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Research article

Task-based modulation of functional connectivity of dorsal attention network in adult-ADHD

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ABSTRACT

Recent studies have prompted a shift in the understanding of attention deficit hyperactivity disorder (ADHD) from models positing dysfunction of individual brain areas to those that assume alterations in large-scale brain networks. Despite this shift, the underlying neural mechanism of ADHD in the adult population remains uncertain. With functional magnetic resonance imaging (fMRI), this study examined brain connectivity of dorsal and ventral attention networks. Adults with and without ADHD completed a Go/No-Go task inside the scanner and the functional connectivity of attention networks was analysed. The generalized psychophysiological interaction analysis indicated differences involving the dorsal attention network. For the ADHD group, an interaction effect revealed altered dorsal attention-default mode network connectivity modulation, particularly between the right frontal eye field and posterior cingulate gyrus. We conclude that dorsal attention network dysfunction may be involved in sustained attention deficits in adult-ADHD. This study sheds light into network-level alterations contributing to the understanding of adult-ADHD, which may be a potential avenue for future research and clinical interventions.

Significance statement

In this study, using functional magnetic resonance connectivity analysis, we found altered connectivity patterns especially involving the dorsal attention network in adults diagnosed with ADHD as compared to healthy individuals.

1. Introduction

Attention deficit hyperactivity disorder (ADHD), characterized by traits like hyperactivity, impulsiveness, and/or inattentiveness, commonly manifests in young children. The estimated global prevalence in school-aged children is twice higher than its prevalence in adulthood [1], suggesting the perception of ADHD as primarily a childhood disorder. However, research has revealed that approximately 65 % of children with ADHD carry these defining traits into adulthood [2]. This transition into adulthood challenges the notion of ADHD as exclusively a pediatric disorder. Surprisingly, adult-ADHD is frequently overlooked

although the disorder lasts into adulthood in over half of cases and its clinical presentation frequently coincides with other psychiatric disorders [3]. Studies indicate that nearly 80 % of adults diagnosed with ADHD also present at least one concurrent mental disorder, including but not limited to personality disorders, substance use disorders, and mood or anxiety disorders [4,5].

Rapid advances in brain magnetic resonance imaging (MRI) techniques, especially in the emerging field of psychoradiology, allow for noninvasive measurement of structural and functional brain features, enhancing our understanding of psychiatric disorders and supporting clinical practice. A recent review highlights that patients with various psychiatric disorders, including ADHD, exhibit both shared and unique changes in brain functional dynamics, which can help elucidate neurophysiological mechanisms and assist in differentiating major psychiatric disorders [6].

Despite these advances, the comprehension of the neural substrates of ADHD remains partial. Initially, research implicated the frontal cortex and basal ganglia in pathophysiological models [7]. Additionally, other

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regions such as the amygdala may be involved in emotional aspects of the disorder such as aversion to delays [8]. However, recently other accounts emerged suggesting dysfunctions in ADHD in large-sage networks rather than individual brain regions [9]. According to these accounts, the pathophysiology of ADHD may not be understood properly unless interactions of brain areas are taken into account. In that sense, functional connectivity (FC) is an important tool to assess such interactions. FC was originally described as the statistical dependencies among neurophysiological events of anatomically distinct brain regions in positron emission imaging [10], and was later applied to functional magnetic resonance imaging (fMRI) [11]. By evaluating the time-domain interdependence among blood-oxygen-level-dependent (BOLD) signals in the brain, fMRI-based FC determines the functional connections between two anatomically separate brain areas [12].

According to a *meta*-analysis of resting state functional connectivity (rs-FC), disrupted connectivity within the default mode network (DMN) is associated with ADHD [13]. Furthermore, a comprehensive *meta*-analysis concentrating on task-based FC showed that a significant number of hyperactivated areas linked to ADHD were found in the ventral attention and frontoparietal networks. The majority of the hyperactive regions associated with ADHD, however, were found in the default mode network, while some hyperactive regions were found in the visual network. However, it's worth mentioning that out of the 55 studies encompassed by this *meta*-analysis, only 16 were conducted with adult-ADHD participants [14]. The predominance of childhood-focused research underscores the ongoing challenge of understanding the pathophysiology including the functional network properties of the adult-ADHD brain.

In the context of the recent transition from an activation-centric into a connectivity-focused perspective in neuroimaging, the exploration of network FC in the adult-ADHD brain becomes increasingly valuable. Considering the diversity and the number of brain networks and the complexity of the data when the whole-brain approach is used, in this study, we narrowed down our analysis to two main attention networks: the dorsal attention network and the ventral attention network. While the ventral attention network (VAN) is engaged in the detection of unexpected changes in the environment, the dorsal attentional network (DAN) is involved in sustained attention and voluntary guidance of attentional focus [15,16].

Prior research has demonstrated structural deficits in these networks. For example, a study found reduced cortical thickness in the DAN subarea of the right temporoparietal junction, suggesting a structural deficit in ADHD [17], while a comprehensive *meta*-analysis revealed a significant ADHD-related hypoactivation in the VAN and DAN compared to healthy subjects [14].

Investigating functional connectivity during the Go/No-Go task in adults with ADHD is particularly important as it provides insight into how network-level interactions underpin cognitive control and attentional processes in real-time. This task-specific approach can reveal unique patterns of connectivity disruptions that may contribute to the persistent attentional deficits observed in adult ADHD, offering a more nuanced understanding of the disorder's neural mechanisms.

