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Hexa-Net: ADHD-specific brain functional reference based on evaluation of the spatiotemporal variability to six resting-state networks

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Abstract: Early identification of Attention-Deficit/ Hyperactivity Disorder (ADHD) is imperative for individuals with this disorder to manage their challenges and improve their quality of life effectively. However, the neural mechanisms and brain network changes underlying ADHD are not yet fully understood. The Human Brain is functionally organised by brain patterns that have spatially distinct but functionally connected that were discovered at rest, known as Resting-state networks (RSNs). Resting-state functional magnetic resonance imaging (rs-fMRI), is an incredible tool that advanced us with detailed insight into those RSNs. Researchers use brain atlases to define RSN nodes for further analysis. Unfortunately, most atlases rely on data from healthy individuals, leading to inconsistencies and a lack of disease-specific atlases tailored for populations with specific medical conditions. Researchers have started developing disease-specific brain atlases or modifying existing ones to represent the disease-specific brain connectivity patterns better. To address the mentioned gaps, this study introduces "Hexa-Net" ADHD-specific brain reference after (1) generating a Master spatial atlas after conducting a systematic comparison of five priori brain atlases and six Network-of-Interests (NoIs) that are frequently referenced in ADHD literature: (Auditory- (AUN), Cognitive Control- (CCN), Dorsal Attention-(DAN), Default Mode-(DMN), Sensorimotor-(SMN), and Ventral Attention-(VAN)) Networks, resulted in overall spatial overlap ranges from (30-97%) across them. (2) demarcating NoIs after measuring the spatial distribution and temporal dynamics of NoIs quantified by the ADHD-200 dataset. Findings reflect a high correlation between the spatial composition of the six RSN associated with Functional Connectivity. Hexa-Net may serve as a valuable tool for future ADHD studies.

Keywords: attention-deficit/ hyperactivity disorder; brain parcellation; resting-state networks; brain disorder; brain networks analysis

1. Introduction

ADHD is an abbreviation of Attention-Deficit/Hyperactivity Disorder, a prominent neurodevelopmental disorder that impacts children and adults; around 60% of children with ADHD continue to experience symptoms into adulthood [1]. Diagnosing ADHD poses a challenge for clinicians due to its presentation heterogeneity, high risk of comorbidity, and inconsistencies in clinical assessments [2]. Routinely, subjective observations and behavioural assessments are used in ADHD diagnosis, which could lead to false diagnoses and lagged treatments [3]. Untreated ADHD could lead to restricted academic achievement, learning disabilities, social difficulties, impaired occupational performance, heightened risk of physical injury, and sleep disorders [4–6].

Neuroimaging investigations utilizing Magnetic Resonance Imaging (MRI) and functional MRI (fMRI) have examined the structural and functional alterations observed in individuals with ADHD. Many studies have used resting-state fMRI (rs-fMRI) as a valuable tool to navigate ADHD brains [7]. Moreover, neuroimaging studies have shown that functional regions in the human brain cannot perform a particular function independently, which makes this tool vital for identifying and examining neurological disorders and syndromes from a network perspective with remarkable precision [8–10].

Brain functional networks have gained popularity in comprehending the functions and diseases of the brain [11]. Previous results provided an improved understanding of resting-state brain activity. They led to the identification of Resting-State Networks (RSNs), which are cortical regions that are anatomically distinct but functionally homogenous [7,12]. Individuals with ADHD experience dysregulation of those RSNs as DAN, DMN, and AUN, not just specific ones, as evidenced by extensive research in this field [13,14].

By adopting a network theoretical perspective in node definition, the analysis of brain connectivity has shown promise in revealing the brain's organizational principles and their complex links to cognitive activities. Correct identification of network nodes is essential for constructing brain connectivity networks for rs-fMRI.

Resting-state networks (RSNs) have various spatial patterns in the brain, and pinpointing these patterns accurately can be challenging. Moreover, a lack of standardized terminologies may lead to functional inconsistencies that are reflected in their spatial variability [12]. To address these drawbacks, RSNs could be identified using brain atlases traditionally; starting with an atlas to perform a controlled clustering with the available data and anatomical definitions, which is a more adaptable method in rs-fMRI data analysis. Brain atlases are highly valuable instruments utilized in the process of partitioning the brain within the context of neuroimaging investigations [15]. Resting-state networks (RSNs) have various spatial patterns in the brain, and pinpointing these patterns accurately can be challenging. Moreover, a lack of standardized terminologies may lead to functional inconsistencies that are reflected in their spatial variability [12]. Traditionally, RSNs could be identified using brain atlases to address these drawbacks. By starting with a brain atlas, researchers can undertake spatially constrained clustering of rs-fMRI data. Brain atlases are highly valuable instruments utilized in partitioning the brain within the context of brain investigations [15]. In the absence of

disorder-specific ground truth for parcellating the cerebral cortex, it is hard to evaluate parcellation algorithms' reproducibility across studies [16]. Currently, there exist numerous structural and functional brain atlases that are being utilized [17]. However, a crucial challenge is that each atlas adopts a different orientation to divide the brain and this disparity in perspectives leads to the “atlases concordance problem”, as shown in Figure 1 [18,19]. This dearth of uniformity, combined with the difficulty in establishing definitive borders for brain regions due to anatomical and functional variations among individuals, hinders the reproducibility of consistent results when dividing the brain into subregions [12]. It is believed that this phenomenon occurs as each atlas relies heavily on pre-existing knowledge during its initial stages of development for cognitive categorization.

