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Attention-Deficit/ Hyperactivity Disorder Brain Functional Reference: Introducing an Inter-subject Consistency Measure and Dual-layer Parcellation

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ABSTRACT

The latest advancements in neuroimaging techniques have contributed to studying the disordered human brain, but still, there is a lack of disease-specific brain reference to localise brain seeds and standardise the comparison across studies. The current study first evaluates the inter-subject consistency across Attention-Deficit/ Hyperactivity Disorder (ADHD) in a publicly accessible resting-state functional magnetic resonance imaging (RS-fMRI) ADHD-200 dataset by

proposing a new voxels similarity index (VSI) that integrates both inter-atlases flexibility (F`) from previous studies with proposed inter-subjects stability (S`) measure to improve outcomes. Secondly, the study employs a dual-layer clustering-based parcellation strategy inspired by the resultant improved Master Atlas networks to examine the ADHD cerebral cortex. The suggested approach to enhancing the ADHD cortex parcellation uses spectral clustering for global structure identification, followed by hierarchical clustering for local refinements and granularity specification. The final connectivity-driven brain reference achieved an average homogeneity of 0.63, and the enhanced Master Atlas with (S') achieved 0.35 homogeneity, surpassing the original Master Atlas with 0.27. This discovery implies that the final brain reference offers a more accurate and reliable framework to examine the connections and functions of the brain in individuals with ADHD.

Keywords: Brain disorder, brain network, functional variability, functional connectivity analysis, Resting-State Networks.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most widespread chronic developmental disorders observed worldwide. It is considered a prominent public health concern and is often registered as an underdiagnosed condition, particularly in adults (Ginsberg et al., 2014; Sarno & Ghozali, 2024).

The traditional diagnostic approach for ADHD typically entails a detailed analysis and assessment of the behaviours and symptoms as described in the DSM-V criteria (Abuse & Administration, 2016). this approach faced limitations due to the situation-dependent nature of ADHD symptoms and the broad variance in ADHD clinical presentation among individuals. Therefore, the DSM-V criteria could be used as a guide for ADHD diagnosis (Grossman & Berger, 2024). Still, it is insufficient to emphasise the pressing need for more nuanced diagnostic and management tools for this condition. Recently, there has been a significant breakthrough since researchers have initiated an exploration of biomarkers for ADHD, with a focus on the brain as one of the key biomarkers to study ADHD (Koutsoklenis & Honkasilta, 2022).

Accordingly, research on ADHD has been ongoing for decades, intending to gain a thorough understanding of brain behaviour and functionality. This emerging research direction holds the promise of creating more precise and effective diagnostic tools and treatment strategies, which could enhance the lives of countless individuals affected by ADHD. Many studies have explored ADHD neuronal interconnections, aiming to identify differences between ADHD and typically developed (TD) brains. The latest advancements in non-invasive neuroimaging techniques have contributed to studying the human brain. In this context, neuroimaging techniques like functional Magnetic Resonance Imaging (fMRI) and their application in studying functional connectivity among brain regions (Fornito et al., 2016; Pereira-Sanchez et al., 2021) are becoming increasingly important.

The fMRI is a specific type of MRI that quantifies brain activity by identifying changes associated with blood flow based on the correlation between cerebral blood flow and neuronal activity since activation of a particular brain region translates to an increase in blood flow to that region leading to a signal called the Blood Oxygen Level-Dependent (BOLD) signal (Lv et al., 2018). There are two categories of fMRI experiments: task-based (i.e., real-time) and resting-state. Resting-state fMRI (rs-fMRI) studies have played a vital role in advancing our understanding of ADHD (Liu et al., 2023; Pereira-Sanchez et al., 2021). Hence, rs-fMRI studies have revealed altered functional connectivity (FC) in ADHD across various brain networks by identifying brain patterns associated with local blood oxygenation to measure brain activity even during rest (Liang et al., 2012; Zhang et al., 2020).

Rs-fMRI studies documented altered resting-state FC (rs-FC) in ADHD throughout multiple brain networks (Smitha et al., 2017; Sutcubasi et al., 2020; Thomson et al., 2022), that often studied through Resting-State Networks (RSNs)- are brain clusters that spatially distinct but functionally connected (dos Santos Siqueira et al., 2014). RSNs have been used to analyse brain connectivity in ADHD, revealing how ADHD impacts various brain networks, including the Default Mode Network (DMN), Dorsal Attention Network (DAN), and Auditory Network (AUN). Harikumar et al. (2021) is one such example that has contributed to this understanding. One significant hurdle in constructing brain networks is delineating and defining those RSNs. This step is crucial given the intricate nature of brain network spatial architecture and terminology variation, which is influenced by the

study perspective of whether it focuses on functional or anatomical connectivity patterns and inter-individual heterogeneity (Doucet et al., 2019; Uddin et al., 2019).