In the current study, we studied the FC of the DAN and VAN networks in the brains of ADHD individuals while completing a Go/No-Go task. Moreover, by examining group-by-condition interaction, our objective is to study the modulation of FC in the two attention networks in adults with ADHD compared to healthy control, during the Go/No-Go task. This analysis can provide insights into how the neural circuits underlying cognitive control and attention may be altered in individuals with ADHD, and how this may differ from healthy individuals. We hypothesized that ADHD individuals will exhibit altered FC for ventral and dorsal attention networks. In addition, we anticipated observing a significant group-by-condition interaction, where the modulation of connectivity will be altered in the ADHD group between Go and No-Go trials. The reason for the latter prediction is that in a Go/No-Go task, the Go and No-Go stimuli represent different task demands. Detection of Go

requires sustained attention resources associated with the DAN, while No-Go stimuli detection involves unexpected stimuli and inhibition associated with the VAN [15,16,18].

2. Method

2.1. Participants

The study enrolled 43 participants, with the experimental group comprising individuals diagnosed with ADHD and the control group consisting of healthy subjects. All participants in the ADHD group had previously received an ADHD diagnosis from a psychiatrist. They were also interviewed before enrolment by a clinical psychologist to confirm the diagnosis according to DSM-5 criteria. Before completing the Go/No-Go fMRI paradigm, each participant underwent assessments using the ADHD DSM Scale, BECK Depression Scale, and BECK Anxiety Scales [19-21]. The participants in the control did not have clinical scores in these questionnaires. Among the initial participants, seven were excluded due to excessive head motion detected during fMRI data quality checks. Specifically, five belonged to the ADHD group, which initially comprised 21 individuals, and two participants were excluded from the control group, originally consisting of 22 individuals. This resulted in a final analysis group of 36 subjects: 16 individuals with ADHD (6 females and 10 males, aged 21-30 years) and 20 healthy controls (11 females and 9 males, aged 18-30 years). Notably, all participants were either attending various universities or had graduated from a university.

There were no significant differences between the groups in terms of sex ($\chi^2=1.092,\,p=0.296$) and age (t = -0.415, p = 0.681). Additionally, there were no significant differences in depression (t = -1.292, p = 0.205) and anxiety scores (t = -0.5, p = 0.62) between groups. However, the groups differed significantly in ADHD scores (t = -7.781, p < 0.001), with significant differences observed in both the attention (t = -3.89, p < 0.001) and hyperactivity (t = 3.53, p = 0.001) subscales (Table 1).

Furthermore, all participants were right-handed and confirmed they were not taking psychiatric medications, except for three subjects from the ADHD group who were using stimulants. Before taking part in the research, each participant provided voluntary and informed consent. None of the subjects had previously experienced psychiatric or neurological conditions apart from ADHD, and none indicated a background of learning disabilities. Those taking stimulant medications were instructed to discontinue usage at least 48 h before the scan.

2.2. Data acquisition

A 1.5 T Philips Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) equipped with a SENSE 8-channel head coil was used for whole-brain imaging at XXXX Hospital. The 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) technique was

Table 1Demographics of ADHD (attention deficit hyperactivity disorder) patients and healthy controls.

	ADHD $(n = 16)$	$control\ (n=20)$	p value
Means (SD), range			
Age (at MRI, in years)	25.25 (± 3.317 , 21–30)	$24.8\ (\pm 3.172,\ 18–30)\ 0.681$	
Scales			
Beck Depression Score	14.46 (±8.6)	10.95 (±7.5)	0.205
Beck Anxiety Score	$11.86~(\pm 10.23)$	$10.20~(\pm 9.38)$	0.62
ADHD DSM Score	11.66 (±3.26)	$4.3~(\pm 2.34)$	0.00
Attention Subtest	4.81 (±3.33)	$1.45~(\pm 1.76)$	< 0.001
Hyperactivity Subtest	5.94 (±3.1)	$2.85\ (\pm 2.13)$	0.001
n (%)			
Sex			
Male (%)	10 (62,5)	9 (45)	0.296
Female (%)	6 (37,5)	11 (65)	

^{*}MRI, magnetic resonance imaging; n, number.

used to acquire high-resolution T1-weighted images, with a collection time of roughly 7 min. The T1-weighted images were acquired with the following settings: a flip angle of 90° , a repetition time (TR) of 8.6 s, an echo time (TE) of 4 ms, a field of view (FoV) measuring 240×240 mm, voxel dimensions of 1.25×1.25 mm 3 , a slice thickness of 1.2 mm, and 140 slices.

Following the structural scan, 198 volumes of Echo Planar Imaging (EPI) data were acquired, taking around 9 min. The EPI imaging parameters were: TR of 2.64 s, TE of 40 ms, FoV of 224 \times 224 mm, voxel size of 3.5 \times 3.5 mm 3 , slice thickness of 4 mm, slice spacing of 4 mm, and 32 slices total.

2.3. Experimental paradigm and procedure

2.3.1. Go/No-Go paradigm

The Go/No-Go paradigm is a goal-oriented test designed to assess sustained attention, selective attention, and response control (response inhibition) in ADHD [22]. During the task, participants were required to respond to all incoming stimuli by pressing a button as quickly as possible, except for when the letter 'X' appeared, which served as the distracting stimulus. The letter 'X' constituted only 18 % of the total stimuli to maintain task complexity and enhance attentional demands.

The Go/No-Go paradigm design employed in this study was implemented using OpenSesame (version 3.3.5), a Python-based software (version 3.7.6). A total of 200 stimuli were presented, consisting of randomly chosen letters from the alphabet (e.g., 'S', 'A', 'D', 'F', etc.) for Go trials, and the letter 'X' for No-Go trials, as shown in Fig. 1. Each letter was displayed on the screen for 300 ms, and the interstimulus interval (ISI) varied between 100 ms and 400 ms. Notably, participants remained unaware of the sequence and repetition of letters, contributing to the task's objectivity. Additionally, the visual cue '+' following each letter effectively prepared participants for the subsequent visual stimulus, thereby reducing the impact of the previous visual presentation.