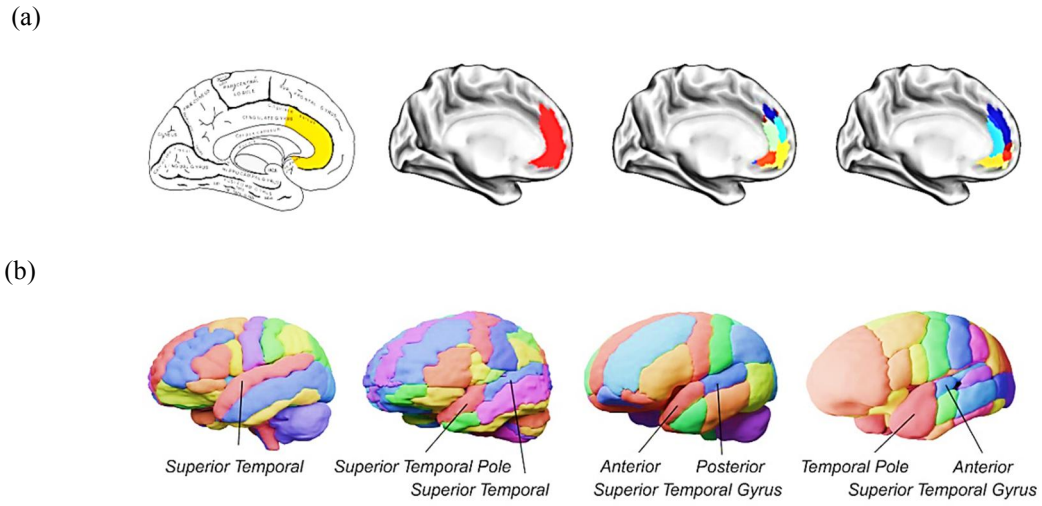


Figure 1. the visual presentation in (a) and (b) were adopted from [18,20] to clarify the “Atlases Concordance Problem”: (a) different presentation to the Anterior Cingulate Cortex (ACC), a brain region set in the frontal lobe, particularly the medial prefrontal cortex which have frequently shown hypoactivation in ADHD children during task [21] (from left-to-right) represented as a single ROI in anatomical brain atlases as in the first two templates, then when delineate and localized it based on functional parcellation, it typically consists of several subregions with varying size as depicted in 3rd and 4th templates; Hence, depending on the subregion and how it interacts with other brain regions, it may have a variety of functions. (b) The Superior Temporal gyrus is defined differently by four atlases that run from (left to right). Label inconsistencies can cause problems for research reproducibility and meta-analysis of brain regions involved in specific diseases; Anatomical parcellations defined fixed resolutions to brain regions while functional brain parcellations are more flexible since it defines brain ROIs based on their functional features.

To tackle the outlined challenges, a highly effective multiple-atlases brain integration framework is introduced here by systematically examining RSNs variations across selected atlases and integrating those Network-of-Interests as a modified form of the method that developed by [17]. In response to the investigation of ADHD studies from a brain networks perspective, we identified six RSNs commonly acknowledged in the literature as the

foundation of our reference, which is recognized here as the networks-of-Interests (NoIs); the contribution of this paper is:

- proposes a pipeline for a comparative analysis of five functional brain atlases frequently employed in ADHD studies, here referred to as the Atlases-of-Interests (AoIs). Subsequently, the six NoIs, are extracted and combined into a spatial master atlas after ensuring the voxel's spatial variation across the AoIs based on a developed algorithm.
- demarcates the NoIs configured in the master atlas by determining the functional connectivity (FC) dynamics in the ADHD-200 dataset using a data-driven approach, then generates the ADHD-specific brain reference called “Hexa-Net brain reference”.

Finally, in the absence of a clear standard to evaluate, the "Hexa-Net" is assessed based on optimal brain parcellation characteristics. The key characteristics we look for are internal evaluation measures.

A discussion about ADHD and how neuroimaging in conjunction with brain atlases could help to diagnose it was presented. The subsequent sections of the paper delve into the topic at hand. In particular, the Related Works section provides an overview of the existing research efforts focused on the identification of ADHD-related Resting State Networks (RSNs). The Data section covers how the data was processed. In the Modelling and Methods section, a comprehensive analysis of the recommended approaches is presented. At the end, the Results and Discussion sections present our findings and discuss the suggested methodologies and limitations. It's worth mentioning that, BrainNet Viewer version 1.7 was used to display and visualize the Hexa-Net and other atlas networks [22].

2. Related works: the state of the art of RSNS connectivity in identifying ADHD

The complicated networks of functional regions in the brain contribute to our identity and cognitive functions. Recent research supports the idea that disruptions in brain communication influence ADHD; for instance, through RSNs or functional connectivity networks [23,24]. However, according to [12], a consensus has yet to be reached over the precise definition of a "large-scale neurocognitive network" that is universally acknowledged in the academic community. This gap in theory has introduced challenges in Network Neuroscience, such as ambiguity in defining terminologies, conflicting insights due to the merging of heterogeneous data, inconsistency in conventions, and methodologies across studies, resulting in a disjointed comprehension.

The terminology for specific brain networks can often vary, it could be functionally-driven based on functional overlap or anatomically-driven based on the network's anatomical description. For example, the “Fronto-Parietal Control Network (FPCN)” is also called the "Cognitive Control Network (CCN)” or referred to as the “Executive Control Network (ECN)” reflected its interrelated cognition process [25,26], also it referred to “working memory network”. On the other hand, the “Ventral Attention Network (VAN)” in [23] also labelled as “Salience Network (SN)” if a study focuses on attention shifts in response to salient stimuli, while the term “Cingulo-Opercular Network” reflects the anatomical regions that emphasize the network connectivity [17,27].

To be concluded, various network definitions in the literature can lead to confusion and ambiguity when comparing results. Three hypotheses are offered here, two of them are based on prior research modelled from the RSNs' perspective while the third is proposed based on state-of-arts findings to advance the study of ADHD Brain Connectivity:

(1) **DMN hypothesis:** probes deep into DMN regions' alterations [28], it is an ADHD-specific network, meaning that it cannot be generalized to other neurological disorders or syndromes [26,29]; According to this hypothesis, DMN is considered as the major Network-of-Interest in ADHD studies [30].

(2) **Tri-Network hypothesis:** originated from Menon's Tri-Network Model who argued that "different forms of psychopathology or symptom profiles are caused by disturbances in the interactions between different Large-scale brain networks"; those brain networks are : DMN, Central Executive Network and Silence Network [31]. What cause a variety of forms of neuropsychiatric or symptom patterns and profiles [32].

