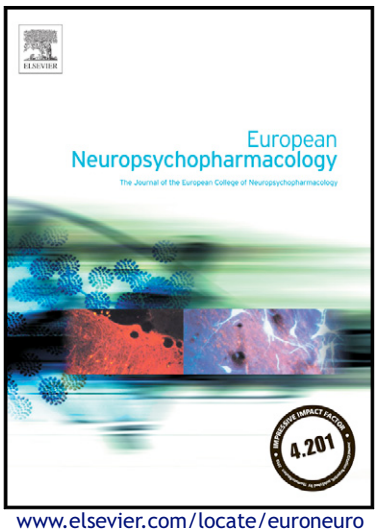
Author's Accepted Manuscript



www.elsevier.com/locate/euroneuro

Methylphenidate and Brain Activity in a Reward/Conflict Paradigm: Role of the Insula in Task Performance

Iliyan Ivanov, Xun Liu, Suzanne Clerkin, Kurt Schulz, Jin Fan, Karl Friston, Edythe D. London, Jeffrey Schwartz, Jeffrey H. Newcorn

PII: S0924-977X(14)00029-7
DOI: http://dx.doi.org/10.1016/j.euroneuro.2014.01.017
Reference: NEUPSY10794

To appear in: *European Neuropsychopharmacology*

Received date: 7 March 2013
Revised date: 29 November 2013
Accepted date: 11 January 2014

Cite this article as: Iliyan Ivanov, Xun Liu, Suzanne Clerkin, Kurt Schulz, Jin Fan, Karl Friston, Edythe D. London, Jeffrey Schwartz, Jeffrey H. Newcorn, Methylphenidate and Brain Activity in a Reward/Conflict Paradigm: Role of the Insula in Task Performance, *European Neuropsychopharmacology,* http://dx.doi.org/10.1016/j.euroneuro.2014.01.017

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Methylphenidate and Brain Activity in a Reward/Conflict Paradigm: Role of the Insula in Task Performance

Iliyan Ivanov[a], Xun Liu[a, c], Suzanne Clerkin[a], Kurt Schulz[a], Jin Fan[a, b, d], Karl Friston[e], Edythe D. London[f, g, h], Jeffrey Schwartz[f], Jeffrey H. Newcorn[a]

[a] Department of Psychiatry and [b] Department of Neuroscience,
Mount Sinai School of Medicine, New York, NY
[c] Key Laboratory of Behavior Science, Institute of Psychology,
Chinese Academy of Science, Beijing, China
[d] Department of Psychology, Queens College,
City University of New York, Flushing, NY
[e]Wellcome Trust Center for Neuroimaging, University College London, London, UK
[f]Department of Psychiatry and Biobehavioral Sciences, [g] Department of Molecular and Medical Pharmacology, and [h]the Brain Research Institute,
University of California Los Angeles, Los Angeles, CA

Corresponding author:
Iliyan Ivanov, MD
Department of Psychiatry
Mount Sinai School of Medicine
One Gustave L. Levy Place, Box 1230
New York, NY 10029
Tel: 646-387-5080
Fax: 212-241- 9311
Email: iliyan.ivanov@mssm.edu

Accepted manuscript

ACCEPTED MANUSCRIPT

Abstract

Psychostimulants, such as methylphenidate, are thought to improve information processing in motivation-reward and attention-activation networks by enhancing the effects of more relevant signals and suppressing those of less relevant ones; however the nature of such reciprocal influences remains poorly understood. To explore this question, we tested the effect of methylphenidate on performance and associated brain activity in the Anticipation, Conflict, Reward (ACR) task. Sixteen healthy adult volunteers, ages 21-45, were scanned twice using functional magnetic resonance imaging (fMRI) as they performed the ACR task under placebo and methylphenidate conditions. A three-way repeated measures analysis of variance, with cue (reward vs. non-reward), target (congruent vs. incongruent) and medication condition (methylphenidate vs. placebo) as the factors, was used to analyze behaviors on the task. Blood oxygen level dependent (BOLD) signals, reflecting task-related neural activity, were evaluated using linear contrasts. Participants exhibited significantly greater accuracy in the methylphenidate condition than the placebo condition. Compared with placebo, the methylphenidate condition also was associated with lessr task-related activity in components of attention-activation systems irrespective of the reward cue, and less task-related activity in components of the reward-motivation system, particularly the insula, during reward trials irrespective of target difficulty. These results suggest that methylphenidate enhances task performance by improving efficiency of information processing in both reward-motivation and in attention-activation systems.

Accepted manuscript

ACCEPTED MANUSCRIPT

1. Introduction

Methylphenidate (MPH) is an indirect agonist that increases intrasynaptic concentrations of dopamine (DA) and noradrenalin (NA) by blocking their reuptake (Kuczenski and Segal, 1997; Seeman and Madras, 1998) which in turn has been postulated to increase signal-to-noise ratio (Robbins and Arnsten 2009, Schulz et al., 2012). Specifically, NA increases signal via activation of α2a-adrenergic receptors, and DA decreases noise via stimulation of D1-receptors (Robbins and Arnsten, 2009). Consistent with these findings, low-dose treatment with MPH increases catecholamine neurotransmission, leading to enhanced cognitive performance (Mehta et al., 2000; Berridge et al., 2006). These effects, suggesting improved efficiency and enhanced task-related information processing in relevant neuroanatomical networks (Arnsten 2006b), are related to cognitive impairments associated with attention deficit-hyperactivity disorder (ADHD), depression, substance use disorders, and other neuropsychiatric conditions. However, improved task performance with MPH has been linked to inconsistent changes in both regional cerebral blood flow and blood oxygen level dependent (BOLD) signals in networks of attention, working memory and reward processing detected by functional magnetic resonance imaging (fMRI). Research has revealed both MPH-induced increases (Knutson et al. 2004; Doddsr et al. 2008; Marquand et al. 2011; Marquand et al. 2012) and decreases in these parameters (Vaidya et al., 1998, Mehta et al., 2000, Knutson et al., 2004, Müller et al., 2005, Dodds et al., 2008, Tomasi et al., 2011), often within the same sample, depending on the tasks employed. As most of the relevant prior fMRI studies have focused on isolating activation patterns in particular networks, the effects of stimulants on the interaction effects between complementary networks remain poorly understood. The goal of this study, therefore, was to evaluate the effects of MPH on activation in both motivation-reward and attention-activation systems in order to clarify the possible mechanisms by which MPH may improve performance. Understanding the effects of stimulants and similar compounds on the interactions of neuronal systems may guide the development of future treatments for attentional and mood syndromes.

The insular cortex is involved in the assessment of the motivational and rewarding aspects of tasks as well as in monitoring of task difficulty and performance (Craig, 2009, Linke et al., 2010, Craig,

ACCEPTED MANUSCRIPT

2011). Further, activity in both the orbitofrontal and the insular cortices has been associated with evaluating the rewarding and aversive aspects of environmental stimuli (London et al., 2000; Rolls, 2008, Grabenhorst and Rolls, 2011). An extensive literature documents the role of these brain regions in responses both to unexpected stimuli and to perceived error (Schwartz and Begley 2002), and also in the pain-alleviating effects of placebo and verbal suggestion (Price et al., 2008). The insula and the orbitofrontal cortex are thus well positioned to participate in integrating the behavioral and physiological aspects of attentional, motivational and reward functions in both normal and pathological settings.

The Anticipation, Conflict, Reward (ACR) task, which has been used to study children and adults (Ivanov et al., 2012; Ivanov et al., 2012), elicits activation in the insula and ortbitofrontal cortex (regions within the motivation-reward network) and in the middle frontal cortex, basal ganglia and thalamus (regions within the attention-activation networks). It therefore is well-suited for assessing interactions between responses to reward and cognitive control stimuli. Here, we studied 16 healthy volunteers with the ACR task to assess the influence of MPH on the activation of these two brain systems. Based on results from other neuroimaging studies with MPH challenge (Vaidya et al., 1998, Mehta et al., 2000, Knutson et al., 2004, Müller et al., 2005, Dodds et al., 2008, Tomasi et al., 2011), we expected less brain activation with MPH treatment than with placebo. We hypothesized that this difference would be evident in brain regions indexed by the reward stimuli (e.g., insula and ortbitofrontal cortex) and by the conflict stimuli of the ACR task (e.g., thalamus, middle frontal gyrus and basal ganglia). Considering the variation in MPH effects in prior studies, it is plausible that reciprocal effects between the motivation-reward and attention-activation networks are not adequately described when the activation of these networks is assessed independently. We suggest that the ability of the ACR task to reveal interactions between brain responses to reward incentives and conflict targets will facilitate the understanding of how stimulants influence the interaction effects of these two complementary systems.

