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Amphetamine Enhances Gains in Auditory Discrimination Training in Adult Schizophrenia Patients

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Targeted cognitive training (TCT) of auditory processing enhances higher-order cognition in schizophrenia patients. TCT performance gains can be detected after 1 training session. As a prelude to a potential clinical trial, we assessed a pharmacological augmentation of cognitive therapy (PACT) strategy by testing if the psychostimulant, amphetamine, augments TCT gains in auditory processing speed (APS) in schizophrenia patients and healthy subjects (HS). HS and schizophrenia patients were tested in a screening session (test 1), followed by a double-blind crossover design (tests 2–3), comparing placebo vs amphetamine (10 mg; 7 d between tests). On each test day, 1 hour of Posit Science "Sound Sweeps" training was bracketed by 2- to 4-minute pre- and post-training assessments of APS. Training consisted of a speeded auditory time-order judgment task of successive frequency modulation sweeps. Auditory system "learning" (APS post- vs pre-training) was enhanced by amphetamine (main effect of drug: $P < .002$; patients: $d = 0.56$, $P < .02$; HS: $d = 0.39$, nonsignificant), and this learning was sustained for at least 1 week. Exploratory analyses assessed potential biomarker predictors of sensitivity to these effects of amphetamine. Amphetamine enhances auditory discrimination learning in schizophrenia patients. We do not know whether gains in APS observed in patients after 1 hour of TCT predict clinical benefits after a full course of TCT. If amphetamine can enhance the therapeutic effects of TCT, this would provide strong support for a "PACT" treatment paradigm for schizophrenia.

Key words: amphetamine/attention/auditory discrimination/cognitive remediation/schizophrenia

Introduction

Functional disability in schizophrenia reflects underlying neurocognitive deficits.[1–3] Antipsychotics blunt acute psychosis, but their impact on negative symptoms or neurocognitive deficits are less dramatic.[4,5] Efforts at remediating cognitive deficits using targeted cognitive training (TCT) generally show efficacy at the group level, yet almost half of all patients demonstrate virtually no cognitive enhancement after prolonged TCT treatment.[6–9]

We proposed pairing drugs with specific cognitive interventions, as a way to enhance schizophrenia patients' ability to benefit from that intervention (pharmacological augmentation of cognitive therapies [PACTs][10,11]), similar to the use of pro-extinction drugs to enhance the response to cognitive therapies in anxiety disorders.[12] Conceivably, pro-cognitive agents might augment the gains from TCT, particularly in subgroups of schizophrenia patients with specific neurobiological and/or genetic characteristics. As a "proof of concept" for the PACT model, we tested the hypothesis that the pro-attention drug, d-amphetamine, will enhance performance on a TCT task—Posit Science "Sound Sweeps"—which is a component of a TCT program known to enhance neurocognition in schizophrenia patients.[6] Because Sound Sweep auditory discrimination performance and learning are associated with attention[13] and neuroplasticity,[6,7] our primary hypothesis was that gains in the performance metric of auditory processing speed (APS) would be augmented by the pro-attention[14] and pro-neuroplastic[15] drug, amphetamine. While APS enhancement is not always associated with neurocognitive gains,[16] such an observation would establish a rationale for testing enhanced therapeutic effects of a PACT paradigm in which amphetamine is paired with TCT.

The extant literature provides strong suggestions that amphetamine can acutely enhance neurocognition in antipsychotic-medicated schizophrenia patients,[17–19] and even that amphetamine can be safely administered to antipsychotic-medicated schizophrenia patients either acutely[17–20]

or daily for 10 weeks.[21] Nonetheless, the decision to use amphetamine in this study was not based on the expectation that it would serve as a primary therapeutic agent for schizophrenia; rather it was based on its known ability to enhance attentional mechanisms, and thus to allow the most straightforward test of the "PACT model" predictions.

Methods

Participants (Ns: healthy subjects [HS] = 35; schizophrenia = 25 [stable antipsychotic doses for >1 mo]; table 1) were carefully screened, to establish appropriate diagnoses and rule out exclusionary conditions (supplementary table S1). Screening and 2 test sessions were conducted approximately 7 days apart (figure 1A).

