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Sex differences in attention deficit hyperactivity symptom severity and functional connectivity of the dorsal striatum in young adults

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) occurs more frequently and manifests with greater symptom severity in men than in women. Although studies have implicated basal ganglia dysfunction, the functional connectivity (FC) of the dorsal striatum (DS), particularly in terms of sex differences, has not been fully investigated in ADHD. Here, using resting state fMRI data of a large sample of adults (n = 744; 395 women; 22–36 years) curated from the Human Connectome Project, we performed seed-based correlations for caudate and lentiform nucleus (LN) FC. ADHD symptom severity was quantified with the Achenbach Adult Self-Report ADHD total score as well as inattention and hyperactivity subscores. Imaging data were processed with published routines and evaluated at a corrected threshold. Men showed significantly higher ADHD total score than women. In men, inattention was negatively associated with LN FC with the right superior frontal gyrus. In women, inattention was negatively associated with caudate FC with the right inferior parietal gyrus and positively with LN FC with the left inferior frontal gyrus, and hyperactivity was positively associated with LN FC with a cluster in the dorsal anterior cingulate cortex and supplementary motor area. Sex differences in most of these connectivity patterns were confirmed by slope tests. Further, *k*-means clustering of FC's identified 3 groups each in men and in women. In men, group 1 showed higher inattention and hyperactivity than both group 2 and 3, and group 2 showed higher inattention than group 3. In women, group 1 showed higher inattention and hyperactivity than group 3 and higher inattention than group 2, and group 2 showed higher hyperactivity than group 3. These findings together suggest sex differences in DS FC as neural markers of ADHD and potentially of ADHD subtypes, with men and women each showing altered FC predominantly in the executive control and ventral attention/saliency networks.

1. Introduction

1.1. Neural markers of ADHD

Attention deficit hyperactivity disorder (ADHD) is characterized by inattention, overactivity and impulsivity (see Konrad and Eickhoff, 2010 for a review) in both children and adults (Faraone et al., 2005; Simon et al., 2009). Numerous studies have implicated fronto-striato-parietal network dysfunction in ADHD (see Rubia et al., 2014 for a review). Meta-analyses showed hypoactivation in the frontoparietal regions as well as dorsal striatum (DS) in response to inhibitory control, working memory, vigilance and attention in individuals with ADHD relative to controls (Cortese et al., 2012; Hart et al., 2013; Lei et al., 2015; McCarthy et al., 2013).

Comprising the caudate and lentiform nucleus (LN), the DS is critical to attention and impulse control (see Balleine et al., 2007 for a review). For instance, neuronal recording in behaving monkeys showed that DS activities were modulated by the demand of attention and memory (Cromwell and Schultz, 2003; Kawagoe et al., 1998). In humans, activation of the caudate and putamen was positively correlated with higher No-go accuracy in the Go/No-go task (Liu et al., 2012), and the caudate showed higher activation during successful stop vs. go (Chevrier et al., 2007) and vs. failed stop (Li et al., 2008) trials in the stop signal task, collectively suggesting a role of the DS in impulse inhibition. In accord

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with impairment in response inhibition, adults with ADHD relative to controls showed reduced activation in the putamen and caudate, inferior frontal cortex, and thalamus during successful stop vs. go trials in a stop task and during successful switch vs. repeat trials in a switch task (Cubillo et al., 2010). Moreover, higher inattention score was associated with less activation of these regions in ADHD patients. Similar findings have been reported in children and adolescents with ADHD during the switch and stop tasks (Pliszka et al., 2006; Rubia et al., 2008; Smith et al., 2006), highlighting the impacts of fronto-striato-parietal dysfunction and deficits in cognitive-motor inhibition in ADHD (Lei et al., 2015).