Accepted manuscript

ACCEPTED MANUSCRIPT

2. Experimental Procedures

2.1. Participants

Sixteen healthy right-handed adults, ages 21 to 45 years, participated in this study (Table 1). Results from the same cohort, performing the ACR task in the placebo condition, have been published (Ivanov et al., 2012b). The study protocol included an initial visit and two subsequent scanning sessions. At the initial visit, all participants received a thorough explanation of the study, and gave written informed consent, as approved by the Mount Sinai Institutional Review Board. Participants were interviewed by a board-certified psychiatrist, and were screened for current/past psychiatric diagnoses using the Structured Clinical Interview for DSM-IV (Spitzers et al., 1992). Those with major psychotic and/or mood/anxiety disorders, ADHD and current substance use disorder(s) were excluded. Participants also underwent a physical examination, including an electrocardiogram and heart rate/blood pressure readings, to exclude any medical contraindications for the administration of MPH. Additional measures included the Symptom Checklist-90-R (SCL-90-R)(Cyr et al., 1988), the Michigan Assessment-Screening Test/Alcohol-Drug (MAST-AD)(Westermeyer et al., 2004), and Conners' Adult ADHD Rating Scale–Self-Report: Long Version (CAARS) (Conners, 2000). The Matrix Reasoning and Vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Ryan et al., 2003) were administered to estimate Full Scale IQ. Exclusion criteria included T-scores of 1.5 SD above age and gender means (i.e., > 65) on the CAARS Total ADHD Symptoms index (indicating the possibility of ADHD) and the SCL-90 Total Severity Index (indicating the possibility of other psychopathology), or an estimated IQ < 80 (indicating low cognitive capacity). Suspected current drug abuse, indicated by a MAST-AD score > 5, was also exclusionary.

2.2. Anticipation, Conflict, Reward (ACR) Paradigm

The ACR task has been described elsewhere (Ivanov et al, 2012b; also see Figure 3 in supplemental materials). In short, this task separately probes reward anticipation, conflict resolution, and reward outcome, using a fixed and a relatively short cue-target interval to minimize the length of each trial and

ACCEPTED MANUSCRIPT

maximize design efficiency (Fan et al., 2005). The task is designed to assess interactions between reward cues and target difficulty, which are the primary factors of interest in this report. In that respect, the fixed cue-target interval is most appropriate for the goal of the current experiment since the use of fixed interval avoids assumptions about delay period activity or sustained neuronal responses, and prior work has shown that a fixed 2250 ms cue-target interval provides sufficient estimates of cue and target-related responses (Clerkin et al., 2009; Schulz et al., 2011).

The ACR contains four 32-trial blocks (each lasting 6-min 20-sec), with 30-second fixation conditions at the beginning and the end of each block. The task contains non-reward and reward trials counterbalanced in each block. Non-reward trials begin with the presentation of a yellow circle, and reward trials begin with presentation of a blue circle. This cue is followed by a target, which is a central arrowhead, flanked by two arrowheads on each side that may point in the same direction (congruent) or in the the opposite direction (incongruent) of the center arrowhead; the two types of targets are counterbalanced within each block. Participants are instructed to respond in the direction of the central arrowhead as soon as possible, while ignoring the flankers, by pressing a button with their right or left index finger, which corresponds to the direction of the central arrowhead. The potential outcomes are: i) correct response in a non-reward trial, yielding $0, as indicated in a light-blue square, ii) correct response in a reward trial, yielding +$1, as indicated in a green square; iii) incorrect or delayed response on both reward and non-reward trials, resulting in -$1 displayed, as indicated in a red square. The running total of wins/losses is presented at the end of each block. Participants must respond to each target regardless of the preceding cue to avoid punishment (i.e. losing $1). Slow responses are defined as button presses longer than 750 msec. As stated in the instructions given to the participants, (Table 4 in supplemental materials), only 50% of the correct responses are rewarded; therefore, the maximum win is $8 for each block , and $32 for the whole task. The monetary rewards associated with the ACR are virtual (not actual money); subjects were told in advance that they would receive a fixed reimbursement upon completion of the task. The ACR contains three components: anticipation (reward vs. no reward cue), conflict (congruent vs. incongruent flankers)

Accepted manuscript

ACCEPTED MANUSCRIPT

and outcome (positive, neutral or negative), and incorporates a nested factorial design (i.e. only anticipation and conflict components are fully balanced) .

2.3. fMRI Procedures

The first fMRI scan was performed during the second study visit; the second scan was performed approximately 2 weeks later. Participants practiced one block of the task on a desktop computer before each scan. The scanning procedure lasted 35-40 min. Participants received one capsule of MPH or placebo orally in a randomized order 1 hour before testing on each of two separate scan days. The dose of MPH was 0.5 mg/kg, which averaged 30 mg for male and 20 mg for female participants.

2.4. Image Acquisition

All image data were acquired on a 3.0-T Siemens Allegra (Siemens Medical Systems) head-dedicated MRI scanner using a high-performance head gradient system. Stimuli were projected via an SVGA system onto a rear-projection screen mounted at the head of the magnet bore. Scan sessions began with shimming and sagittal localization. A high-resolution, T2-weighted, anatomical volume of the brain was acquired with a turbo spin-echo (TSE) pulse sequence with a repetition time (TR) of 4050 ms, echo time (TE) of 99 ms, flip angle of 170°, 240 mm field of view (FOV), and 512 x 336 matrix. Forty axial slices were acquired with a thickness of 4 mm (no gap) and an in-plane resolution of 0.47 x 0.47 mm. Functional T2*-weighted, echo-planar images, indicating blood oxygenation level-dependent (BOLD) signals, were acquired at the same 40 slice locations, with a TR of 2500 ms, TE of 27 ms, flip angle of 82°, FOV of 240 mm, and an acquisition matrix of 64 x 64. Each functional image comprised a brain volume of 40 axial slices with 4-mm thickness (no gap) and an in-plane resolution of 3.75 x 3.75 mm^2. All images were acquired with slices positioned parallel to the anterior commissure – posterior commissure line. All participants completed four runs of 380 seconds each, yielding 152 time points per run.

2.5. Statistical Analysis

2.5.a. Behavioral Analyses The primary measures of performance were reaction time (RT) and accuracy of responses over the four conditions: (i) congruent flanker following non-reward cue; (ii) congruent

Accepted manuscript

ACCEPTED MANUSCRIPT

flanker following reward cue; (iii) incongruent flanker following non-reward cue; and (iv) incongruent flanker following reward cue. A three-way repeated measures analysis of variance (ANOVA), with cue (reward vs. non-reward), target (congruent vs. incongruent) and drug condition (placebo vs. MPH) as the factors, was used to test for main effects and their interactions on RT and accuracy. The nominal false-positive rate for these analyses was set at $p \leq .05$. Behavioral analyses were perfromed using SPSS version 20.

2.5.b. fMRI Analyses Image processing was conducted using statistical parametric mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, U.K.). Pre-processing of the functional time series was performed individually for each subject. The functional scans were slice time-corrected, realigned to the first volume to correct for inter-scan motion, co-registered to the T2 image, normalized to a standard template (Montreal Neurological Institute), and spatially smoothed with an 8 x 8 x 8 mm^3 full-width at half-maximum Gaussian kernel. Neuroimaging results are based on whole-brain analyses. First-level (within subject) analyses were conducted using a general linear model to quantify the relationship between event-related BOLD responses and regressors encoding neural responses as described below. Regressors were created by convolving a train of delta functions – that encoded individual trial types – with the canonical hemodynamic response function, composed of two gamma functions (Friston et al., 1998) . The six movement estimates from the realignment procedure were entered as covariates of no interest. The design matrix comprised nine regressors of interest: two regressors each modeling the main effect of reward vs. non-reward cue over all trials (i.e., anticipation), four regressors to model the effects of reward cue and target congruence (and their interaction) , only for correct trials (note that the presentation of reward cues and flankers was fully orthogonal). The final three regressors modeled outcome effects (reward following reward cue, non-reward following reward cue, and non-reward following non-reward cue).