Traditionally, RSNs could be identified and localised using brain atlases (Genon & Li, 2023). Brain atlases are highly valuable instruments that are widely utilised in the process of parcellating the brain, starting with an atlas to perform controlled clustering with the available data and anatomical definitions, which is a more adaptable method in rs-fMRI data analysis (Yeo et al., 2011). The choice of brain atlas can significantly impact the results of RSN analysis, attributed to atlases concordance issues (Andrew et al., 2021; Bohland et al., 2009). This is because different atlases may not align perfectly and could have misalignments. Some atlases may define the left and right hemispheres, while others may have separate maps for subdivisions of the same RSN. In addition, there are different terminologies with similar networks and different levels of detail, which can also cause issues (Genon & Li, 2023; Nowinski, 2021; Revell et al., 2022).

Publicly accessible brain atlases result from various processing methods that rely on various algorithms and assumptions. However, there is a lack of a unified standard for developing and assessing these atlases across the scientific community. It was impossible for a single brain atlas to capture all of the variations in the brain under investigation by researchers studying neurological and neurodevelopmental disorders. This evidence of variability stems from various factors, such as individual differences, brain disorders, neurocognitive diseases, age, developmental cognitive levels, and technological limitations (Doucet et al., 2021). Therefore, it is recommended to use multiple atlases to avoid incorrect descriptions and gain comprehensive insights (Ming Chen et al., 2019; Salman et al., 2020).

The next section investigates the related works from three perspectives; then, the materials and methods section introduces the dataset, and the proposed methods and describes the validation methods. After that, the results and discussion pronounce the experiments on the selected data. The conclusion is given in the last section.

RELATED WORKS

Various analytical methodologies have been adopted in ADHD rs-fMRI research to understand the condition. Early ADHD research

on rs-fMRI focused primarily on seed-based correlation analysis or region of interest (ROI)-based analysis, the most popular straightforward approach. In contrast, other studies adopted data-driven approaches such as Independent Component Analysis (ICA), clustering-based and graph theory. This part is divided into multiple subsections, addressing distinct and important parts of this study; a short description is provided as follows:

The Role of RSNs in Identifying ADHD Neural Patterns

Understanding the functional connectome can help shed light on various brain disorders' exact aetiology (i.e., causes and origins). However, the inconsistent terminology and labelling across various brain atlases and vast scientific literature complicate research on RSNs. Currently, efforts to investigate the structure and function of the human brain are fragmented due to a lack of standardisation in human brain atlases. These efforts aim to enhance our knowledge of the intricate workings of the brain and find better clinical applications in neurology and psychiatry (Ming Chen et al., 2019).

This inconsistency leads to confusion, discrepancies in understanding RSNs, and disagreement over research methodologies. Uddin et al. (2019) and Bryce et al. (2021) emphasise standardising how RSNs are labelled and identified to achieve more consistent and comparable research results. To fill this gap, a recent study by Doucet et al. (2019) tried to solve this problem by standardising five RSNs defined on six reliable brain atlases by creating a consensual atlas, which will enhance the reproducibility of those RSNs across studies and promote a unified understanding of RSNs in healthy brains, advancing our knowledge of brain function. Furthermore, studies investigating disordered brain mechanisms have underscored the need for disease-specific functional atlases (Al-Ubaidi et al., 2023; Revell et al., 2022).

Numerous studies on ADHD have employed resting-state functional magnetic resonance imaging (rs-fMRI) to investigate FC in RSNs. Harikumar et al. (2021) made significant progress in understanding how ADHD affects the DMN. Besides that, research indicates that ADHD affects interconnected networks, including the DAN, DMN, and AUN (Sutcubasi et al., 2020; Thirion et al., 2014). Studying the brain networks underlying ADHD at the network level is hard because choosing between interpretability and accuracy comes with its difficulty as the problem is too complex and highly dimensional.

In particular, meta-analysis assessments are featured in many studies investigating FC in ADHD; those studies have yielded inconsistent findings (Cortese et al., 2021; Gao et al., 2019; Sonuga-Barke & Castellanos, 2007; Sutcubasi et al., 2020). In contrast, Zhang et al. (2020) utilised (ICA) to investigate RSNs in ADHD adolescents, and it was found that reduced FC within the (DMN) and (DAN) were associated with ADHD symptoms. However, when analysing subjects separately. One drawback is that ICA may miss signal-to-noise ratio (SNR) benefits, which could impact decomposition accuracy.

