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ORIGINAL INVESTIGATION

Amphetamine effects on MATRICS Consensus Cognitive Battery performance in healthy adults

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Abstract
Background Cognitive deficits contribute strongly to functional disability in schizophrenia. The cost of identifying and testing candidate procognitive agents is substantial. Conceivably, candidate drugs might be first identified by positive effects on cognitive domains in sensitive subgroups of healthy subjects. Here, we examined whether the MATRICS Consensus Cognitive Battery (MCCB) detected procognitive drug effects in subgroups of healthy individuals.
Methods The effects of 20 mg amphetamine (AMPH) on MCCB performance were tested in a double-blind, placebo-controlled crossover study of 60 healthy adults. AMPH effects were compared in subgroups of subjects characterized by low vs. high placebo MCCB scores, and by extreme values on personality subscales associated with schizophrenia-relevant biomarkers.
Results AMPH produced autonomic and subjective effects, but did not significantly change MCCB composite scores or individual domain scores across the inclusive sample of 60 subjects. AMPH-induced MCCB changes were significantly (inversely) related to placebo MCCB performance: among individuals with lower placebo scores, AMPH enhanced performance; while among individuals with higher placebo scores, it impaired performance. A potential impact of regression to the mean was assessed and could not be ruled out. Both placebo MCCB performance and AMPH effects on MCCB scores were significantly related to personality domains associated with schizophrenia-linked genetic- and/or neurophysiological substrates.
Conclusions Among healthy adults, AMPH effects on MCCB performance were detected only among specific subgroups, and in specific cognitive domains. Strategies that utilize drug-induced changes in MCCB performance in healthy subjects to screen for candidate procognitive drugs should consider the use of "enriched" subgroups with specific neurocognitive or personality characteristics.

Keywords Amphetamine · Cognition · Schizophrenia · MCCB · MATRICS · Neurocognition

Introduction

Cognitive deficits in schizophrenia (SZ) are a primary determinant of functional disability (Bowie et al. 2008; Cervellione et al. 2007; Gold et al. 2002; Green et al. 2000; Heinrichs et al. 2010; Heinrichs and Zakzanis 1998; Keefe and Harvey 2012; McClure et al. 2007; Williams et al. 2008). The MATRICS Consensus Cognitive Battery (MCCB) was developed to evaluate neurocognition in trials of procognitive drugs and cognitive remediation programs (Kern et al. 2008; Nuechterlein et al. 2008). The MCCB provides measures of cognitive change in repeated testing designs as well as a cognitive reference point for non-intervention studies, and is accepted by the FDA as a primary endpoint for clinical trials targeting cognition in SZ.

The MCCB includes ten tests that assess seven cognitive domains: speed of processing (SP), attention/vigilance (A/V), working memory (verbal and nonverbal) (WM), verbal learning (VerL), visual learning (VisL), reasoning and problem solving (R/PS), and social cognition (SC), and provides a composite score of these domains. In multi-site trials, the MCCB has demonstrated sensitivity to cognitive deficits in all domains, excellent test-retest and inter-site reliability and

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high correlations with measures of functional capacity (Buchanan et al. 2011; Keefe et al. 2011). Despite this sensitivity, many early trials using the MCCB have failed to identify strong procognitive drug effects (Goff et al. 2007; Harvey et al. 2011; Javitt et al. 2012; Marx et al. 2009). Other studies utilizing the MCCB are in progress with a number of other new compounds, as well as atypical antipsychotics (http://clinicaltrials.gov/ct2/results?term=matrics).

There are substantial challenges in the design and implementation of trials to identify procognitive drug effects in SZ patients, ranging from subject recruitment and retention, to complex medication regimens and interactions, and to ethical issues related to the use of placebo (PBO) controls (Barch 2010; Barch and Carter 2008; Correll et al. 2011; Emanuel and Miller 2001; Kemp et al. 2010; Patel 2003; Touwen and Engberts 2012). One productive strategy in studies of the clinical neuroscience of SZ has been to investigate cognitive and neurobiological phenomena in unaffected healthy subjects characterized by personality or other domains that are conceptually or biologically related to psychosis (Koychev et al. 2012; Kumari et al. 2004; Laurent et al. 2002; Smith 1992; Swerdlow et al. 2003b). Indeed, drug challenges in healthy subjects and specific subgroups have identified neurocognitive and neurophysiological changes suggestive of procognitive drug properties (e.g., Barch and Carter 2005; Swerdlow et al. 2009; Talledo et al. 2009). Conceivably, drugs that enhance specific cognitive functions in healthy subjects characterized by psychosis-linked phenotypes may be promising candidates for enhancing cognition in SZ. This study was designed to determine whether the MCCB detects procognitive drug effects in subgroups of healthy individuals distinguished by their levels of neurocognitive performance.

Amphetamine (AMPH) was selected as a “test” procognitive agent based on our understanding of its biological mechanisms and its well-established neurocognitive and neurophysiological profile. AMPH improves cognition in SZ patients as well as in healthy volunteers (Barch and Carter 2005; Pietrzak et al. 2010a, b), and AMPH and other dopamine agonists may be particularly effective in enhancing neurocognition in healthy subjects with low basal performance levels (Kimberg et al. 1997; Kimberg and D’Esposito 2003; Mattay et al. 2000, 2003; Mehta et al. 2001; Swerdlow 2011), and in individuals carrying certain genetic biomarkers or related phenotypes (Ersche et al. 2011; Fleming et al. 1995; Giakoumaki et al. 2008; Hutchison et al. 1999; Kumari et al. 1999; Mattay et al. 2003; Roussos et al. 2009; White et al. 2006). Here, we assessed the effects of a single “challenge” dose of 20 mg AMPH on MCCB performance in a double-blind, PBO-controlled crossover design in 60 clinically healthy adults.