Many studies have characterized structural and other functional abnormalities of the DS in ADHD (see Castellanos et al., 2006 for a review). Meta-analyses of volumetrics identified gray matter reduction in the LN and caudate as the most prominent and replicable findings in both children and adults with ADHD (Ellison-Wright et al., 2008; Nakao et al., 2011). As compared to healthy controls, ADHD adult patients showed diminished activation in the caudate during No-go trials in a continuous performance test and the caudate activity was negatively correlated with ADHD inattention subscore (Schneider et al., 2010). Adolescent ADHD patients showed decreased activation in the putamen and caudate during successful No-go in a Go/No-go task (Rubia et al., 2005). These findings collectively implicate the DS as a critical structure in attentional control in ADHD. An examination of the functional connectivity of the caudate and LN may inform the pathophysiology of ADHD.

1.2. Resting state functional connectivity (FC) as a marker of individual differences and mental illnesses

The brain is organized in functional networks during the resting state (see van den Heuvel and Hulshoff Pol, 2010 for a review). Network organization successfully predicts individual traits (Gordon et al., 2017; Hsu et al., 2018; Plitt et al., 2015) and distinguishes neuropathological from healthy populations (D'Souza et al., 2020; Pariyadath et al., 2014; Rahim et al., 2017). In studies of ADHD, the DS showed resting-state hyperconnectivity with the anterior cingulate cortex (ACC) and insula, in positive correlation with ADHD symptom severity in children and adolescents (Damiani et al., 2021). Children with ADHD relative to controls showed weaker putamen FC with the superior frontal gyrus, temporal gyrus, precuneus, and thalamus (Cao et al., 2009). Children with ADHD also showed stronger positive FC between the striatum and ventromedial prefrontal cortex as compared to developmentally typical children (Rosch et al., 2018). These along with other studies have accumulated to suggest altered resting state DS connectivity in ADHD (Mostert et al., 2016; Oldehinkel et al., 2016; Sörös et al., 2019). On the other hand, the sample sizes of these earlier studies are at best moderate, and few FC studies have specifically examined sex differences.

1.3. Sex differences in the neural markers of ADHD

ADHD is more prevalent and severe in males than in females (Greven et al., 2011; see Rucklidge, 2010 for a review) and sex differences have been identified in brain volumetrics as well as in regional activities in both children and adults with ADHD. Boys but not girls with ADHD relative to controls showed smaller gray matter volumes (GMV) of the caudate and LN (Qiu et al., 2009). In adults with ADHD, men but not women showed smaller caudate GMV, and the caudate GMV was negatively correlated with hyperactivity/impulsivity scores (Onnink et al., 2014). Men but not women with ADHD relative to controls showed less cortical and subcortical including LN activation during verbal working memory (Valera et al., 2010). Additionally, the regional responses to working memory were negatively correlated with hyperactivity and inattention symptoms, respectively, in men and in women with ADHD (Valera et al., 2010). The striatum of girls but not of boys with ADHD relative to controls showed stronger positive FC with the ACC and negative FC with the anterior dorsal prefrontal cortex (Rosch et al., 2018). In contrast, a study of adults with ADHD reported no significant sex differences in the FC of multiple cortical networks (Sörös et al., 2019). There clearly is a need to investigate sex differences in DS FC and how DS FC may relate to inattention and hyperactivity/impulsivity in ADHD.

1.4. ADHD subtypes

According to Diagnostic and Statistical Manual of Mental Disorders-5 (2013) (DSM-5), the diagnosis of ADHD is made of three subtypes: combined (ADHD-C), predominantly inattentive (ADHD-I), and predominantly hyperactive-impulsive (ADHD-H), as determined by inattention and/or hyperactivity symptoms and each with a prevalence rate of approximately 34%, 45%, and 21% in adults (Woo and Rey, 2005). Individuals with different subtypes of ADHD react differently to learning problems (Barnard et al., 2010). Barkley hypothesized more severe deficits in executive functions for ADHD-H and ADHD-C and in attention for ADHD-I (Barkley, 1997). An adult ADHD study reported aberrant attention and inhibition in all three subtypes, greater delay discounting in the ADHD-H only and poorer working memory and verbal fluency in the ADHD-I only (Mostert et al., 2018). Another study compared ADHD-C with ADHD-I adults in executive function, memory and attention and found significant differences in memory only (Dobson-Patterson et al., 2016). A meta-analysis of ADHD adult population also showed memory as the only subtype-differentiating feature whereas executive functioning, attention, and memory distinguished ADHD from control individuals (LeRoy et al., 2019).