An effective approach to tackling this problem is to develop a pipeline that automatically relabels and integrates information from multiple brain atlases, even when they use different labelling protocols, as proposed by (Al-Ubaidi et al., 2023, 2024). Notably, the Auditory Network (AUN), Cognitive Control Network (CCN), Dorsal Attention Network (DAN), Default Mode Network (DMN), Sensorimotor Network (SMN), and Ventral Attention Network (VAN) constituted the networks of interest (NoIs) in our proposed model.

Brain Voxel Analysis as Functional Segregation Measure

The high dimensionality and sparsity of fMRI data pose significant challenges in rs-fMRI analysis, leading to rs-fMRI studies disregarding inter-subject variability and assuming uniformity in spatial and temporal brain activations. However, the human brain's structure and functionality can vary due to various factors. This analysis intends to clarify this issue by adopting a data-driven method to assess individual brain activity differences, specifically in rs-fMRI seed stability analysis. This is crucial for the precise diagnosis of ADHD. Extracting the functional information from specific brain regions or studying the functional connectivity between various brain regions is necessary.

The voxel-wise analysis involves examining numerous measurements within or between voxels features; the widely used metrics in an rs-fMRI study of ADHD: amplitude of low-frequency fluctuation (ALFF), fractional-ALFF (fALFF), regional Homogeneity (ReHo), degree centrality, and voxel-mirrored homotopic connectivity (Alonso et al., 2015; Jiang et al., 2019; Li et al., 2014; Sato et al., 2012; Tan et al., 2017; Wang et al., 2013; Wang et al., 2023; Yang et al., 2011). However, voxel-wise metrics analysis of ADHD using ADHD-200 multiple sites has shown inconsistent findings, indicating a need to

reassess the results regarding spontaneous brain activity (Zhou et al., 2019).

Related to the first goal of this research, two separate studies were conducted to understand inter-subject brain variability in ADHD, each with a different primary focus on different data samples. One study by (Hsieh et al., 2023) utilised a data-driven model to find reliable seeds for diagnosing ADHD. The model selects the four largest clusters as seeds for the whole-brain functional connectivity calculation using a ReHo map. The established model was applied to an ADHD-200 NYU database, including 73 individuals with ADHD and 76 TDs, achieving 83.24 percent accuracy and being unbiased.

In addition to the mentioned data-driven method, another study by Ingabire et al. (2022) has demonstrated that the stability changes in physiological signals can reflect individuals' pathological conditions, including ADHD. This study decomposed resting-state fMRI BOLD signals into Dynamic Modes (DMs) or subsystems to analyse the stability of decomposed subsystems of rs-fMRI BOLD signals. The features related to the stability of those DMs were extracted, and nine common classifiers were used to differentiate healthy controls from ADHD patients. The results showed that almost all features were statistically significant, and the proposed approach outperformed all existing methods with the highest possible precision, recall, and area under the receiver operating characteristic curve of 100 percent.

It is worth mentioning that the data-driven method and Dynamic Mode Decomposition (DMD) approach are highly dependent on the quality and pre-processing of the rs-fMRI data. Any inconsistencies in data acquisition, alignment, co-registration, or pre-processing steps could introduce biases or errors that affect the reliability of the findings. This study measures the variation in brain activity among ADHD individuals using the time courses extracted from the aligned rs-fMRI on the same unified RSN brain mask created by Al-Ubaidi et al. (2023). The analysis incorporates the Voxels Similarity Index (VSI), which considers inter-atlas flexibility (F`) and inter-subject stability (S`).

Data-driven Parcellations

The process of data-driven parcellation is often described as a clustering problem (Arslan et al., 2018). The rs-fMRI-based connectivity-driven

parcellation methodologies involve grouping brain voxels or regions based on their connectivity data to create a reference map useful for standardising data analysis and comparison. It can be generated using healthy or disordered brains as a reference map to identify affected brain regions (i.e., lesion-defined maps). This approach helps to focus the analysis pipeline and reduce data dimensionality and computational load. The frequently used unsupervised clustering algorithms on rs-fMRI are k-means, spectral, hierarchical, and fuzzy clustering (Arslan et al., 2018; Eickhoff et al., 2018; Kaur & Kumar, 2021; Thirion et al., 2014), each with its specific strengths and biases.

