Available online at www.sciencedirect.com

SCIENCE DIRECT®

Schizophrenia Research 77 (2005) 43–58

SCHIZOPHRENIA RESEARCH

www.elsevier.com/locate/schres

Amphetamine improves cognitive function in medicated individuals with schizophrenia and in healthy volunteers

Deanna M. Barch[a,b,*], Cameron S. Carter[c,d,1]

[a]*Department of Psychology, Washington University, United States*
[b]*Department of Psychiatry, Washington University, United States*
[c]*Department of Psychology, University of Pittsburgh, United States*
[d]*Department of Psychiatry, University of Pittsburgh, United States*

Received 22 April 2004; received in revised form 28 December 2004; accepted 30 December 2004
Available online 8 February 2005

Abstract

Background: Recent research on schizophrenia indicates that cognitive deficits in this illness are important predictors of functional outcome, highlighting the need for treatments that have a positive impact on cognitive function. Here we explore the hypothesis that acute administration of D-amphetamine can improve cognitive function in individuals with schizophrenia who are well-treated with typical antipsychotics, as well as in healthy controls performing under dual task conditions designed to elicit performance deficits analogous to those found in schizophrenia.
Methods: Ten individuals with schizophrenia taking haldol or prolixin and 22 healthy controls performed spatial working memory, language production, and Stroop tasks under both placebo and 0.25 mg/kg of D-amphetamine.
Results: D-Amphetamine improved reactions times on the spatial working memory and Stroop tasks for both individuals with schizophrenia and controls, and improved working memory accuracy in schizophrenia. In addition, D-amphetamine improved language production for both individuals with schizophrenia and controls.
Conclusions: These results provide support for the hypothesis that the adjunctive administration of dopamine agonist can improve cognitive in individuals with schizophrenia taking typical antipsychotics. The results are discussed in terms of their implications for understanding the nature of working memory deficits in schizophrenia, and potential future avenues for cognitive enhancement in this illness.

Keywords: Schizophrenia; Working memory; Amphetamine; Language production; Selective attention

1. Introduction

A growing body of research indicates that cognition in schizophrenia is critically important for functional outcome. For example, the severity of cognitive

* Corresponding author. Department of Psychology, Washington University, Box 1125, One Brookings Drive, St. Louis, MO 63130, United States. Tel.: +1 314 935 8729; fax: +1 314 935 4711.
E-mail address: dbarch@artsci.wustl.edu (D.M. Barch).
[1] Department of Psychiatry and Psychology, University of California at Davis.

0920-9964/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2004.12.019

deficits is more predictive of social and vocational outcome in schizophrenia than either positive or negative symptoms (Green, 1996; Harvey et al., 1998; Green et al., 2000; Gold et al., 2002). As has been highlighted by Keefe and Davidson, social and occupational impairments experienced by individuals with schizophrenia lead the largest indirect costs of this illness, both for the individual and for society (Sevy and Davidson, 1995). As such, if we could improve cognition in schizophrenia, and if improved cognition leads to reduced social and occupational dysfunction, such interventions could have a beneficial effect for both individuals with schizophrenia and for society (Davidson and Keefe, 1995).

The growing recognition of the central role of cognition in determining outcome in schizophrenia has lead to a dramatic increase in interest in evaluating whether existing therapies improve cognition, as well on developing new treatments for improving cognition in schizophrenia (Davidson and Keefe, 1995). While there is little evidence that typical antipsychotics improve cognition in schizophrenia (Goldberg and Weinberger, 1996), there is somewhat more evidence that the newer generation of atypical antipsychotics do a better job of improving cognitive function in schizophrenia than the typical antipsychotics (Keefe et al., 1999; Harvey and Keefe, 2001). These are modest effects whose functional significance remains unknown and the interpretation of these effects as specifically related to improved cognitive functioning, rather than an absence of negative side effects in comparison typical agents has also been challenged (Carpenter and Gold, 2002).

Another approach is to examine the use of adjunctive treatments, administered in addition to either typical or atypical antipsychotics, which may specifically target one or more cognitive functions in schizophrenia. For example, one cognitive function that is impaired in schizophrenia is working memory, typically defined as the ability to temporarily maintain and manipulate information (Baddeley, 1986). In part because of the working memory deficits shown by individuals with schizophrenia, there has been interest in agents that influence dopamine function as a potential type of adjunctive treatment for individuals with schizophrenia. This focus on dopamine is driven in large by findings in studies of non-human primates suggesting that optimal dopamine function is critical for working memory performance (Goldman-Rakic et al., 2000). For example, working memory function is impaired in non-human primates following 6-hydroxy-dopamine lesions in PFC (Brozoski et al., 1979), or administration of dopamine antagonists (Sawaguchi and Goldman-Rakic, 1994). In addition, administration of low dose DA agonists can improve working memory in monkeys (Williams and Goldman-Rakic, 1995), especially those with impaired performance (Arnsten et al., 1994; Cai and Arnsten, 1997; Castner et al., 2000).

There is also growing evidence that the administration of dopamine agonists can improve cognition in humans, including working memory. Methylphenidate (Clark et al., 1986; Elliott et al., 1997; Mehta et al., 2000), amphetamine (Mattay et al., 1996; Mattay et al., 2000), bromocriptine (Luciana et al., 1992; Kimberg et al., 1997; Luciana and Collins, 1997; Luciana et al., 1998), and pergolide (Muller et al., 1998; Kimberg and D'Esposito, 2003) have all been shown to improve working memory in healthy human participants. Interestingly, there is also research to suggest that dopamine agonists may be particularly effective for those individuals with the worst performance in the absence of drug (Kimberg et al., 1997; Mattay et al., 2000, 2003; Mehta et al., 2001; Kimberg and D'Esposito, 2003). For example, individuals with the high activity form of the COMT gene (leading to more catabolism of dopamine) have worse working memory performance than individuals with the low activity form of the COMT gene (Egan et al., 2001; Malhotra et al., 2002), and also show the greatest positive benefit of amphetamine (Mattay et al., 2003). Although several of these agents are not selective for dopamine, and it is likely that all of these drugs influence neurotransmitter systems other than the dopamine system, such results are generally consistent with the hypothesis that administration of dopamine agonists can improve working memory. Further, there is evidence that levodopa can improve working memory and related cognitive functions in individuals with impaired dopamine function, such as those with Parkinson's Disease (Cooper et al., 1992; Lange et al., 1995; Kulisevsky et al., 1996, 2000; Cools et al., 2002; Costa et al., 2003).

Interestingly, there is also some evidence that individuals with schizophrenia taking haloperidol

show improved performance on the Wisconsin Card Sort Task with the administration of amphetamine, despite minimal or no exacerbation of positive symptoms (Daniel et al., 1991; Goldberg et al., 1991). Further, individuals with schizotypal personality disorder also show improved performance on the Wisconsin Card Sorting Task and a spatial working memory task with the administration of amphetamine (Siegel et al., 1996; Kirrane et al., 2000). It has been suggested that cognition is improved with schizophrenia with the co-administration of haloperidol and amphetamine because treatment with a typical antipsychotic blocks D2 receptors in subcortical regions, preventing a negative impact of a dopamine agonists of positive symptoms, leaving D1 receptors in regions such as prefrontal cortex free to benefit for enhanced cholinergic transmission (Goldberg et al., 1991).