In addition to behavioral and cognitive features to distinguish the clinical manifestations of ADHD subtypes, imaging studies have aimed to identify structural and functional brain markers of ADHD subtypes (Al-Amin et al., 2018; Park et al., 2015; Shang et al., 2017). For instance, ADHD-I relative to ADHD-C showed greater activation in the superior parietal lobule while both vs. healthy controls showed lower caudate and inferior frontal cortical activation during incongruent versus congruent trials in the Stroop task (Shang et al., 2017). Employing multiple behavioral tasks, a fMRI study explored whole-brain connectivity differences between ADHD subtypes and classified these subtypes based on connectivity measures (Park et al., 2015). ADHD subtypes differed in connectivity measures mainly in the frontoparietal network and the classifier distinguished ADHD subtypes with an accuracy greater than 90%. On the other hand, few studies have investigated resting state FC as a neural measure with respect to the dimensional features of mental illnesses in ADHD (Riaz et al., 2018). It would be of interest to understand how DS FC's may distinguish ADHD subtypes and whether they do so differently between men and women. Elucidation of distinct neural markers of ADHD subtypes may advance our understanding of the pathophysiology of ADHD and ultimately improve the treatment of this chronic mental illness.

1.5. The present study

We examined resting state FC of the caudate and LN in relation to ADHD symptom severity in a large number of adults obtained of the Human Connectome Project (HCP). We focused on the caudate and LN on the premise of a large literature documenting volumetric reduction and altered activity of the caudate and LN in ADHD, as described earlier. The LN comprises putamen and globus pallidus (GP), both heavily connected with the frontal motor cortex (Haber, 2003) and showing co-activation in motor tasks (Marchand et al., 2008). Further, lesions of the putamen or GP caused similar motor impairments (Bhatia and Marsden, 1994), suggesting shared functional roles. Therefore, in the main analyses of the current study, we considered the LN as a seed region. We showed the results of putamen and GP examined separately in the supplement. We performed voxel-wise linear regression analyses of ADHD total score and inattention and hyperactivity subscores for the

entire sample as well as for men and women separately. For the findings obtained in men or women alone, we performed slope tests to confirm sex differences (Zar, 1999). We used *k*-means clustering of the FC features in grouping the subjects and compared the inattention and hyperactivity subscores as well as the FC's between groups, each for men and women. We broadly hypothesized distinct DS FC's in relation to inattention and hyperactivity symptom severity in men and women.

2. Methods

2.1. Dataset: subjects and assessment

We used the clinical, resting state fMRI (rs-fMRI), and structural MRI data of the HCP 1200 Subject Release (S1200) collected from 2012 to 2015 in the current study. The dataset comprised 1096 young adults without severe neurodevelopmental, neuropsychiatric or neurologic disorders. A total of 352 subjects were excluded due to questionable image quality or poor image segmentation (n = 30), missing cardiac and respiratory data (n = 37), or excessive head movements during rs-fMRI (n = 285; see details in "*2.2 MRI data acquisition and preprocessing*"). Thus, the data of 744 participants (395 women, age 22–36 years) were included in the analyses. The ADHD scores of 3 women were missing and replaced with sex-specific mean values. All recruitment procedures and informed consents, including consent to share de-identified data, were approved by the Washington University Institutional Review Board.

ADHD symptom severity was evaluated with the Achenbach Adult Self-Report (ages 18–59) where individual questions were rated on a 3-point Likert scale (0-Not True, 1-Somewhat or Sometimes True, 2-Very True or Often True), including the subscales of inattention (7 items) and hyperactivity (6 items) problems. A higher score indicates more severe symptom severity (Achenbach and Rescorla, 2003). Inattention refers to forgetfulness, inability to concentrate, failure to finish, poor work, disorganization, losing things, and being poor at details (Weiss et al., 2003; Willcutt et al., 2012). Hyperactivity problems include inability to sit still, accidents, impulsivity, rushes, being fidgety, and impatience (Willcutt et al., 2012). The items in the two subscales are consistent with the DSM categories of ADHD symptoms (Achenbach et al., 2003). Inattention (0–14) and hyperactivity (0–12) subscores summed up to ADHD total score (0–26).

