Methylphenidate modulates the connectivity of default mode network in ADHD: a resting-state dynamic causal model analysis

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PURPOSE: As a neurodevelopmental disorder, attention deficit hyperactivity disorder (ADHD) is one of the most common childhood brain disorders and can continue through adolescence and adulthood. Previous studies have reported that ADHD is associated with hyperactivity of default mode network (DMN) and related performance deficits on tasks requiring effortful engagement. Methylphenidate (MPH) has been a prescription treatment to help relieve many symptoms of ADHD. It can be used to modulate the dopamine concentration, and effectively improve subject's task performance, yet the regulation mechanism on brain network is unclear. The current study focuses on the effect of MPH on modulation of default mode brain function. The effective connectivity within DMN regions is investigated for this purpose by using the dynamic causal model with a framework proposed in recent literatures [1].

METHOD: This study included 18 young males with ADHD symptoms, but without any other brain disease. Two subjects were excluded in analysis due to data quality issue. Subject were scanned twice, a control-scan without taking MPH and a drug-scan after taking MPH. Among all subjects, the control-scan was conducted beforehand for 10 of them. The other 8 subjects had the drug-scan first with consideration of a balanced design. The control-scan for these subjects took place in one week after when the drug effect was cleared. Resting-state functional MRI data was acquired on a Siemens 1.5T sonata scanner, with TR=2000ms, TE=40ms, FA=90°, slice-thickness=5mm, gap=6mm, 25 interleaved slices and 180 measurements. Data process and model estimation were implemented in SPM8 on Matlab R2013a. The first 5 frames were discarded before image preprocessing. After slice-timing correction, realignment, spatial normalization and smooth, control-scans and drug-scans were concatenated to form a pseudo-continuous time series. We applied DCM analysis with a similar procedure employed in [1,2] using the DCM10 routine. Fourier series components of sinusoid functions with frequencies of 0.01, 0.02, 0.04, and 0.08 Hz, were used to model the driving input within 0.01–0.08 Hz band of resting-state signals from these regions. Six head motion parameters were also added into the model to remove potential confounding variances caused by head motion. The GLM model also includes an implicit high pass filter of 1/100 Hz to remove ultraslow fluctuations that were due to scanner drift. After estimation of the general linear model, a diagonal F-contrast of all the eight regressors was used to obtain the regions whose variance could be significantly ($p<0.05$) accounted for by the inclusion of the binarized Fourier series regressors. DMN seed regions included medial prefrontal cortex (MPFC) (-4，30，36), posterior cingulate cortex (PCC) (0, -52, 26), left inferior parietal lobule (LIPL) (-50, -63, 32), and right IPL (RIPL) (48, -69, 35). Each volume of interest was defined as spheres centered at selected coordinates above with an 8 mm radius. In order to investigate MPH as a modulatory input onto intrinsic connectivity, a prior causal model of DMN in healthy people was applied to induce a number of generative models. And the additional modulatory input on these five connections between four nodes resulted in 2^5=32 models in total. The expectation maximization algorithm was applied to estimate the expectations of model parameters. At last a Bayesian model selection procedure based on fixed effects assumptions was used to determine the best model after comparing the posterior probability.

RESULT: Bayesian model selection found the modulatory effect on the link from RIPL to MPFC outperformed all other competing models with a posterior probability above 99%. This result was confirmed using post hoc family analysis as well. The final best model is shown in Figure 1, with group averaged endogenous connectivity strength and modulatory parameters. After multiple comparison correction, only the intrinsic link from MPFC to PCC reaches significance threshold (*P=0.001*). Paired t-test also reveals significant reduction on the link parameter from RIPL to MPFC, which is modulated by MPH (*P=0.04*). Predicted and observed responses by this best model in the four selected regions from a representative subject are shown in Figure 2.

DISCUSSION: The brain activity and connectivity at resting state is considered as a baseline condition, and its abnormality could affect attention-demanded task performance. Our preliminary study reveals that the causal connectivity is altered by the dose of MPH, in which the inhibitory link from RIPL to MPFC is significantly enhanced. This finding suggests that MPH could improve individual's awareness of their mistakes, by modulating brain dynamic brain activities in the error-monitoring network.

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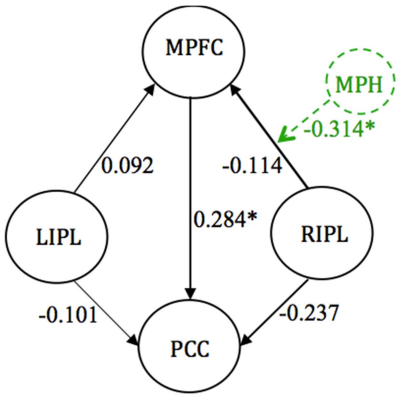

Fig. 1. The best model with group averaged endogenous connectivity strength and modulatory parameters (*$p< 0.05$).

Fig. 2. Observed (in green) and predicted (in blue) responses by the best model in the four ROIs for a representative subject.