Riaz et al. (2018) stated that there is a lack of research that adopted clustering-based mapping algorithms on ADHD-200 in modelling functional connectivity (FC). Recently, interest has increased in using clustering algorithms in conjunction with rs-fMRI to evaluate the brain's FC and to group the brain into several regions, or parcels, with homogeneous features (Craddock et al., 2012). Despite the algorithm differences, most clustering algorithms on rs-fMRI aim to identify the brain's functional and topological characteristics. Brain network analysis adopted graph theory to decompose brain nodes and estimate edges among nodes; the FC power positively correlated with ADHD symptoms, as stated by (Mostert et al., 2016). With the motivation of there is a need for an unbiased and evidence-based methodology, this work suggests a dual-layer parcellation framework, the clustering algorithm is adaptive for the ADHD Connectivity-Driven parcellation.

MATERIALS AND METHODS

The proposed framework consists of several stages, which are conducted in the following manner:

Dataset and Pre-processing

This study included rs-fMRI of 285 ADHD subjects provided by the Neuro Bureau ADHD-200 *(http://neurobureau.projects.nitrc.org/ADHD200/Introduction.html)* to evaluate the proposed methods. The downloaded data is pre-processed using the fmriPrep pipeline by (Esteban et al., 2019), fmriPrep- is a robust fMRI data pre-processing tool designed to handle both task-based and rest-state fMRI data pre-

processing. The data is accessed and downloaded from the Amazon S3 Bucket using Cyberduck software; more details of this pipeline can be found at *(http://www.fmriprep.readthedocs.io/en/latest/workflows.html)*.

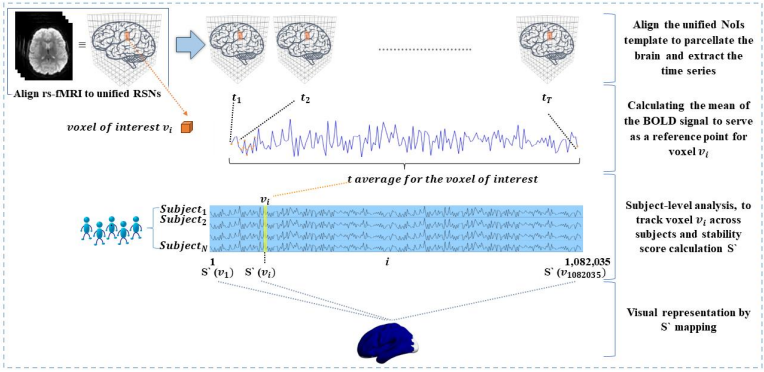
To ensure the quality of the data, the first four time points were excluded to allow for signal stability and participant adaptability. The data is processed using a band-pass filter within the 0.01-0.08 Hz frequency range to eliminate high-frequency interference (Lee et al., 2013). Then, the time signals were extracted for the stability analysis based on the unified RSNs mask from Al-Ubaidi et al. (2023).

The Inter-Subject Voxel Stability Measure

The conceptual framework of the proposed stability measure is depicted in Figure 1. This method focuses on measuring the stability of BOLD signals across ADHD subjects by observing variations in the extracted voxels. This approach aims to determine the variability of the human brain by moving the analysis from Network-of-Interest (NoIs) to voxel-based analysis, and the researcher thoroughly examined the data.

Figure 1

Conceptual Framework Illustrating the Inter-Subject Voxel Stability to measure BOLD consistency across ADHD subjects



For voxel-to-voxel across subjects, a total of around 1,082,035 voxels was extracted and investigated by computing Equation 1; this approach is referred to as S`. Since T= 167, N= 225 ADHD subjects,

and S` is the direct measure of the variability of the BOLD signal values across N subjects for a particular voxel $v_i$. This calculation produced an averaged matrix of S` values for all the participants, as detailed in Algorithm 1. The output of this algorithm is visualised as a 3D map overlaid on a brain mesh as a stability map; check the results and discussions section.

