not be included in the N-back analysis). Compared to placebo (Figure 1), the DAR-0100A group exhibited significantly greater improvement in the PASAT ($t=-2.27$, $df=14$, $p=0.04$), with a very large effect size (Cohen's $d=1.14$).

The effect of DAR-0100A treatment on N-back performance was less clear than that of the PASAT, however. As shown in Table 2, the N-back ratio was significantly improved in the DAR-0100A group relative to placebo ($t=-2.23$, $df=13$, $p=0.04$). Similar to the effect on the PASAT, improvement of N-back ratio was associated with a very large effect size (Cohen's $d=1.14$). However, this effect on the N-back ratio was determined by both a non-significant improvement, with a moderate effect size [Cohen's $d=0.46$], in 2-back performance, as well as a non-significant decrease in 0-back performance, also with a moderate effect size [Cohen's $d=-0.57$]. Given the contribution of the non-significant decrease in 0-back performance to the improvement of the N-back ratio, the significance of improved N-back ratio performance is less clear than that of the PASAT. We suspect that side-effects may have non-specifically led to a possible diminution of non-delayed cognitive processes that underlie 0-back performance. Improvement of N-back ratio performance may suggest DAR-0100A enhanced working memory despite some attenuation of non-delayed perceptual/attentional processes.

DAR-0100A was relatively well tolerated, with no clinically significant adverse events. Side-effects were mild to moderate and transient, consisting of: lightheadedness, sedation,

subjective facial flushing, subjective racing heart, moderate tachycardia and clinically insignificant decreases in systolic blood pressure. No immediate or delayed psychiatric side effects were associated with DAR-0100A treatment, and no LFT changes occurred in any of the participants.

DISCUSSION

This is the first published study to examine the effects of a selective D₁ agonist on salient measures of working memory function in a clinical population with schizophrenia-spectrum cognitive deficits without important confounds such as concurrent psychotropic medication, psychosis, substance abuse, and pervasive functional impairment. While our findings must be interpreted with caution, they do suggest that pharmacological enhancement of D₁ receptor activity may mitigate schizophrenia-spectrum working memory impairments. Important limitations of our study that must be taken into consideration are small sample size, the lack of serum drug concentrations, and the fact that improvement on the N-back ratio in the DAR-0100A treated group was due to a non-significant improvement in the 2-back and a non-significant decline of 0-back performance.

Treatment with DAR-0100A, under our optimized infusion parameters, was not associated with any dose-limiting side effects or significant medical sequelae. DAR-0100A was generally well-tolerated, and side-effects were transient, consisting primarily of facial flushing, lightheadedness, sedation, subjective racing heart, as well as minor increases in heart rate and clinically insignificant hypotension, all of which resolved prior to or soon after completion of drug infusion. No serious cardiovascular or hepatic function abnormalities occurred, and there were no acute or delayed-onset psychiatric side-effects. Specifically, there was no evidence of depression, mania, psychosis, agitation, anxiety, or confusion/disorientation on the days of drug infusion or at a 1-2 week follow-up.

The first reported studies of DHX effects on cognitive function were performed in

primates, and demonstrated cognitive enhancement in young, aged, and reserpine-treated animals (Arnsten et al. 1994), as well as chronic, low dose MPTP-treated primates (Schneider et al. 1994). Furthermore, in rodent models, DHX also was shown to improve both native processes and reverse scopolamine-induced deficits (Steele et al. 1997), as well as attenuate PCP-induced deficits of NMDA-R activity (Lei et al. 2009).

As noted earlier, there have been two prior reported clinical studies with DHX: The first, in Parkinson's disease (Blanchet et al. 1998), showed anti-parkinsonian efficacy in one of four patients who received the highest dose (35 mg/15 minutes, i.v.), but clinically significant hypotension occurred that was dose limiting despite lengthening the infusion time from 15 to 120 minutes. Almost a decade later, administration of a single, subcutaneous dose of 20 mg of DHX was found to be well-tolerated in patients with schizophrenia who were medicated with risperidone (George et al. 2007). In this latter study, DHX treatment was associated with increases in prefrontal, as well as temporal and parietal cortical, perfusion (Mu et al. 2007), and a significant improvement on a 2-back task, but only on the second day after treatment (Johnson, George, et al., personal communication). The latter result is difficult to resolve because of experimental confounds (e.g., neuropsychological testing delayed for many hours after drug; etc.). The current study had several design advantages: First, we used a somewhat higher active dose (i.e., 15 mg of the active enantiomer DAR-0100A rather than 20 mg of the racemate); cognitive testing was done sooner after completion of DAR-0100A infusion; neuropsychological tests were used that were particularly salient to schizophrenia-spectrum working memory deficits; and patients were not receiving concurrent neuroleptics nor did they suffer from pervasive functional impairment. Our data clearly show that a D₁ full agonist can markedly improve schizophrenia-spectrum working memory deficits, at least acutely.