The goal of the current study was to further examine the hypothesis that adjunctive treatment with a dopamine agonist could improve at least some cognitive functions in medicated individuals with schizophrenia. To do so, we conducted a double-blind placebo controlled study of the acute effects of D-amphetamine (D-AMPH) on cognitive function in medicated individuals with schizophrenia and healthy controls. In the individuals with schizophrenia, we examined whether D-AMPH could improve their cognitive function on measures of working memory, language production, and selective attention. We choose measures of language production and selective attention in addition to a working memory measure because of the evidence that both are supported by working memory function in healthy individuals (Levelt, 1989; Cohen et al., 1999), and because language production and selective attention deficits are correlated with working memory deficits in schizophrenia (Docherty et al., 1996; Barch and Carter, 1998; Barch, 1999; Cohen et al., 1999; Kerns and Berenbaum, 2002; Melinder and Barch, 2003). However, we did not expect as strong an influence of D-AMPH in controls on such tasks, as controls typically perform close to ceiling on these measures at baseline. Therefore, we administered versions of each of the tasks to controls that were designed to reduce the their performance via a mechanism conceptually similar to that occurring in schizophrenia, an approach we have used successfully in past research (Barch and Berenbaum, 1994). Specifically, we administered version of the tasks that were designed to reduce the level of working memory capacity available to perform the primary task by asking subjects to simultaneously perform secondary tasks that also engaged working memory resources (e.g., "dual-task" manipulations).

2. Materials and methods

2.1. Participants

Participants were: 10 DSM-IV schizophrenic or schizoaffective patients and 22 normal controls (1 control was missing data on the spatial working memory tasks). The schizophrenic/schizoaffective patients were all outpatients at the Schizophrenia Treatment and Research Center at Western Psychiatric Institute and Clinic. All patients were deliberately selected to be on stable typical antipsychotics (haldol or prolixin) at constant dosages for at least 2 weeks. Patient diagnoses were based on the Structured Interview for DSM-IV (SCID) (Spitzer et al., 1990), and a review of the participant's medical records. Normal controls were recruited through local advertisements and were evaluated using the nonpatient SCID. Diagnostic interviews were completed by one of the authors (DMB, CSC) or a trained research assistant. Controls were excluded if they had any lifetime history of Axis I psychiatric disorder, or any first order family history of psychotic disorders. Potential participants were excluded for: (1) substance abuse within the previous 6 months; (2) neurological illness or history of head trauma with loss of consciousness; (3) mental retardation; (4) non-native English speaker; and (5) color blindness.

The demographic and clinical characteristics of both participant groups are shown in Table 1. The controls were similar to patients for age, gender, and years of parent education (to match approximately for socioeconomic status) and did not differ significantly on any of these variables. As expected, patients had lower education than controls. All participants signed informed consent forms in accordance with the University of Pittsburgh Medical School institutional review board. All participants were paid for their participation.

Table 1
Clinical and demographic characteristics

	Group				
	Healthy controls		Patients with schizophrenia		T-test (X^2)
	M		S.D.	M	
Age (in years)	36.6	8.7	40.3	5.7	1.31, $p>.2$
Sex (% male)	55		67		
Parent's education (in years)	14.4	2.7	13.2	1.8	0.96, $p>.3$
Education (in years)	16	2.6	13.4	2.0	2.64, $p<.05$
Placebo					
Disorganization symptoms	–		6.5	2.1	*−0.20, $p>.8$
Reality distortion symptoms	–		4.4	1.1	*−1.00, $p>.3$
Poverty symptoms	–		12.1	5.6	*0.40, $p>.6$,
Other symptoms	–		15	2.3	*−0.35, $p>.7$
D-Amphetamine					
Disorganization symptoms	–		6.6	1.8	
Reality distortion symptoms	–		4.9	2.2	
Poverty symptoms	–		11.7	6.0	
Other symptoms	–		15.4	2.9	

* Comparing placebo to D-amphetamine.

2.2. Procedure

The design of the study was a double-blind placebo controlled design. Each participant came in for evaluation on two different days, separated by no less than 2 days and no more than 7 days. On one day, participants received a placebo pill and on the other day participants received 0.25 mg/kg of D-AMPH orally, a moderate does similar to that used in prior studies (Mattay et al., 2000). The blinding was administered by the research pharmacy at the University of Pittsburgh Medical School. The study was run at the General Clinical Research Center at the University of Pittsburg Medical School. On each of the two study days, participants entered the GCRC at 8:00 am. Female participants completed a urine pregnancy screen upon admission (a positive test would have been an exclusion). Participants then completed an initial cognitive battery that lasted approximately 1 h to orient them to the tasks and to help equate practice effects at the post-drug/post-placebo testing. For the individuals with schizophrenia, this battery consisted of a structured language production interview, single-trial Stroop task, and a spatial working memory task. For the controls, this consisted of a single-trial Stroop task, a spatial working memory task, an arithmetic task (the secondary task for the dual-task Stroop and Spatial working memory tasks), and brief dual-task versions of a Stroop task and a spatial working memory task. Participants then completed a Profile of Mood States Questionnaire and patients received a brief assessment of clinical symptoms using the Positive and Negative Symptom Scale (PANSS) (Kay, 1991) (23 of 30 questions). Participants then took either the placebo or D-AMPH and rested quietly in their room for two and a half hours to allow the D-AMPH to metabolize and reach peak effect. Participants then completed the post drug/placebo cognitive testing. For controls, this consisted of the following tasks in counterbalanced order: 1) single and dual-task structure language interview; 2) single- and dual-task Stroop tasks; 3) single and dual-task spatial working memory tasks. For patients, this consisted of the following tasks in counterbalanced order: 1) structured language production interview; 2) single-trial Stroop task; and 3) spatial working memory task. After testing, all participants again completed a POMS, and patients were reevaluated with the modified PANSS.

2.3. Materials and tasks

A subset of the items from the PANSS was used to evaluate clinical state in the individuals with schizophrenia on each day of testing. Ratings were completed by two individuals at each day of testing, one of whom was a trained research assistant and one of whom either by a PhD level psychologist (DMB) or a psychiatrist (CSC), all of whom regularly participated in training and reliability sessions. The ratings used in the analyses presented below were the average of the two raters. We used 23 of the 30 PANSS items, eliminating items that we felt would either not be likely to change in response to D-AMPH, or for which we felt change could not be reliability assessed within a short time frame. Excluded items were: 1) passive social withdrawal; 2) difficulty in abstract thinking; 3) somatic concern; 4) uncooperativeness; 5) disorientation; 6) lack of judgment and insight; and 7) active social avoidance. Because we did not have the power to examine each individual symptom, symptoms were grouped into the three factors suggested by Liddle

(Liddle, 1987)—Reality Distortion, Poverty Symptoms, and Disorganization. Based on a review of studies examining the dimensional structure of the PANSS (Cuesta and Paralta, 1995), the following items were chosen for each scale: 1) delusions, hallucinations, suspiciousness, and unusual thought content for Reality Distortion; 2) blunted affect, emotional withdrawal, poor rapport, motor retardation, and lack of spontaneity for Poverty; and 3) conceptual disorganization, mannerisms and posturing, and poor attention for Disorganization. Interrater reliability, measured using intraclass correlations (Shrout and Fleiss, 1979) with raters treated as random effects and the mean of the raters as the unit of reliability, was 0.82 for Reality Distortion, 0.95 for Poverty Symptoms, 0.92 for Disorganization, and 0.78 for the sum of all other items not included in the three subscales.