2.2. MRI data acquisition and preprocessing

All imaging data were acquired on a customized Siemens 3T Skyra with a standard 32-channel Siemens receiver head coil and a body transmission coil. T1-weighted high-resolution structural images were acquired using a 3D MPRAGE sequence with 0.7 mm isotropic resolution (FOV = 224 mm, matrix = 320, 256 sagittal slices, TR = 2400 ms, TE = 2.14 ms, TI = 1000 ms, FA = 8°) and used to register rs-fMRI data to a standard brain space. The rs-fMRI data were collected in two sessions, using gradient-echo echo-planar imaging (EPI) with 2.0 mm isotropic resolution (FOV = 208 × 180 mm, matrix = 104 × 90, 72 slices, TR = 720 ms, TE = 33.1 ms, FA = 52°, multi-band factor = 8). Within each session, oblique axial acquisitions alternated between phase encoding in a right-to-left (RL) direction in one run and phase encoding in a left-to-right (LR) direction in the other run. Each run lasted 14.4 min (1200 frames). Physiological data (i.e., cardiac and respiratory signals) associated with each functional MR scan were also acquired, using a standard Siemens pulse oximeter placed on a digit and a respiratory belt placed on the abdomen. These physiological signals were sampled equally at 400 Hz (~288 samples per frame). More details of the data collection procedures can be found in the HCP S1200 Release Reference Manual.

In the current study, only the first session (two runs: LR and RL) of rs-fMRI data were used and processed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). Images of each participant were first realigned (motion corrected) and a mean functional image volume was constructed from the realigned image volumes. These mean images were co-registered with the high-resolution structural MPRAGE image and then segmented for normalization with affine registration followed by nonlinear transformation. The normalization parameters determined for the structural volume were then applied to the corresponding functional image volumes for each participant. Afterwards, the images were smoothed with a Gaussian kernel of 4 mm at Full Width at Half Maximum.

White matter and cerebrospinal fluid signals, whole-brain mean signal, and physiological signals were regressed out to reduce spurious BOLD variances and to eliminate cardiac- and respiratory-related artifacts. A temporal band-pass filter ($0.009\ \text{Hz} < f < 0.08\ \text{Hz}$) was also applied to the time course to obtain low-frequency fluctuations, as in our previous studies (Zhang and Li, 2018). Lastly, in order to further eliminate global motion-related artifacts, a "scrubbing" method was applied. Specifically, frame-wise displacement given by $FD(t) = |\Delta d_x(t)| + |\Delta d_y(t)| + |\Delta d_z(t)| + |\Delta\alpha(t)| + |\Delta\beta(t)| + |\Delta\gamma(t)|$ was computed for every time point t, where (d_x, d_y, d_z) and (α, β, γ) are the translational and rotational movements, respectively (Power et al., 2012). Moreover, the root mean square variance of the differences (DVARS) in % BOLD intensity $I(t)$ between consecutive time points across brain voxels, was computed as: $DVARS(t) = \text{sqrt}(|I(t) - I(t\text{-}1)|^2)$, where the brackets indicate the mean across brain voxels. Following previous HCP studies, we marked volumes with FD > 0.2 mm or DVARS > 75 as well as one frame before and two frames after these volumes as outliers (censored frames). Uncensored segments of data lasting fewer than five contiguous volumes were also labeled as censored frames (Li et al., 2019). A total of 285 participants who had either BOLD run with more than half of the frames flagged as censored were removed from further analyses.

2.3. Resting state functional connectivity (FC) of the caudate and LN

The masks of the caudate and LN were obtained from the Automated Anatomic Labeling atlas (Tzourio-Mazoyer et al., 2002) and used as the seed regions. Whole-brain voxel-wise analyses were conducted to compute the FC of caudate and LN. For each run, the BOLD time courses of each voxel were averaged, and the correlation coefficient was computed between the average time course of all voxels of the seed and the time courses of all other voxels for individual participants. The correlation matrix was Fisher's z-transformed into z score maps and averaged across the two runs for each participant.