The main effects of the ACR components were quantified with the following contrasts: anticipation (reward cue minus non-reward cue), conflict (incongruent minus congruent targets) (i.e., the main effect of congruency in correct trials) and reward outcomes (anticipated reward minus anticipated non-reward

ACCEPTED MANUSCRIPT

and surprising non-reward minus anticipated non-reward). In addition, the interaction between reward anticipation and congruency (in correct trials) was assessed by contrasting incongruent minus congruent targets under reward cues versus the equivalent contrast under non-reward cues, in both placebo and MPH conditions (Table 5 in supplemental materials). The ensuing contrast images for each participant were entered into second-level (between-subjects) random-effects group analyses, using two sample *t*-tests to produce statistical parametric *t*-maps testing for regionally specific effects of drug (placebo versus MPH) on responses to different levels of the ACR factors. We compared contrasts of the main effect of reward, the main effect of conflict and a contrast testing for conflict by reward interaction, under MPH versus placebo. We restricted our search for drug effects to regions showing main effects of reward, conflict and their interaction (averaged over both drug conditions). We then quantified the effects of MPH vs. placebo by examining the activation changes during reward cues and outcomes and targets using the appropriate contrasts of parameter estimates. The magnitude of activation changes in regions showing significant interactions were then plotted to quantify the underlying (unstandardized) effect sizes. Interactions between reward anticipation and congruency were tested within volumes defined by the (orthogonal) main effects of reward anticipation. The fMRI results are reported at a corrected significance level of $p < .05$ using a random field correction (Nichols, 2012) with cluster extent threshold of 85 voxels (2x2x2 mm^3).

Accepted manuscript

ACCEPTED MANUSCRIPT

3. Results

3.1. Behavioral Results

There was a significant main effect of reward cue on reaction time (RT) ($F_{(1,15)}$=8.75, p ≤0.05) and a significant reward cue by target interaction for RT ($F_{(1,15}$=7.48, p ≤0.05) (Fig 4A in Supplemental materials). RTs were significantly shorter in response to reward than non-reward cues for both congruent and incongruent targets during placebo and for incongruent targets during the MPH condition; RT did not change significantly for reward vs. non-reward cues for congruent targets during the MPH condition. There was a main effect of target with significantly shorter RT for congruent vs. incongruent targets in both placebo and MPH conditions, following both reward and non-reward cues ($F_{(1,15)}$=88.05, p ≤0.05). There was a significant main effect of drug condition on accuracy ($F_{(1,15)}$=4.47, p ≤0.05) and a significant reward cue by medication interaction for accuracy ($F_{(1,15}$=4.50, p ≤0.05) (Fig 4B in Supplemental materials). These findings were associated with higher accuracy during MPH over placebo conditions in reward cue/congruent, reward cue/incongruent and non-reward cue/congruent trials (see Table 2), whereas the accuracy was the same (97.52%) during non-reward cue/incongruent trials for both MPH and placebo conditions. Lastly there was a main effect of target on accuracy ($F_{(1,15)}$=9.20, p ≤0.05), such that congruent targets elicited more accurate responses in both reward/non-reward cue trials. Behavioral data were normally distributed.

3.2. Neuroimaging Results

Compared with placebo, MPH consistently lowered activation in neuronal systems associated with reward processing and executive control, as follows.

3.2.a. Reward Anticipation Contrasts for reward minus non-reward cues showed significantly lower activation in the left insula, left caudate, left thalamus, and right cerebellum in the MPH condition as compared with placebo (Table 3 and Figure1A, B).

3.2.b. Cognitive Conflict The incongruent minus congruent target contrast showed significantly less activity in a widely distributed network, including the left supplemental motor gyrus, the left precuneus, the postcentral gyrus bilaterally and the right cerebellum, in the MPH vs. placebo condition (Table 3).

Accepted manuscript

ACCEPTED MANUSCRIPT

3.2.c. Anticipated Reward The anticipated reward (i.e., reward outcome that followed a reward cue and correct target response) minus anticipated non-reward (i.e., neutral outcome that followed a non-reward cue and correct target response) contrast in the MPH condition was associated with less activation in the mid-occipital and inferior parietal cortex on the left than in the placebo condition (Table 3).

3.2.d. Surprising Non-Reward Contrasts of surprising non-reward (i.e. non-reward outcome following a reward cue and a correct target response) minus anticipated non-reward elicited significantly less activity in the left insula and the left pallidum in the MPH condition (vs. placebo) (Table 3, Figure 1C, D).

3.2.e. Reward Anticipation by Conflict Interaction Significant interactions between anticipation (reward vs. non-reward cue) and conflict (incongruent vs. congruent targets) were mapped at the single-subject level; then the effects of the two medication conditions (placebo vs. MPH) were compared by a same-sample t-test. To characterize the effect of drug on the reward cue-dependent conflict effects, we describe the (three-way) interaction between reward cue, conflict and drug condition in terms of the difference between the two-way interactions (i.e. reward cue and conflict) for the two drug conditions (i.e. placebo and MPH) (Figure 2 A, B, C, D).

Significant interactions were detected in the right thalamus, right insula, right putamen, and the left inferior frontal cortex (Table 2). MPH was associated with less activation (vs. placebo) in these regions in all four conditions (i.e. non-reward cue/congruent target, non-reward cue/incongruent target, reward cue/congruent target, reward cue/incongruent target), but this difference between MPH and placebo varied with whether activation was measured in the attention-activation system or the motivation-reward system. Notably, MPH was associated with less activation than placebo in components of the attention-activation system in response to both congruent and incongruent targets, and this difference was greatest for the non-reward/incongruent trials. This finding is exemplified by no interaction effects in the placebo condition and significant reward cue/incongruent target vs. non-reward cue/incongruent target interactions in the MPH condition in the thalamus, the putamen and the inferior frontal gyrus (Figure 2 A,B,C). These effects were associated with a robust decrease of activation in non-reward/ incongruent trials with MPH. By contrast, differences in activation in the right insula (part of the motivation-reward

Accepted manuscript

ACCEPTED MANUSCRIPT

system) followed a different pattern. Parameter estimates showed that the decrease in insula activation with MPH compared to placebo was more pronounced in reward vs. non-reward trials, regardless of the target type. This finding is illustrated by a significant non-reward/congruent vs. non-reward/incongruent target interaction during the placebo and no interaction effects during the MPH condition. These effects were associated with a robust decrease of activation for both congruent and incongruent reward trials with MPH (Figure 2 D).

Accepted manuscript

ACCEPTED MANUSCRIPT

4. Discussion

4.1. General Considerations

In this study we expanded our previous research as we examined changes in performance on the ACR task in relation to MPH administration and assessed MPH effects on the activation of the attention-activation and motivation-reward systems. The results from this experiment suggest the following considerations. First, the behavioral results show that MPH administration improved accuracy possibly due to improved attention independent of reward cues; in turn reward trials were associated with shorter RT possibly due to increased motivation independent of MPH administration. Neuroimaging results demonstrated that MPH was associated with lower activation in regions that belong to both the attention-activation (Figure 2 A, B, C,) and motivation-reward (Figure 2 D) systems over placebo suggesting improved information processing. The patterns of activation change for these two systems were, however, distinctly different. The changes of activation from placebo to MPH in the attention-activation system possibly reflected improved processing of conflict and interference particularly in incongruent (difficult) targets, and were independent of reward incentives. The lower activation with MPH in the motivation-reward system during reward trials for both easy and difficult targets suggests that in the MPH condition all trials may have been experienced as equally rewarding regardless of the level of difficulty.