2.4. Spatial working memory

In the single-task version of this paradigm, participants were presented with a dot that could appear in one of 18 different locations arrayed in a circle centered in the middle of the computer screen. After the dot appeared, an array of letters appeared with one letter in each of the 18 different locations (the letters appeared in a different random location on each trial, with target locations counterbalanced across visual hemifields). The participant then said which letter was in the location at which the dot had appeared, and the experimenter keyed in the participant's response to the computer. The participant's voice response into a microphone triggered the voice key in a specially constructed PsyScope button box, which recorded reaction time on the computer. Each participant performed one block of 24 trials in which the letter arrayed appeared immediately following the dot (no delay condition) and another block of 24 trials in which the letter array appeared 8 s following the dot (long delay condition). In the dual-task version of this paradigm, participants performed the same task interleaved with a running arithmetic task. In the short delay condition, participants completed a block of 9 "runs" of 4 trials in which the letter array appeared immediately following the dot, interleaved with mental arithmetic, for a total of 36 no delay trials. In the long delay condition, participants completed 24 trials in which the dot appeared, then participants completed a mental arithmetic task during an 8 s delay, after which the letter array appeared. Fewer trials were administered in the dual versus single task version because of the longer length of time needed for no delay trials in the dual task version. See Fig. 1 for the ordering of each run/trial the timing of the

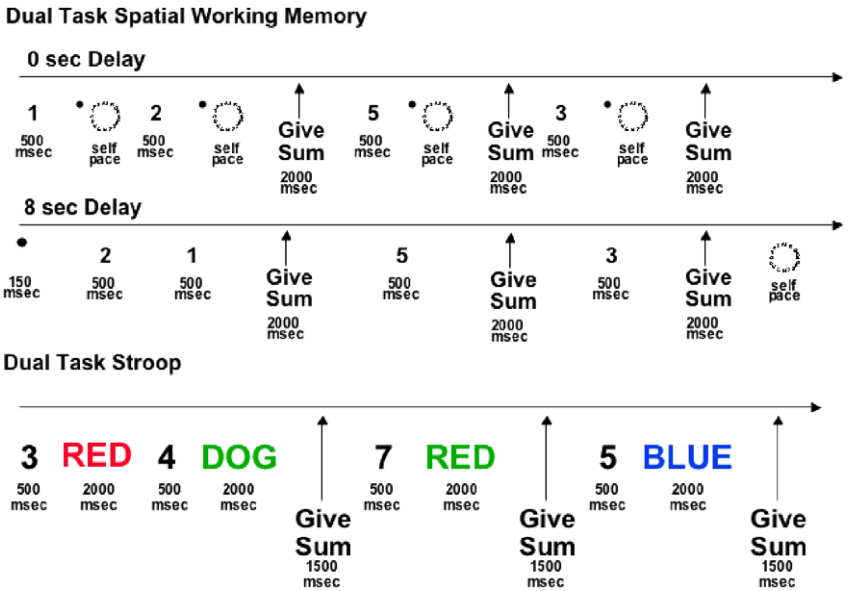

Fig. 1. Time line of events in the dual task versions of the Spatial Working Task and the Stroop task.

events, and the way in which the spatial working memory trials were interleaved with the arithmetic task in both the short and long delay conditions.

2.5. Language production

2.5.1. Structured interview

The patients and controls both completed structured interviews designed to elicit speech samples for assessment of language production disturbances. The patients completed one interview per testing session (a "single-task" interview). The controls completed two interviews at the post drug/placebo testing sessions, one of which was the "single-task" interview and one of which was a dual-task version that we have used in previous studies to examining the influence of reduced working memory capacity on language production (Barch and Berenbaum, 1994; Melinder and Barch, 2003). Four equivalent interviews were constructed. Eight sets of four open-ended questions were created (e.g., "Describe a typical day for you;" "Describe yourself for me;" "Tell me about your childhood:" "Tell me about being in highschool:") and one question from each set was randomly assigned to interview A, B, C, or D. The interview used for a particular session or task was counterbalanced across subjects. Interview questions were asked in the same order for each participant. There was no time limit for the interview. For controls, the dual-task interview was conducted concurrently with a Category Monitoring task (described below). This task requires simultaneous maintenance of target information and processing of incoming stimuli and therefore can be considered a working memory task. If language production also utilizes working memory resources (Levelt, 1989), then the category monitoring task and interview should compete for the same cognitive resources required for maintenance and manipulation of information. Based on the hypothesis that limited working memory capacity leads to at least some of the language disturbance observed in schizophrenia, the dual-task condition should reduce performance on the Category Monitoring task as well as reduce resources available for language production.

2.5.2. Formal thought disorder ratings

Transcripts from each interview were transcribed by an undergraduate research assistant and checked for accuracy by an additional research assistant. Two trained research assistants, blind to interview condition, rated each subtype of thought disorder from the Scale for the Assessment of Thought, Language, and Communication (Andreasen, 1979) using the revised definitions described by Berenbaum, Oltmanns, and Gottesman (Berenbaum et al., 1985). The number of instances of each subtype of thought disorder disturbance was coded for each interview. A dependent variable for formal thought disorder was created by summing the number of instances of each subtype of the TLC (excluding poverty of speech, which is discussed below). Interrater reliability for such total formal thought disorder scores have been excellent in our prior studies (Barch and Berenbaum, 1994, 1995, 1996, 1997; Melinder and Barch, 2003).

2.5.3. Poverty of speech

Poverty of speech was measured in two ways. First, we counted the number of words produced in each interview. Second, we used the poverty of speech item from the TLC, which was rated for each interview.

2.5.4. Syntactic complexity

Syntactic complexity was rated by two advanced linguistics graduate students who coded the number of independent and dependent clauses in each participant's transcribed speech sample. Interrater reliability for these same raters was assessed in a prior study (Melinder and Barch, 2003) using an intraclass correlation coefficient with the raters treated as random effects and the mean of the raters as the unit of reliability, was 0.98 for independent clauses in the single-task and 0.97 in the dual-task, and 0.98 for dependent clauses in the single-task and 0.96 in the dual-task. Syntactic complexity was then calculated by averaging the number of dependent clauses per T-unit. A T-unit is a single independent clause with all of its modifying subordinate clauses (Hunt, 1965).

2.5.5. Filled pauses

Pauses were measured by counting the number of filled pauses (e.g., "um," "ah") in each interview. To correct for opportunity to produce pauses, based on the amount of speech produced, we divided the number of filled pauses by the number of words in each interview.

2.6. Category monitoring task

This category monitoring task was identical to that used in several prior studies (Barch and Berenbaum, 1994; Melinder and Barch, 2003), and was administered once alone and once during the dual-task interview. In this task, participants monitored for the occurrence of words that belonged to a particular category of stimuli, and responded target or non-target to every stimulus. The words appeared one at a time in the middle of the computer screen. Participants were told to press one key on a keyboard for a target stimulus, and another key for a non-target stimulus, using their dominant hand. Two sets of stimuli were created, one in which the targets were animals, and one in which the targets were parts of the body. Each set contained a total of 220 non-targets and 55 targets. Stimuli sets used for the category-monitoring task alone (i.e., single-task) versus the category monitoring concurrent with an interview (i.e., dual-task) were counterbalanced across participants. Stimuli were presented in a pseudo-randomized fashion, such that within every five trials, four non-targets and one target were presented. For the single-task, participants received 160 non-target stimuli and 40 target stimuli, randomly chosen from the full set. Target and non-target words were matched for mean word length and mean frequency (Francis and Kucera, 1982). When run as a dual-task, stimuli were presented until the participant completed the interview. Response timing began with the presentation of the word and ended either when the participant responded or after 3 s, whichever came first. A new word appeared 1 s after termination of the previous trial. To ensure participant's continued attention, a prompt appeared on the screen after every two non-responses.

2.7. Stroop task

For both the single- and dual-task version of the Stroop task, the stimuli were identical to those used by Carter et al. (1992). The single-task version consisted of 96 trials: 24 (25%) congruent trials; 24 (25%) incongruent trials; and 48 (50%) neutral trials. Each trial consisted of a word printed in one of four colors: red, blue, green, or purple. The congruent stimuli consisted of one of the four color names presented in its own color. The incongruent stimuli consisted of each of the four color names presented in one of the three remaining colors. Neutral stimuli were one of four color unrelated words (dog, bear, tiger, or monkey) printed in one of the four colors. The neutral words matched the four-color words in length and frequency and were from a single semantic category to eliminate semantic confounds. Participants enunciated their color naming responses aloud into a microphone, which triggered a voice key relay in a specially constructed PsyScope button box that they recorded reactions times on the computer. The dual-task version consisted of 36 "runs" of 4 Stroop trials in which participants had to do the Stroop task while simultaneously doing a running arithmetic task. Each run contained 2 neutral trials, 1 congruent trial and 1 incongruent trial (in counterbalanced order) for a total of 144 Stroop trials. The ordering of each run, the timing of events, and the way in which Stroop and arithmetic tasks were interleaved is shown in Fig. 1.