Methods

Subject recruitment and testing

Methods were similar to those described in recent reports (e.g., Talledo et al. 2009), approved by the UCSD Human Subjects Institutional Review Board and supported by the NIMH. Sixty R-handed adults (M/F=37:23; mean age=24.2, SD=4.9, range=18–35; Table 1) completed an initial telephone contact and three laboratory visits. Phone screening procedures were identical to those in previous reports (Swerdlow et al. 2003a, b). After passing the phone interview (assessing current and past medical and psychiatric history, medication and recreational drug use, and family history of psychosis), subjects came to the laboratory (for women, within 72 h of menses onset).

During the screening visit, subjects were informed of the potential risks and benefits of the study, read and signed a study consent, underwent a screening medical interview, a modified Structured Clinical Interview for DSM-IV-Non-Patient (SCID-NP), physical examination and electrocardiogram to rule out exclusionary conditions, and urine toxicology test (exclusion for any illicit drug); women underwent a urine-based pregnancy test. Audiometry confirmed hearing threshold <40 dB(A) at 1,000 Hz. Because subjects were also to be tested in measures of acoustic startle for a larger, ongoing study of AMPH effects on this measure, a screening session was used to confirm reliable startle reflex magnitude. The total number of subjects excluded based on the screening visit and the basis for these exclusions are found in Table 2.

Subjects completed several questionnaires based on reported relationships between specific scale scores and dopaminergic function and/or AMPH sensitivity, including: (a) the Tridimensional Personality Questionnaire (TPQ; Cloninger 1987; Novelty Seeking Subscale (NS)); (b) the

Table 1 Subject characteristics (*n*=60; M/F=37:23)

Characteristics	Mean (SD)
Age (y)	24.2 (4.9)
Weight (kg)	77.1 (15.0)
Education (y)	14.5 (1.6)
Caffeine (md/d)	64.1 (89.8)
TPQ: novelty seeking	14.8 (4.5)
SSS: disinhibition	4.2 (2.8)
EPQ: total score	21.4 (4.5)
Smoking (*n*)	
≥20 cigarettes/week	1
≤5 cigarettes/week	2

TPQ tridimensional personality questionnaire, *SSS* sensation seeking scale, *EPQ* Eysenck personality questionnaire

Table 2 Excluded subjects (n=73)

Startle magnitude <50 units[a]	35
Drug history/positive toxicology[b]	12
"No show"/uncooperative	12
Affective disorder history	3
General medical problem	6
Other	5

[a] 1.22 µV/unit

[b] Positive urine toxicology, n=5; substance dependence or abuse by SCID, n=7

Sensation Seeking Scale (SSS; Zuckerman et al. 1972; Disinhibition Subscale (DIS)); and (c) the Eysenck Personality Questionnaire (EPQ; Eysenck and Eysenck 1994; Total Score; Table 1; e.g., Fleming et al. 1995; Ebstein et al. 1996; Benjamin et al. 1996; Hutchison et al. 1999; Kumari et al. 2004; Hamidovic et al. 2009). Subjects who passed screening criteria were tested 5–9 days later and retested 26–30 days after their first test (i.e., for women, at the corresponding date of their next menstrual cycle). This schedule was designed to ensure, to the degree possible, that testing with AMPH and PBO occurred under relatively comparable hormonal states for women. Testing was double-blind, and drug order was randomized.

On test days, subjects arrived at 0830, ate a standardized breakfast, repeated audiometry, urine toxicology (and pregnancy testing in women), and D-amphetamine (20 mg) or PBO was administered at 0900. Heart rate and blood pressure were determined (sitting position, brachial cuff), and subjects completed symptom rating scales at intervals that avoided test interruptions, the first one occurring before pill ingestion. Autonomic measures and visual analog scale (VAS) scores of symptoms across the post-pill intervals were thus anchored by a pre-pill baseline value. VAS scores were designed to assess general somatic and psychological symptoms and level of consciousness (Bond and Lader 1974; Bunney et al. 1999; Norris 1971). Subjects made a single, vertical mark representing their current state along a 100-mm line (0 mm representing "not true" and 100 mm representing "true"). Ratings assessed several states: "happy," "queasy," "dizzy," "drowsy," and perceptual sensitivity. Details of these scales are found in Swerdlow et al. (2002) and included prompts such as "Normal sounds seem unusually intense or loud."

During the 90 min after pill ingestion, subjects completed startle testing as part of a larger, ongoing study (Swerdlow et al. 2003a, b; Talledo et al. 2009) to be reported separately. One hundred and ten min after pill ingestion (at a time known to correspond to bioactivity of this dose of AMPH, based on autonomic and subjective measures of arousal (Swerdlow et al. 2002; 2003a, b; Talledo et al. 2009)), subjects completed the MCCB. As described above, the MCCB measures key cognitive domains relevant to cognitive deficits in SZ. Upon completion of the MCCB, autonomic and subjective VAS ratings were continued until 430 min post-pill. On test day two, subjects also provided blood for future genetic studies. Subjects were paid on completion of each visit. The study sample was considered complete after the 60th subject was tested; this planned "mid-point" analysis is part of a larger anticipated sample of 120 subjects for whom genetic information will also be analyzed.

Data analysis

MCCB T Scores, autonomic measures, and personality scores were treated as continuous measures and analyzed with repeated measure analyses of variance (ANOVAs) with appropriate post-hoc comparisons. VAS scores were not normally distributed and were analyzed via non-parametric statistics. Based on known effects of age, sex and PBO neurocognitive performance (henceforth, "baseline") on either MCCB performance, AMPH sensitivity, or both (e.g., Mattay et al. 2000; Kern et al. 2008; Riccardi et al. 2011), these variables were typically used as either categorical grouping factors (including groupings based on a median or quartile split) or covariates in primary or exploratory analyses. To avoid potential confounding effects of sex differences in neurocognitive function, median and quartile splits were created by ranking variables for male (n=37) and female (n=23) subjects separately. Both ANOVAs and simple regressions were used to explore the relationship between specific personality indices, MCCB performance and AMPH sensitivity. Alpha for planned comparisons and empirical findings were set at 0.05 and 0.01 respectively.