(3) **This research hypothesis:** which is originated based on our exploration of the RSNs connectivity in recent studies; A meta-analysis study by Sutcubasi, *et al.* [26] have focused on interconnectivity within four well-known large-scale networks labelled: Default Mode Network (DMN), Cognitive Control Network (CCN), Ventral Attention Network (VAN), and Affective/Motivational Network (AMN). Recently, Sidlauskaite, *et al.* [33] had discovered hyperconnectivity between DAN-VAN and within DMN and VAN. On the other hand Zhang, *et al.* [34] assumed the idea that ADHD is related to the Auditory Network (AUN), Dorsal Attention Network (DAN), Ventral Attention Network (VAN), and Sensorimotor Network (SMN) [35]. Studies have found that individuals with ADHD tend to have reduced FC within DMN-DAN, along with increased FC between DMN-DAN. It's worth mentioning that, ECN and Attention network are active during task so they show an anticorrelated pattern at rest state [36]. Lin, *et al.* [13] investigated (DAN), (DMN), and (VAN) in ADHD children and they reported that there is hyperconnectivity in (DMN-DAN), (DMN-SMN), (DMN-AUN); No alterations among VAN regions. Compared to controls, those with ADHD were shown to have decreased functional connectivity between their Visual and VAN networks, as published by [37]. However, Icer, *et al.* [10] advised that it is desired studies focus on measuring rs-FC at all RSNs (specifically RSNs that engaged with ADHD pathophysiology) in children with ADHD and TDC (Typical Development Controls or Healthy subjects). Sutcubasi, *et al.* [26] noted that there are no impacts related to ADHD were detected. It is essential to acknowledge that the lack of studies deals with alterations in AUN and SMN, and the limited number of voxels detected at these regions on previous studies, could have various reasons beyond sample size differences. Prior studies revealed that ADHD individuals were more sensitive to noise, which could potentially be linked to an increased FC in the auditory network [34]. Lanzetta-Valdo, *et al.* [38] stated that kids with ADHD exhibit poor Auditory Processing, so that this network would be included to the suggested model.

In light of the aforementioned hypotheses and with the target of reducing confusion and promoting unified research directions, this study sought to introduced Hexa-Net as a brain reference that tailored on ADHD group to be utilized effectively in ADHD research. Moreover, impairments in these RSNs may hold the key in understanding the underlying causes of ADHD and its biomarkers. By identifying these RSNs and giving them a unified name, which are: Auditory Network (AUN), Cognitive Control Network (CCN), Dorsal Attention Network (DAN), Default Mode Network (DMN), Sensorimotor Network (SMN), and Ventral Attention Network (VAN).

3. Data: ADHD-200 dataset

The research data was obtained from Neuro Bureau ADHD-200 dataset, a detailed information related to ADHD-200 dataset can be downloaded from *(https://fcon_1000.projects.nitrc.org/indi/adhd200/*) and [39] supplied more information about ADHD-200. The ADHD-200, a large-scaled fMRI neuroimaging dataset [40], which is the primary source of data used in the ongoing rs-fMRI studies on ADHD [41]. The reason beyond adopting resting state data is that rs-fMRI does not typically include complicated activities other than asking people to open or close their eyes. So, using rs-fMRI is preferable to the task mode since it is challenging for ADHD kids to successfully follow complex instructions on experiment tasks [14]. This work was carried out utilizing the ADHD group only. To guarantee the accuracy of the gathered data, fmriprep pipeline implemented for preprocessing on the ADHD-200; more details of this pipeline could be found in (*http://www.fmriprep.readthedocs.io/en/latest/workflows.html).* To remove high-frequency noise, we filtered the signal using a band-pass filter with a frequency range of 0.01-0.08. Next, the time signals were extracted based on the master brain network-based atlas spatial map that formed later.

4. Modelling and method

As mentioned, this study aims to create a syndrome-specific brain reference based on the consensus of five predefined functional brain parcellations and functional connectivity (FC) analyses of ADHD. The study adheres to significant standards outlined in the literature on brain parcellation to achieve research objectives. Adopting predefined brain templates to segregate the cortex into controlled clusters presents a valuable approach for addressing spatial and temporal dimensionality by means of dimensionality reduction and standardizing taxonomies. The following sections will explain the modelling and methods stages.

4.1. Modeling a brain reference

4.1.1 Picking the atlases-of-interest for this study

For the purpose of creating a comprehensive map of brain impairments associated with ADHD, an in-depth evaluation of the current status of functional brain parcellation will be conducted. An atlas should achieve more than one of the following conditions to be included

in this study: pre-computed, functional, and widely used in ADHD studies. This work focus on five pre-defined resting-state functional atlases, in alphabetic order, CC200 and CC400 from [42] which is widely applied on studies that utilized ADHD-200 dataset [43], Power-264 (was divided into 13 or 10 functional networks using rs-fMRI) from [44], Schaefer 100 from [15] and Yeo 7 from [23] have been chosen by this study (see Figure 2. for original spatial definition of the 5 atlases-of-interests); To find out more about the brain atlases that were examined in this study, please refer to Table 1 for additional information.

Table 1. An overview of the considered brain functional atlases (also can referred to Atlases-of-Interests (AoIs)).

Ref.	Atlas	Alias	#Parcels	Data	Citation rate	Analytical approach
[23]	**Yeo**	**Yeo7**	7-17	*≥1000*	> 6 K	Spectral clustering algorithms;
[44]	**Power**	**PP13**	13	*=264*	> 3.7K	Global similarity approach based on a graph community detection algorithm;
[42]	**CC200**	**CC200**	190-200	*= 41*	> 1.5K	spatially constrained spectral clustering;
[42]	**CC400**	**CC400**	351-400	*= 41*	> 1.5K	Same approach in CC200 spanning to 400 regions;
[15]	**Schaefer**	**Sch100**	100	*= 1489*	> 1.4K	integrated gradient-weighted Markov Random Field (gwMRF) model

Alias= atlases referred name on this study**; citation rate=** cited times by April 25, 2023, according to information available on Google Scholars; **Analytical approach=** The theoretical methodology utilized in constructing them. ***Note:*** the justification beyond selecting CC200 and CC400 are region-based generated using the rs-fMRI [43]; this study grouped them into RSNs depending on AAL brain atlas based on [45].

