Are abnormal regions of structural connectivity connected functionally?
Need *for automatic method for multi-dimensional data-driven meta-analysis*

Assessing the relationship between functional and structural connectivity in the human brain requires large datasets that must be extensively processed through several pipelines, and the utilization of multiple informatics techniques. Although popular software packages allow for piecewise functionality for a local dataset, an in depth understanding of these relationships across disorders and phenotypes calls for more sophisticated algorithms implemented with a meta-analytical approach.

The goal of this project was to assess the relationship between structural and functional connectivity for individuals with ADHD as compared to their healthy counterparts in an effort to utilize a meta-analytical method and assess the ability of the current infrastructure to support this method. Steps included (1) building a machine-accessible database of extracted sMRI (structural MRI) data from ADHD patients, (2) summarizing deficits in structural connectivity, (3) using data-driven methods to infer functional connectivity networks , and (4) finding overlap between patterns of structural abnormality and functional connectivity networks to functionally characterize ADHD deficits. An overview of the method is shown in Figure 1, and a summary of steps detailed below. We suggest that an automatic method for data-driven meta-analysis of functional networks, brain structure, and other variables of interest is needed to better understand biological differences that characterize ADHD and other disorders of interest.

[Figure 1]

(1) Building a machine-accessible database of extracted sMRI (structural MRI) data from ADHD patients: We reviewed all references in four prominent meta-analysis papers pertaining to neuroimaging in ADHD [1,2,4,5], identified a subset of 54 that were relevant to structural differences between ADHD and Control, and then selected studies that detailed gray and white matter volumetric differences, included voxel coordinates or anatomical labels, were done no earlier than 1996, and reported results exclusively comparing ADHD and Control. Our final set included 18 papers with 56 coordinate reports in both MNI and Talairach space, and 82 reports of differences specific to an anatomical region. Out of these 82, we decided that 21 provided enough description to assign a central voxel coordinate, giving us a final set of 77 coordinates from 13 papers, across 937 subjects.

(2) Summarizing deficits in structural connectivity: We converted all of our coordinates into Talairach space and used GingerALE, a tool that identifies significant local maxima of change across the whole brain and many reports, to summarize structural deficits [3,6]. We identified one larger cluster localized to Broadmann areas 3,4,5, and a smaller cluster in Broadmann area 47 that represent significant structural deficits reported in the current literature (Figure 2).

[Figure 2]

(3) Using data-driven methods to infer functional connectivity networks: The International Data Sharing Initiative (INDI) has recently released the ADHD 200 data-set, which contains raw anatomical and resting scans for 285 individuals diagnosed with ADHD, and 491 typically developing individuals across 8 sites. We chose to derive our functional networks from a subset of this data, specifically the sample of 222 subjects from the New York University Child Study Center. We created a package of scripts

controlled by a master submission script that first pre-processes anatomical and functional data, and then performs quality analysis and automatically remove subjects with translational motion greater than 2mm, or rotational motion greater than two degrees in any direction. After quality analysis, our final dataset included 178 subjects (84 ADHD, 94 Control). The package then utilizes multi-session temporal concatenation as an unsupervised method to derive functional networks for the entire group, and finally, runs a dual regression analysis to identify significant differences between ADHD and Control within these functional networks. While a data-driven method would have been preferred and will be suggested in this report, we eliminated components that represent noise or artifact with visual inspection. We then extracted the voxel coordinates of local maxima for each significant difference within a functional network, and converted all coordinates into Talairach space to ascribe an anatomical label, and identify anatomically distinct regions.