Previous neuroimaging studies have provided conflicting results regarding the effects of MPH, with a single-dose MPH challenge either increasing or decreasing task-related activity in brain regions associated with executive functions and inhibitory control, depending on the subject group and the activation paradigm (Vaidya et al., 1998; Knutson et al., 2004). We have observed that MPH treatment (4-6 week daily administration) decreased task-related activity in the ACC and inferior frontal gyrus while increasing task-related activity in regions within the default network (e.g., posterior cingulate cortex) in children and adolescents with ADHD, suggesting that the beneficial effects of MPH may be related to enhanced efficiency of information processing (Schulz et al., 2012). In this respect, this report provides additional evidence that acute (similar to chronic) MPH administration is associated with

Accepted manuscript

ACCEPTED MANUSCRIPT

decreased activation in brain regions linked to reward processing (e.g. insula) and executive control (e.g. ACC, thalamus among others).

The effect of MPH to lower activation in regions of the attention-activation system vs. placebo may reflect augmentation of catecholamine effects to amplify response to salient signals with concomitant suppression of background noise (Foote et al., 1975) with resultant improvement of performance. Here we show that activation in the attention-activation system was lower with MPH during responses to both congruent and incongruent targets, irrespective of the preceding reward cue. The change of activation during incongruent targets in non-reward trials from highest with placebo to lowest with MPH (Figure 3 A, B, C) suggests that the participants were engaged in the task and motivated to exert effort to avoid monetary loss. These neuroimaging results together with the participants' improved accuracy with MPH and significant MPH-by-reward cue interaction (i.e., greater accuracy on difficult reward trials with MPH) suggest that the drug may render the experience of the task as "easier", and also may optimize information processing during conflict, thereby, improving performance.

4.2. Effects of MPH on Executive Control The main effects of the conflict component of the ACR task during the placebo condition suggest that the task engaged regions that have been associated with executive control of attention (i.e. right thalamus, right putamen and left inferior frontal gyrus Figure 2 A, B, C). The MPH-dependent decrease of responses in these regions is consistent with previous reports that during response inhibition tasks healthy volunteers exhibit diminished activation in brain regions such as inferior frontal gyrus, insula and putamen (Costal et al., 2012; Pauls et al., 2012). However, this MPH effect on activation was not linked to changes in RT, as there was no main effect of MPH on RT. In other words, quicker responses were not associated with better performance; it appears that a change of strategy – from minimizing losses during placebo to maximizing money wins with MPH – was most likely related to improved accuracy with MPH administration.

4.3. Effects of MPH on Reward Processing The main effects of MPH during reward cues and outcomes were observed in brain regions associated with both attention and reward-processing. In particular, significant changes in activation during responses to reward cues were observed in the insula and the left

ACCEPTED MANUSCRIPT

caudate (Fig 1). Given a literature that supports a role of the insula in reward processing (Paulus et al., 2003; Linke et al., 2010) and of the caudate nucleus in preparation to act (Opris et al. 2013), the cue component of the ACR task may have been experienced partially as a preparation for response to subsequent targets.

Surprising non-reward outcome (i.e., non-reward following a previously indicated reward cue and correct performance, also see Table 5 Supplemental materials), consistently engaged the insula (Table 3). As this region is involved in monitoring of reward outcomes (Paulus et al., 2003; Linke et al., 2010), our results support the notion of a role of the insula in the assessment of reward-related feedback (Ivanov et al., 2012a). Also of interest is the reward-by-conflict interaction in the insula after MPH (Figure 2 B), which suggests increased efficiency in the processing of both congruent and incongruent targets that followed reward cues. Therefore, decreased reward-related activation in the insula with MPH may reflect improved information processing and heightened sensitivity to monetary wins, which in turn may have boosted motivation and effort. In contrast, the insula activation during placebo was greater with difficult targets that followed non-reward cues, possibly because these targets were experienced as less rewarding. As activation of the insula has been linked to monitoring of performance and error detection (Klein et al., 2007), our findings suggest that in the absence of a stimulant drug the activation of the insula may reflect efforts to optimize overall outcome by minimizing monetary losses whereas the insula activation after stimulant administration may reflect efforts to maximize outcomes by obtaining rewards with both "easy" and "difficult" targets.

4.4. The Role of the Insula in Reward Processing and Executive Control

Interactions between brain regions involving reward and cognitive control has been a subject of significant interest, for example, in work that frames these interactions in terms of intrinsic connectivity networks for salience processing (a term which unites conflict monitoring, interoceptive-autonomic arousal, and reward-processing centers) and executive control (Seeley et al., 2007). Other reports have demonstrated that training focused attention, both within short- and long-term time frames, can enhance functional connectivity between components of the reward-motivation and attention-activation systems,

ACCEPTED MANUSCRIPT

and specifically between the prefrontal-anterior insula cortex and lateral cortical regions (Hasenkamp et al., 2012; Farb et al., 2007).

The insula is now recognized as being involved in functions involving conflict and reward monitoring, error-detection and interoception of autonomic arousal (Craig 2009, 2011, Seeley et al., 2007, Grabenhorst et al., 2011), all of which are highly relevant to the task elements evaluated by the ACR. In theory, improved connectivity between the insula and elements of the executive network may allow for a more efficient switching between the reward-motivation and attention-activation systems and their associated functional states. This report further advances the understanding about the relationship between the unsula region and the executive network. More specifically, we suggest that in the placebo condition insula activations suggest that "difficult" non-reward trials were also associated with greater mental effort (i.e. higher activation in components of the attention- motivation network) as attempts to avoid monetary loss. Alternatively, MPH improved performance accuracy as it simultaneously improves information processing and decreases activation in both attention- motivation and reward-motivation networks. The changes in insula activation in MPH vs. placebo suggest that both "easy" and "difficult " rewards were equally stimulating with MPH, which may be related to the drug ability to improve performance (i. e. possibly relevant to its therapeutic effects in ADHD) and increase motivation for rewards (i.e. possibly relevant to its abuse potential).

4.5. Limitations The sample size (n=16) was small, and there were some limitations related to the ACR. Although the ACR is performance-dependent, the attainment of reward during the task is not linked to actual monetary compensation. Also, the ACR offers only two incentive levels (reward cue signifying a potential $1 win, and a non-reward cue) whereas multiple incentive levels (e.g. 25 cents, 50 cents, $1, $5) seem to engage components of the motivation-reward system more reliably during reward anticipation. These factors may explain why activation was detected in fewer regions of the reward system during the reward cues than other studies. Lastly, we were not able to assess activation during the punishment condition because overall accuracy of performance was very high.

Accepted manuscript

ACCEPTED MANUSCRIPT

4.6. Conclusions This study offers some new insights regarding the effects of MPH and possibly other stimulants on two complementary brain systems that are essential for task performance. The results highlight the importance of the insula as a region engaged in performance-monitoring but also in decision-making related to optimizing performance and outcomes. We further suggest that MPH administration may improve accuracy due to its effects on motivation to obtain reward as well as preparation for action and conflict resolution.

Accepted manuscript

ACCEPTED MANUSCRIPT

Acknowledgements

This project has been supported by a grant from the General Clinical Research Center at Mount Sinai School of Medicine GCO # 05-1129.

Dr. Ivanov has received time support for this project through a NIDA/AACAP K-23 PA-00-003 Career Development grant. Dr. Ivanov has also received nohoraria from Lundbeck pharmaceutical company for work unrelated to this report.

Dr. Newcorn has been a consultant for Alcobra, Biobehavioral Diagnostics, Otsuka, Shire, Eli Lilly and Ortho-McNeil Janssen and as such has received honoraria from these companies for work unrelated to this report.

Dr. London has received research support from NIH/NIDA through RL1 DA024853, P50 DA005010 and R01 DA027633-04 grants, and additional support from Philip Morris USA, the Marjorie Greene Family Trust and the Thomas P. and Katherine K. Pike Chair in Addiction Studies endowments, none of which are related to this report.

Drs. Liu, Clerkin, Schulz, Fan, Friston and Schwartz report no grant support or conflict of unterests related to this report.

Accepted manuscript

ACCEPTED MANUSCRIPT

References

Arnsten A (2006a) Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways**.** J Clin Psychiatry, 67 Suppl 8:7-12.

Arnsten A (2006b) Stimulants: therapeutic actions in ADHD. Neuropsychopharmacology 31: 2376-2383

Berridge C, Devilbiss D, Andrzejewski M, Arnsten A, Kelley A, Schmeichel B at al. (2006) Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biol Psychiatry 60: 1111-1120.

Clerkin S, Schulz K, Halperin J, Newcorn J, Ivanov I, Tang C et al. (2009) Guanfacine potentiates the activation of prefrontal cortex evoked by warning signals. Biological Psychiatry Aug, 15;66(4):307-12.

