Brain connectivity differences between typically developed and ADHD subjects using Energy Landscape Analysis of resting-state fMRI data

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Abstract– Functional magnetic resonance imaging (fMRI) is an effective tool used to study neural systems and functional connectivity patterns within brain networks. Using resting-state fMRI data, we can uncover the functional connectivity differences in people with typically developed brains and brains of people with attention deficit hyperactivity disorder (ADHD). Segmenting the human brain into networks and analyzing the internetwork connectivity can help us identify which brain network regions are engaged and if they are working together. In this study, we used energy landscape analysis, a method that calculates and interprets multivariate time series data, such as resting-state fMRI, to investigate brain activity differences in typically developed, ADHD-Hyperactive/Impulsive, ADHD-Inattentive, and ADHD-Combined subjects. The functional connectivity differences between the subgroups, analyzed separately, could be attributed to internetwork activity, and can possibly help identify biomarkers of ADHD. The internetwork connections consisted of the auditory network (AUD), attention network (ATN), default-mode network (DMN), frontoparietal network (FPN), salience network (SAN), sensorimotor network (SSM), and visual network (VIS). The activity patterns and disconnectivity graphs are obtained for each subject and the differences between groups are compared. Results suggest that DMN and VIS are strongly coupled for females with ADHD, whereas FPN and SAN are strongly coupled for males with ADHD. These cognitive differences may attribute to neural deficits and cognitive dysfunction in ADHD, such as trouble paying attention and inability to control behavior. The energy landscape analysis technique is a powerful tool for identifying differences between typically developed and ADHD subjects, which could help validate and encourage treatment options.

Keywords-- ADHD, functional connectivity, energy landscape analysis, biomarker, fMRI

I. Introduction (Heading 1)

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that affects at least 5-10% of all school-aged children in the United States [1], [4]. Children with ADHD may have trouble paying attention and controlling impulsive or hyperactive behaviors [1], [4], [9]. Symptoms of ADHD can be mistaken for emotional or disciplinary problems or missed entirely in quiet well-behaved children, leading to a delay in diagnosis [1], [4], [9]. There are three types of ADHD identified and analyzed in this study: 1) hyperactive or impulsive form of ADHD revealing no significant inattention, 2) inattentive form of ADHD revealing no significant hyperactive-impulsive behavior, and 3) combined form of ADHD revealing the struggle(s) of paying attention and regulating behavior. The cause of ADHD is not entirely known, although some cases of ADHD are purely attributed to genes [1], [4], [9]. Other research studies suggest that ADHD is also caused by environmental factors and interactions [4], [9].

A. Characterizing Brain Function Associated with ADHD

In the past, ADHD diagnosis focused primarily on screening tests, such as neuropsychological testing and questionnaires, however, these assessments lacked sensitivity and specificity [9]. Functional magnetic resonance imaging (fMRI) helps researchers think about co-occurring conditions which may include: 1) underlying circuits or brain systems such as dynamics, and 2) the non-linear relationships between brain systems and psychiatric diagnosis that may explain various conditions [1], [4], [9]. Combining fMRI analysis with academic performance and clinical measures (e.g., rating scales) can better assess the brains of people with ADHD while revealing the cognitive differences of neurotypically developed brains [1], [4], [9].

Researchers from the MIND Institute at the University of California, Davis discovered that the brains of people with ADHD may activate compensatory brain regions that are less efficient than their peers on some cognitive tasks [1]. The brain system involved in the pleasure response or "reward center," is associated with both ADHD and substance use disorders. ADHD is associated with more variable responses and the variability is linked to reduced functioning in the brain's "default mode network", [1]. Adolescent impatience decreases with increased brain frontostriatal connectivity [1]. In another study, ADHD and healthy subjects performed an adapted go/no-go task using a voluntary response button [6]. Frontal brain responses were reduced in ADHD patients compared to controls, whereas parietal brain functions seemed to be unaffected [6]. This may indicate dysfunctions, predominantly in frontal brain regions in ADHD patients.

B. Brain Connectivity Using Energy Landscape Method

The energy landscape is an analysis tool used to calculate and interpret multivariate time series data, such as resting-state fMRI, and helps identify energy values at local minimums to understand the changes between state transitions [7].

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TABLE I
TOTAL SUBJECTS ANALYZED

	Female	Male
Typically Developed	31	28
ADHD-Combined	7	20
ADHD-Hyperactive/Impulsive	2	2
ADHD-Inattentive	5	29

In this study, I investigated functional connectivity and brain activity differences between ADHD-Hyperactive/Impulsive, ADHD- Inattentive, and ADHD-Combined subjects using an energy landscape analysis technique. The differences in functional behavior between these groups could be attributed to internetwork activity.