As with any drug, the question is whether the effect we have found with DAR-0100A can be ascribed solely to activation of D₁ receptors. There are two primary off-target receptors that should be considered in the actions of DHX: the dopamine D₂ and the α_2 -adrenergic receptor

(Mottola et al. 2002). The one of greater importance is the D_2 since DHX is only ten-fold $D_1:D_2$ selective (Mottola et al. 2002). As noted earlier, however, DHX has unique functionally selective properties at D_2 receptors, having full agonist effects at D_2 -dependent inhibition of adenylate cyclase versus little or no intrinsic activity at G protein-coupled inwardly rectifying potassium channels (Gay et al. 2004; Kilts et al. 2002; Mailman 2007; Mottola et al. 2002). This probably explains why, even at very high doses, DHX does not have amphetamine-like actions *in vivo* (Darney, Jr. et al. 1991) as would be expected from a drug activating both D_1 and D_2 receptors. Moreover, the turning induced by DHX in unilateral 6-OHDA rats is completely blocked by selective D_1 antagonists, but not decreased by D_2 antagonists (in contrast to the typical $D_2:D_1$ agonist apomorphine where each type of antagonist will attenuate the turning). In addition, DHX lessens psychomotor activity (an effect attenuated by D_1 but not D_2 , antagonists), actually antagonizing amphetamine-induced increases in motor activity, and causes immediate early gene expression changes in the medial prefrontal cortex that are sensitive to D_1 but not D_2 antagonists (Isacson et al. 2004).

The other potentially important off-target locus is the α_2 -adrenergic receptor. It is not known what the functional characteristics of dihydrexidine are at this receptor, but we do know the drug is ~50-fold $D_1:\alpha_2$ selective. PET studies have shown that D_2 occupancy is unlikely to be important with clinical doses of DHX (Slifstein et al. 2011), and since the α_2 -adrenergic affinity is five-times lower than the D_2 , it seems unlikely that the current data were affected by α_2 -adrenergic effects. Nonetheless, more detailed future studies with dihydrexidine and with newer D_1 agonists will be needed to provide a conclusive test of this hypothesis.

It is also important to take into consideration that the animal studies of working memory functional effects of D_1 agonists demonstrate an inverted U-shaped dose-response curve rather than a plateauing. Based on the published pharmacology of DAR-0100A in humans, the doses we used result in very low blood concentrations that are almost certainly in the ascending phase

of the dose-response curve of this drug, being less than those which cause cognitive enhancement in non-human primates (Arnsten et al. 1994; Schneider et al. 1994). Nonetheless, this assumption will need to be tested in further studies in which a therapeutic range for DAR-0100A and other D_1 agonists is determined, as this has significant implications for the clinical utility of this class of drug.

Although there have been many selective full D_1 agonists discovered during the past 25 years, only two compounds (DHX and ABT-431) have resulted in reports of clinical studies. ABT-431 is a prodrug of A-86929 that has *in vitro* pharmacology almost identical to DHX (Michaelides et al. 1995; Mottola et al. 1992). The data from both compounds allows us to speculate on other side effects that are attributed to dopamine agonists as a general class, including nausea, the exacerbation of psychoses, and drug-abuse related behaviors. There is a sizable literature that suggests that nausea and psychosis exacerbation are largely mediated by D_2 receptors. The issue of drug abuse liability is more complex as some studies in murine species suggest D_1 agonists have potential liability (Graham et al. 2007). On the other hand, it has been reported that ABT-431 actually decreased cocaine craving (Giardina and Williams 2001) suggesting that clinically this will not be problematic.