Conners K (2000) Conners' Rating Scales-Revised Technical Manual. Multi Health Systems. North Tonawanda, New York.

Costa A, Riedel M, Pogarell O, Menzel-Zelnitschek F, Schwarz M, Reiser M, Möller H et al. (2102) Methylphenidate Effects on Neural Activity During Response Inhibition in Healthy Humans. Cereb Cortex in press

Craig A (2009) How do you feel--now? The anterior insula and human awareness. Nat Rev NeurosciJan;10(1):59-70.

Craig A (2011) Significance of the insula for the evolution of human awareness of feelings from the body. Ann N Y Acad Sci Apr;1225:72-82

Cyr J, Doxey N, Vigna C, Vigna M (1988) Factorial composition of the SCL-90--R. Journal of Social Behavior & Personality, 3(3), 245-252.

Dodds C, Mueller U, Clark L, van Loon A, Cools R, Robbins T (2008) Methylphenidate has differential effects on blood oxygenation level-dependent signal related to cognitive subprocesses of reversal learning. J Neurosci 28, 5976-5982.

Accepted manuscript

ACCEPTED MANUSCRIPT

Fan J, McCandliss BD, Fossella J, Flombaum JI, Posner MI (2005) The activation of attentional networks NeuroImage 26; 471 – 479

Farb NA.S, Segal, ZV., Mayberg H, Bean J, McKeon D, Fatima Z, Anderson AK.(2007).Attending to the present: mindfulness meditation reveals distinctneural modes of self-reference. *Soc. Cogn.Affect.Neurosci.* 2, 313–322.

Foote S, Freedman R, AP. O (1975) Effects of putative neurotransmitters on neuronal activity in monkey auditory cortex. Brain Res Mar 21;86(2):229-42

Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998) Event-related fMRI: characterizing differential responses. Neuroimage 7:30-40.

Grabenhorst F, Rolls E (2011) Value, pleasure and choice in the ventral prefrontal cortex. Trends in *Cognitive Sciences, February, 15(2):56-67.*

Hasenkam,p W & Barsalou LW. (2012) Effects of meditation experience on functional connectivity of distributed brain networks. Frontiers in Human Neuroscience March: 6 (38).

Ivanov I, Liu X, Shulz K, Fan J, London E, Friston K et al. (2012a) Parental substance abuse and function of the motivation and behavioral inhibition systems in drug-naïve youth. Psychiatry Res Feb 28;201(2):128-35

Ivanov I, Liu X, Clerkin S, Friston K, Newcorn J, Fan J (2012b) Effects of Motivation on Reward and Attentional Networks: an fMRI Study. Brain and Behavior 10.1002/brb3.80

Klein T, Endrass T, Kathmann N, Neumann J, Cramon D, Ullsperger M (2007) Neural correlates of error awareness. Neuroimage 2007;34:1774–1781.

Knutson B, Bjork J, Fong G, Hommer D, Mattay V, Weinberger D (2004) Amphetamine modulates human incentive processing. Neuron 43, 261-9.

Kuczenski R, Segal DS. (1997) Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem;68:2032–7.

Accepted manuscript

ACCEPTED MANUSCRIPT

Linke J, Kirsch P, King A, Gass A, Hennerici M, Bonger A et al. (2010) Motivational orientation modulates the neural response to reward. Neuroimage 49:2618-2625.

London E, Ernst M, S Grant S, K Bonson K, Weinstein A. (2000): Orbitofrontal cortex and human drug abuse: functional imaging. Cerebral Cortex 10:334-342 [

Marquand A, De Simoni S, O'Daly O, Williams S, Mourão-Miranda J, Mehta M (2011) Pattern classification of working memory networks reveals differential effects of methylphenidate, atomoxetine, and placebo in healthy volunteers. Neuropsychopharmacology 36, 1237-1247.

Marquand A, O'Daly O, De Simoni S, Alsop D, Maguire R, Williams S et al. (2012) Dissociable effects of methylphenidate, atomoxetine and placebo on regional cerebral blood flow in healthy volunteers at rest: A multi-class pattern recognition approach. NeuroImage 60 (2012) 1015-1024.

Mehta M, Owen A, Sahakian B, Mavaddat N, Pickard J, Robbins T (2000) Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci 20, 6.

Müller U, Suckling J, Zelaya F, Honey G, Faessel H, Williams S et al. (2005) Plasma level-dependent effects of methylphenidate on task-related functional magnetic resonance imaging signal changes. Psychopharmacology, Aug;180(4):624-33.

Nichols TE. (2012) Multiple testing corrections, nonparametric methods, and random field theory. Neuroimage. 15;62(2):811-5.

Opris I, Santos L, Gerhardt GA, Song D, Berger TW, Hampson RE, Deadwyler SA. (2013) Prefrontal cortical microcircuits bind perception to executive control. Sci Rep. 2013;3:2285.

Pauls A, O'Daly O, Rubia K, Riedel W, Williams S, Mehta M (2012) Methylphenidate effects on prefrontal functioning during attentional-capture and response inhibition. Biol Psychiatry Jul 15;72(2):142-9.

Paulus M, Rogalsky C, Simmons A, Feinstein J, Stein M (2003) Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. Neuroimage 49:2618-2625.

Accepted manuscript

ACCEPTED MANUSCRIPT

Price D, Finniss D, Benedetti F (2008) A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought. Annu Rev Psychol 59:565-90.

Rapoport JL, Inoff-Germain G (2002). Responses to methylphenidate in attention-deficit/hyperactivity disorder and normal children: update. J Atten Disord 6: S57–S60.

Robbins T, Arnsten A (2009) The Neuropsychopharmacology of Fronto-Executive Function:Monoaminergic Modulation. Annu Rev Neurosci 32:267-87.

Rolls E (2008) Functions of the orbitofrontal and pregenual cingulate cortex in taste, olfaction, appetite and emotion. . Acta Physiologica Hungarica, Volume 95 (2), pp 131–164.

Ryan JJ, Carruthers CA, Miller LJ, Souheaver GT, Gontkovsky ST, Zehr MD (2003) Exploratory factor analysis of the Wechsler Abbreviated Scale of Intelligence (WASI) in adult standardization and clinical samples. Appl Neuropsychol 10:252-256.

Schulz K, Bédard A, Czarnecki R, Fan J (2011) Preparatory activity and connectivity in dorsal anterior cingulate cortex for cognitive control. Neuroimage, Jul 1;57(1):242-50.

Schulz K, Fan J, Bedard A, Clerkin S, Ivanov I, Tang C et al. (2012) Common and Unique Therapeutic Mechanisms of Stimulant and Nonstimulant Treatments for Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry, 69(9):952-961.

Schwartz JM, Begley S (2002) The Mind and The Brain: Neuroplasticity and the Power of Mental Force. Harper Collins, New York, NY

Seeley WW, MenonV, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL,Greicius MD. (2007).Dissociable intrinsic con- nectivity networks for salience processing and executive control. *J.Neurosci.* 27, 2349–2356.

Seeman P, Madras BK (1998) Anti-hyperactivity medication: methylphenidate and amphetamine. Mol Psychiatry 3:386 –396.

Spitzer RL, Williams JB, Gibbon M, First MB (1992) The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 49:624-629.

Accepted manuscript

ACCEPTED MANUSCRIPT

Swanson JM, Volkow ND (2003) Serum and brain concentrations of methylphenidate: implications for use and abuse Neuroscience and Biobehavioral Reviews 27 (615–621

Tomasi D, Volkow N, Wang G, Wang R, Telang F, Caparelli E et al. (2011) Methylphenidate enhances brain activation and deactivation responses to visual attention and working memory tasks in healthy controls. Neuroimage Feb 14;54(4):3101-10.

Vaidya C, Austin G, Kirkorian G, Ridlehuber H, Desmond J, GH. G, Gabrieli J (1998) Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. Proc Natl Acad Sci November 24; 95(24): 14494-14499

Westermeyer J, Yargic I, Thuras P (2004) Michigan assessment-screening test for alcohol and drugs (MAST/AD): evaluation in a clinical sample. Am J Addict 13:151-162.