Because sensitivity to the neurocognitive effects of amphetamine have been reported to be moderated by catechol-*O*-methyl transferase (COMT[22–24]; but see Wardle et al[25]), this experiment also explicitly tested the hypothesis that COMT function—regulated by the COMT single nucleotide polymorphism (SNP) rs4680[26]—might predict sensitivity to amphetamine effects on TCT performance. Specifically, we hypothesized that rs4680 Val/Val homozygotes—previously reported to be most sensitive to the pro-cognitive effects of amphetamine[22]—would be most sensitive to the learning-enhancing effects of amphetamine. Saliva was collected from community samples of HS and schizophrenia patients to identify rs4680 homozygotes (Val/Val: "GG" or Met/Met: "AA"), who were then studied to permit an efficient assessment of this SNP as a moderator of TCT and amphetamine sensitivity; to understand the basis of statistical interactions of diagnosis × genotype, "wait-listed" heterozygous ("AG") subjects were subsequently added to the sample (see supplementary methods).

In addition to rs4680, screen day measures tested 5 potential biomarkers of sensitivity to "pro-learning" effects of amphetamine on TCT: Attention/Vigilance domain of the MATRICS Consensus Neurocognitive Battery (MCCB), event-related potentials (ERPs) measures of mismatch negativity (MMN) and P3a (amplitude and latency), and prepulse inhibition (PPI) of acoustic startle (see supplementary methods). The power of a PACT paradigm would be greatly enhanced by predictive biomarkers, and thus we tested a set of secondary hypotheses, focusing on these 5 measures, which are known to be robust and reliable indices of attentional or pre-attentional dysfunction in schizophrenia patients[cf.27–29] that in some cases predict TCT performance[cf.30] or gains from other cognitive interventions.[31]

Screen day (figure 1A) measures served as no-drug "baselines." Test days (on which placebo or amphetamine were administered) included measures of TCT, MCCB, startle, and subjective[32] and autonomic drug effects (figure 1A); measures of startle on test days will be reported separately. Test days 2 and 3 were identical except: (1) the pill administered 210 minutes prior to TCT (based on time course studies in HS[33,34]) was either placebo or amphetamine (10 mg) and (2) alternative MCCB

Table 1. Subject Characteristics

Diagnoses[46] (n)	SZ[a] (25)	HS (35)	P
Age (y), mean (SD)	39.2 (8.9)	31.6 (11.7)	<.01
Weight (kg), mean (SD)	90.4 (21.6)	71.6 (15.6)	<.0003
Sex, M:F	12:13	24:11	NS
Smoker:nonsmoker	10:15	2:33	<.002
Race, % White	31.8%	42.9%	NS
Daily caffeine (mg), mean (SD)	198.6 (183.4)	121.0 (145.8)	NS
WRAT, mean (SD)	93.1 (9.4)	103.1 (9.7)	<.0003
Education (y), mean (SD)	12.1 (1.7)	15.1 (1.8)	<.0001
Duration of illness (y), mean (SD)	18.4 (8.3))		
Age of onset (y), mean (SD)	20.8 (7.6)		
GAF, mean (SD)	66.0 (6.9)		
PANSS score, mean (SD)			
Positive	20.9 (4.5)		
Negative	19.8 (3.9)		
Psychopathy	44.4 (8.2)		
Total	85.0 (14.0)		
Chlorpromazine equivalents (mg), mean (SD)	456.0 (436.2)		
Anticholinergic load (pmol/ml), mean (SD)	11.1 (23.5)		
Antipsychotic medications (n)			
	FGA only (2)		
	SGA only (20)		
	FGA + SGA (3)		