Algorithm 1: **Voxel-wise Stability in rs-fMRI data for ADHD subjects**

Input:
Subjects= [S_1, S_2, S_3, ..., S_N]: a list of pre-processed rs-fMRI data for each subject: *N*= the number of subjects used in the experiment;
num_voxels: the total number of voxels in the brain unified map;
Output:
S`: the voxel-wise Stability degree map;
Initialisation:
For each subject (s) in the dataset
Align the unified NoIs template to parcellate the brain;
Step (1): Extract raw BOLD Signals for each voxel across subjects
For each subject (S_j) in 'Subjects'
For each voxel (v_i) in the 'num_voxels'
Extract the BOLD signal time courses for the current (v_i)
Store this time-series in voxel_info [S_j, v_i]

Step (2): Calculation of Standard Deviation for each voxel across subjects
For each (v_i) in the 'num_voxels'
Extract voxel_info [:, v_i] // which contains the time-series of this voxel for all subjects
Calculate S` as the standard deviation of these values across subjects

$$S` = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}(BOLD_{tj} - \overline{BOLD}_t)^2} \quad (1)$$

: N=no of Subjects, and t represents the time point in the BOLD signal

Store the S` value at the position corresponding to voxel v_i
Return the Stability map;

Step (3): Apply a threshold (optional)

Visualisation: The spatial distribution map of the stable voxels
display the stability results on a 3D map to show the stable voxels across ADHD-200 subjects.

Following this step, a voxel similarity index (VSI) is introduced to gauge voxel-wise consistency and variability by factoring in both inter-atlas flexibility (F`) calculated from (Al-Ubaidi et al., 2023) and inter-subjects stability (S`), as seen in Equation 2. By overlaying information from inter-atlas flexibility (F`) and inter-subject stability (S`) maps, the Master Atlas is improved.

$$VSI_{(v)} = S`(F`_{(v)}) \quad (2)$$

At the end of this phase, the Master atlas is enhanced to comprehensively represent the integrated information (voxels) from the two perspectives.

The Dual-layer Connectivity-Driven Parcellation

This phase introduces a dual-layer parcellation framework to segregate the ADHD cortex, utilising two distinct clustering approaches applied to the ADHD-200 dataset. The first layer employed the normalised cuts (N-Cut) spectral clustering algorithm to group vertices into large homogeneous and non-overlapped clusters at group-level parcellations for ADHD by performing the connectivity analysis at the voxel level on the localised networks from the enhanced Master Atlas. On the second layer, agglomerative nesting hierarchical clustering is adopted to obtain high-similarity clusters by cutting the hierarchical tree at the required level.

The first process involved representing voxels (*V)* obtained from the alignment of the rs-fMRI to enhanced Master Atlas template, reducing the data dimensionality and limiting the algorithm's search space. Those voxels were identified using a *4 mm x 4 mm x 4 mm* resolution. For each ADHD, the edges were estimated within each voxel using Pearson's correlation coefficient *(r)*, a commonly used approach for this task, as defined in Equation 3.

The *r* value would be between [-1,1], our focus on positive values. This calculation yielded a 15,832 × 15,832 correlation matrix of Fisher's r-to-z-transformed coefficients. A weighted correlation matrix was built for averaged subjects by applying a cut-off value of 0.5 to filter out weak and negative connections that may not be significant. The resulting connectivity matrix was then subjected to a

spectral clustering based on the normalised cuts (N-Cut) algorithm to group vertices into large homogeneous and non-overlapping clusters to obtain high similarity across different group-level parcellations for ADHD. Then, the RSN clusters were determined using an automated process that aligned them according to spatial correlation and the FC analysis. Therefore, on the second layer, parcels were merged, utilising an agglomerative hierarchical clustering algorithm while preserving their functional uniformity.

Algorithm 2: **Dual-Layer Clustering Algorithm for ADHD Cortex Parcellation**

Layer 1: N-Cut spectral clustering algorithm based on hybrid similarity measure

Input:

V= [*v*1, *v*2, ..., *vn*]: A set of brain voxels of pre-processed rs-fMRI data: n= *n* is the number of brain voxels in the experiment; V is imported from Master Atlas;

k= the number of clusters*;*

Output:

k clusters: *c*1*, c*2 . . . *ck;*

Initialisation:

Initialise the similarity matrix **S** as an $n \times n$ zero matrix;

Step (1): Construct the functional similarity matrix (BoSM)

Construct the brain voxels' BoldSignal similarity matrix *BoSM* by computing pairwise Pearson's correlation coefficients using Equation 3

$$r_{(v_i,v_j)} = \frac{\sum_{l=0}^{L}((v_{il}-\overline{V_i})(v_{jl}-\overline{V_j}))}{(L-1)\,\sigma_i\sigma_j} for\ 0 \le l \le L \quad (3)$$

Filter *BoSM* by removing values 0.5

Step (2): Construct the brain voxels' Spatial similarity matrix (SpSM)

Perform the Euclidian distance of spatial locations between each pair of voxels (Spatial Similarity based on voxels coordinated), as in Equation 4;

$$D(V_i, V_j) = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2} \quad (4)$$