Accepted manuscript

ACCEPTED MANUSCRIPT

Conflicts of Interest

Dr. Ivanov has received time support for this project through a NIDA/AACAP K-23 PA-00-003 Career Development grant. Dr. Ivanov has also received nohoraria from Lundbeck pharmaceutical company for work unrelated to this report.

Dr. Newcorn has been a consultant for Alcobra, Biobehavioral Diagnostics, Otsuka, Shire, Eli Lilly and Ortho-McNeil Janssen and as such has received honoraria from these companies for work unrelated to this report.

Dr. London has received research and salary support from NIH/NIDA through 5 T32, 5 RL1 DA024853, P50 DA005010 and R01 DA027633-04 grants, and additional support from Philip Morris USA, and The Marjorie Greene Family Trust and Thomas P. and Katherine K. Pike Chair in Addiction Studies endowments, none of which is related to this report.

Drs. Liu, Clerkin, Schulz, Fan, Friston and Schwartz report no grant support or conflict of unterests related to this report.

Accepted manuscript

ACCEPTED MANUSCRIPT

Contributors

Drs. Ivanov, Schulz, Fan and Newcorn designed the study and wrote the protocol. Drs Clerkin, Liu, Fan and Friston undertook the statistical analysis. Drs. London and Schwartz managed the literature searches and contributed to the manuscript writing and editing. . Dr. Ivanov wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Accepted manuscript

ACCEPTED MANUSCRIPT

Legend for Tables and Figures

Table 1. Demographics

Variables	Mean	SD
Age	30.63	± 7.44
SCL Global Severity Index	37.91	± 9.04
SCL Positive Symptom Total	41.42	± 12.57
CAARS – ADHD Index	40.81	± 5.66
MAST –AD	1.81	± 4.49
Gender	Male = 8	Female = 6

Note: T scores >1.5 SD on SCL and CAARS and MAST raw scores > 5 were considered abnormal.

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 2. Behavioral results

Variables	**Trial Type**			
	Congruent Target		Incongruent Target	
	Reward Cue	*Nonreward Cue*	*Reward Cue*	*Nonreward Cue*
Reaction Time PL (Mean, SD)	518.35 (± 83.92)	523.40 (± 96.65)	567.05 (± 95.17)	584.77 (±103.48)
Reaction Time MPH (Mean, SD)	510.63 (± 92.34)	506.02(± 86.02)	550.83 (± 83.78)	571.10 (±105.22)
Accuracy (%) PL	98.43	98.82	96.87	97.52
Accuracy (%) MPH	99.60	99.08	99.21	97.52

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 3. Activation with ACR Task

ACR Components	PL vs. MPH	MNI coordinates	Cluster size	Z
Anticipation				
L Thalamus	PL>MPH	-18 -16 10	393	4.06
L Insula		-32 0 12	393	3.57
R Cerebellum crus 6		14 -70 -28	393	3.11
L Caudate		-4 24 2	101	3.79
Conflict				
Supplemental motor gyrus	PL>MPH	-20 -8 66	3579	3.90
L Precuneus		-12 -62 52	4590	4.54
R Cerebellum crus 9		14 -56 -50	4590	3.77
L Post central		-62 -4 30	3579	3.83
R Post central		34 -36 52	3579	4.18
Expected Reward	PL>MPH			
L Mid Occipital		-26 -58 38	511	3.98
L Inferior Parietal		-34 -52 46	511	2.98
Surprising Non-Reward	PL>MPH			
L Insula		-40 16 10	786	4.49
L Pallidum		-22 -4 -4	766	3.86
L Insula		-32 12 8	766	3.81
Interactions	NA			
R Putamen		28 -6 14	686	3.74
R Insula		40 2 -10	686	3.22
L Inferior Frontal		-32 32 10	338	3.04
L Middle Frontal		-24 46 20	338	3.04
R Thalamus		12 -16 6	686	3.04

Accepted Manuscript

ACCEPTED MANUSCRIPT

Figure 1. Activation with Reward Components of the ACR Task
Statistical parametric maps in axial views showing significant blood oxygenation level-dependent (BOLD) signal changes:

A – BOLD signal increase in the left insula in the placebo vs. MPH condition during the *reward – non-reward* cue contrast;

B – BOLD signal increase and the left caudate in the placebo vs. MPH condition during the *reward – non-reward* cue contrast;

C – BOLD signal increase in the left insula in the placebo vs. MPH condition during the *surprising non-reward – expected non-reward* outcome contrasts.

D - BOLD signal increase in the left palidum in the placebo vs. MPH condition during the *surprising non-reward – expected non-reward* outcome contrast.

The figures were thresholded at $p < .05$ (corrected); the color bar indicates color-coded significance of the *t*-test values.

Accepted manuscript

ACCEPTED MANUSCRIPT

Figure 2. Interaction Effects during ACR task

Estimated percent change in the BOLD signal during congruent and incongruent flankers of the ACR task in relation to the preceding cue (i.e. reward vs. non-reward) in placebo and MPH conditions in:

A) right thalamus

B) right putamen

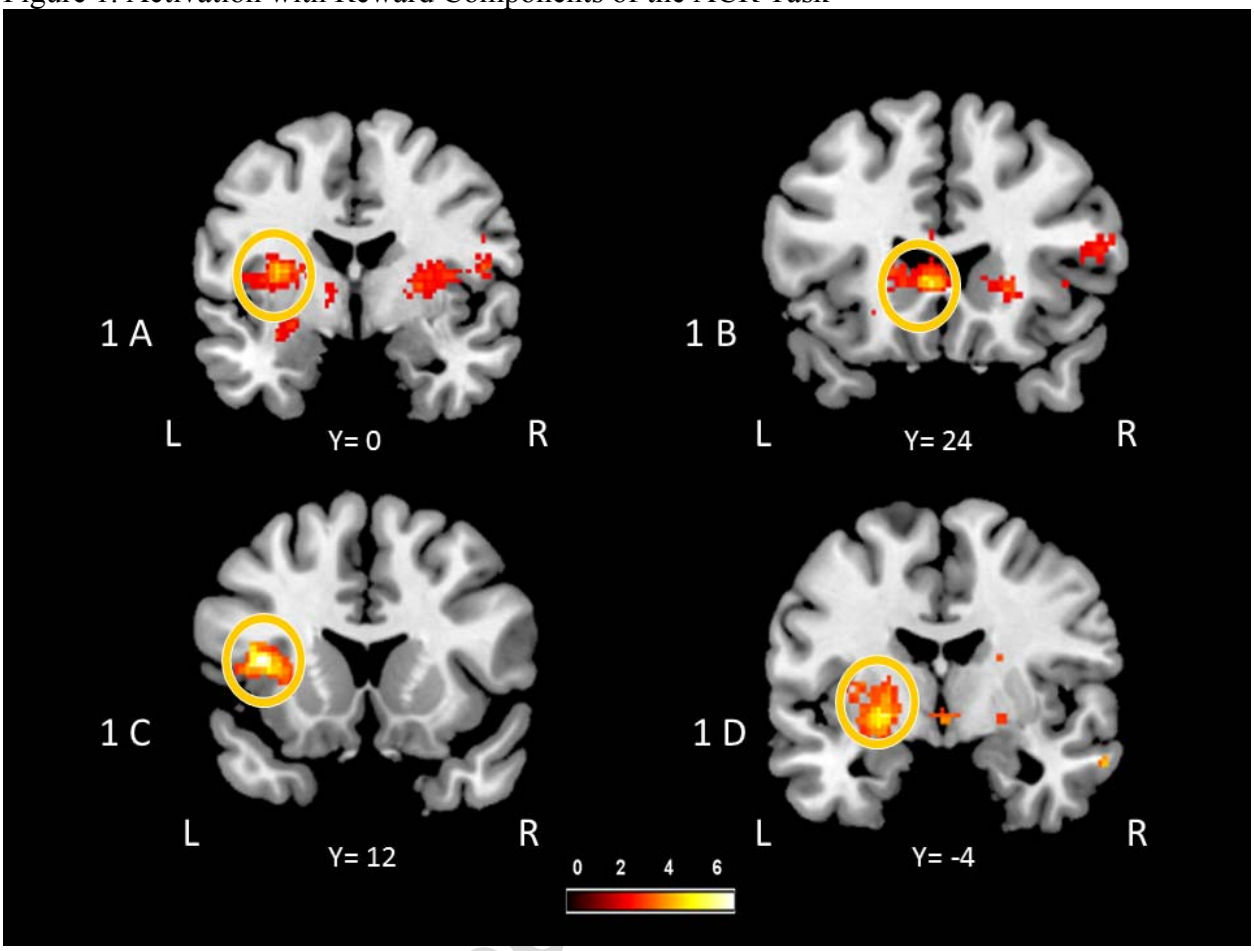
C) left inferior frontal gyrus
D) right insula

The SPMs were thresholded at $p < .05$ corrected; the color bar indicates color-coded significance of the *t*-test values.