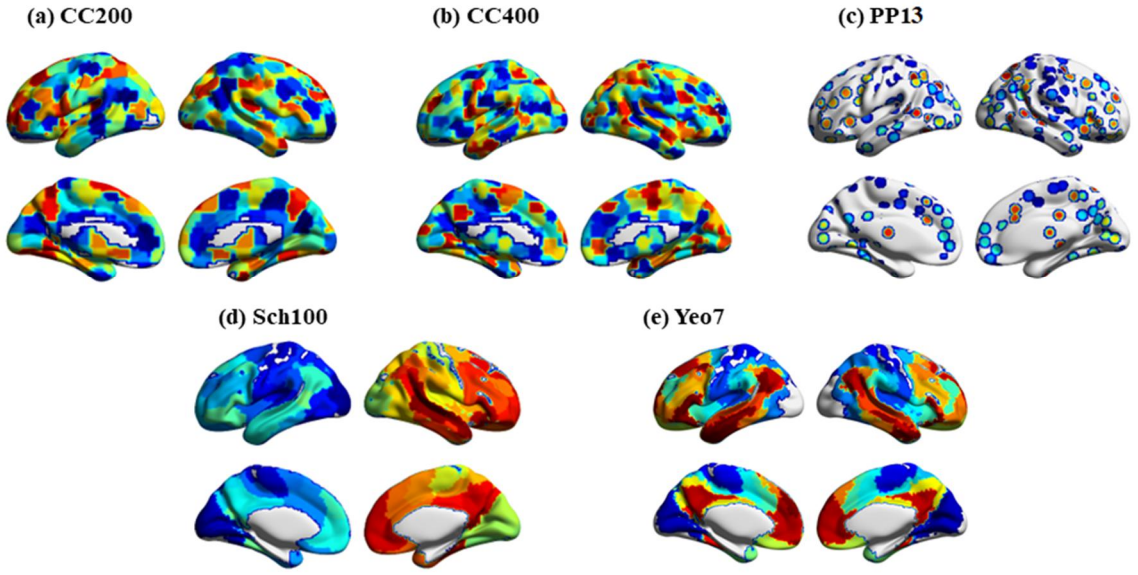


Figure 2. The entire brain spatial definition maps of the original five brain atlases-of-Interest (AoIs); different color represents different network or regions. Description provided in Table 1.

4.1.2 AoIs registration and resampling

To ensure consistency across the five atlases, they were resampled to a uniformed template by registering them to Montreal Neurological Institute 152 Nonlinear 2009 volumetric brain reference (abbreviated MNI152NLin)- Asymmetric version, on (1.0 x 1.0 x 1.0 mm) resolution; utilizing the same registration template that used for the individual subjects on dataset is strongly recommended.

4.1.3 Establishing the "Hexa-Net" based on Six predominant Network-of-Interests (NoIs)

Drawing from the findings stated previously, this research introduces the term "Hexa-Net" to represent this collective reference to the six primary RSNs under investigation; with the prefix "Hexa-" signifying the six identified RSNs (AUN, CCN, DAN, DMN, SMN, and VAN).

4.2. Constructing Hexa-Net brain reference

4.2.1 Overall spatial overlap across multiple brain Atlases

As a way to assess the reproducibility of picked parcellations produced by different research teams and labs, this study utilized a well-known technique that is the Adjusted Rand Index (ARI) [46]; This method is utilized to evaluate the level of similarity between two atlases in an objective manner by treating them as complete entities. It provides a straightforward measure of parcellation agreement between atlases-of-interests (AoIs) with varying numbers of parcels [20]. Moreover, the ARI was chosen here to overcome the limitation of the original Rand Index (RI) by considering the possibility of random pairings; refer to equation (1) for ARI between parcellation pairs. Please check Figure. 4 for the presented results.

$$ARI\ (A,B) = \frac{2(aa\ bb - \ ab\ ba)}{(aa + ab)(ab + bb) + (aa + ba)(ba + bb)} : -1 \ \leq \text{ARI} \leq 1 \qquad (1)$$

For parcellations A and B, aa: represents the number of parcels that are belong to distinct clusters in both; bb: represents the number of parcels that are assigned to same cluster in both; ab: the number of pairs allocated to the same parcel in A but different in B; ba: the number of pairs given to the same parcel in B but different parcels in A; an ARI score of 1 signifies a complete agreement between AoIs.

Subsequently, this study proposed a scoring and normalized weighting scheme as stated in equations (2) and (3). Equation (2) calculates the average similarity of the atlas (A_i) against other AoIs; This posited as an effective strategy for and a comprehensive perspective of the level of agreement between an atlas and the others in the picked collection. The atlas weights that have been calculated in equation (3) will be utilized to determine the significance of each atlas. The higher weight reflects the greater influence and more representative of that particular atlas on the overall analysis.

$$Score(A_i)_{ARI} = \frac{1}{N-1} \sum_{j=1, j \neq i}^{N} ARI(A_i, A_j) \qquad (2)$$

(*N-1)* refers to the exclusion of any similarity between an item and itself.

$$Atlas(A_i)_w = Score(A_i)_{ARI} / \sum_{k=1}^{N} Score(A_k)_{ARI} \ , i = 1 \ to \ N \quad (3)$$

It's worth mentioning that, the sum of these weights will always result in 1, indicating a reliable probability distribution. The weight of each atlas will guide how much significance and contribution each atlas has to the master atlas.