2.4. fMRI analysis

2.4.1. Pre-processing

Visualization and conversion of raw data from dicom to nifti format were performed using the MRIcron-based DCM2NII program. Results included in this manuscript come from analyses conducted with the CONN toolbox (version 22.a.) [23]. The functional and anatomical data underwent preprocessing, including realignment with susceptibility

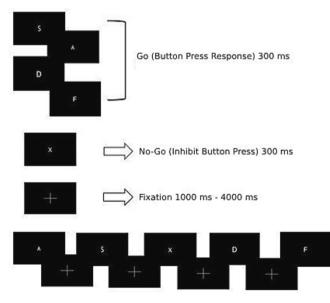


Fig. 1. Schematic illustration of the Go/No-Go task used in the study.

distortion correction, detection of outliers, segmentation, normalization into MNI space, and smoothing [24]. For the functional data, realignment was conducted using the SPM realign & unwarp procedure [25]. This process aligned all scans to the first scan of the initial session as a reference image, employing a least squares method and a 6-parameter rigid body transformation [26]. Additionally, b-spline interpolation was used to resample the data, effectively correcting for motion and magnetic susceptibility interactions.

Outlier scans were identified using the ART method, which flagged scans with framewise displacement higher than 0.9 mm or global BOLD signal changes exceeding 5 standard deviations as potential outliers [27–29]. Subsequently, a baseline BOLD image was computed for each participant by averaging all scans, with the exception of the outliers.

The functional and structural data underwent normalization, followed by segmentation into categories of gray matter, white matter, and cerebrospinal fluid (CSF) tissues. The data were then resampled to achieve 2 mm isotropic voxels, employing a direct normalization technique [30,31]. These procedures were implemented through the unified segmentation and normalization algorithm in SPM [32,33]. Finally, the functional data underwent smoothing through spatial convolution with FWHM Gaussian kernel size 8 mm.

To denoise the functional data, a standard denoising was employed, involving regression of potential confounding effects [34]. These impacts were defined using white matter timeseries, CSF timeseries, motion parameters along with their derivatives, flagged scans, and linear trends within every functional run. Following this, a high-pass filter was employed on the BOLD time-series to retain frequencies above 0.008 Hz [28,35,36]. To derive the CompCor noise components from white matter and CSF, the mean BOLD signal was calculated along with the most significant principal components orthogonal to the average BOLD signal, motion parameters, and flagged scans. These calculations were performed within each subject's eroded segmentation masks [37,38].

2.4.2. gPPI connectivity

Seed-to-voxel Analysis

The examination of FC was carried out through the application of the generalized psychophysiological interaction (gPPI) technique, utilizing the CONN toolbox. Unlike the conventional PPI analysis, which combines contrast information while constructing a psychological regressor, the gPPI methodology involves convolving the BOLD signal with the canonical hemodynamic response function for each specific condition prior to forming the contrast. This approach yields distinct psychological regressors for each condition, a technique demonstrated to enhance the fitting of the regression model for event-related fMRI data. This particular approach proves suitable for analysing the Go/No-Go task employed in our study [39].

Regions of Interest (ROIs): The regions of interest (ROIs) pertinent to our study were selected based on functional relevance to attention networks, and all served as **seed regions**. These included the right frontal eye field (FEF [+30—6+64]), left frontal eye field (FEF [-27—9+64]), right intraparietal sulcus (IPS [+39—42+54]), left intraparietal sulcus (IPS [-39—43+52]) for the DAN, as well as the right inferior frontal gyrus (IFG [+54+28+1]), right supramarginal gyrus (SMG [+62—35+32]), and right posterior superior temporal gyrus (pSTG [+59—42+13]) within the VAN. These coordinates were determined using the CONN toolbox.

The IPS and FEF are considered core regions of the DAN, and thus were selected as ROIs within the DAN network in our study [40,41]. The DAN is generally considered to have no hemispheric lateralization, which is why we included bilateral ROIs for this network [42]. In contrast, the VAN has been demonstrated to be right-lateralized based on existing evidence, which is why we included only the right-sided ROIs for VAN in our analysis [16,43,44].

Initially, we computed the average BOLD time course across specific voxels for each Region of Interest (ROI) and utilized it as a physiological regressor. For every combination of seed and target regions, we

established a gPPI model [39,45]. This model employed the seed BOLD signals as physiological factors, the boxcar signals characterizing individual task conditions convolved with an SPM canonical HRF as psychological factors, and the product of the two as psychophysiological interaction terms. The assessment of FC changes across conditions was accomplished by examining the multivariate regression coefficient of the psychophysiological interaction terms in each model. Following this, the results underwent a conversion into z-scores through Fisher's z-transformation before calculating a group-level averaged FC. This methodology allowed us to explore task-related FC between the selected seed regions and whole brain voxels.

Group-level analyses were conducted utilizing a General Linear Model (GLM) [46]. For each voxel, a unique GLM was estimated, with first-level connectivity measures being treated as dependent variables. In this approach, each participant contributed an individual sample for each task or experimental condition if applicable, while independent variables were represented by groups or other subject-level identifiers.

To evaluate voxel-level hypotheses, multivariate parametric statistics were employed, considering both random-effects across subjects and the estimation of sample covariance across multiple measurements. Statistical significance was assessed at the level of individual clusters. Cluster-level inferences relied on parametric statistics derived from Gaussian Random Field theory [30,47]. The achieved outcomes were subjected to thresholding, employing both a voxel-level threshold of p < 0.001 to form clusters, and a cluster-size threshold of familywise corrected p-FDR <0.05/7 (FDR <0.05/ number of ROIs) [48].

The main effects of the groups during Go and No-Go tasks, as well as group-by-task interactions were analysed. These analyses were conducted across all ROIs, including brain regions within the DAN and the VAN. For all analyses, we used only correct responses (e.g. GoCorrect, No-GoCorrect). However we inserted Go correct, No-Go correct and errors into the model, even though we were not interested in errors as including all of the regressors was demonstrated to be more accurate [39].