Accepted manuscript

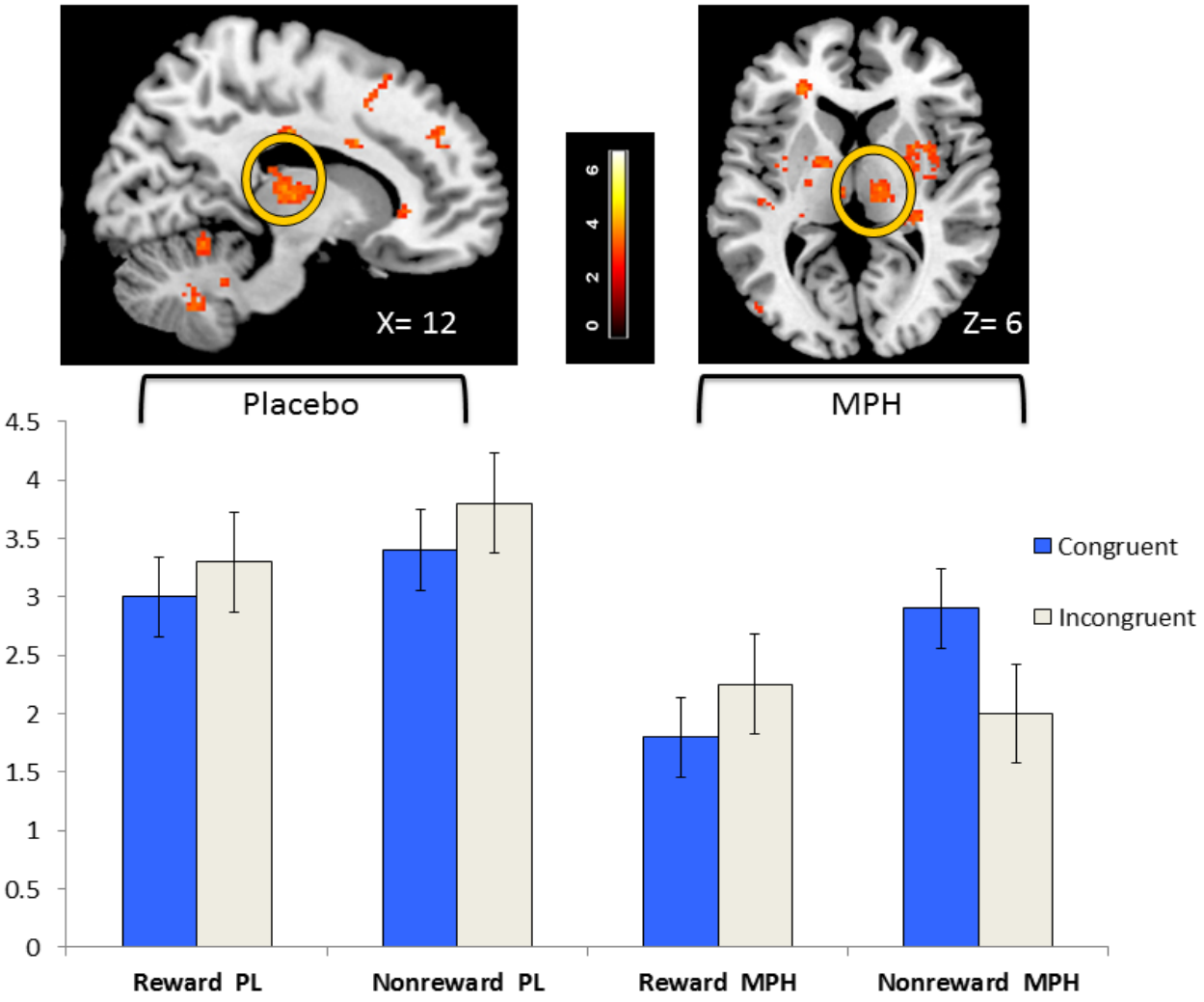
ACCEPTED MANUSCRIPT

Figure 1. Activation with Reward Components of the ACR Task



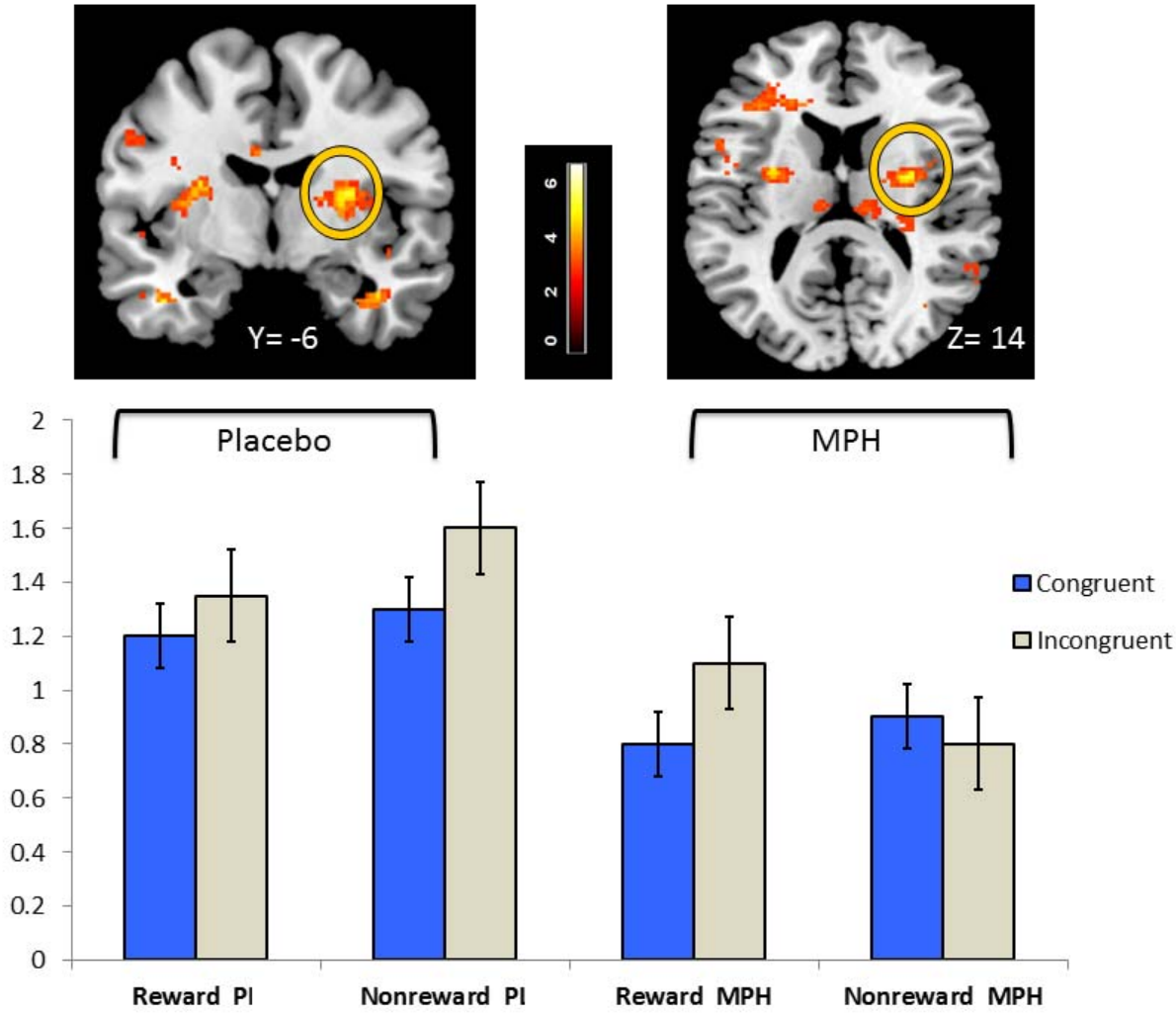
Accepted

Figure 2A.