SpSM= D

Filter *SpSM* by removing out values > 15 // to exclude nodes of far distance

Normalise values of *SpSM* //to be between 0 and 1 (for compatibility with BoSM)

(continued)

Algorithm 2: **Dual-Layer Clustering Algorithm for ADHD Cortex Parcellation**

Step (3): Construct the final similarity matrix FS

$$FS(V_1, V_2) = \delta * BoSM(V_1, V_2) + (1 - \delta) * SpSM(V_1, V_2) \quad (5)$$

// δ ranged between [0.1 – 0.9]; what is the best value? Best value of δ is 0.65 (specified in the experiment)

Step (4): Construct a weighted graph (G)

assigning weights to the final similarity matrix FS, given that *n* is the number of brain voxels;

W= FS

G=(V, W)

Step (5): Construct the normalised Laplacian matrix

$$L = D^{-1/2} W D^{-1/2}$$

:D is the diagonal matrix, where each element contains the sum of ith row weight matrix W;

Step (6): Find k largest eigenvectors of L, and construct the matrix X $\in R^{n*k}$ by assembling the eigenvectors in columns;

Step (7): Construct the matrix T from X by normalising rows of X;

Step (8): Process rows of T as data points, then cluster them into k clusters by the K-means algorithm;

Layer 2: Agglomerative Hierarchical Clustering

Input:

k clusters from Layer 1.

Output:

Refined clusters based on hierarchical clustering representing the final parcellations of the ADHD cortex;

Step (1): Apply an agglomerative hierarchical clustering method to the results of Layer 1 by treating each cluster from Layer 1 as an individual node;

Step (2): Cut the hierarchical tree at a specified level to achieve desired granularity in clustering;

Step (3): Merge clusters as needed while preserving functional uniformity based on data similarity;

Step (4): Continue merging until the desired level of hierarchy is achieved;

Model Validation

Without ground truth, effectiveness evaluation techniques are the optimal choice for evaluating the properties of the derived Brain Master Atlas and the generated map using dual-layer connectivity-

driven parcellation. Researchers advised using clustering validation metrics to quantify the resultant parcellation validity (Arslan et al., 2018; Moghimi et al., 2022). A key challenge in brain parcellation is how evaluating and comparing various parcellation algorithms are applied to different data from different perspectives. Therefore, homogeneity *(h)*- a popular parcellation evaluation technique- is used as a clustering validity measure to determine the clustering accuracy for the resultant parcellation maps. The effective parcellation should have higher homogeneity values representing the ideal characteristic of functional brain parcellation.

For parcellation *P,* the homogeneity is calculated using Equation 6 as follows:

$$h_{(p)} = \frac{1}{n_p(n_p-1)} \sum_{i,j \in P_p, i \neq j} s(v_i, v_j) : -1 \leq h_{(p)} \leq 1$$
$$: n_p = number\ of\ voxels\ in\ parcel\ P_p \quad (6)$$
$$and\ s(v_i, v_j) \text{ is measured using r between two voxels}$$

RESULTS AND DISCUSSIONS

This paper presents its contributions in the following manner: It adopts a dual-layer parcellation strategy, drawing inspiration from the Master Atlas networks from previous studies. Firstly, it improves the accuracy of the Master Atlas constructed using the method in Al-Ubaidi et al. (2023) by introducing a new data-driven metric, the Voxel Stability Measure (S`), and overlying it with the Voxel Flexibility Measure (F`) further to improve the consistency and reliability of the atlas. Secondly, adding a clustering process ensures the consistency of Functional Connectivity (FC) patterns across ADHD-200 subjects (i.e., the fidelity of the voxel to the underlying data).

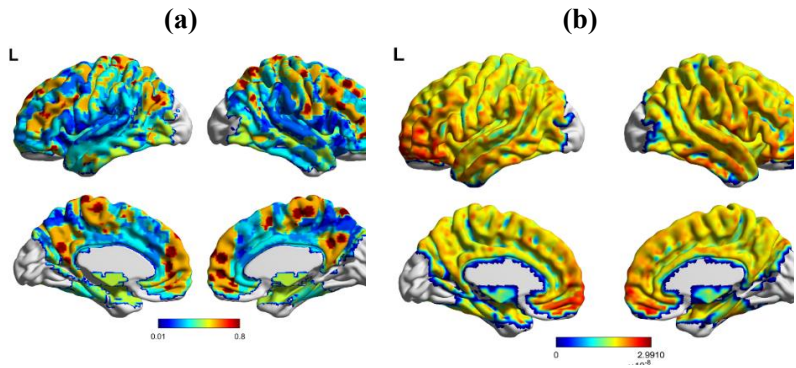
The ADHD rs-fMRI group was co-registered on the enhanced Master Atlas from the previous phase to enhance the algorithm's efficiency without affecting the final parcellation. Furthermore, it reduces the dimensionality and limited search space. Algorithm 1. identified the consistent patterns of brain activity across individuals, correlated them with cognitive processes, or identified lesions associated with ADHD. This study emphasises balancing voxel accuracy and stability in voxel selection. While inter-subject stability (S`) voxel selection frameworks can provide more interpretable subsets of features, they may sacrifice accuracy to some extent. This trade-off could impact

