Imaging Stimulant and Non-Stimulant Treatments fro ADHD: A Network-Based Approach

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Statistical Analysis Plan

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5.5.2. SPECIFIC AIMS

Despite a general convergence of findings from neuroimaging studies implicating several key brain regions in the pathophysiology of attention deficit hyperactivity disorder (ADHD) and data regarding the acute neurobiological effects of stimulant medications, the mechanisms by which ADHD treatments produce clinical improvement are not well understood. We recently completed an NIMH-funded R01 supplement comparing the mechanisms of action of methylphenidate (MPH) and atomoxetine (ATX) using functional magnetic resonance imaging (fMRI) over 7 weeks of treatment. Findings indicate that the two medications produce clinical improvement through common and unique mechanisms in regions of the anti-correlated 'task-positive' fronto-striatal and 'task-negative' cingulate-precuneus networks.[3,4] Symptomatic improvement with both medications was associated with reduced activation in motor cortex, but there were divergent effects in inferior frontal cortex (IFG), anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC) – with increased activation for ATX and decreased activation for MPH. Based on these findings, we have developed a model which posits that ATX primarily works by increasing activation (i.e., signal) in the 'task-positive' fronto-striatal network, with resultant increase in PCC activity to maintain competitive balance between the networks, while MPH primarily produces improvement by decreasing activity (i.e., noise) in the 'task-negative' default network (i.e., PCC), with resultant decreases in activation (i.e., increased efficiency) in the fronto-striatal network. We are very excited by these findings, which we believe offer a window into the neurophysiological basis of differential response to stimulant and non-stimulant treatments. However, to more thoroughly understand the mechanisms through which these treatments exert their effects requires in-depth investigation of neural networks (rather than single brain regions) before and after treatment, and consideration of whether clinical improvement is achieved via normalization of pathophysiology or other compensatory changes. We are therefore proposing a network-based study of the effects of MPH and ATX treatment in a large sample of ADHD youth scanned with fMRI before and after treatment (to determine comparative treatment effects on brain function), and a group-matched sample of healthy controls (to establish 'normal' connectivity). We will investigate three specific aims:

Aim 1: Delineate functional impairments in 'task-positive' and 'task-negative' neural networks in youth with ADHD. Emergent findings[5,6 7-10] implicate functional disconnections within and between the 'task-positive' (i.e., IFG, caudate nucleus, ACC) and 'task-negative' (i.e., PCC, precuneus, medial prefrontal cortex [MPFC]) networks in the pathophysiology of ADHD. We predict that impaired response inhibition in youth with ADHD versus normal controls will be associated with reduced functional connectivity (i.e., co-activation) between:

a) 'Task-positive' regions: IFG, caudate, ACC, and related structures (e.g., frontal operculum, dorsolateral prefrontal cortex [DLPFC], motor cortex);
b) 'Task-negative' regions: PCC, precuneus, MPFC and related areas (e.g., posterior inferior parietal lobule);
c) 'Task-positive' regions (i.e., ACC, IFG, caudate) and 'task-negative' regions (i.e., PCC, precuneus, MPFC).

Aim 2: Determine the common brain mechanisms which underlie successful treatment with stimulant and non-stimulant medications. Our previous findings and pilot data suggest that successful treatment involves certain common features, including both 'normalization' of pathophysiology and compensatory changes. We hypothesize that symptomatic improvement for both ATX and MPH will be related to:

a) Normalization of reduced IFG connectivity with caudate nucleus and reduced IFG inhibition of motor cortex, which may reflect the suppression of pre-potent responses;
b) Compensatory increases in the functional connectivity of ACC with PCC and IFG with precuneus – 'task-positive' and 'task-negative' regions that are typically anti-correlated.

Aim 3: Determine the specific mechanisms by which MPH and ATX produce clinical improvement. Our previous findings and pilot data suggest that MPH and ATX produce clinical benefits via distinct mechanisms in 'task-positive' and 'task-negative' networks. We predict that improvement will be differentially associated with:

a) Normalization of reduced ACC-DLPFC and IFG-frontal operculum connectivity for ATX, and PCC-precuneus and PCC-MPFC connectivity for MPH;
b) Compensatory increases in functional connectivity between IFG and MPFC for ATX and between ACC and MPFC for MPH – 'task-positive' and 'task-negative' regions that are typically anti-correlated.

The proposed investigations are both innovative and unique; we know of no other data comparing mechanisms of stimulant and non-stimulant medications. Our research has yielded important findings regarding common and distinct effects of MPH and ATX, which we have used to develop a model positing divergent mechanisms in 'task-positive' and 'task negative' networks. Validation of this model would constitute important progress in delineating the neurobiological basis of differential response to stimulant and non-stimulant medications, and offer a scientific basis on which to develop research examining individualized approaches to treatment.