Note: FGA, first-generation antipsychotic agent; GAF, Global Assessment of Functioning; HS, healthy subjects; NS, nonsignificant; PANSS, Positive and Negative Syndrome Scale; SGA, second-generation antipsychotic agent; SZ, schizophrenia patients; WRAT, Wide Range Achievement Test.
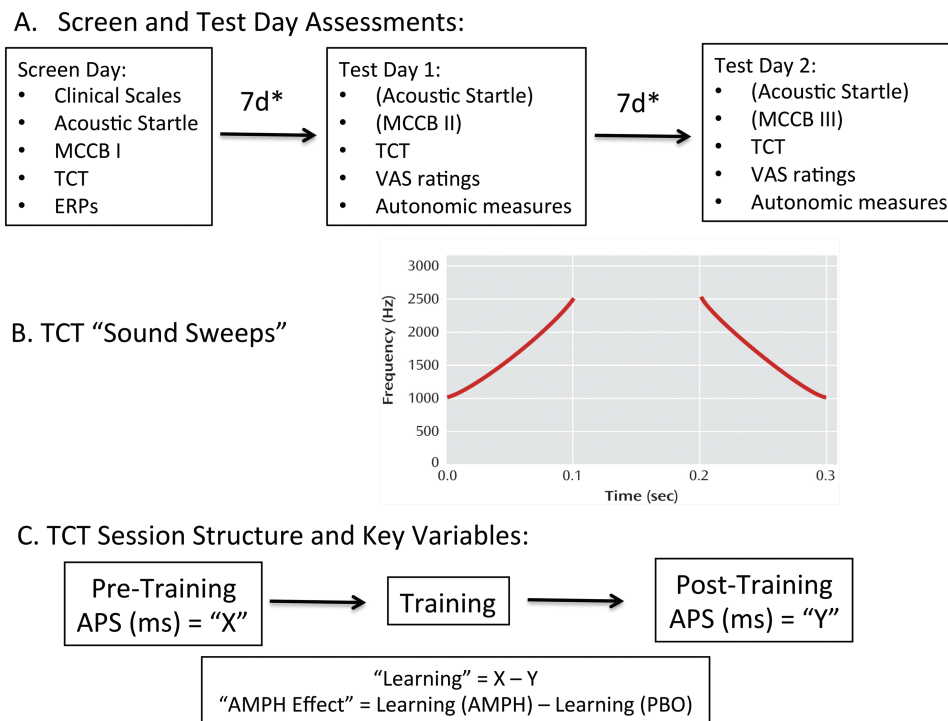[a]Schizophrenia (n = 23); schizoaffective disorder, depressed (n = 2).

A. Screen and Test Day Assessments:

B. TCT "Sound Sweeps"

C. TCT Session Structure and Key Variables:

Fig. 1. (A) Test schedule (*±5 d); MCCB I, II, III = alternate versions; tests in parentheses not reported herein. (B) "TCT Sound Sweeps": Subjects identify each of 2 successive sound sweeps as either "up" or "down." Sweep duration and interstimulus interval are modified as performance improves (adapted from Fisher et al[6]). (C) TCT structure and critical variables of APS "learning" and "amphetamine effect." AMPH, amphetamine; APS, auditory processing speed; ERP, event-related potential; MCCB, MATRICS Consensus Neurocognitive Battery; PBO, placebo; TCT, targeted cognitive training; VAS, Visual Analogue Scale.

forms were used to diminish practice effects.[28] This choice of amphetamine dose and post-pill test time is based on published findings of amphetamine-enhanced neurocognition in schizophrenia patients.[18,19]

TCT (Posit Science; brainhq.com) is a computerized cognitive training program targeting both low-level auditory perceptual processes and higher-order cognitive operations. This study utilized 1 training exercise, "Sound Sweeps": an auditory frequency discrimination time-order judgment task. Participants heard pairs of frequency-modulated sound "sweeps" and indicated whether they perceived each sweep as becoming higher or lower in pitch[6] (figure 1B). Sweep duration, frequency range, and interstimulus interval become shorter after correct responses, but longer after incorrect responses. On screen and test days, subjects completed 1 hour of TCT, monitored by a research assistant. APS was calculated based on the shortest duration of stimuli that participants discriminated correctly. Before and after each training session, participants completed an APS assessment, to quantify learning (APS pre- minus post-training [ms]). For both the APS assessment and the training, stimulus duration ranged from 13 to 1000 ms, with smaller scores indicating better APS. Our group reported that baseline APS is associated with better functioning across specific cognitive domains: auditory attention, working memory, verbal memory, and executive functioning.[13]