the method's effectiveness in accurately diagnosing ADHD, as a model that is too stable but not accurate enough may miss critical diagnostic information. This work addresses the need for a reliable metric to quantify stability across subjects. Without a standardised and reliable metric for stability measure, evaluating and comparing the effectiveness of different feature selection approaches in the context of ADHD diagnosis using rs-fMRI data could be challenging. This approach reduces the difficulty of seed selection and improves the search for an effective seed.

One of the main benefits of using (S') as a direct measurement of variability in brain activity is its simplicity and ease of use. Calculating the standard deviation of BOLD signals at the voxel level is relatively straightforward and intuitive. It does not require complex modelling, seed selection, or high computational costs, which makes it more accessible for researchers and clinicians with varying levels of expertise. The voxel similarity index comprehensively measures each voxel's reliability and importance; see Figure 2 for the generated F` and S` maps. The VSI produced an enhanced Master Atlas by identifying brain voxels with low flexibility and high stability values across multiple atlases and subjects.

Figure 2

(a) the Flexibility Map from previous work; (b) the Stability Map based on the inter-subject

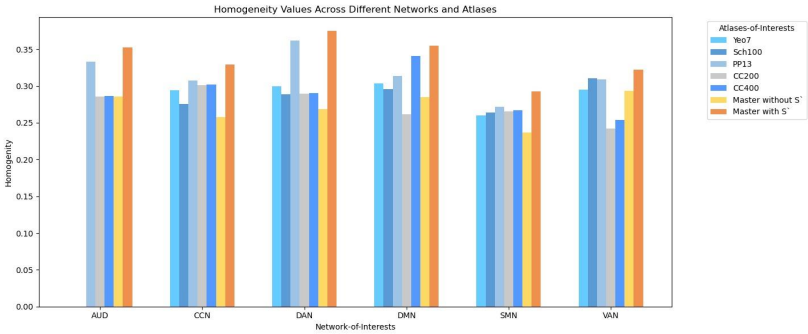


Constructing the Master Atlas by employing stability as a new feature, in conjunction with flexibility, improved the results as demonstrated in Figure 3 that the Master Alas with S` strategy outperforms other Atlases-of-Interests as well as the Master Atlas without S` in terms of Homogeneity.

The evaluation results for the enhanced version of the Master Atlas are presented first; see Figure 3. By assessing the effectiveness of the parcellation scheme (denoted as Master Atlas with S`) compared to five pre-defined functional brain atlases (CC200, CC400, Power, Schafere, and Yeo) and the original Master Atlas without S`.

Figure 3

Homogeneity values across the RSNs and atlases in addition to the Master Atlas based on the ADHD-200 rs-fMRI functional data representing the Functional Connectivity



The resultant Master Atlas could contain clinically significant clusters tailored to individual ADHD subjects by reducing the high dimensionality of rs-fMRI data, a major challenge in multi-voxel pattern analysis of rs-fMRI that affects the reliability and accuracy of ADHD diagnosis and limits the studies' replication. This can make feature selections and identify informative voxels for the classification of complex tasks.

The dual-layer clustering algorithm is grounded in a data-driven approach that avoids bias in selecting specific voxels or ROIs; the brain map is visualised in Figure 4. The positive correlation between FC power and ADHD symptoms informs this methodology. Table 1 listed the homogeneity *(h)* values as it is clear that the developed brain reference using the dual-layer parcellation outperforms all previous models. However, for the final connectivity-driven brain reference, an average of 0.63 offers the highest homogeneity among results, while the unbiased enhanced Master Atlas with stability was 0.35, which outperformed the original Master Atlas, which was 0.27. It is important to note that the *h* value represents the fidelity of the parcellation to the

employed data. The *h* map of the dual-layer parcellation is presented in Figure 5.