C.5. DATA PREPARATION

C.5.1. Behavioral variables.

C.5.1.1. Symptomatic improvement. Percent change in the ADHD-RS-IV total score over treatment will serve as the measure of clinical improvement in the multiple linear regression. Percent change on the ADHDRS-IV is calculated individually for each subject by subtracting the post-treatment score from the pre-treatment score, dividing the difference by the pre-treatment score, and multiplying the quotient by 100. The ADHD-RS-IV change scores for the 36 subjects described in the Preliminary Studies section were normally distributed, with a mean (SD) of 56 (28). If the scores are not normally distributed or there are visible outliers, log transformations will be considered or nonparametric procedures will be utilized.

C.5.1.2. Task performance. The effects of treatment on go/no-go performance will be tested to inform the interpretation of the fMRI results. The percentage of commission errors on no-go trials (false alarms) will serve as the measure of response inhibition. Differences in go/no-go task performance between youth with and without ADHD will be tested with a linear 2-level mixed models, in which Group (MPH vs. ATX vs. control) will serve as the between-subjects factor and Time (baseline vs. endpoint) will be the within-subjects factor.

C.5.2. Functional images. Preprocessing and modeling the fMRI data replicate the MACRO supplement.

C.5.2.1. Preprocessing of functional images. The six functional time series for the go/no-go task acquired at baseline and endpoint for each ADHD and control subject will be separately realigned, co-registered to the high-resolution T2 images, co-registered to each other, normalized, and then smoothed.

C.5.2.2. First-level analysis: within-subject modeling of activation. We will use a within-subjects design to model activation in the baseline and endpoint time series for each subject individually, as a prelude to extracting PPI data. The relationship between the observed event-related BOLD signals and regressors that represent expected neural responses to events will be determined with a general linear model (GLM).[87] Four regressors representing correct and incorrect no-go and go events will be entered in the GLM. Six motion correction parameters will also be entered as covariates of no interest.[88] The appropriate linear contrasts will be applied to the parameter estimates for correct no-go events minus correct go events in the baseline scan for control subjects only (see next section) and in the endpoint minus baseline scans for all subjects. The endpoint minus baseline contrast maps will be used to extract PPI data (see next section).

C.5.2.3. First-level analysis: within-subject modeling of psychophysiological interaction (PPI). PPI is a regression-based method of functional connectivity that tests for differences in the regression slope of activation between brain regions due to differential responses in one region (seed) to different experimental contexts.[69,70] An initial one-sample t-test will identify regions activated/deactivated for response inhibition at baseline in the control subjects to determine 'normal' levels of activity and connectivity. PPI will be calculated using the methods described in Fan et al.[68] and Schulz et al.[89] Briefly, seed volumes of interest (VOI) will be extracted for all subjects from 8-mm radius spheres centered on the maximal local peak in the regions identified by the t-test. The appropriate linear contrasts will be applied to the parameter estimates for the PPI regressor in the baseline and endpoint scans, resulting in 'baseline connectivity' and 'endpoint connectivity' contrasts maps for all subjects. In addition, linear contrasts will be applied to parameter estimates for the PPI regressor in the post-treatment minus baseline scans for ADHD subjects only ('post–baseline connectivity').

C.6. STATISTICAL ANALYSIS

C.6.1. Second-level group analysis. We have adopted a two step approach to hypothesis testing. We will first use analyses of covariance (ANCOVA) to test for connectivity changes over treatment and then use multiple linear regression to test the association of these changes with clinical improvement. Statistical significance will be set at a height (intensity) threshold of $p < 0.01$ and an extent (cluster) threshold of 100 contiguous voxels to correct for multiple comparisons at $p < 0.01$.[90]

C.6.1.1. Analysis of covariance (ANCOVA). The 'baseline connectivity' and 'endpoint connectivity' contrast maps for all subjects will be entered into a random-effects GLM, in which Group (ATX vs. MPH vs. control) will serve as the between-subjects factor and Time (baseline vs. endpoint) will be the within-subjects factor. Age of subjects will be entered as a covariate to remove any developmental effects. The concepts of 'normalization' and 'compensation' in Aims 2 and 3 are defined as Group × Time interactions that indicate differences in connectivity at baseline but not endpoint and at endpoint but not baseline, respectively (see Fig. 3).