II. METHODS

A. Data Source

I used the freely available ADHD-200 data, a subset of neuroimaging data obtained from the 1000 Functional Connectomes Project. This New York University study contained a total of 222 subjects: 99 Typically Developed (TD) controls, 77 ADHD-Combined (ADHD-C), 44 ADHD-Inattentive (ADHD-I), and 2 ADHD-Hyperactive/Impulsive (ADHD-HI) patients. Each subject had an anatomical scan and one or two resting-state fMRI scans. During data acquisition, participants were asked simply to remain still, close their eyes, think of nothing systematically and not fall asleep. A black screen was presented to them. The dataset also contains information pertaining to sex (79 females, 142 males, and 1 unreported sex), handedness, and age (7-17 years of age). For this research, I utilized the first resting-state scan only and omitted subjects that did not have this data. In this report I focused on 122 subjects containing the following characteristics: 1) 31 TD females, 28 TD males, 5 ADHD-C females, 29 ADHD-C males, 0 ADHD-HI females, 2 ADHD-HI males, 7 ADHD-I females, and 20 ADHD-I males, as indicated in Table 1.

B. Data Preprocessing

The resting-state fMRI data was initially in the NIfTI file format (a commonly used format for multi-dimensional neuroimaging data), which contained voxels with 3D (x, y, z) and 1D (time) coordinates. Once the NIfTI files were unzipped, I used MATLAB to read each file. To obtain the necessary regions for a specific brain network, I parsed the data using the 90-region Automated Anatomical Labeling (AAL) atlas as shown in Table 2. The region of interest (ROI) time series is then extracted from the data using REX, a MATLAB-based toolkit used to extract connectivity values within the ROI. The REX software relies on spatial parametric mapping (SPM), allowing us to investigate the mean activity of a particular region of the brain.

C. Energy Landscape Analysis

The energy landscape toolbox interpreted brain activity of internetwork connections among the 7 networks, including auditory network (AUD), attention network (ATN), default

TABLE II
DATA PARCELED INTO 7 REGIONS USING THE 90 ROI AAL ATLAS

Region	Number
VIS	7
SSM	6
SAN	5
FPN	4
DMN	3
AUD	2
ATN	1

– mode network (DMN), frontoparietal network (FPN), salience network (SAN), sensorimotor network (SSM), and visual network (VIS). This was interpreted based on the properties and functions of each brain region and subsequent network. The energy landscape is achieved by 1) binarization of the data, 2) maximum entropy model from Boltzmann distribution, 3) disconnectivity graph and basin of energy local minimum(s), and 4) dynamics of energy landscapes [7]. We constructed activity patterns and disconnectivity graphs for each subject using the Energy Landscape toolbox to interpret the multivariate fMRI data.

The Boltzmann distribution is denoted by

$$P(\boldsymbol{\sigma} \mid \boldsymbol{h}, \mathbf{J}) = \frac{\exp[-E(\boldsymbol{\sigma} \mid \boldsymbol{h}, \mathbf{J})]}{\sum_{\sigma'} \exp[-E(\boldsymbol{\sigma}' \mid \boldsymbol{h}, \mathbf{J})]'} \tag{1}$$

with energy, E

$$E(\boldsymbol{\sigma} \mid \boldsymbol{h}, \mathbf{J}) = \sum_{i=1}^{N} h_i \sigma_i - \frac{1}{2} \sum_{i=1}^{N} \sum_{\substack{j=1 \\ j \neq i}}^{N} J_{ij} \sigma_i \sigma_j \tag{2}$$

maximum likelihood

$$(\boldsymbol{h}, \mathbf{J}) = \arg\max_{\boldsymbol{h}, \mathbf{J}} \mathcal{L}(\boldsymbol{h}, \mathbf{J}) \tag{3}$$

and likelihood, $\mathcal{L}(\boldsymbol{h}, \mathbf{J})$

$$\mathcal{L}(\boldsymbol{h}, \mathbf{J}) = \prod_{t=1}^{t_{max}} P(\boldsymbol{\sigma}(t) \mid \boldsymbol{h}, \mathbf{J}) \tag{4}$$

D. Local Minimums

The local minimums are states that have lower energy (more frequent) relative to their neighboring nodes, N. Two minimums are in different sets if the highest energy transitions state (a local maximum) or lowest energy pathway between them exceeds energy, E [7]. The number of local energy minimum (attractor states) is estimated and the disconnectivity graph shows the positions of the local minimum states and their relationships [7]. The numbers on the x-axis of the activity patterns and disconnectivity graphs labeling the energy local minimum states are consistently used in both panels. White and black cells represent variables or ROIs that are active and inactive, respectively.