Analyses progressed in a systematic fashion. We first compared our sample's baseline performance with published MCCB patterns, examining sample characteristics, and the effects of age, sex, years of education, and personality measures on MCCB performance. We next assessed the fidelity of our intervention (drug) by examining evidence of bioactivity (autonomic response, VAS of subjective experience), and the fidelity of our measurements by examining test-retest reliability. With this assurance of bioactivity and measurement fidelity, we then examined the effect of AMPH on MCCB performance using a difference score (AMPH performance minus PBO performance), starting with the most global metric: the MCCB composite score. Based on previous findings, the two a priori factors included in this analysis were: (a) sex and (b) baseline performance. We then proceeded to a finer-grain analysis of AMPH's effects on individual MCCB domains, using the same analytic strategy (i.e., difference score and factors). Lastly, we explored correlations between MCCB effects of AMPH and (a) measures of AMPH bioactivity and (b) personality scale scores associated with dopaminergic function and/or AMPH sensitivity.

Some patterns detected in our results were consistent with a regression to the mean (RTM), i.e., based on chance, high scorers in one condition (e.g., AMPH) were more likely to score lower in the other condition (e.g., PBO), and vice versa (Barnett et al. 2005). We thus assessed whether baseline (PBO)-dependent effects of AMPH on MCCB performance were attributable to RTM using permutation tests. For each of the seven MCCB domains, data were first residualized based on a linear mixed effects model (LME) with each domain in turn as the dependent variable and treatment (AMPH vs. PBO) and test number as independent variables along with their interaction. For each residualized measure, high scoring subjects were selected based on surpassing the median of residualized scores. For each of these subjects, the difference between their scores in the AMPH and PBO conditions was computed. The mean differences between conditions for high AMPH scorers were then computed. To determine if this mean difference was greater or smaller than expected by usual RTM, we performed a permutation test, randomly permuting the treatment label (AMPH or PBO) within each subject and computing the mean difference for high AMPH scorers for each permutation; the permutations give the distribution of differences for high scorers under the null hypothesis that the difference is unrelated to treatment assignment. The same permutation test procedure was repeated for AMPH low scores, and PBO high and low scorers.

Results

Subject demographics

As seen in Table 1, the subjects were generally college-aged, well-educated, non-smokers and moderate caffeine consumers.

Baseline MCCB

Measures of baseline MCCB performance—T Scores of each of the seven MCCB domains after PBO—are seen in Fig. 1a; values ranged from 47.68 (range 13–69) in SC to 59.7 (range 34–66) in VisL. Baseline performance was consistent with previously reported MCCB patterns related to age (Fig. 1b; e.g., main effect of age (median split): $F=12.01$, df 1,58, $p=0.001$; composite T Score vs. age, $R=-0.52$, $p<0.0001$) and sex (Fig. 1c; Kern et al. 2008). ANOVA of domain T scores with sex as a between-subject factor revealed no significant effect of sex ($F<1$) and a significant effect of domain ($F=17.23$, df 6,348, $p<0.0001$), and a significant interaction of sex x domain ($F=2.15$, df 6, 348, $p<0.05$). Post hoc comparisons across the seven domains detected no significant main effect of sex in any single domain. MCCB performance was not significantly related to years of education in this sample ($R=0.10$), likely reflecting a restrictive "ceiling effect." Expected significant correlations among the different MCCB domains were also confirmed for SP vs. WM ($R=0.64$, $p<0.0001$) and VerL vs. VisL ($R=0.57$, $p<0.0001$). The full seven-domain correlation matrix is found in Supplemental Table 1.

Personality measures

The impact of TPQ NS, SSS DIS, and EPQ total scores on MCCB performance is seen in Fig. 2. Primary analyses focused on these scales based on specific reported relationships to AMPH sensitivity or dopaminergic neural mechanisms (e.g., Fleming et al. 1995; Ebstein et al. 1996; Benjamin et al. 1996; Hutchison et al. 1999; Kumari et al. 2004; Hamidovic et al. 2009). Performance on individual MCCB domains appeared to be impacted by elevated NS (elevated WM scores) and DIS scores (elevated A/V scores), while MCCB scores were more globally impaired among individuals with elevated EPQ Total scores. Significant negative correlations were detected between EPQ Total Scores and T Scores on domains of WM ($R=-0.31$; $p<0.02$), R/PS ($R=-0.38$; $p<0.003$) and SC ($R=-0.38$; $p<0.003$).

MCCB test-retest reliability

Independent of drug condition, test performance for subjects across test days was highly correlated (composite T score, $R=0.92$, $p<0.0001$; T scores for seven individual domains, R's$=0.482$–0.749, with all $p<0.0001$). Also independent of drug condition, MCCB scores increased significantly with retesting: ANOVA revealed a significant main effect of test day ($F=61.05$, df 1,59, $p<0.0001$), and a significant domain x test day interaction ($F=2.38$, df 6,354, $p<0.03$). Post-hoc comparisons revealed significant test day effects for domains of SP ($p<0.015$), A/V ($p<0.04$), VerL ($p<0.0001$), and VisL ($p<0.0001$). Effect sizes for practice effects on performance in all MCCB domains are found in the "Supplemental materials" section, as a function of low vs. high baseline performance.