A number of important study limitations need to be addressed: The sample size was modest; we did not assess serum drug concentrations; and cognitive domains other than those related to working memory (such as attention, executive function, and declarative memory) were not examined. Although we did collect serial blood samples during the second day of drug/placebo infusion, these will not be analyzed until a later date once we have accrued enough samples to send out for analysis. In our current funded study, however, we are assessing a broad array of cognitive processes, and therefore, we will be able to assess the specificity of effects of DAR-0100A.

An additional matter worthy of addressing is that improvement of the N-back ratio was due to non-significant increases and decreases, respectively, of 2-back and 0-back

performance. Taking into account that performance on the PASAT was significantly improved in the DAR-0100A treated group, a plausible explanation for the mixed result on the N-back is that working memory function may have been enhanced despite a possible attenuation of non-delayed attentional/perceptual processes. It is also possible that the N-back (a visual, verbal working memory task) is not as sensitive to enhancement by DAR-0100A as is the PASAT (an auditory, verbal working memory task). This is consistent with our recent finding that frontocortical D₁ receptor availability in patients with SPD was negatively correlated with PASAT performance, but not that of the 2-back (Thompson et al. 2014). We speculate that any attenuation of non-delayed attentional/perceptual processes (e.g., 0-back performance) in the DAR-0100A group may have been due to side-effects such as sedation, and light-headedness. However, it is also possible that the 15 mg dose was too high and eroded cognitive improvement, given the inverted-U dose response function of D₁ agonists. This issue could be addressed in future studies where side effects are minimized by supportive measures, or lower doses are assessed for effects on cognition.

Although side effects were mild, transient and without significant clinical impact, their potential for breaking the blind is an additional study limitation. Anecdotal evidence from our Columbia colleagues (Girgis, personal communication) suggests participants were unable to correctly identify whether they were receiving DAR-0100A or placebo. Furthermore, in this study, the physician who performed clinical monitoring did not administer the working memory tests; and, research personnel who did administer neuropsychological testing were not monitoring side effects and vital signs. Nevertheless, we cannot rule-out the possibility that failure to absolutely maintain the blind may have confounded our results.

In an effort to confirm our findings and address these limitations, we are currently conducting a large, randomized, placebo-controlled, cross-over trial of DAR-0100A in patients with SPD using a more comprehensive neuropsychological battery of working memory and verbal learning tasks, as well as those assessing more basic cognitive processes, and serial

assessment of serum drug levels. Even within the current limitations, the findings of this study should provide an impetus for the discovery and development of novel D₁ agonists that would have improved pharmacokinetic properties including longer half-life and greater oral bioavailability and may ultimately be helpful in psychiatric and neurologic disorders characterized by working memory impairment including schizophrenia spectrum disorders and attention deficit related disorders.

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Dr. Mailman has a conflict-of-interest as it relates to existing and pending patents in the D₁ agonist area, and has an equity interest in Effipharma Inc. that is the assignee of one patent application. He has received compensation in the last three years as a consultant in related areas from Pfizer and Roche. His conflict-of-interests are managed by a standing committee at the Penn State College of Medicine, and he was not involved in the subject testing for this study or the primary data analysis. The remaining authors declare no conflict of interest; however, the following authors have relationships with pharmaceutical companies; specifically: Dr. Barch has consulted for Amgen, Roche, and Pfizer and received compensation. Dr. Harvey has served as a consultant to AbbVie, Boehringer Ingelheim, En Vivo, Genentech, Otsuka-America, Roche, Sunovion, and Takeda Pharmaceuticals. Dr. Harvey is also doing contract research for Genentech. Dr. Girgis receives research support from Otsuka Pharmaceuticals. Dr. Abi-

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TABLES

Table 1. Demographics of Subjects

	Placebo Group	DAR-0100A Group	<i>p</i> value ¹
Age (years)	32.1 (10.4)	39.8 (13.3)	0.22
n (Male:Female)	5:3	6:2	1.0

Note. Values represent mean (SD).

¹ *p* values derived from t-tests, except for M:F ratio comparisons, chi-square was used.