In group analyses, a whole-brain regression of seed-based FC (caudate or LN) each against ADHD total score, inattention subscore, or hyperactivity subscore was conducted in men and women separately, with years of age as a covariate. The results were evaluated at voxel $p < 0.001$, uncorrected, in combination with a cluster $p < 0.05$, corrected for family-wise error (FWE) of multiple comparisons, on the basis of Gaussian random field theory, as implemented in SPM, following the reporting standards (Poldrack et al., 2008). In addition to reporting the peak voxel Z value, we computed the effect size by approximating Cohen's d from the t-statistics using the expression $d = \frac{2t}{\sqrt{df}}$ (Kleber et al., 2016). Although we aimed primarily to examine sex differences, we also conducted the analyses for men and women combined and showed the results in the Supplement. Likewise, as we were interested in the distinct neural correlates of inattention and hyperactivity, we reported the regression results on ADHD total score in the Supplement, too.

For the regions of interest (ROIs) identified from linear regressions in men or women alone, we computed the β estimates of the FC with caudate or LN for all subjects. We then tested sex differences in the regressions using slope tests, with age as a covariate (Zar, 1999). Note that the slope tests of sex differences were not "double-dipping" (Dhingra et al., 2020; Ide et al., 2020; Le et al., 2019), as the regression maps were identified with a threshold and a cluster showing correlation in men could also show a correlation in women that just missed the threshold,

and vice versa. Thus, direct tests of the slopes were needed to confirm sex differences.

2.4. K-means clustering of resting state FC for ADHD subtypes

To examine whether the FC features of caudate and LN characterized inattention and hyperactivity subtypes, we applied *k*-means clustering to the β estimates of the FC derived from the regressions (Deen et al., 2011) for men and women separately. The *k*-means algorithm was repeated 100 times. The *k*-means clustering partitioned the observations into 1 to *n* sets and provided a criterion value for each partitioning. The optimal number (*k*) of clusters was determined by the solution that minimized sum of squared distances from the mean vector (centroid) of each cluster, which yielded the greatest criterion value. We then compared the inattention and hyperactivity subscores and FC β values pair-wise among the *k* clusters of participants in an independent *t*-test with age as a covariate.

3. Results

3.1. Sex differences in ADHD scores

The distribution of ADHD total score, inattention and hyperactivity subscore of men and women is presented in the left panels of Fig. 1A, **1B** and **1C**, respectively. With age as a covariate, two-sample *t* tests (two-tailed) showed that ADHD total score was significantly higher [$t(742) = 2.02, p = 0.044$] (Fig. 1A, right panel) but the inattention [$t(742) = 1.82$, $p = 0.069$] and hyperactivity [$t(742) = 1.69, p = 0.091$] subscores were only marginally higher in men than in women (Fig. 1B and C, right panels).

In pairwise regressions with age as a covariate, ADHD total score was significantly correlated with inattention ($r = 0.898$, $p < 0.001$) and hyperactivity ($r = 0.861$, $p < 0.001$) subscore in men. The inattention and hyperactivity subscore were also significantly correlated, though with a smaller effect size ($r = 0.550$, $p < 0.001$). Likewise, ADHD total score was significantly correlated with inattention ($r = 0.886, p < 0.001$) and hyperactivity ($r = 0.838, p < 0.001$) subscore in women. Inattention and hyperactivity subscores were also significantly correlated albeit with a smaller effect size in women ($r = 0.491$, $p < 0.001$).

3.2. Caudate and LN FC in relation to ADHD scores

For men and women combined, the whole-brain connectivity of caudate and LN against ADHD scores is shown in Supplementary Figs. S1 and S2, respectively. The clusters are summarized in Supplementary Table S1. Stronger caudate FC with the left middle frontal gyrus was associated with higher ADHD total score and inattention subscore. Stronger LN FC with the left inferior frontal gyrus (IFG) was associated with higher ADHD total score and inattention subscore; stronger LN FC with the right superior occipital gyrus was associated with lower inattention score; and stronger LN FC with the left posterior cingulate cortex was associated with lower hyperactivity subscore.