Bioactivity

Measured immediately upon MCCB completion, heart rate, diastolic and systolic blood pressure were all significantly elevated by AMPH (F's$=21.08$, 17.04 and 55.50; p's<0.0001, respectively (Supplemental Figure 1)); at this time point, more subjects reported greater reductions in drowsiness and perceived sound intensity, and a near-significant increase in the ability to focus attention with AMPH vs. PBO (paired sign tests, $p<0.036$, 0.029, and 0.06, respectively). In contrast, this dose of AMPH had no significant effect on perceived queasiness, happiness, or dizziness (all NS).

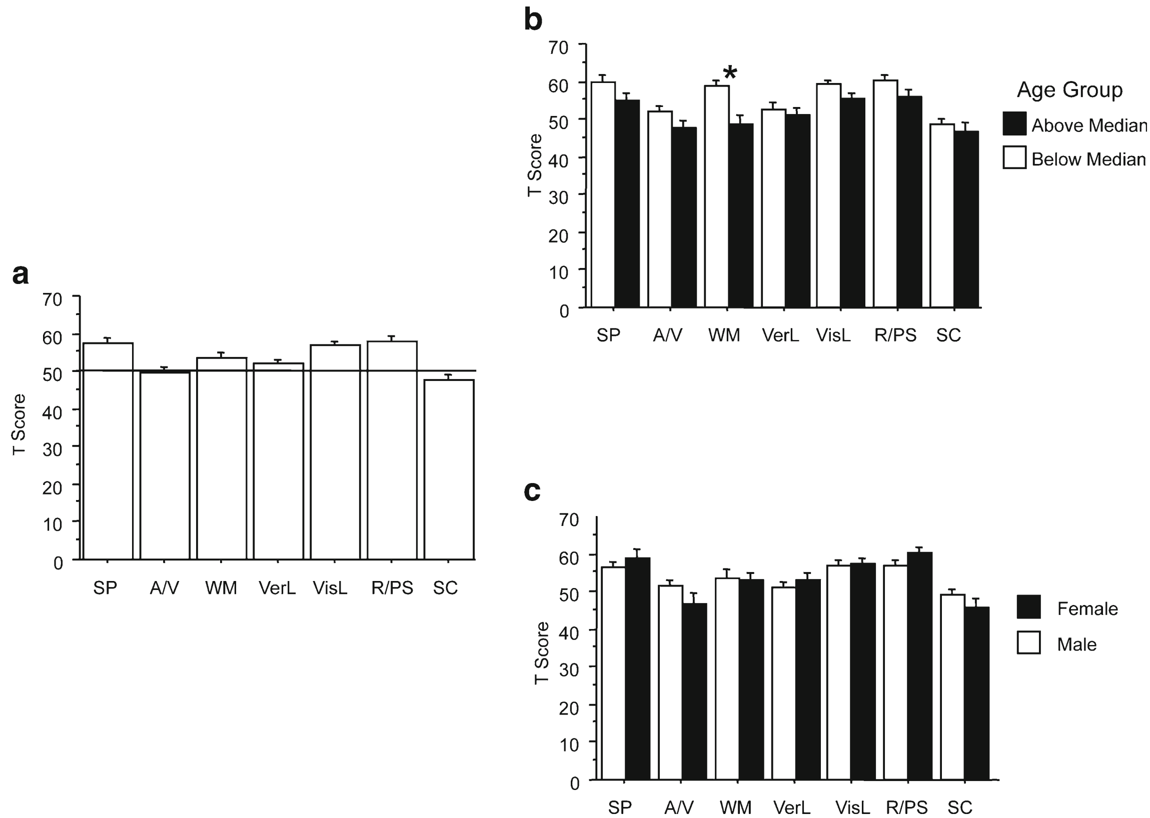

Fig. 1 Baseline MCCB performance. **a** Mean T scores in each of the seven MCCB domains after PBO ingestion. **b** Mean T scores of subjects below and above median age. *Asterisk* indicates significant main effect of age by ANOVA (below median age > above median age). **c** Mean T-score values of subjects divided by sex

AMPH effects on MCCB performance

A simple ANOVA of the MCCB Composite Score using AMPH dose as a within-subject factor revealed no significant main effect of AMPH ($F<1$). Thus, in the inclusive study sample, AMPH had no significant effects on overall MCCB performance.

Sex and baseline performance

Two variables reported to impact AMPH effects on a variety of measures, including neurocognition, are sex (cf. Becker et al. 2001; Riccardi et al. 2011) and baseline performance (Mattay et al. 2000). ANOVA of MCCB Composite Score using sex and low vs. high baseline MCCB performance (based on a median split of PBO MCCB values) revealed no significant effect of sex ($F<1$) or AMPH dose ($F<1$), or sex x AMPH dose interaction ($F<1$). The median produced the expected significant effect of baseline MCCB performance ($F=66.54$, *df* 1,56, $p<0.0001$), and a significant interaction of AMPH dose x baseline MCCB performance ($F=4.73$, *df* 1,56, $p<0.035$). This interaction reflected the tendency for AMPH to increase MCCB composite scores among subjects with low baseline performance, and to decrease MCCB composite scores among subjects with high baseline performance. This relationship was supported statistically by a significant negative correlation between the magnitude of the AMPH effect on MCCB performance (calculated as a difference score: AMPH minus PBO) and baseline MCCB composite score ($R=-0.43$, $p<0.001$).

Regression to the mean

Conceivably, "rate-dependent" effect of AMPH might be due to a "regression to the mean" (RTM), i.e., a likelihood that, if two populations differ by random chance in the PBO (baseline) test, subjects scoring low in the PBO test are likely to score higher in the AMPH test, and vice versa. The RTM hypothesis is a challenging one to "falsify" in a within-subject, cross-over design (Barnett et al. 2005; Nesselroade et al. 1980), but can be explored via other properties of the data. We first explored the RTM hypothesis using two known "non-random" sources of low MCCB Composite Score in this sample: higher age, and higher EPQ score. We next tested whether the distribution of AMPH effect scores among subjects scoring above or below the median of each drug condition differed from permuted null distributions.