(4) finding overlap between patterns of structural abnormality and functional connectivity networks to functionally characterize ADHD deficits. Visual investigation and common anatomical labels revealed overlap of structural deficits with two maps of functional network deficits. The first group of deficits was localized to the Precentral Gyrus (Broadmann area 3 and 4) and Medial Frontal Gyrus (Broadmann area 47) in the Frontal Lobe, and the Inferior Parietal Lobe (Broadmann area 40). Further investigation of the functional network from which these significant differences were derived revealed a network between (region names here), clearly an attention network (Figure 3). The second group of deficits was localized to the Cingulate Gyrus (Broadmann area 31 and 32), and the Paracentral Lobule (Broadmann area 5). The functional network associated with these areas includes (insert region names here), arguably another network involved with attention.

[Figure 3]

MAKING IT BETTER

We aim to propose an infrastructure with machine-accessible anatomical and functional data tagged with study specific meta-data to allow for streamlined, accurate analysis from a secured browser environment. Raw data might be added to the system for automatized preprocessing, quality analysis, and tagging, or result maps might be submitted for tagging and query. The system would utilize ontologies to tag data with anatomical regions and functional networks, allowing for user query and the combination of multiple datasets and analysis across imaging modalities. The following section attempts to address how each step might be improved. Questions that the proposed infrastructure would easily answer are in green.

(1) Building a machine-accessible database of extracted sMRI (structural MRI) data from ADHD patients: The manual extraction of coordinates and anatomical regions is time-consuming and calls for a more efficient method. Text mining the current literature is a proposition utilized by projects such as NeuroSynth [7], however it is clear from our manual extraction that releasing algorithms to mine coordinates from tables is not an accurate enough approach. Many papers report results approaching significance, and unclear or multiple coordinate spaces or contrast labels. A more accurate approach would be to summarize structural differences via machine-accessible raw anatomical

data, allowing for user query of specific populations and data types provided by meta data.

How many studies have found gray matter deficits in females with ADHD?
What age groups have been examined for white matter deficits in the past ten years?

(2) Summarizing deficits in structural connectivity: Ascribing an anatomical label to a cluster or voxel coordinate requires manipulation of the finding to the correct orientation and coordinate space, and utilization of a visual atlas (FSLview) or automatic tool (Talaraich demon or AAL) to be done. When done manually, this procedure is highly prone to bias or error, and unfortunately, a label in absence of an ontology lacks context in its location in the brain. Our proposed infrastructure would utilize raw data to automatically derive significant structural differences, and automatically provide labels for the result based on voxel coordinates. Results would automatically be tagged with these labels as well as with study specific meta data and other imaging markers such as cluster size and average intensity to allow for user query. Utilization of an ontology would ensure that a user searching for “Precuneus” or “attention network” would also be informed of results pertaining to “Broadmann area 7.”

How does white matter integrity compare between ADHD and control in the frontal lobe?
Do individuals with ADHD have gray matter deficits anywhere in the prefrontal cortex?

(3) Using data-driven methods to infer functional connectivity networks: The proposed infrastructure would automate and parallelize all pre-processing, quality analysis, group multi-session temporal concatenation, and dual regression analysis, a series of distinct procedures that might take months to implement and run, providing the user with these results from the onset. Most importantly, data across modalities and sites would be labeled to allow for instant user query.

Show me functional connectivity differences between ADHD and control?
Show me all functional deficits that involve the amygdala, for males, females, and both?

(4) finding overlap between patterns of structural abnormality and functional connectivity networks to functionally characterize ADHD deficits. A system with query-able structural and functional results across many groups would allow for the retrieval of user-specified results, and calculation of correlations across imaging maps, and with other behavioral and genetic data.

Do correlations between significant functional and structural deficits differ between ADHD subtypes?
Do structural deficits in ADHD compare to structural deficits in ASD, and if so, are functional networks effected in the same manner?

INFRASTRUCTURE EXTENSION

Further, we propose that this infrastructure would be easily extended to allow for the application of **machine learning** methods. Machine accessible, labeled data would allow for a user to make an observation at the group level, and then query specified single-subject data to extract time-series and perform custom **correlation analysis.** Combined with clinical data, a user could test the ability of a functional or structural

marker combined with **genetic** and **behavioral** measures to predict a particular diagnosis.