2.8. Data analysis

We analyzed the data in two stages. First, we compared the performance of the individuals with schizophrenia to the performance of healthy controls on both placebo and D-AMPH, using only the data from the single task version of all tasks (since the individuals with schizophrenia did not complete the dual-task versions of any of the tasks. Then we compared single and dual task performance for the controls under both placebo and D-AMPH. Data from each of the tasks were analyzed using error rates and RTs as the dependent measures of interest. Analyses of the error data were confirmed using data normalized by an arcsine transformation (Neter et al., 1990). The arcsine transformation did not change any of the results, so analyses using raw data are presented below. Median RTs were examined for correct responses only, unless otherwise noted.

3. Results

3.1. Schizophrenia patients versus healthy controls

3.1.1. Spatial working memory

The error and RT data from the spatial working memory task were analyzed using 3-Factor ANOVAs,

with group as a between subject factor, and both session (placebo, D-AMPH) and delay (0 s, 8 s) as within-subject factors. For errors, the ANOVA revealed a main effect of delay, $F(1,29)=61.5$, $p<0.001$, with both groups performing worse at the long delay. There was also a group by session interaction, $F(1,29)=4,1$, $p=0.05$. As shown in Table 2, the patients were impaired compared to controls on placebo ($p=0.06$) at a trend level, but not on D-AMPH ($p>0.45$). In other words, accuracy improved for patients with D-AMPH as compared to placebo, both for the short and long delay. However, accuracy did not change for controls with D-AMPH. For RT, the ANOVA revealed main effects of group, $F(1,29)=7.5$, $p<0.05$, delay, $F(1,29)=57.4$, $p<0.001$, and session, $F(1,29)=7.4$, $p<0.05$. There were no significant interactions. Patients were overall slower than controls, both groups were faster at the short than the long delay, and both groups were faster on D-AMPH as compared to placebo. In sum, on the spatial working memory task, both individuals with schizophrenia and controls were significantly faster with D-AMPH compared to placebo, and individuals with schizophrenia were also more accurate on D-AMPH as compared to placebo.

3.1.2. Language production

We used a series of 2-factor ANOVAs to analyze the dependent variables from the single-task structured language interviewers, with group (patient, controls) as a between-subject factor and session (placebo, D-AMPH) as a within subject factor (though caution should be used in interpreting these analyses given the lack of formal thought disorder in controls on placebo). For formal thought disorder, the ANOVA revealed main effects of group, $F(1,30)=12.3$, $p<0.001$) and session, $F(1,30)=12.3$, $p<0.001$), that were modified by a group×session interaction, $F(1,30)=17.8$, $p<0.001$). As shown in Table 3, planned contrasts indicated that the patients showed significantly more formal thought disorder than controls on placebo ($p<0.05$), formal thought disorder was improved among patients on D-AMPH as compared to placebo ($p<0.05$), and patients no longer showed significantly more formal thought disorder than controls on D-AMPH ($p>0.5$). For number of words, the ANOVA revealed a significant main effect of session, $F(1,30)=4.3$, $p<0.05$, such that both groups produced more words under D-AMPH as compared to placebo, but no significant main effect of group or group by session interaction (ps>0.17). For poverty of speech ratings, the ANOVA revealed main effects of group, $F(1,30)=17.7$, $p<0.001$) and session, $F(1,30)=22.1$, $p<0.001$, that were modified by a group X session interaction, $F(1,30)=11.1$ $p<0.01$. As shown in Table 3, planned contrasts indicated that the patients received significantly higher poverty of speech ratings than controls on placebo ($p<0.05$), poverty of speech was improved among patients on D-AMPH as compared to placebo ($p<0.05$), and patients

Table 2
Spatial working memory

Variable	Group							
	Healthy controls				Individuals with schizophrenia			
	Placebo		D-Amphetamine		Placebo		D-Amphetamine	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Single task								
0 s delay errors (%)	6	7	4	6	9	11	4	5
8 s delay errors (%)	15	13	16	12	26	15	20	9
0 s delay RT (ms)	715.9	191.0	664.4	98.9	904.0	209.3	860.0	177.7
8 s delay RT (ms)	1034.4	308.3	952.2	179.2	1150.2	204.0	1078.0	128.8
Dual task								
0 s delay errors (%)	6	7	5	7	–	–	–	–
8 s delay errors (%)	26	17	24	15	–	–	–	–
0 s delay RT (ms)	716.7	106.1	675.8	87.5	–	–	–	–
8 s delay RT (ms)	898.8	136.7	873.1	177.2	–	–	–	–

Table 3
Language production

Variable	Group							
	Healthy controls				Individuals with schizophrenia			
	Placebo		D-Amphetamine		Placebo		D-Amphetamine	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Single task interview								
Formal thought disorder	0	0	0.05	0.2	0.5	0.5	0	0
Number of words	246.4	128.7	362.8	237.1	202.7	190.0	228.3	185.0
Poverty of speech	0.23	0.4	0.1	0.3	1.2	0.8	0.4	0,5
Syntactic complexity	0.30	0.15	0.31	0.14	0.29	0.17	0.31	0.16
Filled pauses per word	0.06	0.04	0.04	0.03	0.05	0.03	0.04	0.03
Dual task interview								
Formal thought disorder	0.08	0.28	0.08	0.28	–	–	–	–
Number of words	202.7	131.6	251.2	150.0	–	–	–	–
Poverty of speech	0.59	0.67	0.36	0.50	–	–	–	–
Syntactic complexity	0.20	0.11	0.32	0.17	–	–	–	–
Filled pauses per word	0.07	0.03	0.05	0.03	–	–	–	–

no longer received significantly higher poverty of speech ratings than controls on D-AMPH ($p>0.5$). For syntactic complexity, the ANOVA did not reveal any significant main effects or interactions. For filled pauses, there was a significant main effect of session, $F(1,30)=4.3$ $p<0.05$, such that both groups showed reduced filled pauses under D-AMPH as compared to placebo. However, there was no significant main effect of group or group by session interaction (ps>0.67). Thus, in summary, for both patients and controls, D-AMPH increased the number of words produced and decreased the number of filled pauses produced. Additionally for patients, D-AMPH reduced formal thought disorder and poverty of speech ratings such that patients no longer differed from controls on D-AMPH.

3.1.3. Stroop task

The Stroop data (errors and RT) were analyzed using 3-Factors ANOVA with group as a between subject factor and both session (placebo, D-AMPH) and condition (congruent, neutral, incongruent) as within subject factors. For errors, the ANOVA revealed a main effect of group, $F(1,30)=8.7$, $p<0.01$ and condition, $F(1,30)=16.0$, $p<0.001$), that was modified by a group by condition interaction, $F(2,60)=11.2$, $p<0.001$. There were no main effects of session or interactions with session. As shown in Table 4, planned contrasts indicated that the group by condition interaction reflected the fact that patients made more errors than controls in the incongruent condition ($p<0.01$), but not in the neutral or congruent conditions ($p>0.05$). For RT, the ANOVA revealed main effects of group, $F(1,30)=11.5$, $p<0.01$), session, $F(1,30)=14.9$, $p<0.01$), and condition, $F(2,60)=142.1$, $p<0.001$), that were modified by a group by condition interaction, $F(2,60)=8.4$, $p<0.01$). The main effect of session reflected the fact that both patients and controls were faster on D-AMPH as compared to placebo. Similar to the results of our prior Stroop studies, the group by condition interaction reflected the fact that patients showed a larger overall Stroop effect than controls (Incongruent–Congruent), which was primarily due to a larger RT Facilitation among patients than controls (127 ms versus 37 ms; $p<0.01$) and not to greater RT interference (109 ms versus 106 ms; $p>0.9$). Thus, in summary, both groups were faster at the Stroop task on D-AMPH, without a loss of accuracy.