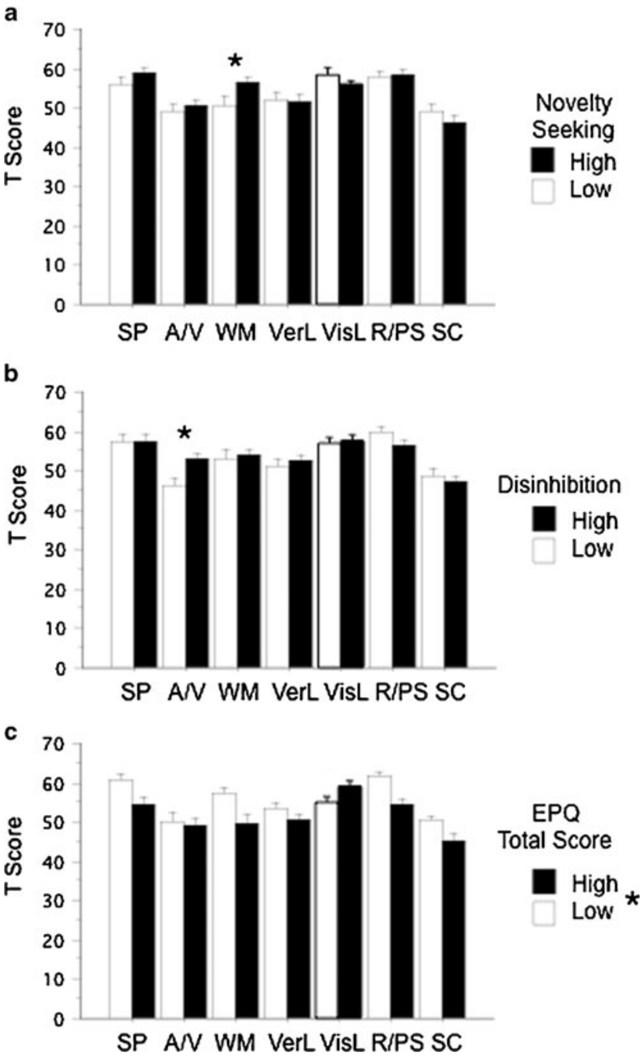

Fig. 2 T scores in each of the seven MCCB domains as a function of median split in personality measures of **a**. TPQ Novelty Seeking (*asterisk*) significant difference in WM, $p<0.05$, after significant domain x median split interaction by ANOVA. **b** SSS disinhibition. **c** EPQ total score. *Asterisk* indicates significant main effect of EPQ score by ANOVA (low score > high score)

RTM, age and EPQ score

We first examined whether the effect of AMPH on MCCB Composite scores (i.e., "AMPH minus PBO" difference score) was related to known sources of low MCCB scores, independent of any selection for extreme values. We fit linear regressions with AMPH difference score as the dependent variable and either age or EPQ Total score as independent variables, controlling for mean MCCB Composite score (averaged across the two test days). There was a trend toward higher age predicting higher differential scores (coef=0.025, se=0.014, p=0.086), and higher EPQ scores significantly predicted lower differential scores (coef=−0.036, se=0.015, p=0.020). Thus, independent of baseline performance, older subjects tended to exhibit a greater effect of AMPH on MCCB performance, while subjects with elevated EPQ scores exhibited a significantly diminished effect of AMPH on MCCB performance.

Permuted null distributions

We next computed the null distribution of differences in cognitive outcomes between conditions (PBO vs. AMPH) for AMPH high scorers for all seven MCCB domains using permutation tests. The mean difference of cognitive scores was contained within the 95 % confidence intervals of the null permutation distributions for all seven domains, indicating no evidence that the mean "AMPH minus PBO" difference in AMPH high scorers differed from that predicted by an RTM effect. We repeated the analysis for AMPH low scorers (below the median of scores in the AMPH condition) and on PBO high and low scorers. As with AMPH high scorers, all results were within the bounds of the 95 % permutation null distributions, indicating no significant departures from a model based on RTM.

AMPH effects on individual MCCB domains

Analyses next proceeded with the seven MCCB domains. ANOVA of domain T Scores with AMPH dose and domain as within-subject factors and sex as a between-subject factor revealed no significant main effects of AMPH dose (F= 1.56, df 1,58, ns) or sex (F<1), and no interaction of AMPH dose x sex (F<1). There was a significant effect of domain (F=26.35, df 6,348, p<0.0001), but no other significant two- or three-way interactions (Fig. 3a).

Based on findings of significant interactions of baseline MCCB performance and age on AMPH effects on the Composite MCCB Score, we next assessed the impact of these variables on AMPH effects within individual MCCB domains (Fig. 3b, c and Table 3). ANOVAs revealed significant main effects of baseline score (median split) for each domain on the AMPH difference score for that domain (Fig. 3b), with AMPH-induced decreases in subjects with baseline scores above the median, and AMPH-induced increases in subjects with baseline scores below the median. Using a more extreme criterion of 1 SD above or below the PBO mean, AMPH significantly decreased performance among high baseline subjects in MCCB domains of SP (p<0.002), WM (p<0.025), VerL (p<0.002), Vis (p<0.01), and SC (p<0.006), and significantly increased performance among low PBO scorers in MCCB domains of A/V (p<0.03), VerL (p<0.03), and R/P (p<0.01). Effect sizes for AMPH effects on performance in all MCCB domains are shown in Supplemental Table 2, as a function of low vs. high baseline performance. Assessing effects of age on AMPH sensitivity, ANOVA with age (above vs. below median) as a grouping factor detected significant effects only on WM (p=0.01; Fig. 3c).