2.5. Statistical analysis

The calculation of between-group differences in the demographic and clinical variables was conducted using the JASP toolbox (Version 0.16.2.0). Age and Neuropsychiatric Scales, and Go/No-Go task results were analysed using independent samples t-tests. Furthermore, the sex distribution was compared using Pearson's chi-square test (see Table 1). The p values of connectivity analysis were corrected using the false discovery rate as implemented within the CONN toolbox. Afterward, Bonferroni correction was applied to control further for the number of ROIs used in the analysis.

3. Results

3.1. Behavioural results

The independent samples T-test revealed non-significant group

differences in Go (t = -0.59; p = 0.559) and No-Go (t = 0.72; p = 0.474) accuracy scores. There was also no significant difference in the RT of Go trials between the two groups (t = 0.72; p = 0.474).

3.2. Functional connectivity results

Table 2 presents the FC results. We found a significant main effect of the group during Go and No-Go conditions and an interaction effect only within the right FEF. Whereas no significant effect was found for the left FEF, right IPS, left IPS, right IFG, right SMG, and right pSTG.

3.2.1. The main effect of group-Go condition

Frontal Eye Field (FEF) right seed: regions showing a significant main effect of the group included right central opercularis and cingulate gyrus, see Table 2. Participants with ADHD showed significantly decreased FC between the right eye field and right central opercularis [t = 5.10, p = 0.001], and the right eye field and cingulate gyrus in Go condition as compared to healthy controls [t = 5.02, p = 0.003], see Fig. 2.

3.2.2. The main effect of group- No-Go condition

Frontal Eye Field (FEF) right seed: region showing significant group main effect during No-Go condition was right superior lateral occipital cortex (sLOC). We observed a significantly increased FC between FEF right and sLOC right during No-Go conditions in the ADHD group as compared to healthy subjects [$t=5.63,\,p=0.006$], see Fig. 3.

3.2.3. Diagnosis-by-condition interaction

Finally, we observed a significant interaction between the FEF right seed and posterior cingulate gyrus connectivity, see Table 2 [t = -4.85, p = 0.005], see Fig. 4. During Go trials, the FEF and posterior cingulate of controls were anti-correlated. However, in the ADHD group, they were positively correlated.

4. Discussion

In the present study, we investigated the FC in the dorsal and ventral attention networks during the Go/No-Go task in ADHD adults and healthy controls. We observed abnormality in DAN both as a main effect of the group during the Go and No-Go conditions, as well as in interaction between task and condition.

4.1. Main effects

4.1.1. DAN/Go Condition

We found a significant main effect of the group in **Go** condition in the Go/No-Go task in DAN, where the ADHD individuals had reduced FC between right FEF and right central operculum, and right FEF and cingulate gyrus as compared to healthy subjects during the Go condition, where the participant has to respond fast and accurately to a particular stimulus. Notably, these results are consistent with the literature, where reduced FC involving DAN in the ADHD population was

Table 2Seed and target brain regions with significant FC differences.

Network	Seed	Condition (Contrast)	target(s)	Peak MNI coordinates (x,y,z)	Size	EDD corr p	т
						FDR corr p value	value
Dorsal attention Network	Right FEF (+30—6 + 64)	Go (ADHD < Control)	Right central opercularis	+54—14 + 06	336	0.001	-5.17
			Cingulate gyrus	+04+02+48	258	0.003	-5.17
		No-Go (ADHD > Control)	right superior lateral occipital cortex (sLOC)	+28-62 + 36	203	0.006	4.65
		Interaction (ADHD <	Posterior cingulate gyrus	+06—44 + 24	218	0.005	-4.65
		Control&No-Go > Go)					

^{*}Note. All regions are FDR-corrected and further correction for the number of ROIs was applied (p-FDR = 0.05/7). Nonsignificant region within the dorsal and ventral attention networks are not included in the table. Size is represented by number of voxels. FEF = frontal eye field; MNI = Montreal Neurological Institute; FDR = false discovery rate.

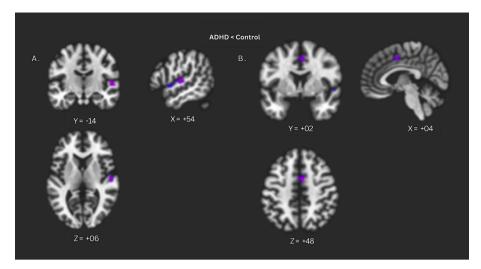


Fig. 2. Main effect of group (ADHD < Control) during Go condition. Purple-blue colors represent decreased connectivity in the ADHD group. **A.** Decreased functional connectivity between right FEF and right central opercularis in ADHD subjects; **B.** Decreased functional connectivity between right FEF and cingulate gyrus in ADHD subjects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

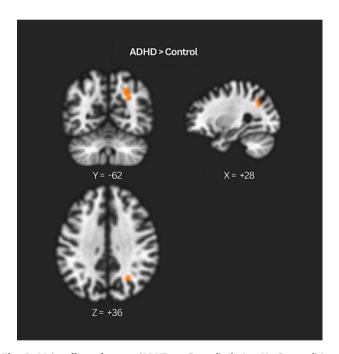


Fig. 3. Main effect of group (ADHD > Control) during No-Go condition. Yellow-red colors represent increased connectivity in the ADHD group (Increased functional connectivity between right FEF and right sLOC in ADHD subjects). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reported [14,49,50]. In addition to task-based studies, resting-state fMRI investigations conducted with children and adults with ADHD have revealed diminished DAN FC [51,52]. In that sense, diminished connectivity between the dorsal attention network and other key areas involved in attention (operculum and cingulate gyrus) may be responsible for sustained attention deficits in ADHD.