4.2.2 Network-of-interests determination and extraction

As previously mentioned, several brain atlases have the same brain regions but may use different terms to describe them. Additionally, some atlases provide maps for both the left and right hemispheres of the same RSN, while others do not [12,18]. These issues have been resolved here by consolidating RSN labels, convert ROIs-based (e.g., CC200 and CC400) into their respective RSNs by grouping regions, and integrating those that were previously separated based on brain hemisphere. This study focused on the analysis of six RSNs: AUN, CCN, DAN, DMN, SMN, and VAN, which have been commonly acknowledged in ADHD studies. The initial step to examine the spatial configuration to RSNs across AoIs, involve generating a labelling dictionary for a unified set of RSNs.

This was done to ensure consistency across all RSNs and guarantee accurate results. Then obtaining binary map to the NoIs spatial distribution from the selected AoIs. For each RSN binary map the *Dice's similarity coefficient* (D) is calculated [47], if NoI_i and NoI_j present two RSNs in atlas i and j then D between NoI_i and NoI_j is given by equation (4); as a popular measure to quantify the spatial overlap between two labelled networks (i.e., parcels at same resolution).

$$D_{(NoI_i, NoI_j)} = 2\,|NoI_i \cap NoI_j| / |NoI_i| + |NoI_j| \ \ 0 \leq D \leq 1 \quad (4)$$

Figure 5(a) and (b) depicted a result snippet, strong similarity implied by $D = 1$ which reflect higher overlap and consistency in the spatial representation of RSNs and vice versa. Then a standardized RSNs spatial map is formed containing elements exhibiting the highest degree of overlap. Figure 6 visualize the spatial overlap maps of the six NoIs across the five atlases.

4.2.3 Voxel spatial allocation guided by selected brain Atlases

This step aims to determine the fidelity of a given voxel by examining how it is categorized across multiple atlases. Voxel-wise variability is a widely recognized phenomenon that describes the differences in specific features of RSNs in various atlases.

The flexibility coefficient (F) [48] is often used to measure a voxel's flexibility across various atlases in a quantitative manner (check equation (5)); high F suggests that the voxel frequently changes its membership across different atlases, while a low F indicates that the voxel remains consistent. To improve the accuracy of the results, the weighted integration algorithm ($\acute{F}$) (as seen in equation (6)) is suggested here. This algorithm considers the

predetermined weight (as calculated in equation (3)) of each atlas, which helps assess the reliability and significance of each atlas. This means that more trustworthy atlases will significantly influence the flexibility coefficient, thus making the findings more reliable and robust.

$$F_{v\,(i)} = \frac{Actual\ \_Changes}{Total\ Possible\_Changes} \tag{5}$$

$$\acute{F}_{v\,(i)} = \sum (Atlas(A_i)_w \text{ } change) / \sum Atlas(Ai)_w \tag{6}$$

To this point, a master atlas is formed from the spatial maps representing the six RSNs with unified coordinate system that includes a complete collection from all atlases considered in this study. The Master atlas visualized in Figure 8(b). Each voxel in the master atlas is assigned to a RSN based on its weighted flexibility coefficient.

4.3. Generating the Hexa-Net reference based on multi-source RSNs integration

Research on Functional Connectivity (FC) networks could help explain the neurological basis of the primary symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD). Therefore, the present study claimed that (FC) would exhibit variability based on the distinct physiological composition of the (RSNs) across the vertex is grouped with high similarity. The preprocessed ADHD-200 rs-fMRI data was registered with a Master atlas to ensure consistency in a spatial context. For hierarchical clustering, a similarity matrix is computed. Then it is converted into a distance matrix. After that, we applied the ward's hierarchical clustering algorithm using the distance matrix. The result of this process, a FC map was created as an ADHD group representative. In general, the Hexa-Net brain reference is generated by contouring the master atlas based on the temporal parcellation (ADHD FC map) that reflects the functional organization of the NoIs in ADHD, as stated in equation (7). Figure 3 illustrates the different modeling stages used to develop the Hexa-Net brain reference.

$$Hexa\text{-}Net = Master\ Atlas\ map \cap FC\ map \tag{7}$$

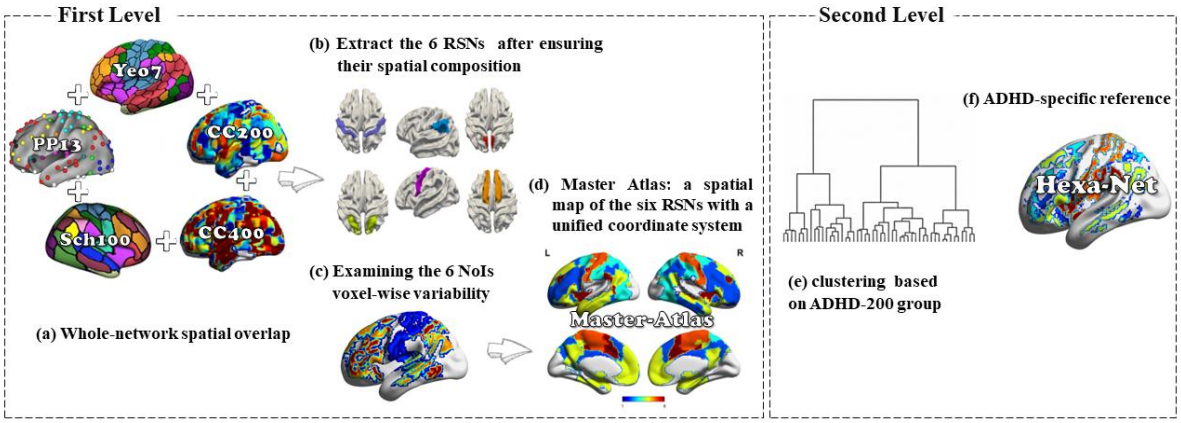


Figure 3. Graphical illustration of the two level parcellation framework for producing Hexa-Net brain parcellation. First Level or spatial level: initial step: identifying five pre-existing brain atlases and Six RSNs based on literature; (a) assessing the spatial similarity of the entire network across the five atlases, (b) evaluating the spatial overlap of the six RSNs at the network-level, (c) Voxel-wise variability examination (d) Master atlas, a unified coordinate map of the 6 NoIs. Second Level or temporal level: (e) is a data-driven map based on registering ADHD-200 group representative into the Master atlas; and (f) The process of obtaining Hexa-Net an ADHD-specific parcellations at the intersection agreements between the spatial and temporal maps.