3.1.4. Symptom ratings for patients

We compared the PANSS subscale scores for placebo and D-AMPH using paired sample t-tests. As shown in Table 1, there were no significant effects of D-AMPH for disorganization symptoms, reality distortion symptoms, poverty symptoms, or other symptoms. Thus, individuals with schizophrenia did

Table 4
Stroop task errors and RT

Variable	Group							
	Healthy controls				Individuals with schizophrenia			
	Placebo		D-Amphetamine		Placebo		D-Amphetamine	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Single task Stroop								
Congruent errors (%)	1	2	1	2	0	0	0	0
Neutral errors (%)	1	1	1	2	1	2	1	2
Incongruent errors (%)	4	5	3	4	14	16	12	13
Congruent RT (ms)	652.3	127.8	618.0	128.5	807.7	178.7	735.3	128.5
Neutral RT (ms)	694.3	115.8	655.5	102.2	899.3	213.9	831.4	217.9
Incongruent RT (ms)	804.2	148.3	768.8	128.2	1069.8	298.2	972.5	212.5
Dual task Stroop								
Congruent errors (%)	5	7	2	4	–	–	–	–
Neutral errors (%)	3	4	2	2	–	–	–	–
Incongruent errors (%)	10	11	8	8	–	–	–	–
Congruent RT (ms)	724.9	135.7	698.5	122.4	–	–	–	–
Neutral RT (ms)	761.3	149.1	721.6	120.4	–	–	–	–
Incongruent RT (ms)	850.7	155.9	844.8	163.3	–	–	–	–

not show an increase in symptoms, either positive or negative, with D-AMPH.

3.2. Healthy controls: single task versus dual task

3.2.1. Spatial working memory

The error and RT data from the spatial working memory tasks were analyzed using 3-Factor ANOVAs with task type (single, dual), delay (0 s, 8 s) and session (placebo, D-AMPH) as within subject factors. For errors, the ANOVA revealed significant main effects of task, $F(1,20)=33.2$, $p<0.001$, delay, $F(1,20)=75.7$, $p<0.001$, and a task type by delay interaction, $F(1,20)=15.7$, $p<0.001$. There were no other significant main effects or interactions. As shown in Table 2, the task type by delay interaction reflected the fact that participants made more errors in the dual as compared to single task version, but only for the long delay. For RT, the ANOVA revealed significant main effects of delay, $F(1,20)=69.0$, $p<0.001$ as well as a trend level main effect of task type, $F(1,20)=3.4$, $p=0.08$, and task type by delay interaction, $F(1,20)=3.8$, $p=0.07$. Participants were actually faster at the long delay for the dual as compared to the single task, but did not differ at the short delay. There was also a significant main effect of session, $F(1,20)=6.1$, $p<0.05$, such that participants were faster on D-AMPH as compared to placebo. Again, this increase in speed on D-AMPH did not come at the expense of accuracy on the spatial working memory task. In addition, this increase in speed did not come at the expense of performance on the secondary task, as errors (placebo=4.4%, D-AMPH=4.9%) were similar on D-AMPH and placebo.

3.2.2. Language production

We analyzed the data for the language production variables using 2-Factor ANOVAs, with both session (placebo, D-AMPH) and task type (single, dual) as within subject factors. For formal thought disorder, the ANOVA did not indicate any significant main effects of session or task type, or an interaction between session and task type (all ps>0.3. For number of words, the ANOVA indicated significant main effects of task type, $F(1,21)=7.8$, $p<0.05$, and session, $F(1,21)=8.6$, $p<0.01$, and a marginal session by task type interaction, $F(1,21)=2.9$, $p=0.10$. As shown in Table 3, participants produced fewer words during the dual versus single task interaction, produced more words with D-AMPH as compared to placebo, and D-AMPH tended to increase word output more for the single than the dual task. For poverty of speech, the ANOVA indicated significant main effects of task type, $F(1,21)=10.9$, $p<0.01$, and session, $F(1,21)=5.5$,

$p<0.05$, but no significant task type by session interaction ($p>0.5$). As shown in Table 3, participants had higher poverty of speech ratings during the dual as compared to single task interview, but lower poverty of speech ratings during D-AMPH versus placebo. For syntactic complexity, the ANOVA indicated significant main effects of task type, $F(1,21)=5.0$, $p<0.05$, and session, $F(1,21)=6.0$, $p<0.05$, and a trend level task type by session interaction, $F(1,21)=4.0$, $p=0.06$. As shown in Table 2, participants produced less syntactically complex speech during the dual as compared to the single task interview, but only on placebo. Speech was as syntactically complex during the dual as the single task interview with D-AMPH. For filled pauses, the ANOVA indicated significant main effects of task type, $F(1,21)=8.1$, $p<0.01$ and session, $F(1,21)=6.6$, $p<0.05$, but no significant task type by session interaction ($p>0.75$). As shown in Table 2, participants produced more filled pauses during the dual as compared to single task interview, and fewer filled pauses with D-AMPH as compared to placebo. In summary, the addition of the secondary task (designed to compete for working memory resources) reduced the amount of speech and the syntactic complexity of speech, and increased the frequency of filled pauses, language production impairments also often found in individuals with schizophrenia. Further, the administration of D-AMPH helped ameliorate these dual-task induced language production deficits. Of note, these improvements in language production during the dual-task interview did not come at the expense of performance on the secondary task (category monitoring), as errors (placebo=7%; D-AMPH=6%) and RTs (placebo=938.0 ms; D-AMPH=946.0 ms) were similar under placebo and D-AMPH.

3.2.3. Stroop task

The error and RT data from the single and dual-task Stroop paradigms was analyzed using 3-Factor ANOVAs with task type (single, dual), session (placebo, D-AMPH), and condition (congruent, neutral, incongruent) as within subject factors. For errors, the ANOVA revealed significant main effects of task type, $F(1,21)=11.1$, $p<0.01$, and condition, $F(2,42)=18.1$, $p<0.001$, as well as a trend level main effect of session, $F(1,21)=3.4$, $p<0.08$. There was also a significant task type by condition interaction, $F(2,42)=4.3$, $p<0.05$. As shown in Table 4, the task type by condition interaction reflected the fact that participants made more errors in the dual versus single task version of the Stroop in all conditions, though this error increase was greater in the congruent and neutral conditions than the incongruent condition. In addition, the trend level effect of session reflected the fact that participants made fewer errors with D-AMPH as compared to placebo for both the single and dual task version of the Stroop. For RTs, the ANOVA indicated significant main effects of task type, $F(1,21)=36.7$, $p<0.001$, and condition, $F(2,42)=103.6$, $p<0.001$, as well as a trend level main effect of session, $F(1,21)=3.4$, $p=0.08$. As shown in Table 4, participants were slower with the dual as compared to single task Stroop and participants showed the typical RT Stroop interference effect. Further, participants tended to be faster on D-AMPH as compared to placebo, along with the trend level increase in accuracy described above. Again, this increase in speed with D-AMPH did not come at the expense of accuracy on the secondary arithmetic task (placebo=4.9%, D-AMPH=4.8%).

4. Discussion

The goal of the current study was to further examine the hypothesis that agents that augment the function of the dopamine system would be effective at improving cognition in individuals with schizophrenia who were being treated with typical antipsychotics. Consistent with this hypothesis, we found that the acute administration of D-AMPH improved: 1) spatial working memory in individuals with schizophrenia, reflected in both accuracy and speed; 2) language production, both the amount of speech and formal thought disorder; and 3) Stroop task performance, at least in terms of speed. Moreover, these cognitive improvements occurred in the absence of an increase in psychotic symptoms as a function of D-AMPH. In healthy controls we found that the addition of secondary tasks designed to reduce working memory capacity elicited performance deficits analogous to those shown by individuals with schizophrenia. Further, we found that D-AMPH reduced some of these dual task induced cognitive deficits in healthy

controls. Each of these results will be discussed in more detail below.