The cingulate gyrus plays a role in various cognitive functions including emotion regulation, attention, and decision-making. Both structural and functional alterations in the entire cingulate were observed in ADHD [53]. The FC between FEF and the PCG has been previously documented in human and macaque monkeys during rest [54]. The right central operculum, which is part of DAN, is involved in processing sensory and motor information, contributing to attention and

decision-making. Its functional impairment has been previously reported in ADHD [55], which can be related to disrupted integration of sensory and motor signals, potentially contributing to attentional deficits and impulsive behavioural characteristic of the disorder. To the best of our knowledge, alteration in task-based FC between the right FEF and right central opercularis in ADHD has not been reported. Therefore, our finding of reduced task-based FC during the Go condition between the right FEF- and right central operculum is intriguing and requires further attention.

4.1.2. No-Go condition

We also looked for the main effect of the group in the No-Go condition in DAN, and found a significantly increased FC between FEF right and sLOC right in adults with ADHD during the No-Go condition as compared to healthy subjects. Increased connectivity in the DAN network in ADHD is not consistent with the existing literature, where the decreased connectivity of DAN is routinely reported in ADHD. Only a few studies similar to our findings reported an increased DAN connectivity in children and adult subjects with ADHD [49,56]. The increased DAN connectivity observed in our findings can be interpreted as "inefficient" since it may require more energy to achieve similar performance for ADHD subjects as compared to healthy individuals. This inefficient top-down attentional deployment by the DAN could be responsible for the symptoms of inattention.

Particularly, the increased FEF right sLOC connectivity in ADHD adults aligns with a previous study that also reported increased resting-state FC between the bilateral FEF and occipital regions in ADHD adults [49]. Moreover, increased resting state FC in occipital regions in ADHD has been previously associated with difficulties in inhibiting sensory perception [57]. It has been proposed that individuals with ADHD may exert more effort in inhibitory control tasks compared to controls due to the lack of connectivity within the VAN, which they may attempt to compensate for [49,58]. However, in task-based paradigms examining FC, bilateral occipital lobes have shown both increased and decreased connectivity in ADHD [51], indicating an abnormality in occipital lobe connectivity that warrants further investigation.

4.1.3. Interaction effect

Finally, we found a diagnosis-by-condition interaction involving the right FEF that further underscores the complex interplay of connectivity dynamics in response to different task conditions in ADHD adults. We observed that while the controls showed anti-correlated connectivity between FEF and Posterior Cingulate Gyrus (PCG) during the Go

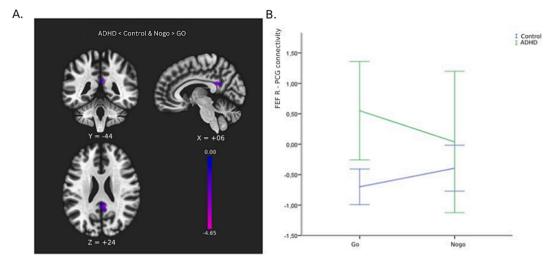


Fig. 4. A. Diagnosis-by-condition interaction (ADHD < Control&Nogo > Go) in functional connectivity between right FEF and posterior cingulate gyrus (PCG). B. The plot of FEF-PCG functional connectivity for group and condition differences with mean \pm error.

condition, the ADHD group showed a positive correlation. An alteration of FEF-PCG connectivity has been previously reported in children with ADHD [50]. The posterior cingulate gyrus has been associated with nongoal-directed processes. Furthermore, the PCG serves as a hub within the DMN. Consequently, our discovery implies a potential modification in FC between the DAN and DMN in individuals with ADHD. This aligns with previous research indicating that ADHD is characterized by abnormal connectivity between networks rather than isolated brain region abnormalities [59]. Lin et al. proposed that the disrupted FC between local regions associated with the DAN and DMN could be a pathophysiological mechanism of ADHD. While Lin observed this in children, our study investigated this in adults, which suggests that this may be a shared neural mechanism of ADHD [56]. It is possible that while healthy individuals' DMN do not engage with FEF during sustained attention, the ADHD brain is not able to suppress this engagement.

4.1.4. VAN

In addition, we also examined VAN and found no significant effect of the Go/No-Go task on the FC differences within the network. Regarding VAN connectivity in ADHD, previous studies showed inconsistent results. Though certain studies have documented a reduction in rs-FC within the VAN among children diagnosed with ADHD [49], contrasting findings have emerged indicating no such decrease [56]. A Metanalysis of 55 fMRI studies failed to detect any alteration of VAN connectivity in ADHD adults, whereas there were abnormalities in ADHD children [14]. The discrepancy in findings of VAN connectivity between ADHD adults and ADHD children, suggests that VAN characteristics may differ across different ages. It is possible that the adults may not have problems with attending to unexpected stimuli, while they have still problems with sustained attention.

5. Limitation and conclusion

Our study is subject to limitations, particularly it's relatively small sample size for more reliable inferences and increased generalizability of the results, a larger sample-size study needs to be further conducted.

Another limitation pertains to the lack of differentiation among ADHD presentations in our study. While this approach allowed for an exploration of broader network connectivity patterns, future investigations could delve into these distinctions to uncover potentially unique connectivity profiles within specific ADHD subgroups.

Additionally, although the sex ratio and age of the two groups did not significantly differ, we recognize that these factors can influence

functional connectivity results. Future studies should consider matching or statistically controlling for these variables to ensure more accurate results.

Finally, we used a 1.5 T device due to its availability in our hospital. While we acknowledge the limitations of a 1.5 T device, particularly the lower signal-to-noise ratio, which can be a disadvantage in fMRI studies, it also has advantages, such as reduced sensitivity to artifacts compared to 3 T and higher intensity devices [60]. We recommend that future studies use higher intensity devices, such as 3 T scanners, to further confirm our findings and potentially overcome the limitations associated with lower field strength.

Despite these limitations, our study contributes to the understanding of functional network dynamics in adults with ADHD. In particular, these findings highlight the role of the dorsal attention network in sustained attention in ADHD, which in turn pave the way for more targeted interventions in clinical settings.