It's worth noting that, the master atlas contains around 1,003,482 non-zero voxels, while the Hexa-Net has around 242,360 non-zero voxels. Consequently, this approach can be considered an aspect of dimensionality reduction. Hexa-Net is presented in Figure 8(c).

5. Results

5.1. Hexa-Net construction

ARI discovered that the CC200-CC400 and Sch100-Yeo7 pairs had the highest level of spatial overlap. The degree of similarity among the five AoIs ranged from 0.17 to 0.9. The similarities observed among the five atlases cannot be solely attributed to the analytical methodology used in creating each atlas. Please refer to Figure 4 for further details.

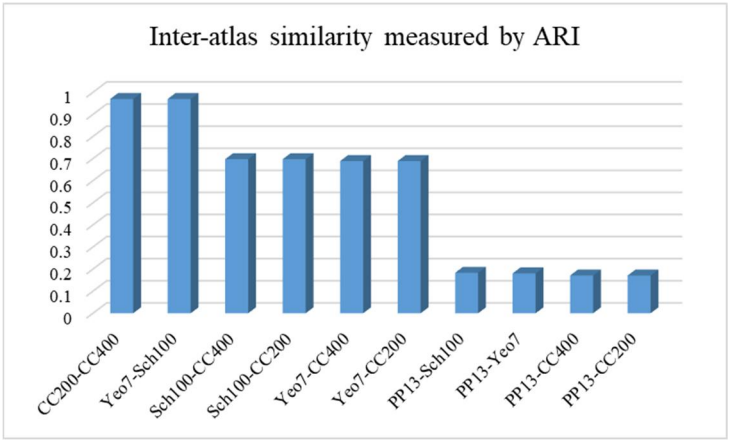
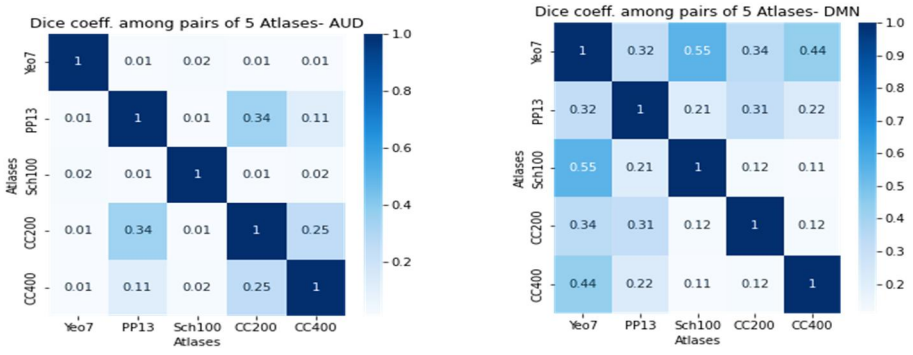


Figure 4. Overall similarity of the original atlases pairs in sorting order; greater values indicate a closer match and vice versa.

Considering the selected brain atlases' consistency by evaluating their network variability, the picked atlases share a significant amount of RSNs with each other based on calculated weights. Among them, the DMN has the highest spatial overlap, with D ranging from 11% to 55%. The highest value is defined between DMN in Yeo7 and Sch100, while the lowest value is defined by CC400 and Sch100 (see Figure 5(a)). The Auditory Network (AUN) had the lowest D value ranging from 11% to 34% across AoIs as visualized in Figure 5(b). This is because AUN is absent in Yeo7 and Sch100, resulting in values near zero. The CCN also shows spatial overlap, with D ranging from 13% to 41%. The RSNs defined by Yeo7 and Sch100 are highly similar, but those defined by PP13 are the lowest ones. Regarding DAN, D ranges from 27% to 44%, with the highest value between CC200 and CC400. SMN D value ranges from 26% to 39%, and in VAN D value ranges from 31% to 49%.



(a) (b)

Figure 5. The Dice coefficients Similarity map across the five atlases (a) AUN (b) DMN as an example.

Figure 6 represents the spatial overlap maps of NoIs over the selected atlases.