As noted in the Introduction, a great deal of animal and human literature supports the hypothesis that intact function of the dopamine system is important for optimal spatial working memory function (Brozoski et al., 1979; Clark et al., 1986; Luciana et al., 1992, 1998; Arnsten et al., 1994; Sawaguchi and Goldman-Rakic, 1994; Williams and Goldman-Rakic, 1995; Mattay et al., 1996, 2000, 2003; Cai and Arnsten, 1997; Elliott et al., 1997; Kimberg et al., 1997; Luciana and Collins, 1997; Muller et al., 1998; Castner et al., 2000; Goldman-Rakic et al., 2000; Mehta et al., 2000; Kimberg and D'Esposito, 2003). Individuals with schizophrenia commonly demonstrate deficits on working memory tasks, which have been hypothesized to be related to impaired dopamine levels. Our results are consistent with these hypotheses in several respects. First, we found that under placebo, the individuals with schizophrenia showed impaired accuracy and RT on the spatial working memory task. Second, the acute administration of D-AMPH improved both accuracy and speed on a spatial working memory task in individuals with schizophrenia. Third, the addition of a secondary task designed to reduce working memory resources impaired spatial working memory performance in controls, particularly when the delay between the cue and the probe was long. Fourth, the administration of D-AMPH helped ameliorate these dual task induced spatial working memory performance deficits in controls, at least in terms of speed of responding.

However, our results indicated that the patients with schizophrenia were impaired both on the no delay and 8 s delay conditions of the task, and that D-AMPH improved accuracy and RT on both delay conditions in patients. These results suggest that D-AMPH might be improving working memory performance through an effect on encoding information into working memory rather than through mechanisms involving storage. Other investigators have also suggested that working memory deficits in schizophrenia reflect encoding rather than (or in addition to) storage deficits (Javitt et al., 1997; Wexler et al., 1998; Javitt et al., 2000; Rabinowicz et al., 2000; Tek et al., 2002; Lencz et al., 2003), and this interpretation would be consistent with the idea that dopamine may serve to enhance signal-to-noise ratios that could improve encoding of the cue representation into memory (Barch et al., 1996; Cohen and Servan-Schreiber, 1992; Braver et al., 1999). Whether or not this turns out to be the case, we believe that our results are particularly germane at the present time in that they demonstrate a consistent pattern of improvement in cognitive function among individuals with schizophrenia under acute D-AMPH administration.

A number of researchers have also hypothesized that language production impairments in schizophrenia may also reflect deficits in working memory function, including both negative thought disorder (reduced amount and complexity of speech, increased pausing) (Barch and Berenbaum, 1994, 1996, 1997; Barch, 1997; Melinder and Barch, 2003) and positive formal thought disorder (Barch and Berenbaum, 1994, 1996; Docherty et al., 1996; Kerns and Berenbaum, 2002; Melinder and Barch, 2003). Consistent with this we found that patients had higher poverty of speech and positive formal thought disorder ratings than controls on placebo, though they did not differ significant in the number of words produced or syntactic complexity. Further, they showed an increase in the amount of speech and a decrease in formal thought disorder with D-AMPH. Also consistent with prior research, we found that the addition of secondary task designed to reduce working memory resources reduced the amount and complexity of speech among controls, though it did not elicit formal thought disorder (Barch and Berenbaum, 1994). As described in the Introduction, our hypothesis was the language production and the category monitoring task compete for the same working memory resources, reduced the amount available for language production. We should note, however, that we cannot rule out the possibility that language production and the category monitoring tasks compete for processes or resources other than working memory capacity (e.g., attentional resources). Similar to the individuals with schizophrenia, the administration of D-AMPH improved these language production deficits induced by the addition of a secondary task. For controls, the administration of D-AMPH not only increased the amount of speech (a results that is not particular surprising given the influence of D-AMPH on arousal), but also significantly improved the syntactic complexity of speech. The latter results is more

suggestive of an impact of D-AMPH on working memory functions, given the large literature suggesting that syntactic complexity processing is associated with working memory capacity (Just and Carpenter, 1992; Condray et al., 1996; Bagner and Barch, 2003). Taken together, such results are indirectly consistent with the hypothesis that language production disturbances in schizophrenia are associated with working memory deficits, and thus amenable to improvement by agents that have a positive impact on working memory function.

In our prior research we have also argued that selective attention deficits and working memory disturbances in schizophrenia are related, and may reflect a common deficits in the representation of context. As in a number of prior studies (Carter et al., 1992; Taylor et al., 1996; Barch et al., 1999a,b; Cohen et al., 1999; Elvevag et al., 2000; Chen et al., 2001; Henik et al., 2002) we again found that individuals with schizophrenia demonstrated Stroop performance deficits that were reflected in increased errors in the incongruent condition and an increased RT facilitation (but no increased RT interference). The performance of individuals with schizophrenia was faster on the Stroop task with D-AMPH with no loss of accuracy. However, D-AMPH did not reduce the magnitude of RT facilitation for individuals with schizophrenia in comparison to controls. For controls, the addition of a secondary task designed to reduce working memory resources elicited more errors in the incongruent conditions, an aspect of Stroop performance also found in individuals with schizophrenia. However, the addition of the secondary task did not change the relative magnitude of either RT facilitation or interference in comparison to the single task condition. The performance of controls was faster under D-AMPH as compared to placebo, with a trend towards improved accuracy. However, D-AMPH did not change the pattern of RT facilitation or interference as compared to placebo. Thus, performance on the Stroop task was speeded for both controls and patients by D-AMPH, and accuracy was somewhat improved for controls. However, D-AMPH did not have an impact on the pattern of Stroop effects shown by either group.

In summary, the current data provide renewed support for the hypothesis that cognition in individuals with schizophrenia well treated on typical antipsychotics can be improved by the acute administration of D-AMPH, without a concomitant worsening of either positive or negative symptoms. However, several questions remain unanswered. First, amphetamines do not have a selective effect only on the dopamine system, but also influence other neurotransmitter systems such as norepinephrine. Thus, further research using more selective agents is needed to determine whether the results we obtained are medicated by influences on dopamine per se, or also by influences in other neurotransmitter systems. Second, it is not clear whether these results reflect a positive impact of amphetamine on a disturbance of the dopamine system that is an integral part of the disease process. Instead, it may be that amphetamine is simply reversing dopamine antagonism induced by typical antipsychotics. On a related note, it is not clear whether we would find the same pattern of results with individual taking atypical antipsychotics, as such agents may not provide the same degree of D2 blockade as provided by typical antipsychotics. As such, it is possible that administering D-AMPH to individuals on atypicals may lead to increase in psychotic symptoms in addition to cognitive enhancement. Finally, it is important to note that we would not recommend adjuvant therapy with D-AMPH or other stimulants as a therapy for impaired cognition in schizophrenia. However we believe that the present work represents further proof of concept work that enhancement of dopaminergic neurotransmission may be a viable strategy in our efforts to develop effective therapies for impaired cognition in schizophrenia and hope that these results will provide further impetus for those efforts.

Acknowledgements

Dr. Barch is supported by the National Institute of Mental Health, the National Alliance for Research on Schizophrenia and Depression, and the Dana Foundation; Dr. Carter is supported by the National Institute of Mental Health and the National Alliance for Research on Schizophrenia and Depression. The present work was supported by a Seed grant from the Conte Center for the Neuroscience of Mental Disorders (PI D Lewis MD) to Dr Carter.

References

Andreasen, N.C., 1979. Thought, language, and communication disorders: clinical assessment, definition of terms, and evaluation of their reliability. Archives of General Psychiatry 36, 1315–1321.

Arnsten, A.F., Cai, J.X., Murphy, B.L., Goldman-Rakic, P.S., 1994. Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. Psychopharmacology 116, 143–151.

Baddeley, A.D., 1986. Working Memory. Oxford University Press, New York.