For men and women examined separately, brain regions functionally connected to caudate or LN in relation to ADHD scores are shown in Supplementary Figs. S3–S5, and the clusters are also summarized in Supplementary Table S1.

In men, no clusters showed caudate FC in significant correlation with ADHD total score or subscores. Stronger LN FC with the right superior frontal gyrus (SFG; x = 16, y = 16, z = 48, peak voxel $Z = -4.71$, Cohen's $d = 0.51$; volume = 1360 mm^3) was associated with lower ADHD total score, and stronger LN FC with the right SFG (x = 16, y = 14, z = 46, peak voxel $Z = -4.90$, Cohen's $d = 0.53$; volume = 2352 mm^3)

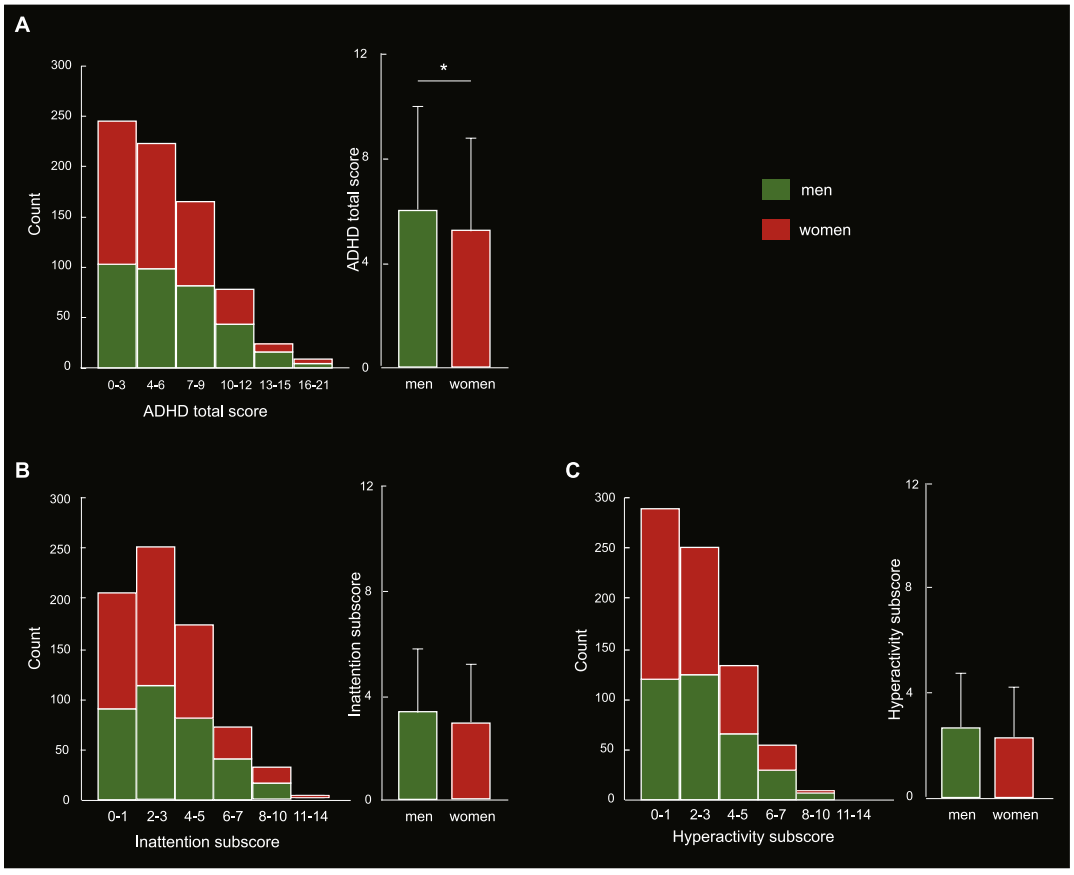

Fig. 1. The distribution (left panels) and mean ± SD (right panels) of **(A)** ADHD total score, **(B)** inattention subscore, and **(C)** hyperactivity subscore for men (green) and women (red). *$p < 0.05$, two-sample *t*-test with age as a covariate.

was also associated with lower inattention subscore.

