NeuroImage 81 (2013) 213–221

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Distributed effects of methylphenidate on the network structure of the resting brain: A connectomic pattern classification analysis

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ARTICLE INFO

Article history:
Accepted 9 May 2013
Available online 16 May 2013

Keywords:
Methylphenidate
fMRI
Resting state
Multivariate pattern classification
Connectome
Intrinsic connectivity networks

ABSTRACT

Methylphenidate is a psychostimulant medication that produces improvements in functions associated with multiple neurocognitive systems. To investigate the potentially distributed effects of methylphenidate on the brain's intrinsic network architecture, we coupled resting state imaging with multivariate pattern classification. In a within-subject, double-blind, placebo-controlled, randomized, counterbalanced, cross-over design, 32 healthy human volunteers received either methylphenidate or placebo prior to two fMRI resting state scans separated by approximately one week. Resting state connectomes were generated by placing regions of interest at regular intervals throughout the brain, and these connectomes were submitted for support vector machine analysis. We found that methylphenidate produces a distributed, reliably detected, multivariate neural signature. Methylphenidate effects were evident across multiple resting state networks, especially visual, somatomotor, and default networks. Methylphenidate reduced coupling within visual and somatomotor networks. In addition, default network exhibited decoupling with several task positive networks, consistent with methylphenidate modulation of the competitive relationship between these networks. These results suggest that connectivity changes within and between large-scale networks are potentially involved in the mechanisms by which methylphenidate improves attention functioning.

Introduction

Methylphenidate (MPD) is a psychostimulant medication that is a highly efficacious and widely prescribed treatment for attention deficit hyperactive disorder (ADHD). MPD produces improvements in attention, motoric control, executive processing, and memory (Swanson et al., 2011)—cognitive functions associated with distributed neurocognitive systems. Previous studies have emphasized MPD effects on specific brain regions during tasks specifically tailored to elicit selective activation (Cortese et al., 2012). More global patterns of MPD effects on connectivity across distributed brain networks are still poorly understood.

Intrinsic connectivity networks (ICNs) consist of distributed brain regions exhibiting coherent activity (Greicius et al., 2003), and which are reliably detected (Damoiseaux et al., 2006) from low-frequency oscillations of the blood oxygenation level dependent (BOLD) signal during the resting state. Convergent evidence indicates that ICNs constitute fundamental organizational elements of human neural architecture (Beckmann et al., 2005; Laird et al., 2011). Individual ICNs have been implicated in specific neurocognitive functions such as attention control and somatomotor processing (Menon and Uddin, 2010; Yeo et al., 2011). Moreover, aberrant connectivity within specific ICNs is linked to clinically-relevant symptom dimensions across psychiatric disorders (Menon, 2011). Thus investigating alterations in ICNs during the resting state constitutes a powerful method to understand distributed effects of acute drug administration.

A number of specific ICNs may be targets of MPD effects. The default mode network (DMN) is a network of midline and lateral parietal regions that is implicated in internally directed mentation (Raichle et al., 2001) and lapses of attention (Weissman et al., 2006), and it exhibits a competitive relationship with task-positive networks (Corbetta and Shulman, 2002), such as dorsal and ventral attention networks and frontoparietal control network. Previous task-based fMRI studies (Liddle et al., 2011; Nagano-Saito et al., 2008; Peterson et al., 2009; Tomasi et al., 2011)

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http://dx.doi.org/10.1016/j.neuroimage.2013.05.016

have suggested that the competitive relationship between these networks (Fox et al., 2005) is enhanced by dopamine. Thus we hypothesized that MPD would produce greater segregation between DMN and task-positive networks during the resting state. We also had a priori hypotheses about MPD effects on motor processing networks and visual network. Existing circuit models propose dopamine-mediated interactions between striatum and motor cortex (Alexander et al., 1986) as well as striatum and cerebellum (Hoshi et al., 2005), and previous fMRI studies with acute administration of dopamine modulators [L-dihydroxyphenylalanine (L-Dopa), cocaine] found altered connectivity in multiple motor regions including striatum, cerebellum, and motor cortex (Cole et al., 2012; Kelly et al., 2009; Li et al., 2000). Additionally, Li et al. (2000) found that cocaine reduced connectivity within visual cortex, with evidence suggesting that greater decoherence in visual cortex is associated with high attention states (McAvoy et al., 2012; Nauhaus et al., 2009). Thus we predicted that MPD would modulate resting state connectivity in motor regions including striatum, somatomotor network, and cerebellum, and would reduce connectivity within visual network.

Seed-based methods are commonly used to investigate functional connectivity. These methods have the advantage of identifying connectivity changes at well-defined regions, but they are also restricted to investigating a single, or a handful, of selected regions, and require potentially arbitrary choices of which a priori regions to investigate. In this study we coupled two methods that help to overcome restrictions with standard seed-based methods. We used connectomic imaging methods to identity functional connectivity pairwise between 1080 regions of interest (ROIs) placed at regular intervals throughout the brain. Additionally, we used multivariate pattern classification, which allows connectivity across multiple regions and networks to simultaneously inform classification decisions (Heinzle et al., 2012).