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Table 2. Comparison of Change Scores Between DAR-0100A and Placebo Groups

Cognitive Test	Placebo		DAR-0100A		Change Score (%)		Group Comparison		
	<i>Baseline</i>	<i>Post-Infusion</i>	<i>Baseline</i>	<i>Post-Infusion</i>	<i>Placebo</i>	<i>DAR-0100A</i>	<i>Cohen's d</i>	<i>t (df)</i>	<i>p</i>
PASAT ¹	32.1 (11.9)	31.6 (13.6)	28.5 (12.2)	34.6 (12.6)	1.69 (26.5)	26.0 (14.7)	1.14	-2.27 (14)	0.04
N-back ^{2,3} :									
<i>2-back:0-back ratio</i>	0.92 (0.07)	0.95 (0.11)	0.84 (0.15)	0.93 (0.11)	3.12 (6.03)	12.1 (9.48)	1.14	-2.23 (13)	0.04
<i>2-back</i>	0.88 (0.11)	0.89 (0.10)	0.78 (0.14)	0.82 (0.13)	1.82 (7.92)	5.66 (8.77)	0.46	-0.89 (13)	0.39
<i>0-back</i>	0.95 (0.07)	0.94 (0.06)	0.94 (0.06)	0.89 (0.09)	-1.03 (8.83)	-5.54 (6.74)	-0.57	1.10 (13)	0.29

Note. Values represent mean (SD). PASAT=Paced Auditory Serial Addition Test.

¹ PASAT values represent number of correct answers -- highest possible score is 49.

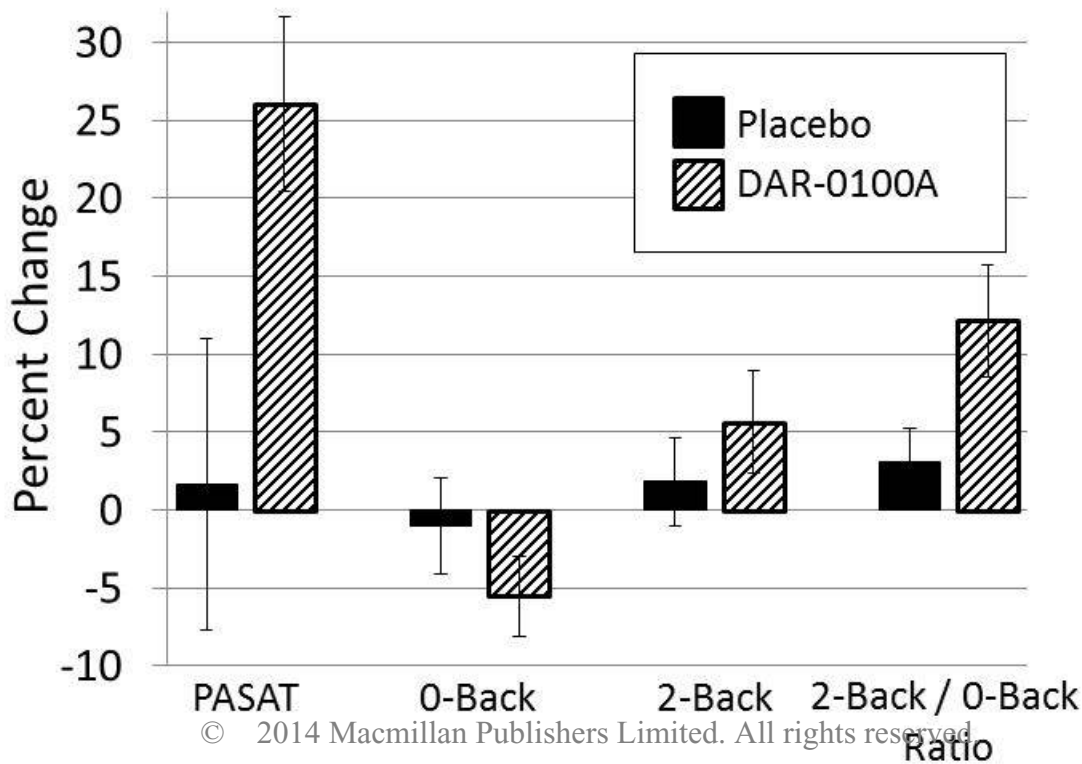
² N-back values represent proportion of correct answers.

³ n=7 for DAR-0100A N-back owing to loss of one participant's data because of computer error

FIGURE LEGEND

Figure 1. Percent-change scores for the PASAT, 0-back, 2-back, and N-back ratio (2-back / 0-back). Scores for the PASAT and N-back ratio were significantly greater in the group treated with DAR-0100A compared to placebo. Error bars represent the standard error of the mean.

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