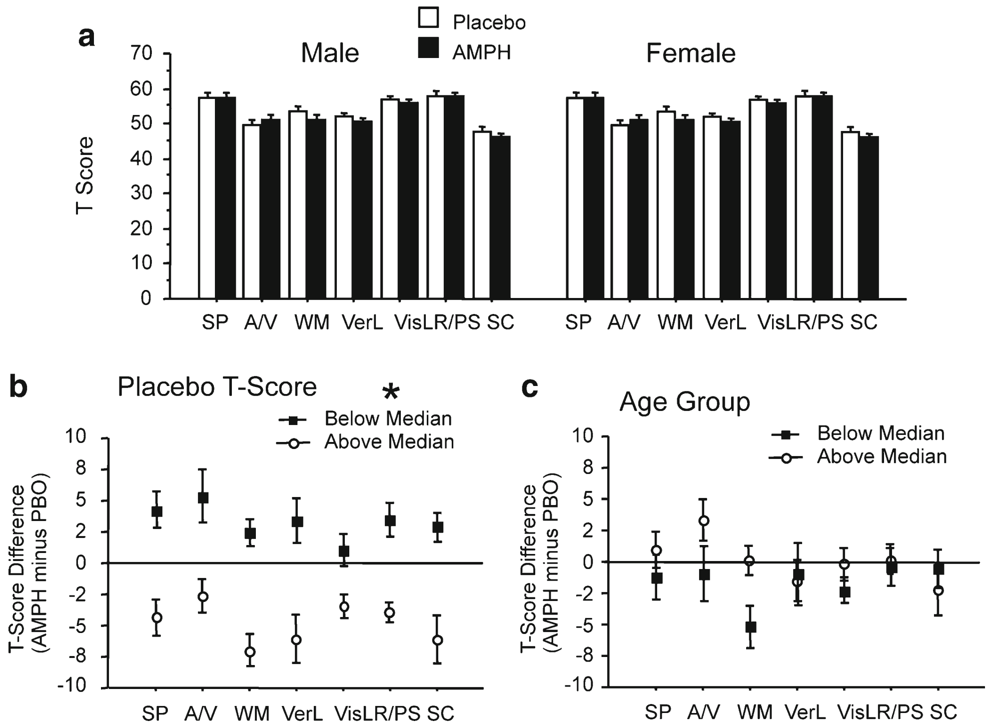

Fig. 3 Effect of drug (PBO vs. 20 mg AMPH) on the seven MCCB domains. **a** All subjects, divided by sex. **b** T-score difference (AMPH minus PBO) divided by median split of PBO T scores; *asterisk* indicates significant main effect of PBO T score by ANOVA. **c** T-score difference (AMPH minus PBO) divided by median split of age. *SP* speed of processing, *A*/*V* attention/vigilance, *WM* working memory (verbal and nonverbal), *VerL* verbal learning, *VisL* visual learning, *R*/*PS* reasoning and problem solving, *SC* social cognition

As with the Composite MCCB score, ANCOVAs with AMPH effect on domain scores as the dependent variable and EPQ score as a covariate suggested substantial shared variance with EPQ score (i.e., a loss of significant effect of baseline MCCB performance) for all domains except WM and SP. For WM, the main effect of baseline MCCB performance remained statistically significant ($p<0.02$); conversely, the significant relationship between WM and baseline MCCB performance was lost when age was entered as a covariate. For SP, the main effect of baseline MCCB performance remained significant with covariates of both EPQ score and age (*p's*<0.007 and 0.002, respectively); both covariates interacted significantly with baseline MCCB performance (*p*'s<0.04 and 0.008, respectively).

While AMPH did not exhibit significant main effects on any individual MCCB domain across the inclusive study sample, subjects exhibiting AMPH-induced increases (or decreases) on one MCCB domain were more likely to exhibit similar AMPH-induced changes on other domains. AMPH difference scores were significantly correlated between domains in 5 out of 21 possible pair-wise comparisons (*p*'s<0.02–0.0002), with trend level correlations in 3 additional pairings ($p<0.10$–0.05). In total, of the 21 possible comparisons (*R*), 20 were positive, and one was −0.10; this distribution exceeds a chance probability (Sign test, $p<0.0001$). The full correlation matrix of AMPH difference scores across MCCB domains is found in Supplemental Table 3.

AMPH bioactivity and MCCB effects

Simple regressions revealed no strong correlations between AMPH effects on autonomic measures and its effects on MCCB Composite or individual domain scores: of the 24 correlations, only 2 achieved nominal alpha values (social cognition vs. change in heart rate ($R=0.26$, $p<0.05$) and vs. change in diastolic blood pressure ($R=-0.32$, $p<0.015$)), neither of which survived correction for multiple comparisons. Because VAS scores for change in drowsiness were not normally distributed, Spearman Rank Correlations were used to assess the relationship between this measure of "central" AMPH bioactivity and AMPH effects on MCCB scores. Significant correlations for reduced drowsiness and increased MCCB scores were detected for MCCB Composite Score (*R*'s=0.28, $p<0.04$), SP (*r*'s=0.31, $p<0.02$), VerL (*R*'s=0.30, $p<0.02$) and R/PS (*R*'s=0.30, $p<0.025$), but not A/V, WM, VisL, or SC (*R*'s=0.00–0.15). No consistent pattern emerged when subject weight (as a proxy for dose in mg/kg) was included as a predictor of AMPH effects.