6. Ethics statement

The study was conducted in adherence to the ethical standards set by the Uskudar University's ethical committee and was approved under reference number 99102440.

CRediT authorship contribution statement

Baris Metin: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation, Conceptualization. Secil Damla Kayaalp: Writing – original draft, Visualization, Software, Formal analysis, Data curation, Conceptualization. Shams Farhad: Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Investigation, Data curation. Elvan Ciftci: Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. Buse Gocmen Er: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. Nevzat Tarhan: Writing – review & editing, Writing – original draft, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

References

- [1] S. Victoria, P. Czobor, S. Balint, A. Meszaros, I. Bitter, Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis, Br. J. Psychiatry 194 (3) (2009) 204–211, https://doi.org/10.1192/bjp.bp.107.048827.
- [2] S.V. Faraone, J. Biederman, E. Mick, The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies, Psychol. Med. 36 (2) (2006) 159–165, https://doi.org/10.1017/S003329170500471X.
- [3] M.A. Katzman, T. Bilkey, P.R. Chokka, A. Fallu, L.J. Klassen, Re: is adult attention-deficit hyperactivity disorder being overdiagnosed? Can. J. Psychiatry. 61 (1) (2016) 60–61, https://doi.org/10.1177/0706743715620143.
- [4] E. Sobanski, D. Bruggemann, B. Alm, S. Kern, M. Deschner, T. Schubert, M. Rietschel, Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). European Archives, Psychiatry Clin. Neurosci. 257 (7) (2007) 371–377, https:// doi.org/10.1007/s00406-007-0712-8.
- [5] T. Torgersen, B. Gjervan, K. Rasmussen, ADHD in adults: a study of clinical characteristics, impairment and comorbidity, Nord. J. Psychiatry 60 (1) (2006) 38–43, https://doi.org/10.1080/08039480500520665.
- [6] L. Luo, W. You, M.P. DelBello, Q. Gong, F. Li, Recent advances in psychoradiology, Phys. Med. Biol. 67 (23) (2022), https://doi.org/10.1088/1361-6560/ac9d1e. PMID: 36279868.
- [7] F.X. Castellanos, Toward a pathophysiology of attention-deficit/hyperactivity disorder, *clin. Pediatr. (phila) 36 (7) (1997) 381–393, https://doi.org/10.1177/ 000992289703600702.
- [8] L. Jurgen, M. Danckaerts, W. Van Hecke, M.A. Mehta, R. Peeters, S. Sunaert, E. Sonuga-Barke, Brain activation to cues predicting inescapable delay in adolescent attention deficit/hyperactivity disorder: an fMRI pilot study, Brain Res. 1450 (2012) (2012) 57–66, https://doi.org/10.1016/j.brainres.2012.02.027.
- [9] F.X. Castellanos, E. Proal, Large-scale brain systems in ADHD: beyond the prefrontal-striatal model, Trends Cog. Scie. 16 (1) (2012) 17–26, https://doi.org/ 10.1016/j.tics.2011.11.007.
- [10] K.J. Friston, Functional and effective connectivity in neuroimaging: A synthesis, Human Brain Mapping 2 (1–2) (1994) 56–78, https://doi.org/10.1002/ hbm.460020107.
- [11] B. Biswal, F.Z. Yetkin, V.M. Haughton, J.S. Hyde, Functional connectivity in the motor cortex of resting human brain using echo-planar MRI, Magn. Reson. Med. 34 (4) (1995) 537–541. https://doi.org/10.1002/mrm.1910340409.
- [12] Functional Connectivity via Feature Extraction. Scie. Rep. 10*(1), (2020) 1298. doi:10.1038/s41598-020-57915-w.
- [13] B. Sutcubasi, B. Metin, M.K. Kurban, Z.E. Metin, B. Beser, E. Sonuga-Barke, Resting-state network dysconnectivity in ADHD: A system-neuroscience-based meta-analysis, World J. Biol. Psych. 21 (9) (2020) 662–672, https://doi.org/10.1080/15622975.2020.1775889.
- [14] S. Cortese, C. Kelly, C. Chabernaud, E. Proal, A. Di Martino, M.P. Milham, F. X. Castellanos, Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies, Am. J. Psych. 169 (10) (2012) 1038–1055, https://doi.org/10.1176/appi.aip.2012.11101521.
- [15] M. Corbetta, G.L. Shulman, Control of goal-directed and stimulus-driven attention in the brain, Nat. Rev. Neurosci. 3 (3) (2002) 201–215, https://doi.org/10.1038/ nrn755.
- [16] M. Corbetta, G. Patel, G.L. Shulman, The reorienting system of the human brain: from environment to theory of mind, Neuron 58 (3) (2008) 306–324, https://doi. org/10.1016/j.neuron.2008.04.017.
- [17] W. You, Q. Li, L. Chen, N. He, Y. Li, F. Long, Y. Wang, Y. Chen, R.K. McNamara, J. A. Sweeney, M.P. DelBello, Q. Gong, F. Li, Common and distinct cortical thickness alterations in youth with autism spectrum disorder and attention-deficit/hyperactivity disorder, BMC Med. 22 (1) (2024) 92, https://doi.org/10.1186/s12916-024-03313-2. PMID: 38433204; PMCID: PMCI0910790.
- [18] L. Wright, J. Lipszyc, A. Dupuis, S.W. Thayapararajah, R. Schachar, Response inhibition and psychopathology: a meta-analysis of go/no-go task performance, J Abnorm Psychol. 123 (2) (2014) 429–439, https://doi.org/10.1037/a0036295. Epub 2014 Apr 14 PMID: 24731074.
- [19] B. Metin, Z. Alpuğan, H. Burkovik, S. Cengel, E. Yılmazer, M. Aydın, M. Sunar, I. Esenkaya, L. Arslan, S. Metin, K. Tarhan, Reliability and validity of the Turkish version of the ADHD DSM Scale, J. Neurobehiev. Scie. 2018 (2018) 1, https://doi. org/10.5455/JNBS.1522419592.
- [20] N. Hisli, Beck Depresyon Envanteri'nin Üniversite Öğrencileri için Geçerliği, Güvenirliği. Psy. J. 6 (23) (1989) 3–13.
- [21] M. Ulusoy, N. Hisli Sahin, H. Erkmen, Turkish version of the beck anxiety inventory: psychometric properties, J. Cog. Psychother. Internat. Quart. 12 (1998).
- [22] M. Criaud, P. Boulinguez, Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review, *neuroscie. & Biobehav. Rev. 37 (1) (2013) 11–23, https://doi.org/ 10.1016/j.neubiorev.2012.11.003.
- [23] S. Whitfield-Gabrieli, A. Nieto-Castanon, Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks, Brain Connect. 2 (3) (2012) 125–141, https://doi.org/10.1089/brain.2012.0073.