Statistical Approach

Repeated measure ANOVAs identified main and interaction effects of diagnosis, dose (placebo vs 10 mg), and in some cases genotype (AA vs GG) on the dependent measures. These ANOVAs (main effects and 2- and 3-way interactions) were used to test the primary hypotheses (eg, amphetamine will enhance APS learning in patients). Post hoc analyses assessed specific effects of variables (eg, age) on the primary outcomes and evaluated more complex explanations for the findings (eg, state-dependent learning). Once ANOVAs detected significant effects of amphetamine on APS learning, post hoc exploratory correlations were assessed among a measure of APS amphetamine sensitivity and baseline (screening) measures of ERPs, PPI and neurocognition, and subjective and autonomic drug responses and clinical variables. PPI data were not available from 5 startle "non-responders" ($n = 4$ HS, $n = 1$ patient). TCT day 2 post-assessment data were lost from 1 HS due to computer failure. In addition, for 1 patient, placebo-day learning exceeded levels in the patient group or the inclusive group of all subjects, by 4.73 SD and 6.35 SD, respectively; this "outlier" value did not alter main statistical effects (main effect of drug on APS) but did impact correlations, and thus all APS data from this subject were omitted. To test primary hypotheses, alpha was .05. To test secondary hypotheses (5 predictive biomarkers), alpha was adjusted to $.05/5 = .01$.

Additional descriptive statistics are reported for demographics and autonomic and subjective measures not directly linked to a specific hypothesis.

Results

Subject Characteristics

In general, patients were functionally impaired, symptomatic, and taking second-generation antipsychotics (with 2 exceptions); group differences were detected in sex distribution, age, education, premorbid intelligence, and smoking status (tables 1 and 2).

Screen Day

Screen day neurocognitive and neurophysiological results are described in the supplementary results. TCT performance during screen day training was impaired in patients vs HS, based on previously established metrics (average best APS [ms][13]: $F = 10.01$, $df = 1,57$, $P < .003$; $d = 0.88$)

(figure 2A). The amount of TCT "learning" (pre- minus post-training APS) did not differ significantly across the inclusive HS vs patient groups ($F = 1.07$, $df = 1,57$, nonsignificant [NS]). Clinical, experimental and genetic (rs4680) correlates of screen day performance are reported in supplementary results.

Test Days

Bioactivity of amphetamine is described in the supplementary results. Despite this bioactivity, subjects correctly identified the active drug on amphetamine test days only at chance levels (HS: 57.1%; patients: 48.0%; $\chi^2 = 0.49$, NS). Training session APS (figure 2C) was impaired in patients vs HS ($F = 11.19$, $df = 1,57$, $P < .002$); there were near-significant APS-improving effects of amphetamine ($F = 3.84$, $df = 1,57$, $P < .06$), but no diagnosis × amphetamine interaction ($F = 1.08$, $df = 1,57$, NS). In analyses limited to patients, amphetamine had no significant effect on APS ($F = 1.75$, $df = 1,23$, NS).

Table 2. Correlations (R) vs AMPH-Enhanced Learning

	HS	SZ	All Subjects
Age (y)	0.52[b]	−0.01	0.25
Weight (kg)	0.02	−0.09	−0.08
Education (y)	−0.10	0.20	−0.11
WRAT[47]	−0.16	−0.11	−0.22
GAF	—	0.00	—
Duration of illness (y)	—	−0.13	—
Chlorpromazine equivalents (mg)	—	−0.10	—
Anticholinergic load[48,a]	—	Rs = 0.08	—
PANSS positive[49]	—	0.09	—
PANSS negative	—	0.30	—
PANSS psychopathy	—	−0.02	—
PANSS total	—	0.10	—
MCCB composite	−0.41[c]	−0.21	−0.35[d]
MCCB Attention/Vigilance	−0.15	−0.24	−0.29[e]
%PPI (60 ms)	0.23	0.22	0.15
MMN (µV)	0.18	0.34	0.28[f]
P3a amplitude (µV)	−0.12	−0.02	−0.08
P3a latency (ms)	0.13	−0.43[f]	−0.15
AMPH-enhanced HR	−0.13	0.06	−0.08
AMPH-enhanced SBP	−0.31	0.08	−0.10
AMPH-enhanced DBP	−0.17	−0.11	−0.16
AMPH-enhanced "drowsiness"	0.38[e]	0.12	0.19
AMPH-enhanced "happiness"	−0.30	−0.11	−0.14
AMPH-enhanced "concentration"	−0.23	−0.25	−0.23
AMPH-enhanced "anxiety"	−0.06	0.10	0.07
Screen day APS (ms)	0.52[b]	0.20	0.32[c]
Screen day "learning" (ms)	0.28	−0.27	−0.15