Do correlations between significantly impaired functional networks in ADHD combined with genetic marker X predict ADHD diagnosis?

FIGURE 1

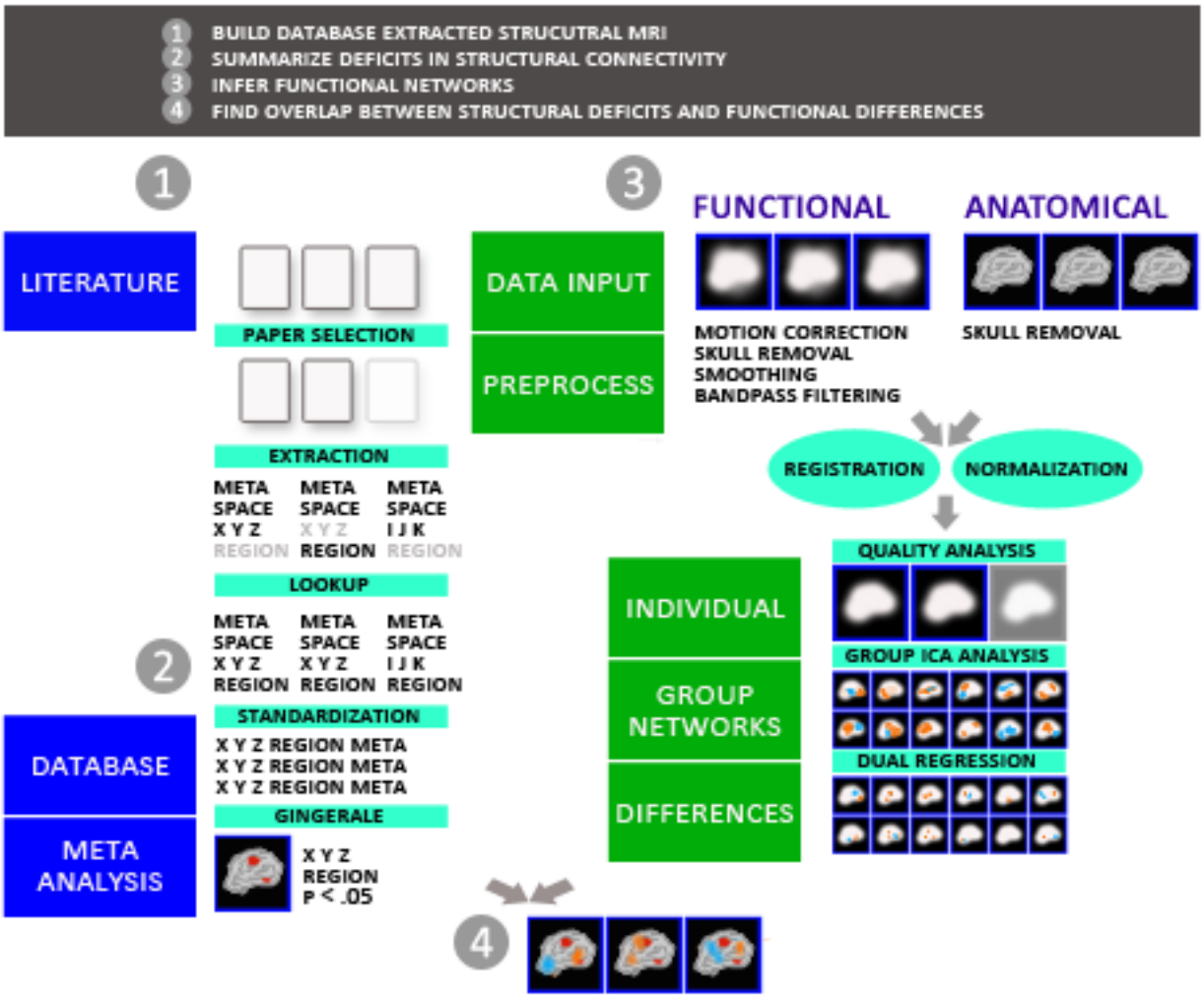