III. RESULTS

The averaged results from the activity patterns and disconnectivity graphs were generated for each subgroup. The

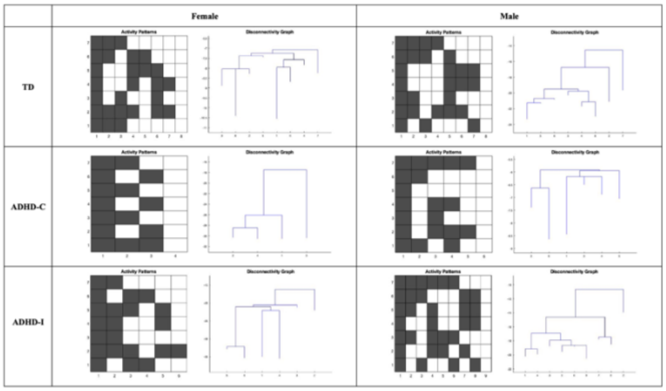

Fig.1: Activity Patterns and Disconnectivity Graphs, obtained from energy landscape analysis, for 31 TD females, 28 TD males, 5 ADHD-C females, 29 ADHD-C males, 7 ADHD-I females, and 20 ADHD-I males, averaged across all 7 networks.

internetwork results show that for both TD females and males, 8 states were identified as local minimums. For ADHD-C females, 4 states were identified as local minimums, whereas for ADHD-C males, 6 states were identified as local minimums. For ADHD-I females, 6 states were identified as local minimums, whereas for ADHD-I males, 9 states were identified as local minimums. On average, 2 states were identified as local minimums for ADHD-HI males. For ADHD-HI Subject 1, 5 states were identified as local minimums and for ADHD-HI males, 7 states were identified as local minimums. Since there were only two ADHD-HI subjects in the data, it was simple to represent the activity patterns and disconnectivity graphs for both subjects.

IV. Discussion

Based on the activity patterns displayed in Figure 1, ATN and VIS are correlated (both are activated at the same time) in TD females. Whereas FPN and SAN are correlated in TD males. DMN, SAN, and VIS are correlated, and simultaneously AUD, FPN, and SSM are correlated in ADHD-C females. For ADHD-C males, there was no correlation between internetworks. DMN and VIS are correlated, and simultaneously ATN and SSM are correlated for ADHD-I females. For ADHD-I males, there was no correlation between internetworks. Results for ADHD-HI are shown in Figure 2. On average, AUD and VIS are correlated, and simultaneously ATN, DMN, FPN, SAN, SSM, and VIS are correlated for the 2 ADHD-HI subjects. For ADHD-HI Subject 1, AUD and VIS are correlated, and simultaneously DMN, FPN, and SAN are correlated. For ADHD-HI Subject 2, DMN and FPN are correlated. Overall, the data suggest that DMN and VIS are strongly coupled for females with ADHD, whereas FPN and SAN are strongly coupled for males with ADHD. This data concludes that the VIS region is prevalent in TD females and may associate with higher visual processing. In TD males, the FPN is prevalent and may associate with language processing and motor cognition. The SSM region, which explains free will or the ability or inability to control actions, is easily separable for TD subjects

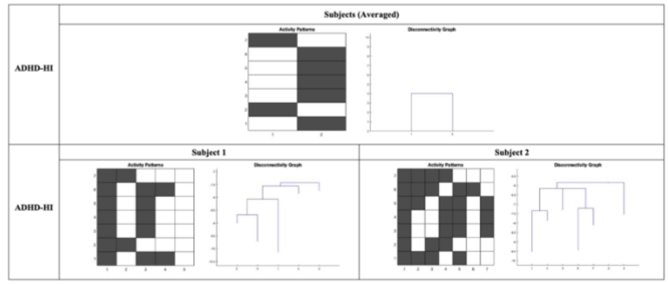

Fig. 2: Activity Patterns and Disconnectivity Graphs, obtained from energy landscape analysis, for 2 ADHD-HI males across all 7 networks, as averaged and shown as individual subjects.

but not for subjects with ADHD. To separate, one must have awareness and training, and self-awareness is the hallmark of attentiveness. Consistent training helps to form a local minimum which represents habits, thus controlling behavior.

V. Conclusion

The energy landscape analysis technique has been employed to identify brain connectivity biomarkers that can possibly separate TD and ADHD subjects. Potential biomarkers were identified, and their corresponding meanings were interpreted, showing that the analysis technique is an effective method for brain connectivity biomarker extractions. Future work would require analysis of the intranetwork connections to understand better the brain dynamic differences and characteristics of the data. It is important to note that ADHD is primarily associated with behavior, so other factors such as stress, trauma, drugs, chemicals, and diet or obesity were not included in this study but could be analyzed in the future. Therefore, underlying brain systems may predispose individuals to several conditions rather than one isolated condition.

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