Figure 4

The Resultant Brain Map Based on the Proposed Dual-Layer Connectivity-Driven Parcellation Approach

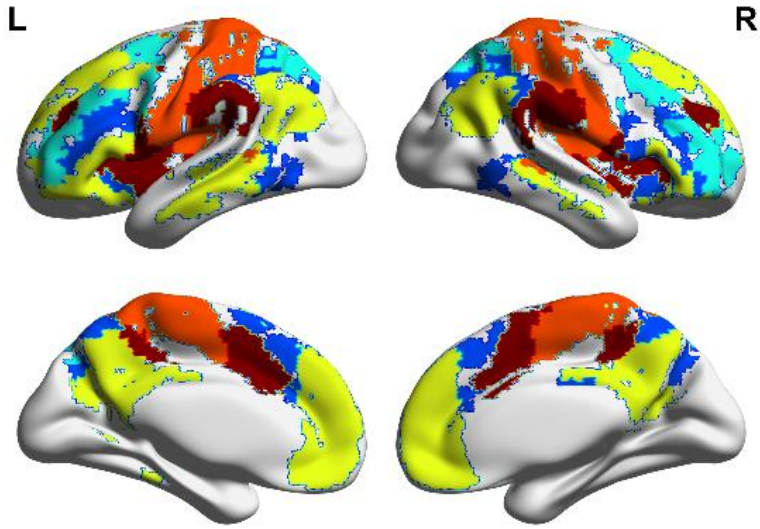


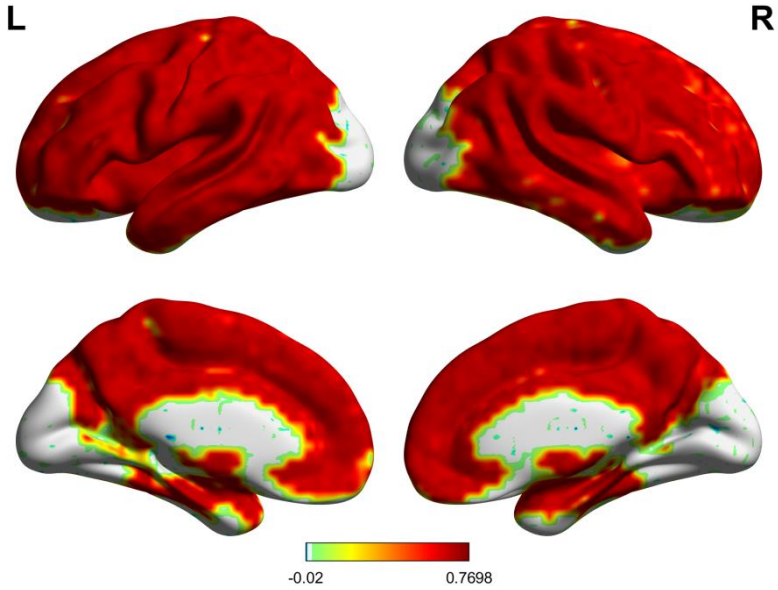
Table 1

The parcellation effectiveness represented by (h) values across the NoIs and the resultant brain references in comparison to the original Master atlas

NoIs	Original Master Atlas (without S`)	Enhanced Master Atlas (with S`)	The dual-layer Connectivity-Driven parcellation
AUN	0.286	0.369	0.67
CCN	0.257	0.347	0.619
DAN	0.269	0.398	0.70
DMN	0.285	0.378	0.596
SMN	0.237	0.311	0.623
VAN	0.293	0.349	0.601

Figure 5

The homogeneity map at the voxel level was constructed using the Connectivity-Driven Strategy, and h values are higher on average, reflecting the effect of granularity



CONCLUSION

These research endeavours are dedicated to identifying specific brain activation patterns and comprehending the broader structure of functional interactions within the brain's network. The proposed method utilises a data-driven model to identify reliable seeds, with a focus on diagnosing ADHD by analysing rs-fMRI data from the ADHD-200 dataset, offering a novel data-driven seed selection method based on a Master Atlas RSNs map for ADHD future studies. Using S` directly measures the variability in brain activity, which provides a key aspect of interest when studying ADHD. This approach reduces the difficulty associated with manual seed of interest selection and has the potential to enhance the accuracy and relevance of brain connectivity studies. The enhanced Master Atlas with S` is a subject-based brain reference integrating multiple source voxels employed here to limit the search space of the clustering algorithm. The parcellation created

in this study can be utilised to model the functional organisation of the ADHD brain, allowing for the extraction of distinct features for further network analysis in the context of ADHD or other brain disorders.

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