Accepted

Figure 2B.



Accepted

Figure 2C

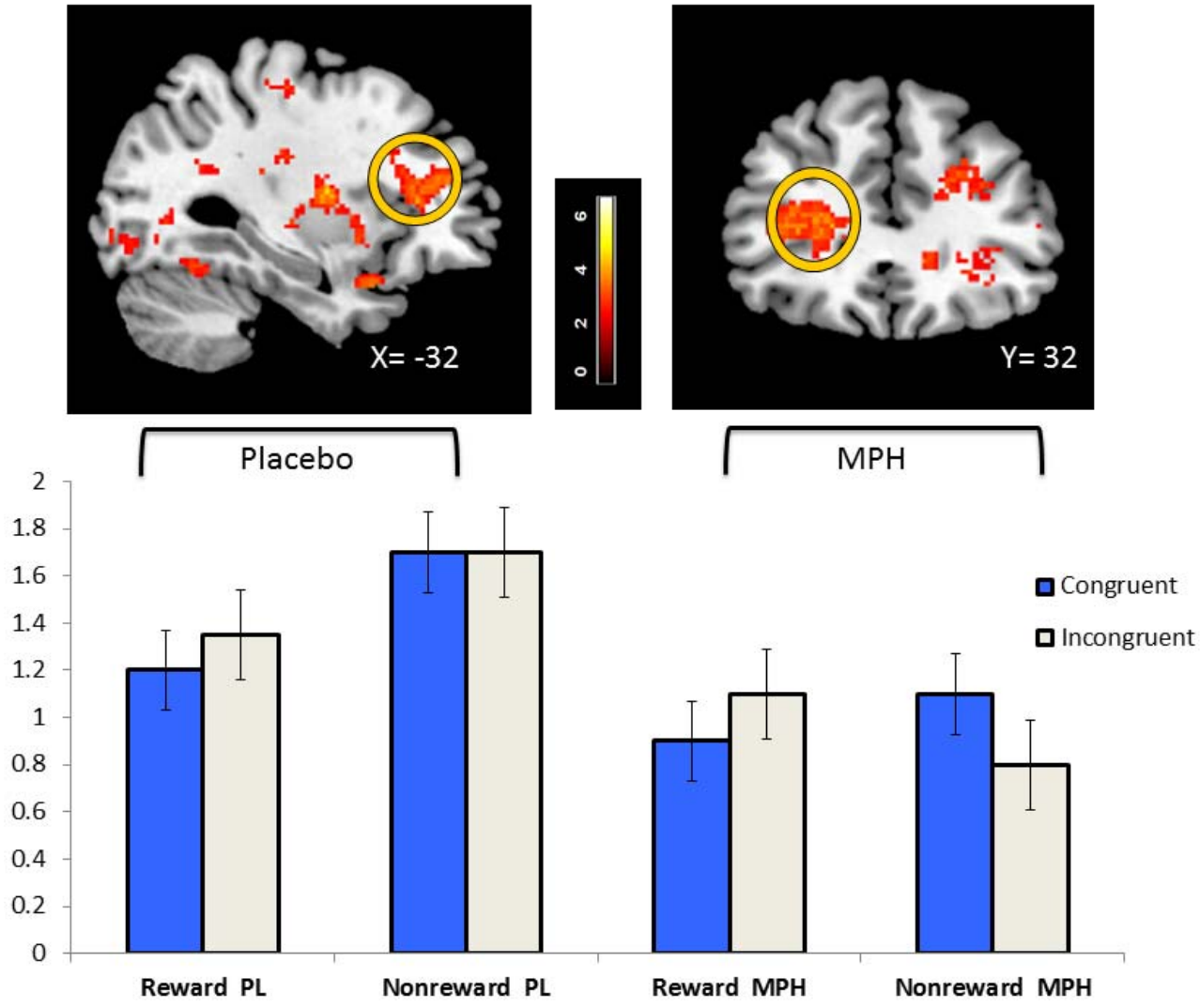
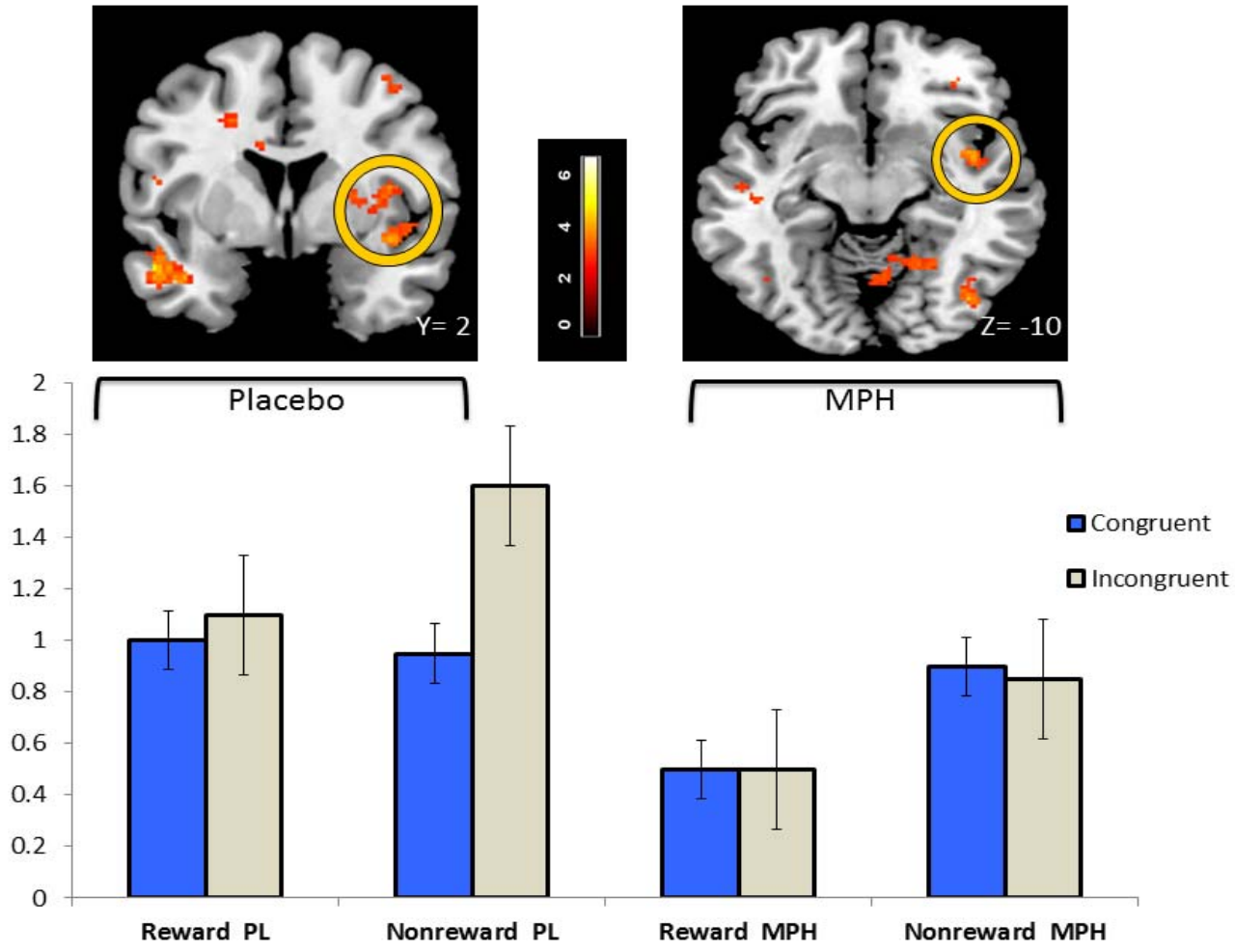

X= -32
0 2 4 6
Y= 32
Placebo
MPH
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Congruent
Incongruent
Reward PL
Nonreward PL
Reward MPH
Nonreward MPH

Figure 2D.



Accep

ACCEPTED MANUSCRIPT

Accepted manuscript