Personality measures and AMPH sensitivity

As noted above, baseline performance in individual MCCB domains was impacted significantly by elevated Novelty Seeking (NS), Disinhibition (DIS), and EPQ Total scores. Simple regressions also revealed significant correlations between these personality measures and AMPH effects on MCCB performance within specific domains: NS score and

Table 3 Correlation (R) between age and baseline MCCB performance vs. AMPH effect (difference scores)

	SP	A/V	WM	VerL	VisL	R/PS	SC
Age	0.24	0.29*	0.41**	0.09	0.12	0.13	0
Baseline MCCB	−0.46***	−0.54****	−0.57****	−0.66****	−0.36**	−0.51****	−0.60****

*p<0.03; **p<0.005; ***p<0.0005; ****p<0.0001

SP speed of processing, *A*/*V* attention/vigilance, *WM* working memory (verbal and nonverbal), *VerL* verbal learning, *VisL* visual learning, *R*/*PS* reasoning and problem solving, *SC* social cognition

DIS scores vs. AMPH effects on SP (R=0.32 and 0.31, respectively; p<0.015 and <0.02, respectively); and EPQ Total score vs. VisL (R=−0.29, p<0.025). Correlations of personality measures and AMPH effects on individual MCCB domains among individuals with low vs. high baseline performance scores are found in Supplemental Table 4.

Discussion

Evolving therapeutic strategies for SZ are requiring new approaches to experimental designs. Efforts to "augment" antipsychotic therapies with procognitive agents have largely proven unsuccessful, and trials have now instead begun to focus on the ability of drugs to enhance the therapeutic impact of cognitive therapies by targeting specific cognitive abilities that are engaged or otherwise required by those therapies (Swerdlow 2011). Importantly, the process of matching candidate drugs and cognitive interventions, and testing them for additive or synergistic therapeutic impact in patients is extremely time- and resource-intensive, given the 12–26 weeks required for many cognitive interventions, and the logistical complexities of already medicated and severely ill patients with heterogeneous symptom profiles and a high propensity for study attrition (cf. Rosenheck et al. 2011). Predictive information garnered from preclinical studies in healthy populations could thus have a very significant impact on the efficiency and viability of this discovery process (http://www.nimh.nih.gov/about/director/2012/experimental-medicine.shtml). Here, we report the effects of the known procognitive agent and psychostimulant, AMPH, on MCCB performance in 60 healthy adults; this study was undertaken as part of a larger investigation of dopamine agonist effects on psychophysiological and neurocognitive measures and their relationship to genotype.

AMPH generated evidence of bioactivity, including autonomic activation, and subjective reductions in drowsiness and self-reported increases in attentional capacity. In our past reports, this dose of AMPH also resulted in significant changes in prepulse inhibition (PPI) of the startle reflex; a preliminary inspection confirmed significant AMPH-induced increases in PPI among subjects in the present study (data to be reported as part of a larger sample (n=120)).

Despite this evidence of robust autonomic and CNS effects of AMPH, its impact on MCCB performance was subtle—detected only among specific subgroups, and on specific MCCB domains. This is perhaps not surprising based on the overall high level of MCCB performance within this highly educated, clinically healthy sample. Nor does the overall insensitivity of the MCCB to AMPH effects suggest that the MCCB does not detect meaningful drug-induced improvements in neurocognition in all healthy individuals: ceiling effects in this inclusive sample of high functioning individuals might be expected to obviate any but the most robust AMPH-mediated cognitive enhancement. Because the goal of this preclinical strategy is to identify drugs that might enhance cognition in cognitively impaired SZ patients—rather than in an inclusive sample of high functioning healthy subjects—it was our a priori design to focus on drug effects among subgroups of subjects who are conceptually linked to SZ, either through their relatively poor MCCB performance, or through psychological or other markers associated with SZ. We previously used this strategy in psychophysiological measures of several drug effects (Swerdlow et al. 2006, 2009; Talledo et al. 2009). One might argue that neurocognitive performance in a sample of healthy adults should be expected to be insensitive to improvement, because "healthy" neurocognition has been optimized by evolutionary forces (Hills and Hertwig 2011). An alternative strategy to "taking all comers" would be to screen subjects for a single characteristic, e.g., exclude all but the lowest MCCB scorers. However, this strategy would not be optimal for examining multiple contributors to AMPH MCCB sensitivity, e.g., personality scale scores or age, would limit performance range and thereby hinder the detection of correlations among performance-predicting variables, and also would preclude detection of potential deleterious effects of AMPH on performance in higher scoring subgroups.

Among individuals with relatively poor baseline MCCB performance, AMPH increased MCCB scores; this was true to varying degrees, depending on the threshold defining "poor performance": e.g., lowest 50 % or 25 %, or 1 SD below the sample mean. For comparison, values 1 SD below the present sample mean for T Scores in the seven MCCB domains were 46.82, 39.17, 41.95, 42.41, 52.02, 49.01, and

37.17 for SP, A/V, WM, VerL, VisL, R/PS, and SC, respectively. These values roughly compare with means reported for a somewhat older sample of SZ outpatients for some domains (e.g., A/V, SC), but remain elevated compared to other SZ domain scores (e.g., VisL, R/PS; Kern et al. 2011). As is perhaps best illustrated in Fig. 3b, it is clear that across all MCCB domains, individuals who scored in the lower part of the present distribution at baseline tended to have their scores elevated under AMPH conditions. How to interpret this effect, and particularly the potential role of "regression to the mean" in this apparent AMPH-induced cognitive improvement, is less straightforward.

On the one hand, we demonstrated rate-dependent effects of AMPH in this same sample that are not easily attributable to an RTM explanation. Specifically, we determined that in older subjects, AMPH tended to have a greater effect on MCCB performance, while in subjects with elevated EPQ scores, AMPH has a significantly diminished effect on MCCB performance. Because these analyses were not based on extreme values of baseline MCCB performance, these relationships cannot be explained on the basis of a RTM. On the other hand, using permutation tests, we found no significant differences of observed rate-dependent effects of AMPH from those predicted by RTM. More definitive assessments on whether observed effects constitute RTM or actual AMPH effects can be determined from other study designs, such as those using three or more time points (Nesselroade et al. 1980). For example, under usual psychometric assumptions of measurement error independence, if a third measurement of MCCB performance was obtained, it would then be possible to determine if any drug effect detected across the previous two measurements were "real" (i.e., whether low baseline performers performed significantly better in the AMPH condition).