Bagner, D., Barch, D.M., 2003. Working memory and language comprehension in schizophrenia. Schizophrenia Research 60, 299–309.

Barch DMaB, H., 1997. Language generation in schizophrenia and mania: the relationships among verbosity, syntactic complexity, and pausing. Journal of Psycholinguistic Research 26, 401–412.

Barch, D.M., 1999. The role of working memory in language production and its disturbance in schizophrenia. Schizophrenia Research 36, 160.

Barch, D.M., Berenbaum, H., 1994. The relationship between information processing and language production. Journal of Abnormal Psychology 103, 241–251.

Barch, D.M., Berenbaum, H., 1995. The categorization of thought disorder. Journal of Psycholinguistic Research 24, 349–376.

Barch, D.M., Berenbaum, H., 1996. Language production and thought disorder in schizophrenia. Journal of Abnormal Psychology 105, 81–88.

Barch, D.M., Berenbaum, H., 1997. The effect of language production manipulations on negative thought disorder and discourse coherence disturbances in schizophrenia. Psychiatry Research 71, 115–127.

Barch, D.M., Carter, C.S., 1998. Selective attention in schizophrenia: relationship to verbal working memory. Schizophrenia Research 33, 53–61.

Barch, D.M., Carter, C., Perlstein, W., Baird, J., Cohen, J., Schooler, N., 1999a. Increased Stroop facilitation effects in schizophrenia are not due to increased automatic spreading activation. Schizophrenia Research 39, 51–64.

Barch, D.M., Carter, C.S., Braver, T.S., Sabb, F.W., Noll, D.C., Cohen, J.C., 1999b. Overt verbal responding during fMRI scanning: empirical investigations of problems and potential solutions. NeuroImage 10, 642–657.

Barch, D.M., Cohen, J.D., Servan-Schreiber, D., Steingard, S., Steinhauer, S., van Kammen, D., 1996. Semantic priming in schizophrenia: An examination of spreading activation using word pronunciation and multiple SOAs. Journal of Abnormal Psychology 105, 592–601.

Berenbaum, H., Oltmanns, T.F., Gottesman, I.I., 1985. Formal thought disorder in schizophrenics and their twins. Journal of Abnormal Psychology 94, 3–16.

Braver, T.S., Barch, D.M., Cohen, J.D., 1999. Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biological Psychiatry 46, 312–328.

Brozoski, T.J., Brown, R.M., Rosvold, H.E., Goldman, P.S., 1979. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 205, 929–931.

Cai, J.X., Arnsten, A.F.T., 1997. Dose-dependent effects of the dopamine D1 receptor agonists A77636 or SKF81297 on spatial working memory in aged monkeys. Journal of Pharmacology and Experimental Therapeutics 283, 183–189.

Carpenter, W.T., Gold, J.M., 2002. Another view of therapy for cognition in schizophrenia. Biological Psychiatry 51, 972–978.

Carter, C.S., Robertson, L.C., Nordahl, T.E., 1992. Abnormal processing of irrelevant information in schizophrenia: selective enhancement of Stroop facilitation. Psychiatry Research 41, 137–146.

Castner, S.A., Williams, G.V., Goldman-Rakic, P.S., 2000. Reversal of antipsychotic induced working memory deficits by short term dopamine D1 receptor stimulation. Science 287, 2020–2022.

Chen, E.Y.H., Wong, A.W.S., Chen, R.Y.L., Au, J.W.Y., 2001. Stroop interference and facilitation effects in first-episode schizophrenia patients. Schizophrenia Research 48, 29–44.

Clark, C.R., Geffen, G.M., Geffen, L.B., 1986. Role of monoamine pathways in the control of attention: effects of droperidol and methylphenidate on normal adult humans. Psychopharmacology 90, 28–34.

Cohen, J.D., Servan-Schreiber, D., 1992. Context, cortex and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychological Review 99, 45–77.

Cohen, J.D., Barch, D.M., Carter, C., Servan-Schreiber, D., 1999. Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. Journal of Abnormal Psychology 108, 120–133.

Condray, R., Steinhauer, S.R., Van Kammen, D.P., Kasparek, A., 1996. Working memory capacity predicts language comprehension in schizophrenic patients. Schizophrenia Research 20, 1–13.

Cools, R., Stefanova, E., Barker, R.A., Robbins, T.W., Owen, A.M., 2002. Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. Brain 125, 584–594.

Cooper, J.A., Sagar, J.H., Doherty, S.M., Jordan, N., Tidswell, P., Sullivan, E.V., 1992. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease: a follow-up study of untreated patients. Brain 115, 1701–1725.

Costa, A., Peppe, A., Dell'Agnello, G., Carlesimo, G.A., Murri, L., Bonuccelli, U., Caltagirone, C., 2003. Dopaminergic modulation of visual–spatial working memory in Parkinson's disease. Dementia and Geriatric Cognitive Disorders 15, 55–66.

Cuesta, M.J., Paralta, V., 1995. Psychopathological dimensions in schizophrenia. Schizophrenia Bulletin 21, 473–482.

Daniel, D.G., Weinberger, D.R., Jones, D.W., Zigun, J.R., Coppola, R., Handel, S., Bigelow, L.B., Goldberg, T.E., Berman, K.F., Kleinman, J.E., 1991. The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. Journal of Neuroscience 11, 1907–1917.

Davidson, M., Keefe, R.S., 1995. Cognitive impairment as a target for pharmacological intervention in schizohprenia. Schizophrenia Research 17, 123–129.

Docherty, N.M., Hawkins, K.A., Hoffman, R.E., Quinlan, D.M., Rakfeldt, J., Sledge, W.H., 1996. Working memory, attention, and communication disturbances in schizophrenia. Journal of Abnormal Psychology 105, 212–219.

Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., Weinberger, D.R., 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proceedings of the National Academy of Science of the United States of America 98, 6917–6922.

Elliott, R., Sahakian, B.J., Matthews, K., Bannerjea, A., Rimmer, J., Robbins, T.W., 1997. Effects of methylphenidate on spatial working memory and planning in healthy young adults. Psychopharmacology 131, 196–206.

Elvevag, B., Duncan, J., McKenna, P.J., 2000. The use of cognitive context in schizophrenia: an investigation. Psychological Medicine 30, 885–897.

Francis, W.N., Kucera, H., 1982. Frequency Analysis of English Usage: Lexicon and Grammer. Houghton Mifflin, Boston.

Gold, J.M., Goldbert, R.W., McNary, S.W., Dixon, L.B., Lehman, A.F., 2002. Cognitive correlates of job tenure among patients with severe mental illness. American Journal of Psychiatry 159, 1395–1402.

Goldberg, T.E., Weinberger, D.R., 1996. Effects of neuroleptic medications on the cognitive of patients with schizophrenia: a review of recent studies. Journal of Clinical Psychiatry 57, 62–65.

Goldberg, T.E., Bigelow, L.B., Weinberger, D.R., Daniel, D.G., Kleinman, J.E., 1991. Cognitive and behavioral effects of the coadministration of dextroamphetamine and haloperidol in schizophrenia. American Journal of Psychiatry 148, 78–84.

Goldman-Rakic, P.S., Muly, E.C., Williams, G.V., 2000. D1 receptors in prefrontal cells and circuits. Brain Research Reviews 31, 295–301.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? American Journal of Psychiatry 153, 321–330.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophrenia Bulletin Special Issue: Psychosocial Treatment for Schizophrenia 26, 119–136.

Harvey, P.D., Keefe, R.S., 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. American Journal of Psychiatry 158, 176–184.

Harvey, P.D., Howanitz, E., Parrella, M., White, L., Davidson, M., Mohs, R., Hoblyn, J., Davis, K.L., 1998. Symptoms, cognitive functioning and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. American Journal of Psychiatry 155, 1080–1086.