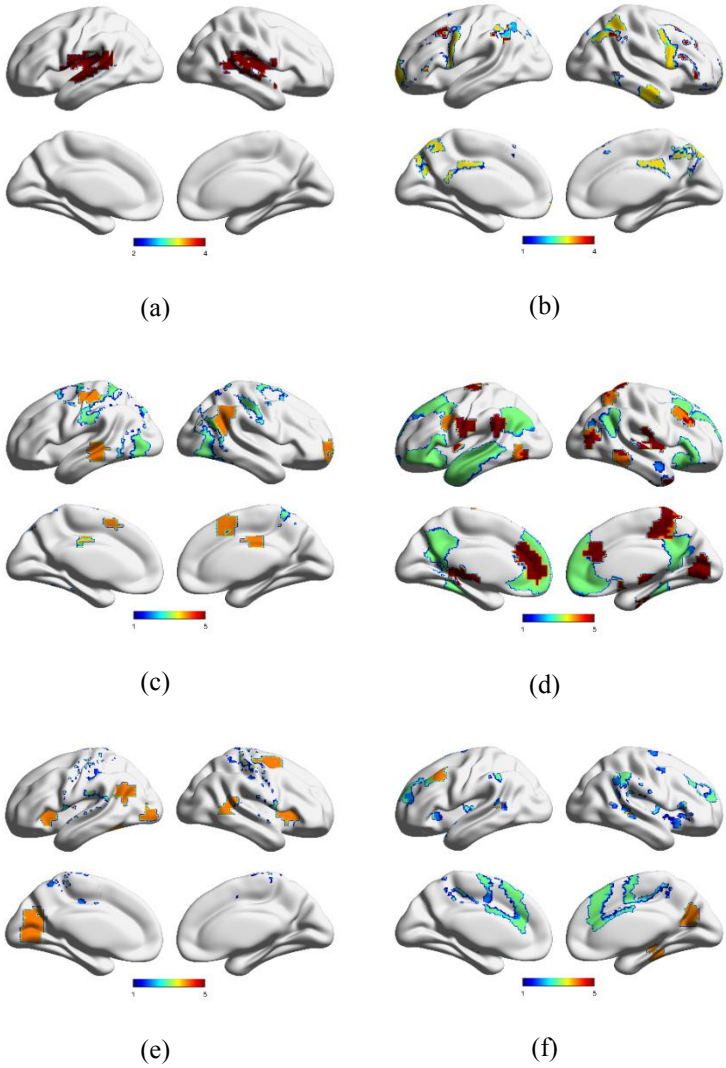


Figure 6. The spatial overlap maps of the six NoIs across the five atlases, (a) referred to spatial overlap of the AUN and it occurred clearly only in three atlases (CC200, CC400, and PP13) (b) is the CCN and it occurred across the five atlases while in (c) (d) (e) and (f) are the DAN, DMN, SMN and VAN sequentially, and all of them are occurred at the five elected atlases.

5.2. Hexa-Net evaluation

Different measures are used to compare parcellations, among them we applied the Dice index to compare Hexa-Net and AAL; AAL is reliable atlas commonly referenced in ADHD studies so that it utilized as a ground truth here. Then to measure the homogeneity of the six networks based on ADHD-200 group. These metrics allowed us to evaluate the spatial overlap and FC similarity, respectively. To calculate the homogeneity of networks (X) in Hexa-Net by utilizing Pearson's correlation (r) using the following formula:

$$P_{(X,Y)} = \frac{Cov(X, Y)}{\sigma_X \cdot \sigma_Y} \tag{8}$$

The Spearman's correlation coefficient (r_s) is used to demonstrate the relation between spatial overlap and homogeneity. To test the association between the spatial overlap measured measured by D of the six RSNs in Hexa-Net brain reference and AAL and the homogeneity of Hexa-Net. Results found that the (r_s)=0.74 and p=3.4 x 10^{-5} that indicate strong spatial overlap between the six RSN in both atlases is associated with the homogeneity.

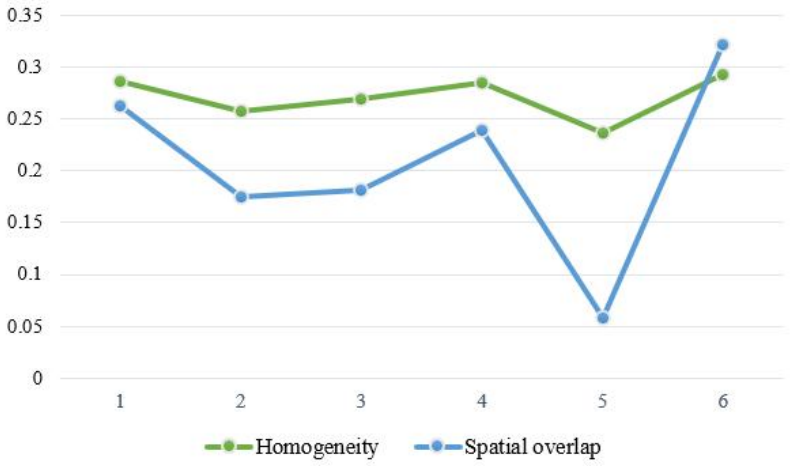


Figure 7. Result of functional homogeneity and Dice similarity of the six RSN; 1= Auditory Network (AUN), 2= Cognitive Control Network (CCN), 3= Dorsal Attention Network (DAN), 4= Default Mode Network (DMN), 5= Sensorimotor Network (SMN), and 6= Ventral Attention Network (VAN) based on ADHD-200 dataset.

6. Discussion

The essence of Hexa-Net brain reference is it combines the structural integrity of the Master Atlas with the FC map that captures functional variability in ADHD subjects. This study contributes to the literature by constructing an ADHD-specific spatiotemporal brain reference that reflects the ADHD brain's network topology. The most analogous work to our approach is another multi-atlas RSNs by [17], which solely adopted the spatial assessment technique to evaluate the spatial variability of five major RSNs across brain functional atlases and provide a new consensual atlas. Firstly, the foundation principles of the chosen atlases were heterogeneous and incompatible; the delineated AoIs are based on different aspect (e.g., some of them network-based and others are region-based that required further process and consolidations), different numbers of RSNs and not all encompassed the RSNs under our consideration, diversity in definition schemes and abstraction levels posed significant challenges to accurately measuring agreement among the AoIs. Secondly, our work utilized a broader disordered population (i.e., ADHD-200) as temporal data for FC analysis in the second phase. In contrast, [17] used a healthy one regarding homogeneity evaluation to their atlas. Thirdly, the researchers accounted the voxel flexibility by using a weighted criterion. This approach empowers us to confidently choose atlases of higher relevance and reliability. Lastly, our approach introduces an unbiased mechanism to evaluate voxel variability across

diverse atlases. This enables a systematic comparison of different (AoI) and allows for the accurate quantification of voxel agreement across the atlases.

The highest spatial overlap between the CC200-CC400 and Sch100-Yeo7 pairs indicates an apparent convergence in brain regions delineation within these atlases. Notably, the similarity values among the five AoIs exhibit a significant range from 0.17 to 0.9 points with varying levels of agreement between these atlases. It is imperative to note that these observed similarities cannot be solely attributed to methodological nuances, there by suggesting the existence of commonalities in the neuroanatomical features they capture. In order to enhance the reliability of the Master atlas, a methodological approach is by introducing atlases' scoring and weighting metrics to assess the contribution of individual atlases. This step aims to prioritize more dependable atlases, increasing their influence within the comprehensive analysis.