FIGURE 2

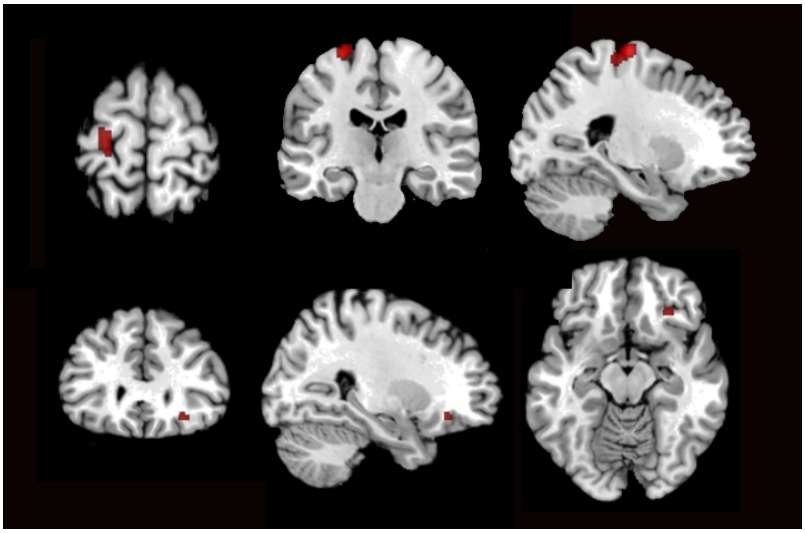
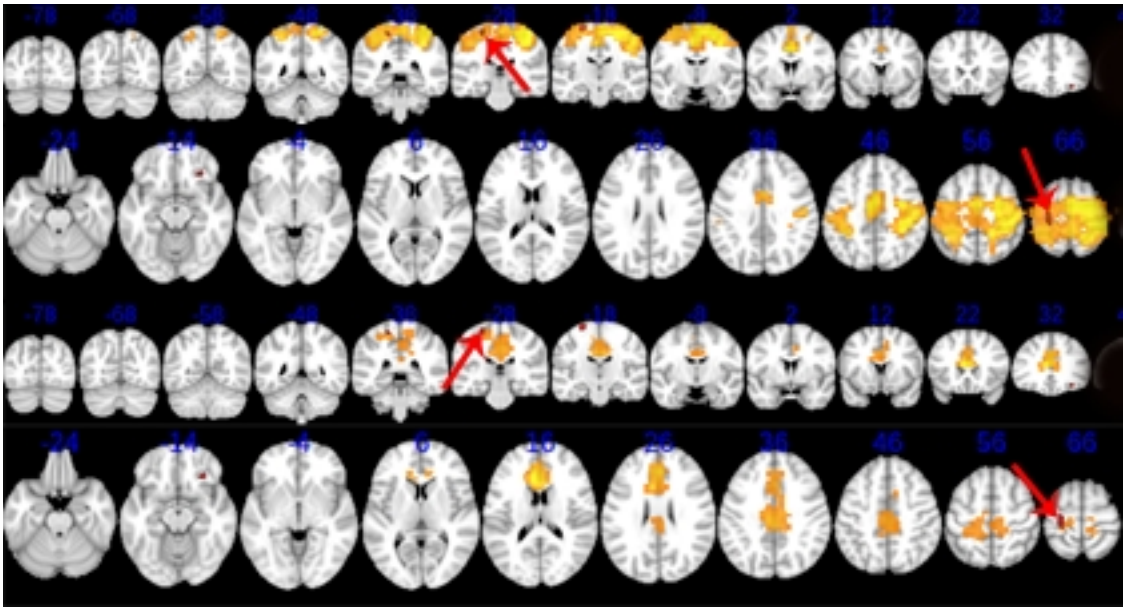


FIGURE 3



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