While there is not absolute clarity to the basis for the current observation of AMPH-enhanced MCCB performance among "low baseline" subjects, our findings are consistent with previous reports of dopamine agonist effects on neurocognition. In both SZ patients and healthy comparison subjects, AMPH has been shown to improve cognition (Barch and Carter 2005; Pietrzak et al. 2010a, b; Rapoport et al. 1980). Of most relevance to our present findings, Mattay et al. (2000) reported that AMPH enhanced WM among healthy subjects with low baseline WM performance, but worsened performance among subjects who had high baseline WM scores. This same pattern of baseline-dependent drug effects was reported by Kimberg et al. (1997) with the D2 agonist, bromocriptine. Other reports have identified an "inverted-U" relationship between baseline performance and AMPH or other DA agonist effects on forebrain-mediated psychophysiological measures such as prepulse inhibition of startle (Bitsios et al. 2005; Talledo et al. 2009) and antisaccade latency (Allman et al. 2010). Mechanisms responsible for the baseline-dependent impact of DA agonists on neurocognitive and other forebrain-mediated processes are a focus of investigation, and may involve differential levels of DA catabolism effected the COMT Val158-Met polymorphism (Hamidovic et al. 2010; Mattay et al. 2003).

We examined other variables that might moderate MCCB performance and/or AMPH effects on neurocognition: sex, personality measures and bioactivity. The MCCB did not detect significant sex differences in any domain, nor were there sex differences in AMPH sensitivity on these measures. By contrast, personality measures—NS, DIS, and EPQ Total Score—were found to significantly moderate both baseline MCCB scores and AMPH effects on MCCB performance. Previous studies reported distinct cognitive performance and drug sensitivities among groups of normal subjects differing in several of these same personality dimensions (Fleming et al. 1995; Hutchison et al. 1999; Corr & Kumari 2000; Koychev et al. 2012; Kumari et al. 2004; Roussos et al. 2009; Soubelet and Salthouse 2011); to our knowledge, this is the first report of the relationship between personality dimensions and MCCB performance in healthy individuals. Fleming et al. (1995) reported that among healthy women, AMPH disrupted verbal memory performance in high NS individuals, but enhanced performance in low NS subjects; interestingly, in our present sample, higher NS scores predicted MCCB-enhancing effects of AMPH for composite MCCB performance, and particularly for specific MCCB domains. Hutchison et al. (1999) reported that DIS significantly moderated the subjective effects of AMPH, with higher scores predicting greater AMPH-induced subjective stimulation and elation; in our present sample, higher DIS scores were associated with greater AMPH-induced increases in speed of processing (SP) domain of the MCCB. We previously reported significant differences in AMPH effects on sensorimotor gating of the startle reflex among healthy women distinguished by low vs. high NS or DIS scores. Mechanisms mediating the relationship between personality dimensions and AMPH sensitivity on subjective, cognitive or neurophysiological measures have been explicated at the levels of endocrine reactivity (White et al. 2006), differential neural circuit effects (Kumari et al. 2004) and genetic polymorphisms (Roussos et al. 2009).

To the degree that AMPH does enhance MCCB performance in a particular subgroup of healthy subjects, this effect might reflect either primary drug actions (e.g., stimulation of dopamine release in prefrontal areas regulating attention) or secondary drug actions (e.g., reducing drowsiness to permit better test performance). While no measures of primary drug effects on brain chemistry were used, it was possible to detect significant correlations between positive AMPH effects on MCCB performance and reduced drowsiness. These correlations do not preclude the possibility that both changes in performance and drowsiness might both be correlated with one or more primary drug effects, such as prefrontal dopamine release. At the least, it appears that reduced drowsiness might be one parsimonious mechanism by which AMPH enhances MCCB performance in this sample.

There are rational reasons why AMPH might raise concerns as a drug to augment the therapeutic impact of cognitive therapies in SZ patients, even though AMPH has been shown to enhance neurocognition in antipsychotic-medicated SZ patients (Daniel et al. 1991; Pietrzak et al. 2010a, b) and is not associated with an exacerbation of psychosis in these patients who received a single challenge dose (Barch and Carter 2005; Goldberg et al. 1991). Nonetheless, in the absence of antipsychotic medications, there are at least theoretical reasons to believe that AMPH might carry a risk of triggering psychotic symptoms in SZ patients. Given the pragmatic difficulties of ensuring antipsychotic adherence in SZ patients, it is viewed by some as problematic to prescribe a drug (AMPH) that might activate psychosis in the absence of antipsychotics. Other psychostimulants, such as modafinil, are being investigated for their potential procognitive effects (Bobo et al. 2011; Kane et al. 2010; Scoriels et al. 2012), and might also prove to enhance the therapeutic impact of cognitive interventions.

The present study tested a strategy—the use of healthy populations to predict the potential for drug-enhanced neurocognition in SZ patients. The findings suggest that, in a sample of clinically healthy, young adults, the MCCB is only modestly sensitive to procognitive effects of a dose of AMPH that shows evidence of both bioactivity and central activation, and which is known to enhance SZ neurocognition in other studies. However, the present findings also suggest that by identifying a priori subgroups of interest, it is possible to detect significant positive cognitive effects of AMPH; conceivably, drug effects in these subgroups may be most relevant to their potential activity in SZ patients. Our larger study, for which the present sample is a planned "first wave," may identify specific genetic predictors of such drug effects. Until definitive biomarkers are available, the use of healthy populations to predict "procognitive therapy" candidate drugs may be enhanced by designs that minimize potential "RTM" effects and that focus on population subgroups characterized by low baseline levels of neurocognitive performance or extreme values of specific SZ-linked personality indices.

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