- [24] A. Nieto-Castanon, fMRI minimal preprocessing pipeline, in: M. Filippi (Ed.), Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN, Hilbert Press, 2020, pp. 3–16.
- [25] J.L. Andersson, C. Hutton, J. Ashburner, R. Turner, K. Friston, Modelling geometric deformations in EPI time series, Neuroimage 13 (5) (2001) 903–919, https://doi. org/10.1006/nimg.2001.0746.
- [26] K.J. Friston, J. Ashburner, C.D. Frith, J.B. Poline, J.D. Heather, R.S.J. Frackowiak, Spatial registration and normalization of images, Human Brain Mapp. 3 (3) (1995) 165–189, https://doi.org/10.1002/hbm.460030303.
- [27] S. Whitfield-Gabrieli, A. Nieto-Castanon, S. Ghosh, 2011. Artifact detection tools (ART). Cambridge, MA. Release Version, 7(19), 11.
- [28] J.D. Power, A. Mitra, T.O. Laumann, A.Z. Snyder, B.L. Schlaggar, S.E. Petersen, Methods to detect, characterize, and remove motion artifact in resting state fMRI, Neuroimage 84 (2014) 320–341, https://doi.org/10.1016/j. neuroimage.2013.08.048.
- [29] A.Nieto-Castanon, (submitted). Preparing fMRI Data for Statistical Analysis. In M. Filippi (Ed.), fMRI Techniques and Protocols Springer. doi:10.48550/ arXiv.2210.13564.
- [30] A.A. Nieto-Castanon, Cluster-level inferences, in: M. Filippi (Ed.), Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN, Hilbert Press, 2020, pp. 83–104.
- [31] V.D. Calhoun, T.D. Wager, A. Krishnan, K.S. Rosch, K.E. Seymour, M.B. Nebel, K. Kiehl, The impact of T1 versus EPI spatial normalization templates for fMRI data analyses, Human Brain Mapp. 38 (11) (2017) 5331–5342, https://doi.org/ 10.1002/hbm.23737.
- [32] J. Ashburner, A fast diffeomorphic image registration algorithm, Neuroimage 38 (1) (2007) 95–113, https://doi.org/10.1016/j.neuroimage.2007.07.007.
- [33] J. Ashburner, K.J. Friston, K., Unified segmentation, Neuroimage 26 (3) (2005) 839–851, https://doi.org/10.1016/j.neuroimage.2005.02.018.
- [34] A. Nieto-Castanon, FMRI denoising pipeline, in: Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN, Hilbert Press, 2020, pp. 17–25.
- [35] K.J. Friston, S. Williams, R. Howard, R.S. Frackowiak, R. Turner, Movement-related effects in fMRI time-series, Magn. Reson. Med. 35 (3) (1996) 346–355, https://doi.org/10.1002/mrm.1910350312.
- [36] M.N. Hallquist, K. Hwang, B. Luna, The nuisance of nuisance regression: spectral misspecification in a common approach to resting-state fMRI preprocessing reintroduces noise and obscures functional connectivity, Neuroimage 82 (2013) 208–225, https://doi.org/10.1016/j.neuroimage.2013.05.116.
- [37] Y. Behzadi, K. Restom, J. Liau, T.T. Liu, A component based noise correction method (CompCor) for BOLD and perfusion based fMRI, Neuroimage 37 (1) (2007) 90–101, https://doi.org/10.1016/j.neuroimage.2007.04.042.
- [38] X.J. Chai, A.N. Castanon, D. Ongur, S. Whitfield-Gabrieli, Anticorrelations in resting state networks without global signal regression, Neuroimage 59 (2) (2012) 1420–1428, https://doi.org/10.1016/j.neuroimage.2011.08.048.
- [39] D.G. McLaren, M.L. Ries, G. Xu, S.C. Johnson, A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches, Neuroimage 61 (4) (2012) 1277–1286, https://doi.org/10.1016/j.neuroimage.2012.03.068.
- [40] M.D. Fox, M. Corbetta, A.Z. Snyder, J.L. Vincent, M.E. Raichle, Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems, PNAS 103 (26) (2006) 10046–10051, https://doi.org/10.1073/pnas.0604187103. Bibcode:2006 PNAS..10310046F. PMC 1480402. PMID 16788060.
- [41] Kristafor Farrant, Lucina Q. Uddin, Asymmetric development of dorsal and ventral attention networks in the human brain, Dev. Cognit. Neurosci. 12 (2015) 165–174, https://doi.org/10.1016/j.dcn.2015.02.001. ISSN 1878-9293. PMC 4396619. PMID 25797238.
- [42] S.V. Astafiev, G.I. Shulman, C.M. Stanley, A.Z. Snyder, D.C. Van Essen, M. Corbetta, Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing, J. Neurosci. 23 (11) (2003) 4689–4699, https://doi.org/ 10.1523/JNEUROSCI.23-11-04689.2003. PMC 6740811. PMID 12805308.
- [43] M. Thiebaut de Schotten, et al., A lateralized brain network for visuospatial attention, Nat. Neurosci. 14 (2011) 1245–1247.
- [44] J. Downar, A.P. Crawley, D.J. Mikulis, K.D. Davis, A multimodal cortical network for the detection of changes in the sensory environment, Nat. Neurosci. 3 (2000) 277–283.
- [45] K.J. Friston, C. Buechel, G.R. Fink, J. Morris, E. Rolls, R.J. Dolan, Psychophysiological and modulatory interactions in neuroimaging, Neuroimage 6 (3) (1997) 218–229, https://doi.org/10.1006/nimg.1997.0291.
- [46] A. Nieto-Castanon, General Linear Model. In Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN, Hilbert Press, 2020, pp. 63–82.
- [47] K.J. Worsley, S. Marrett, P. Neelin, A.C. Vandal, K.J. Friston, A.C. Evans, A unified statistical approach for determining significant signals in images of cerebral activation, Human Brain Mapp. 4 (1) (1996) 58–73, https://doi.org/10.1002/ (SICI)1097-0193(1996)4:1<58::AID-HBM4>3.0.CO;2-O.
- [48] J. Chumbley, K. Worsley, G. Flandin, K. Friston, Topological FDR for neuroimaging, Neuroimage 49 (4) (2010) 3057–3064, https://doi.org/10.1016/j. neuroimage.2009.10.090.
- [49] H. McCarthy, N. Skokauskas, A. Mulligan, G. Donohoe, D. Mullins, J. Kelly, T. Frodl, Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood, JAMA Psychiatry 70 (12) (2013) 1329–1337, https://doi. org/10.1001/jamapsychiatry.2013.2174.
- [50] J. Salmi, M. Metwaly, J. Tohka, K. Alho, S. Leppamaki, P. Tani, M. Laine, ADHD desynchronizes brain activity during watching a distracted multi-talker