Methods and materials

Participants and pharmaco-fMRI design

In this within-subject, double-blind, placebo-controlled, randomized, counterbalanced, cross-over study, 32 right-handed healthy volunteers (16 females; age 20.6 ± 2.0 years, range 18–27) participated in two fMRI scanning sessions separated by approximately 1 week. Participants received either 40 mg MPD or PBO 60 min prior to resting state scanning. The dose of MPD was higher than typically used in clinical practice in order to enhance blood levels, and predicted psychological and neural effects, in an acute dosing context, consistent with recent studies (Clatworthy et al., 2009; Schlosser et al., 2009).

All participants completed a Visual Analogue Scale (VAS) immediately prior to drug ingestion as well as 30, 60, and 140 min afterwards (Fig. 1). This scale consists of 20 items that measure cognitive and emotional state using adjective descriptors (e.g., 'stimulated', 'drowsy'), and responses were recorded on 4-inch bars anchored with 'Not At All' and 'Extremely'. Post-ingestion measures were adjusted by subtracting baseline responses immediately prior to drug ingestion. They were then compared between PBO versus MPD sessions via repeated measures ANOVA.

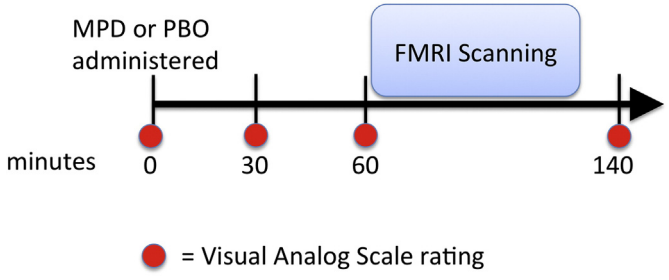

Fig. 1. Sequence of events during pharmaco-fMRI experiment.

Resting state paradigm

During resting state scans, a black fixation cross on a white background was displayed in the center of the screen for 6 min. Participants were instructed to relax and keep their eyes open and fixed on the cross. Participants next completed an attention control task and a decision-making task, which are described in a separate report. Heart rate and respiration measurements were acquired for group comparisons using paired *t*-tests.

Magnetic resonance imaging

Image acquisition

MRI scanning occurred on a Philips 3.0 Tesla Achieva X-series MRI (Best, The Netherlands). We obtained a medium resolution T1-weighted anatomical scan, 180 functional volumes with a T2*-weighted, echoplanar acquisition sequence [GRE; repetition time, 2000 ms; echo time, 25 ms; flip angle, 90°; field of view, 22 cm; 42 slice; thickness/skip, 3.0/0 mm matrix size equivalent to 64 × 64], and a high-resolution T1-weighted scan for anatomic normalization [26 cm FOV; thickness/skip, 1.0/0 mm].

Preprocessing

A standard series of processing steps was performed using statistical parametric mapping (SPM8; www.fil.ion.ucl.ac.uk/spm). Scans were reconstructed, slice-time corrected (sequential ascending), and realigned to the first scan in the experiment to correct for head motion, and co-registered with the high-resolution T1-weighted image (the medium-resolution T1-weighted image was co-registered with the functional scans as an intermediate step and then the high-resolution T1-weighted image was coregistered with the medium-resolution T1-weighted image). Normalization was performed using the voxel-based morphometry toolbox implemented in SPM8. The high-resolution T1-weighted image was segmented into tissue types, bias-corrected, registered to MNI space, and then normalized using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Ashburner, 2007). Smoothing of functional data was performed with an 8 mm^3 kernel. Motion parameters were checked in order to identify and exclude all scans with greater than 2 mm movement. Summary motion statistics were calculated (mean displacement, mean angle) and were compared across drug conditions via paired samples Wilcoxon signed rank tests to account for non-normally distributed data.

In order to produce a whole-brain resting state functional connectome, we placed 4.25 mm radius ROIs encompassing 19 3 × 3 × 3 mm voxels in a regular grid spaced at 12 mm intervals throughout the brain, yielding 1080 ROIs in total. Spatially averaged time series were extracted from each of these ROIs. White matter and cerebrospinal fluid masks were generated from the VBM-based tissue segmentation step noted above, and eroded using FSL-erode to eliminate border regions of potentially ambiguous tissue-type. Next, regression was performed to remove the effects of nuisance variables, including six motion regressors generated from the realignment step, as well as their first derivatives, and the top five principal components of the BOLD time series extracted from each of the white matter and cerebrospinal fluid masks—a method that has been demonstrated to also effectively remove signals arising from the cardiac and respiratory cycles (Glover et al., 2000). The time-series for each ROI was band-passed filtered in the .01–.10 Hz range, and Pearson product-moment correlation coefficients were then calculated pairwise between time courses for each of the 1080 ROIs, yielding 582,120 total