Note: AMPH, amphetamine; APS, auditory processing speed; DBP, diastolic blood pressure; HR, heart rate; MCCB, MATRICS Consensus Neurocognitive Battery; MMN, mismatch negativity; PPI, prepulse inhibition; SBP, systolic blood pressure; the rest of the abbreviations are explained in the first footnote to table 1.
[a]Anticholinergic load (pmol/ml) not normally distributed.
[b]$P < .002$.
[c]$P < .02$.
[d]$P < .007$.
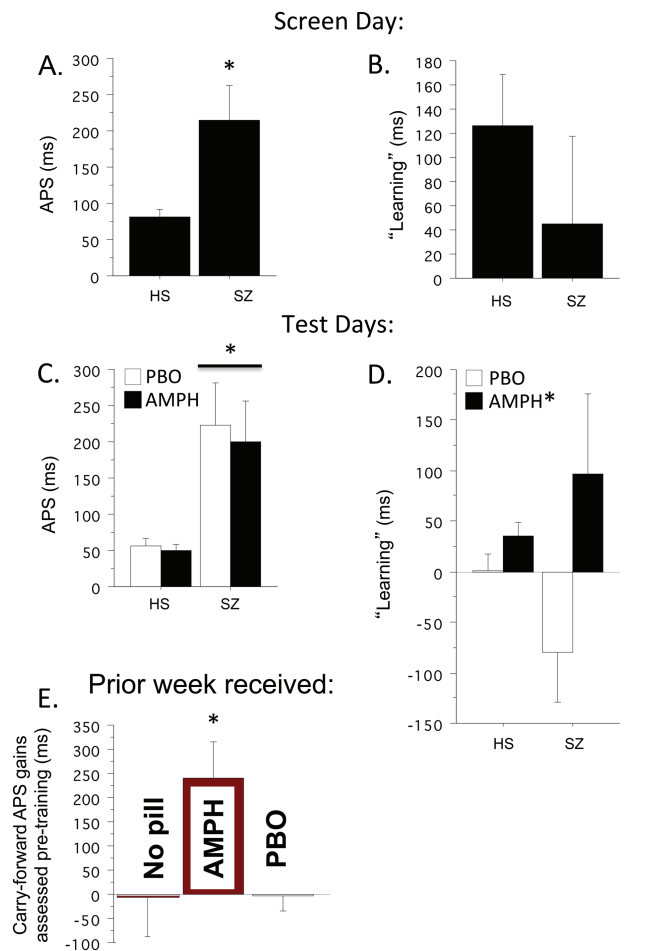[e]$P < .03$
[f]$P < .035$.

Fig. 2. Targeted cognitive training (TCT) performance. (A) Screen Day TCT performance during the 1-h training is impaired in patients ($n = 24$) vs HS ($n = 35$), seen by significantly longer discrimination thresholds. (B) Screen Day "learning," measured by the change in APS from pre- to post-training, measured during the 2- to 4-min pre- and post-training epochs. A positive number indicates more "learning" over the course of training. No significant effects of diagnosis on TCT learning were detected (SZ: $n = 24$; HS: $n = 35$). (C) Test Day APS (ms) during training in patients ($n = 24$) and HS ($n = 35$); *significant effect of diagnosis. (D) On Test Days, amphetamine increased "learning" during TCT, demonstrated by faster APS post- vs pre-assessment. ANOVA detected significant effects of amphetamine (*$P < .002$) and amphetamine × diagnosis interaction ($P = .03$) (SZ: $n = 24$; HS: $n = 35$). (E) Amphetamine-enhanced learning was not state dependent in patients: amphetamine-enhanced APS learning "carried forward" from test day 1 to test day 2. On test days 2 vs 1, APS learning "carried forward" to the pre-training assessment was greater among patients who received amphetamine on test day 1 ($n = 13$), than among patients who received PBO on test day 1 ($n = 11$) (*$P < .009$). Learning carried forward from screen day is shown as "No Pill" ($n = 24$). AMPH, amphetamine; APS, auditory processing speed; HS, healthy subjects; PBO, placebo; SZ, schizophrenia patients.