C.6.1.2. Multiple linear regression. The 'post-baseline connectivity' contrast maps for ADHD subjects only will be entered into a random-effects GLM with three regressors: (i) Medication (MPH vs. ATX); (ii) ADHD-RS-IV change score; and (iii) an interaction predictor, which is the product of the Medication variable with the ADHD-RS-IV change

score. Age of subjects will initially be entered as a covariate; secondary analyses will include age as a regressor crossed with both Medication and ADHD-RS-IV change score to explore potential development effects. A mask will restrict the analyses to regions that showed significant Group × Time interactions in the ANCOVA. The ADHD-RS-IV change score and the interaction predictor identify connectivity changes that are associated with improvement across the whole sample (i.e., common effects) and differentially in the MPH and ATX groups (i.e., unique effects). The medication regressor is of no interest since it is not linked to improvement. The interaction predictor involves a between-group contrast that subtracts-out changes shared by the ATX and MPH groups – including practice, expectation, and other non-specific factors.

C.6.2. Hypothesis testing.

C.6.2.1. Hypotheses 1a-c: Youth with ADHD have reduced connectivity between and within 'task-positive' and 'task-negative' networks compared to controls would be confirmed by significant Group × Time interactions in the ANCOVA indicating that the two ADHD groups have lower connectivity compared to controls at baseline: a) between IFG and caudate, motor cortex, and frontal operculum and between ACC and DLPFC (within the 'task-positive' network); b) between PCC and MPFC and precuneus (within the 'task-negative' network); and c) between ACC and PCC and MPFC, and between IFG and precuneus and MPFC (between the two networks).

C.6.2.2. Hypothesis 2a: Symptomatic improvement for both ATX and MPH is associated with normalization of reduced connectivity within the 'task-positive' network would be confirmed by finding: i) significant Group×Time interactions in the ANCOVA indicating lower IFG-caudate and IFG-motor cortex connectivity in both the ATX and MPH groups compared to controls at baseline but not endpoint; and ii) positive associations between the ADHD-RS-IV change score and IFG-caudate and IFG-motor cortex connectivity in the regression.

C.6.2.3. Hypothesis 2b: Symptomatic improvement for both ATX and MPH is associated with compensatory increases in connectivity between 'task-positive' and 'task-negative' networks would be confirmed by findings of both: i) significant Group × Time interactions in the ANCOVA indicating lower ACC-PCC and IFG-precuneus connectivity in both the ATX and MPH groups compared to controls at endpoint but not baseline; and ii) positive associations between the ADHD-RS-IV change score and ACC-PCC and IFG-precuneus connectivity in the regression. These results would reflect increased connectivity between anti-correlated networks.[3,4]

C.6.2.4. Hypothesis 3a: Symptomatic improvement is associated with normalization of reduced 'task-positive' network connectivity for ATX and reduced 'task-negative' network connectivity for MPH would be confirmed by findings of: i) significant Group × Time interactions in the ANCOVA indicating lower ACC-DLPFC and IFG-frontal operculum connectivity for ATX-treated subjects compared to MPH-treated subjects and controls at baseline, but not endpoint; ii) significant Group × Time interactions in the ANCOVA indicating lower PCC-precuneus and PCC-MPFC connectivity for MPH compared to ATX and controls at baseline but not endpoint; and iii) positive associations between the interaction predictor and IFG-caudate and IFG-motor cortex connectivity for ATX and PCC-precuneus and PCC-MPFC connectivity for MPH in the multiple regression.

C.6.2.5. Hypothesis 3b: Symptomatic improvement is associated with compensatory increases in connectivity between 'task-positive' and 'task-negative' networks would be confirmed by findings of: i) significant Group × Time interactions in the ANCOVA demonstrating lower IFG-MPFC for ATX compared to MPH and controls at endpoint but not baseline; ii) significant Group × Time interactions in the ANCOVA indicating lower ACC-MPFC for MPH compared to ATX and controls at endpoint but not baseline; and iii) associations between the interaction predictor and IFG-MPFC connectivity for ATX and ACC-MPFC connectivity for MPH in the multiple regression. These results would reflect increased connectivity between typically anti-correlated networks.[3,4]

C.6.2.6. Exploratory Aim 1: Establish direct causal models of the therapeutic actions of ATX and MPH. The PPI results will be used to inform direct causal modeling (DCM) of the directionality or effective connectivity of the therapeutic actions of ATX and MPH on interactions between and within the 'task-positive' and 'task-negative' networks, as described in Fan et al.[68] and Wang et al.[67]

C.6.2.7. Exploratory Aim 2: Changes in connectivity associated with improvement on neurocognitive measures of treatment outcome. Percent change in the Digit Span, Finger Windows and Attention Network (ANT) Tests (neuropsychological outcome measures of attention and executive function) will be used in the two step analytic model described above to identify changes in connectivity as*sociated with various cognitive outcomes.*