Henik, A., Carter, C.S., Salo, R., Chaderjian, M., Kraft, L., Nordahl, T.E., Robertson, L.C., 2002. Attentional control and word inhibition in schizophrenia. Psychiatry Research 110, 137–149.

Hunt, K., 1965. Grammer Structures Written at Three Grade Levels. NCTE, Urbana, IL.

Javitt, D.C., Strous, R.D., Grochowski, S., Ritter, W., Cowan, N., 1997. Impaired precision, but normal retention, of auditory sensory ("echoic") memory information in schizophrenia. Journal of Abnormal Psychology 106, 315–324.

Javitt, D.C., Shelley, A., Silipo, G., Lieberman, J.A., 2000. Deficits in auditory and visual context-dependent processing in schizophrenia. Archives of General Psychiatry 57, 1131–1137.

Just, M.A., Carpenter, P.A., 1992. A capacity theory of comprehension: individual differences in working memory. Psychological Review 99, 122–149.

Kay, S., 1991. Positive and Negative Symptoms in Schizophrenia. Brunner/Marzel, New York.

Keefe, R.S., Perkins, S., Silva, S.M., Lieberman, J.A., 1999. The effect of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophrenia 25, 201–222.

Kerns, J.B., Berenbaum, H., 2002. Cognitive impairments associated with formal thought disorder in people with schizophrenia. Journal of Abnormal Psychology 111, 211–224.

Kimberg, D.Y., D'Esposito, M., 2003. Cognitive effects of the dopamine receptor agonist pergolide. Neuropsychologia 41, 1020–1027.

Kimberg, D.Y., D'Esposito, M., Farah, M.J., 1997. Effects of bromocriptine on human subjects depend on working memory capacity. NeuroReport 8, 381–385.

Kirrane, R.M., Mitropoulou, V., Nunn, M., New, A.S., Harvey, P.D., Schopick, F., Silverman, J.M., Siever, L.J., 2000. Effects of amphetamine on visuospatial working memory performance in schizophrenia spectrum personality disorder. Neuropsychopharmacology 22, 14–18.

Kulisevsky, J., Avila, A., Barbanoj, M., Antonijoan, R., Berthier, M.L., Gironell, A., 1996. Acute effects of levodopa on neuropsychological performance in stable and flucuating Parkinson's disease patients at different levodopa plasma levels. Brain 199, 2121–2132.

Kulisevsky, J., Garcia-Sanchex, C., Berthier, M.L., Barbanoj, M., Pascual-Sedano, B., Gironell, A., Estevez-Gonzalez, A., 2000. Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: a two year follow-up study of previously untreated patients. Movement Disorders 15, 613–626.

Lange, K.W., Paul, G.M., Naumann, M., Gsell, W., 1995. Dopaminergic effects on cognitive performance in patients with Parkinson's disease. Journal of Neural Transmission 46, 423–432.

Lencz, T., Bilder, R.M., Turkel, E., Goldman, R.S., Robinson, D., Kane, J.M., Lieverman, J.A., 2003. Impairments in perceptual competency and maintenance on a visual delayed match-to-sample test in first-episode schizophrenia. Archives of General Psychiatry 60, 238–243.

Levelt, W.J.M., 1989. Speaking: From Intention to Articulation. MIT Press, Cambridge, MA.

Liddle, P.F., 1987. Syndromes of chronic schizophrenia: a re-examination of the positive–negative dichotomy. British Journal of Psychiatry 151, 145–151.

Luciana, M., Collins, P.F., 1997. Dopamine modulates working memory for spatial but not object cues in normal humans. Journal of Cognitive Neuroscience 4, 58–68.

Luciana, M., Depue, R.A., Arbisi, P., Leon, A., 1992. Facilitation of working memory in humans by a D_2 dopamine receptor agonist. Journal of Cognitive Neuroscience 4, 58–68.

Luciana, M., Collins, P.F., Depue, R.A., 1998. Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions. Cerebral Cortex 8, 218–226.

Malhotra, A.K., Kestler, L.J., Mazzanti, C.M., Bates, J.A., Goldberg, T.E., Goldman, D., 2002. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. American Journal of Psychiatry 159, 652–654.

Mattay, V.S., Berman, K.F., Ostrem, J.L., Esposito, G., Van Horn, J.D., Bigelow, L.B., Weinberger, D.R., 1996. Dextroamphetamine enhances "neural network-specific" physiological signals: a positron-emission tomography rCBF study. Journal of Neuroscience 15, 4816–4822.

Mattay, V.S., Callicott, J.H., Bertolino, A., Heaton, I., Frank, A.J., Coppola, R., Berman, K.F., Goldberg, T.E., Weinberger, D.R., 2000. Effects of dextroamphetamine on cognitive performance and cortical activation. NeuroImage 12, 268–275.

Mattay, V.S., Goldberg, T.E., Fera, F., Hariri, A.R., Tessitore, A., Egan, M.F., Kolachana, B.S., Callicott, J.H., Weinberger, D.R., 2003. Catechol *O*-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proceedings of the National Academy of Sciences 100, 6186–6191.

Mehta, M.A., Owen, A.M., Sahakian, B.J., Mavaddat, N., Pickard, J.D., Robbins, T.W., 2000. Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. The Journal of Neuroscience 20, 1–6.

Mehta, M.A., Swainson, R., Gogilvie, A.D., Sahakian, B.J., Robbins, T.W., 2001. Improved short-term spatial memory but impaired reversal learning following the dopamine D2 agonist bromocriptime in human volunteers. Psychopharmacology 159, 10–20.

Melinder, M.R.D., Barch, D.M., 2003. Working memory manipulations of language production in schizophrenia. Schizophrenia Bulletin 29, 473–484.

Muller, U., von Cramon, Y., Pollmann, S., 1998. D1- versus D2-receptor modulation of visuospatial working memory in humans. The Journal of Neuroscience 18, 2720–2728.

Neter, J., Wasserman, W., Kutner, M.H., 1990. Applied Linear Statistical Models. Irwin Press, Boston.

Rabinowicz, E.F., Silipo, G., Goldman, R.S., Javitt, D.C., 2000. Auditory sensory dysfunction in schizophrenia: imprecision or distractibility. Archives of General Psychiatry 57, 1131–1137.

Sawaguchi, T., Goldman-Rakic, P.S., 1994. The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. Journal of Neurophysiology 71, 515–528.

Sevy, S., Davidson, M., 1995. The cost of cognitive impairment in schizophrenia. Schizophrenia Research 17, 1–3.

Shrout, P.E., Fleiss, J.L., 1979. Intraclass correlations: uses in assessing rater reliability. Psychological Bulletin 86, 420–428.

Siegel, B.V., Trestman, R.L., O'Faithbheartaigh, S., Mitropoulou, V., Amin, F., Kirrane, R.M., Silverman, J.M., Schmeidler, J., Keefe, R.S., Siever, L.J., 1996. D-amphetamine challenge effects on Wisconsin card sort test performance in schizotypal personality disorder. Schizophrenia Research 20, 29–32.

Spitzer, R.L., Williams, J.B., Gibbon, M., First, M.B., 1990. Structured clinical interview for DSM-III-R-patient edition (SCID-P, version 1.0). American Psychiatric Press, Washington, DC.

Taylor, S.F., Kornblum, S., Tandon, R., 1996. Facilitation and interference of selective attention in schizophrenia. Journal of Psychiatric Research 30, 251–259.

Tek, C., Gold, J.M., Blaxton, T., Wilk, C., McMahon, R.P., Buchanan, R.W., 2002. Visual perceptual and working memory impairments in schizophrenia. Archives of General Psychiatry, 146–153.

Wexler, B.E., Stevens, A.A., Bowers, A.A., Sernyak, M.J., Goldman-Rakic, P.S., 1998. Word and tone working memory deficits in schizophrenia. Archives of General Psychiatry 55, 1093–1096.

Williams, G.V., Goldman-Rakic, P.S., 1995. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature 376 (17), 572–575.