ANOVA of APS "learning" (pre- minus post-training) revealed no significant effect of diagnosis ($F < 1$), a significant pro-learning effect of amphetamine ($F = 11.01$, $df = 1,56$, $P < .0017$), and a significant amphetamine ×

diagnosis interaction, reflecting arithmetically larger pro-learning effects in patients vs HS ($F = 4.96$, $df = 1,56$, $P = .03$). In patients, these effects of amphetamine were significant ($P < .02$; $d = 0.56$); the effect in HS missed significance ($d = 0.39$; $P < .10$). Post hoc analyses assessed factors that might contribute to pro-learning effect of amphetamine and differential amphetamine effects across groups (see supplementary results) and rejected potential confounding effects of group differences in age, sex, weight, race, smoking status, or baseline learning levels. Our within-subject design involved 2 different test orders (amphetamine day 1 vs 2); including this variable in the ANOVAs of either APS or learning had no impact on the critical findings: for measures of learning, this yielded no significant effect of test order ($F = 1.04$), with persistent main effects of amphetamine ($P < .0025$) and amphetamine × diagnosis interaction ($P < .038$). Assessing APS learning only on test day 1 confirmed greater learning among amphetamine vs placebo subjects ($P < .037$; $d = 0.77$).

Predictors of Amphetamine-Enhanced Learning?

Analyses limited to rs4680 homozygotes confirmed the patterns detected in the inclusive sample (diagnosis: $F < 1$; drug: $F = 28.83$, $df = 1,41$, $P < .0001$ [in patients, $d = 0.85$]; diagnosis × drug interaction: $F = 16.39$, $df = 1,41$, $P = .0002$). There was also no significant effect of genotype or other 2- or 3-way interactions (all $Fs < 1$).

Other potential predictors of the magnitude of amphetamine-enhanced learning were assessed, by calculating the "amphetamine effect" on APS ((APS gains after amphetamine) minus (APS gains after placebo)) (see supplementary results). No robust predictors were identified. Amphetamine sensitivity in patients did correlate significantly with P3a latency ($R = -.43$, $P < .035$); categorical (median split) analyses revealed that HS and patients with higher screening PPI levels subsequently exhibited more amphetamine-enhanced TCT "learning" ($F = 5.43$, $df = 1,51$, $P < .025$; d: HS = 0.49; schizophrenia = 0.74).

State-Dependent Learning?

To determine whether amphetamine-enhanced APS learning is "state-dependent," ie, present only under a "state" of amphetamine action vs generalized to non-amphetamine states, we examined APS during "pre-assessment" in each of the 3 TCT sessions, before any additional learning from that session could take place. Among patients, there were no APS gains from screening to test day 1, regardless of whether they subsequently received placebo vs amphetamine on test day 1 ($F < 1$). However, compared to APS during day 1 pre-assessment, APS during day 2 pre-assessment (1 wk later) was faster among patients who received amphetamine on test day 1, but not among patients who received placebo on test day 1 (mean day 2 vs day 1 reduction in APS [SEM] = 241.77

[73.66] ms vs −3.64 [30.97] ms, respectively; $F = 8.29$, $df = 1,22$, $P < .009$; $d = 1.33$) (figure 2E). Thus, APS gains after being trained under amphetamine conditions generalized (ie, "carried forward") to the pre-assessment phase of the subsequent test, 1 week later, ie, were not "state-dependent."

Discussion

Amphetamine (10 mg) acutely enhanced auditory discrimination learning in schizophrenia patients, and these gains persisted for at least 1 week. These effects were selective for APS learning, rather than task performance per se. A similar, though weaker effect in HS suggests that amphetamine's benefits in patients may reflect an enhancement of "normal" brain mechanisms, in the service of the attentional demands of training.[14,cf.30] The observation that learning can be acutely enhanced in severely impaired schizophrenia patients provides evidence of intact resources for positive neuroplastic changes, which might be harnessed for clinical gains. Conceivably, by enhancing auditory discrimination learning, amphetamine might accelerate or potentiate the therapeutic response to this form of TCT; if these amphetamine effects on APS learning reflect enhanced attention rather than an auditory-specific process, then such amphetamine effects might generalize to other forms of TCT.