Investigating network variability in selected brain atlases provides insights into the consistency of their RSNs representations. High spatial overlap within DMN, SMN and DAN showed the highest D similarity because these networks are mainly made up of sensory and motor regions with consistent anatomical morphology across individuals [12,17], which also affects their FC. Maximum spatial overlap between DMN in Yeo7 and Sch100 atlases underscores strong convergence in defining this network. The absence of the Auditory Network (AUN) in Yeo7 and Sch100 emphasizes the importance of network presence in contributing to the spatial overlap metric. So, the AUD spatial distribution totally depends on CC200, CC400 and PP13.

It is essential to control voxel flexibility in brain parcellation to achieve reduced variability and enhance homogeneity [49]. This leads to more reliable, interpretable, and clinically relevant parcellations for neuroscience investigations and practical implementations. Considering precalculated Atlases' ARI-based weight in measuring voxel flexibility would likely indicate the reliability or importance of that atlas in the overall analysis. The atlas weight is employed in the flexibility assessment step, which assesses the variability of each voxel across atlases to ensure consistently labelled regions receive priority. The outcome of this process is a unified representation, referred to as a Master atlas, which offers a balanced and comprehensive spatial view of the elected NoIs. The final brain parcellation process will benefit from controlling voxel flexibility to achieve increased homogeneity, a vital feature of optimal parcellation.

Last but not least, this research paper introduces an ADHD brain reference called "Hexa-Net", the prefix "Hexa-" signifies the number six, reflecting the incorporation of the six NoIs. Hexa-Net generated by an intersecting the master atlas with the connectivity-driven map that produced by the hierarchical clustering via grouping voxels based on their functional connectivity patterns. To ensure consistency and obtain standard region labels across all computed parcellations, each parcel was renamed into uniform labels to avoid potential issues with evaluation measures. Numerous scholarly works have established a set of RSNs that associated to ADHD, precisely the AUN, CCN, DAN, DMN, SMN, and VAN networks [30,33,34,38], which have been commonly detected in studies on ADHD and have been related to alterations in the ADHD brain. The present study relies on the investigation done

in the related work section to establish a uniform terminology used here to describe the RSNs, which has been achieved based on empirical evidence; This evidence indicates that certain atlases utilize distinct terminology to describe (RSNs) that consist of the same anatomical regions [12]. Further elaboration on this matter can be found in the related work section.

If someone utilizes this process, it is recommended to work within specific parameters as ensuring all atlases are spatially aligned to the same space, and including a smoothing step in the algorithm is advisable. Still, it is not restricted because the selected smoothing parameters can impact the final algorithm map.

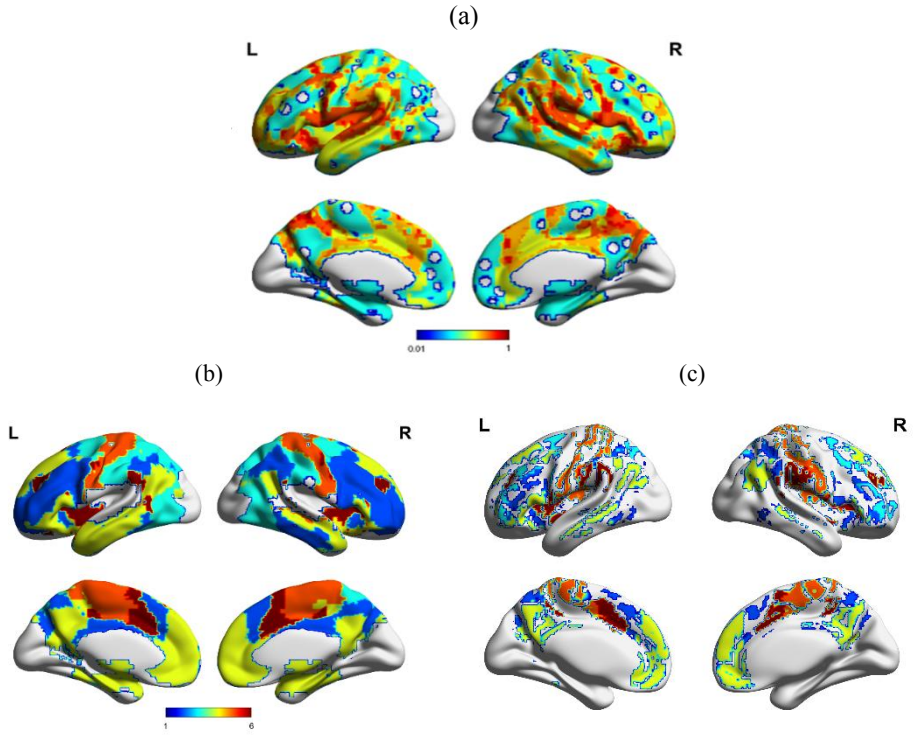


Figure 8. Hexa-Net an ADHD fresh Brain reference. (a) the spatial distribution map of the voxel quantified by $(\acute{F})$; (b) presents the spatial distribution of the six NoIs as formed in the Master Atlas; (c) The Master atlas and FC map of a group representative of ADHD-200 were combined to create Hexa-Net, a network-based reference.

7. Conclusion

With the fact that parcellation templates may substantially reduce the data dimensionality and enhance the reproducibility of findings across the human connectome studies, revealing new insights into how the brain's regions interact and how these connections give rise to higher-order cognitive functions with a minimum computational cost. This research contributes to the field by introducing the Hexa-Net, a novel spatiotemporal ADHD-specific brain reference that integrates the spatial composition of six RSNs formed master atlas with the obtained FC map into one brain reference to get more understanding of ADHD-related brain connectivity patterns. To create the Master atlas, a comparison of the spatial overlap and similarity of six NoIs followed by a developed ARI-based weighting schema to control the voxel flexibility. This Master atlas intersected with the constructed FC map that employed

ADHD-200 led to "Hexa-Net". This approach adds depth and reliability to further analysis, making it a valuable resource for future investigations in ADHD research and beyond. Hexa-Net accomplishes the study goals and opens up fresh opportunities for comparing different atlases to identify ADHD or other brain disorders. Along this, it might also be generalized to assess the reliability of an atlas employed in a particular psychological experiment. Fulfilling evaluation criteria in practical scenarios can be difficult, as trade-offs often exist between different factors.

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