- conversation, Neuroimage 216 (2020) 116352, https://doi.org/10.1016/j.neuroimage.2019.116352.
- [51] O.S. Kowalczyk, M.A. Mehta, O.G. O'Daly, M.B. Criaud, Task-based functional connectivity in attention-deficit/hyperactivity disorder: A systematic review, Biol. Psychiatry Glob Open Sci. 2 (4) (2022) 350–367, https://doi.org/10.1016/j. bpsgos.2021.10.006.
- [52] C.Z. Zhu, Y.F. Zang, Q.J. Cao, C.G. Yan, Y. He, T.Z. Jiang, Y.F. Wang, Fisher discriminative analysis of resting-state brain function for attention-deficit/ hyperactivity disorder, Neuroimage 40 (1) (2008) 110–120, https://doi.org/ 10.1016/j.neuroimage.2007.11.029.
- [53] B.A. Vogt, Cingulate impairments in ADHD: Comorbidities, connections, and treatment, HandB. Clin. Neurol. 166 (2019) 297–314, https://doi.org/10.1016/ B978-0-444-64196-0.00016-9.
- [54] R.M. Hutchison, T. Womelsdorf, J.S. Gati, S. Everling, R.S. Menon, Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques, Human Brain Mapp. 29 (7) (2008) 757–770, https://doi. org/10.1002/blm.20529
- [55] P. Soros, E. Hoxhaj, P. Borel, C. Sadohara, B. Feige, S. Matthies, A. Philipsen, Hyperactivity/restlessness is associated with increased functional connectivity in adults with ADHD: a dimensional analysis of resting state fMRI, BMC Psychiatry 19 (1) (2019) 43, https://doi.org/10.1186/s12888-019-2031-9.
- [56] H. Lin, Q. Lin, H. Li, M. Wang, H. Chen, Y. Liang, X. Huang, Functional connectivity of attention-related networks in drug-naive children with ADHD, J. Atten. Disord. 25 (3) (2021) 377–388, https://doi.org/10.1177/1087054718802017.

- [57] Y.F. Zang, Z. Jin, X.C. Weng, L. Zhang, Y.W. Zeng, L. Yang, S.V. Faraone, Functional MRI in attention-deficit hyperactivity disorder: evidence for hypofrontality, Brain Dev. 27 (8) (2005) 544–550, https://doi.org/10.1016/j. hrsinder.2004.11.009
- [58] C. Fassbender, J.B. Schweitzer, Is there evidence for neural compensation in attention deficit hyperactivity disorder? A review of the functional neuroimaging literature, Clin. Psycho. Rev. 26 (4) (2006) 445–465, https://doi.org/10.1016/j. com/2006.01.003
- [59] J. Sidlauskaite, E. Sonuga-Barke, H. Roeyers, J.R. Wiersema, Altered intrinsic organization of brain networks implicated in attentional processes in adult attention-deficit/hyperactivity disorder: a resting-state study of attention, default mode, and salience network connectivity, Eur. Arch. Psychiatry Clin. Neurosci. 266 (4) (2016) 349–357, https://doi.org/10.1007/s00406-015-0630-0.
- [60] J.M. Wardlaw, W. Brindle, A.M. Casado, K. Shuler, M. Henderson, B. Thomas, J. Macfarlane, S. Muñoz Maniega, K. Lymer, Z. Morris, C. Pernet, W. Nailon, T. Ahearn, A.N. Mumuni, C. Mugruza, J. McLean, G. Chakirova, Y.T. Tao, J. Simpson, A.C. Stanfield, H. Johnston, J. Parikh, N.A. Royle, J. De Wilde, M. E. Bastin, N. Weir, A. Farrall, M.C. Valdes Hernandez, SINAPSE Collaborative Group. A systematic review of the utility of 1.5 versus 3 Tesla magnetic resonance brain imaging in clinical practice and research, Eur Radiol. 22 (11) (2012 Nov) 2295–2303, https://doi.org/10.1007/s00330-012-2500-8. Epub 2012 Jun 9. PMID: 22684343.