Safety Issues

We detected no adverse consequences of exposure to 10 mg of amphetamine, consistent with the reported literature documenting the safety, and symptomatic and neurocognitive benefits, of amphetamine in antipsychotic-mediated schizophrenia patients.[17–21,35] For example, in a controlled trial,[21] amphetamine (5.9–20.8 mg/d) was administered daily for 10 weeks to antipsychotic-medicated schizophrenia patients, without elevated risks of adverse events either during treatment or upon withdrawal, and with evidence for some clinical gains. In another randomized, controlled trial, Modell and Hussar[36] reported a lack of pressor effects of 20 mg daily amphetamine in obese antipsychotic-medicated schizophrenia patients. In the present study, self-ratings identified mild positive effects of amphetamine on both alertness and hedonic state in HS and patients. Positive pressor and chronotropic effects of amphetamine were evident in HS, but consistent with Modell and Hussar[36] were blunted in patients, presumably due to peripheral effects of antipsychotics. Unlike HS, patients tended to experience reduced anxiety after amphetamine vs placebo, and self-assessment measures of psychological or somatic distress, or perceptual anomalies, detected no effects of amphetamine in patients. Notwithstanding our current findings, and those of previous reports,[17–21,35] it remains clear that amphetamine can have a propensity for precipitating psychosis in vulnerable individuals, particularly in the absence of antipsychotic medication.

The present findings clearly do not justify the use of amphetamine as a "stand-alone" pro-cognitive agent for schizophrenia patients, but do provide a rationale for further testing a "PACT" application of amphetamine + TCT. While some effects of amphetamine are known to exhibit tolerance, pro-attentional effects of amphetamine in clinical populations can persist far longer than the 10 weeks necessary to complete a typical course of TCT.[37,38]

Predicting Amphetamine Sensitivity

Despite suggestive findings in humans[39] and rodents,[40] rs4680 status was not a robust predictor of sensitivity to amphetamine in patients or HS. Greater amphetamine-enhanced TCT learning was modestly associated with faster screening P3a latency and higher screening levels of PPI, but these findings must be viewed with caution until replicated in larger samples. Consistent with our past report in healthy adults,[41] positive effects of amphetamine were associated with lower baseline MCCB performance, though this effect reached significance only in HS (Composite T score) or combined HS and patient groups (Composite and Attention/Vigilance domain T scores), and not among patients alone.

The underlying mechanisms for amphetamine's enhancement of APS learning were not the focus of this study. Amphetamine enhances simple sensory-based learning and underlying cortical reorganization[15]; conceivably, similar phenomena might account for our observed facilitation of APS learning; however, such "neuroplastic" processes would seem more relevant to changes in neurocognition, symptoms, and function observed over repeated training sessions, or perhaps to the sustained APS learning detected 1 week after training, rather than changes detected within the amphetamine-day training period per se. Perhaps a more parsimonious explanation for amphetamine-enhanced "learning" in this TCT paradigm is that amphetamine enhances attentional engagement with the auditory discrimination task. Indeed, an extensive literature demonstrates that amphetamine can acutely raise arousal, increase attention, and enhance performance and learning.[cf.41,42] Anecdotally, test subjects are often challenged to maintain full attention throughout the hour-long auditory "sweeps" task, and conceivably, a low dose of amphetamine might help subjects stay "on task." However, no empirical evidence indicated that the TCT-enhancing effects of amphetamine in patients were associated significantly with either low basal levels of attention (as measured by the MCCB), neurophysiological markers associated with the integrity of attentional or pre-attentional resources (eg, MMN, P3a amplitude), changes in levels of "drowsiness," or other evidence of sympathetic arousal. More generally, there was no evidence that the pro-learning effects of amphetamine

reflected a "reversal" of an antipsychotic-induced learning deficit, as: (1) patients did not exhibit baseline APS learning deficits, either during screening or placebo test days; (2) amphetamine tended to enhance APS learning in HS ($d = 0.39$), who were not taking antipsychotics; and (3) neither baseline learning nor amphetamine sensitivity was associated with antipsychotic dose (either chlorpromazine equivalents or levels of anticholinergic activity; see supplementary results). While neither antipsychotic dose ($R = -.10$) nor duration of illness ($R = -.13$) predicted the pro-learning effects of amphetamine in the present study, it is conceivable that both of these variables might be important moderators of stimulant effects on cognition in a clinical setting.

Limitations

There are several potential limitations to this study. First, this study is not a clinical trial, and thus these findings cannot support the use of amphetamine within a PACT strategy for schizophrenia. At best, the present study supports the rationale of conducting such a clinical trial, based on the evidence that amphetamine enhances learning of an auditory discrimination task that is associated with clinical gains from TCT. It cannot be assumed that enhanced APS learning is relevant to the processes underlying the clinical benefits associated with a full course of TCT, though such a hypothesis can be tested empirically in a randomized clinical trial. Second, trying to understand the neural basis of amphetamine-enhanced APS learning in schizophrenia patients is complicated by the fact that all patients in this study were maintained on stable doses of antipsychotic medications, which presumably block the effects of amphetamine within some but not other dopamine terminal fields that regulate neurocognition and learning. Metrics of antipsychotic dosing, including chlorpromazine equivalents and anticholinergic activity units, were not associated with amphetamine effects on APS learning. Third, this study tested only 1 dose of amphetamine, and only 1 post-pill time point. Full dose-response effects should be characterized before moving this PACT paradigm towards a clinical trial, both because amphetamine has "inverted-U" dose-response properties,[cf.42] and so that the lowest effective dose of amphetamine can be used in patients. While the current time of TCT testing (210 min post-pill) is a point of near-maximal amphetamine bioactivity by several metrics, it is possible that pro-learning effects of amphetamine might have a more rapid onset; any shortening of the PACT-TCT protocol will greatly facilitate its implementation in a clinical setting. Fourth, the trends for amphetamine to also enhance APS learning in HS suggest that its effects are not "diagnostically specific." In fact, one basis for the selection of amphetamine for the first test of this PACT design is that its pro-attentional effects are not diagnostically specific, with the expectation that its impact on APS learning in patients would reflect its action on intact brain mechanisms.[30] If clinical trials confirm the value of amphetamine in a TCT-PACT regimen, there will be a rationale to evaluate other pro-attentional interventions, some of which may be more specifically tailored to attentional processes of relevance to schizophrenia.

Next Steps

The most critical next steps are to determine whether amphetamine-enhanced TCT "learning" (ie, gains in APS) in patients enhances clinical benefits from a full course of 30–50 hours,[6] and whether such clinical benefits can be predicted by specific biomarkers. In fact, there are reasons to anticipate a complex relationship between enhanced APS learning and neurocognitive and clinical gains. Cain et al[16] reported that schizophrenia patients taking the pro-extinction *N*-methyl-D-aspartate agonist, D-cycloserine (DCS), exhibited significant gains in APS learning and negative symptom reduction during an 8-week trial of TCT. Interestingly, placebo- but not DCS-treated patients exhibited significant gains in MCCB performance. Thus, enhanced APS learning was associated with symptom reduction but not neurocognitive gains. Clearly, the many differences in the neurochemical and nootropic mechanisms of DCS (pro-extinction[43] or perhaps "memory-enhancing"[44]) vs amphetamine (pro-attentional[14]) make it impossible to know the relevance of these DCS findings to a proposed amphetamine PACT regimen. Nonetheless, it is clear that amphetamine-enhanced TCT gains might be most evident in some but not all outcome metrics (symptoms, neurocognition, function), even in the face of robust increases in APS learning.

It is important to emphasize that the therapeutic model being developed here involves the acute use of a pro-learning drug paired directly with a session of a cognitive intervention, in the context of a stable regimen of antipsychotic medications. Many hurdles must be cleared before this "PACT" model—with amphetamine or any other "pro-cognitive" intervention—is ready for clinical use in schizophrenia patients, including assessing and understanding potential effects of state-dependent learning, interactions of PACT medications and antipsychotics, and the underlying mechanisms of action. Alternate approaches, including the use of aerobic exercise to augment TCT effects, are also being piloted.[45] Nonetheless, if it is demonstrated that a pro-cognitive intervention such as amphetamine can enhance the therapeutic effects of TCT, then this "PACT" approach could ultimately become a useful addition to the treatment options for schizophrenia.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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