In women, stronger caudate FC with the right inferior parietal gyrus (IPG; x = 28, y = −46, z = 52, peak voxel $Z = -4.95$, Cohen's $d = 0.51$; volume = 848 mm^3) was associated with lower inattention subscore; stronger LN FC with the mid-cingulate cortex (two clusters: x = −10, y = 8, z = 70, peak voxel $Z = 4.66$, Cohen's $d = 0.48$; volume = 816 mm^3; and x = −2, y = −10, z = 44, peak voxel $Z = 4.49$, Cohen's $d = 0.37$; volume = 1552 mm^3) was associated with higher ADHD total score; stronger LN FC with the left IFG (x = −48, y = 28, z = 18, peak voxel $Z = 4.17$, Cohen's $d = 0.42$; volume = 832 mm^3) was associated with higher inattention subscore; and stronger LN FC with a cluster in the dorsal ACC/supplementary motor cortex (dACC/SMA; x = 2, y = 8, z = 46, peak voxel $Z = 4.20$, Cohen's $d = 0.42$; volume = 2568 mm^3) was associated with higher hyperactivity subscore.

For each of the four ROIs identified in relation to inattention and hyperactivity subscores in men or in women alone, we computed the correlations between FC β values and ADHD subscores with age as a covariate and conducted slope tests to examine sex differences in the correlations. The results confirmed sex differences in all except for the regression of LN FC with left IFG against inattention score (Fig. 2). The statistics are summarized in Supplementary Table S2.

In addition, for men and women combined and separately, we also examined the whole-brain connectivity of putamen and GP against ADHD scores. The clusters are summarized in Supplementary Table S3.

3.3. Inattention and hyperactivity subtypes

For men only, the *k*-means clustering was applied to the $FC_{LN\text{-}SFG\text{-}R}$ since this is the only significant feature identified from the whole-brain functional connectivity analyses in men alone. An optimal solution of 3 clusters was identified with a criterion value of 359.96 (Fig. 3A). The $FC_{LN\text{-}SFG\text{-}R}$ β value as well as inattention and hyperactivity subscores are shown for the three subgroups in Fig. 3B and C, respectively. With age as a covariate, one-way ANOVA showed significant differences in $FC_{LN\text{-}SFG\text{-}R}$ [$F(2,346) = 359.30$, $p < 0.001$], inattention [$F(2,346) = 20.15$, $p < 0.001$] and hyperactivity [$F(2,346) = 9.12$, $p < 0.001$] subscore between the three groups. Bonferroni post-hoc tests confirmed significant differences in $FC_{LN\text{-}SFG\text{-}R}$ between the three groups in men: M1: n = 19, mean ± SD = −0.19 ± 0.10; M2: n = 213, −0.01 ± 0.04; M3: n = 117, 0.11 ± 0.07 (all p's < 0.001). The inattention subscore of M1 (6.16 ± 3.32) was significantly higher than M3 (2.68 ± 2.00) and M2 (3.46 ± 2.33) (both p's < 0.001) and the inattention subscore of M2 was also significantly higher than M3 ($p = 0.009$). The hyperactivity subscore of M1 (4.58 ± 2.04) was significantly higher than M3 (2.57 ± 2.00) ($p = 0.030$) and M2 (2.56 ± 2.05) ($p = 0.001$) but was not significantly different between M2 and M3 ($p = 1.000$).

For women only, *k*-means clustering was applied to three features identified in the whole-brain analyses, i.e., the $FC_{caudate\text{-}IPG\text{-}R}$ and $FC_{LN\text{-}IFG\text{-}Tri\text{-}L}$ β values identified in regression to the inattention subscore and the $FC_{LN\text{-}dACC/SMA}$ β value in regression to the hyperactivity subscore. An optimal solution of 3 clusters (left panel) was identified with a criterion value of 124.21 and inattention and hyperactivity subscores of the 3 groups (right panel) are shown in Fig. 4A. With age as a covariate, one-way ANOVA showed significant differences in inattention [$F(2,392) = 6.64$, $p = 0.001$] and hyperactivity [$F(2,392) = 6.42$, $p = 0.002$] subscore between the three groups in women. Bonferroni post-hoc tests

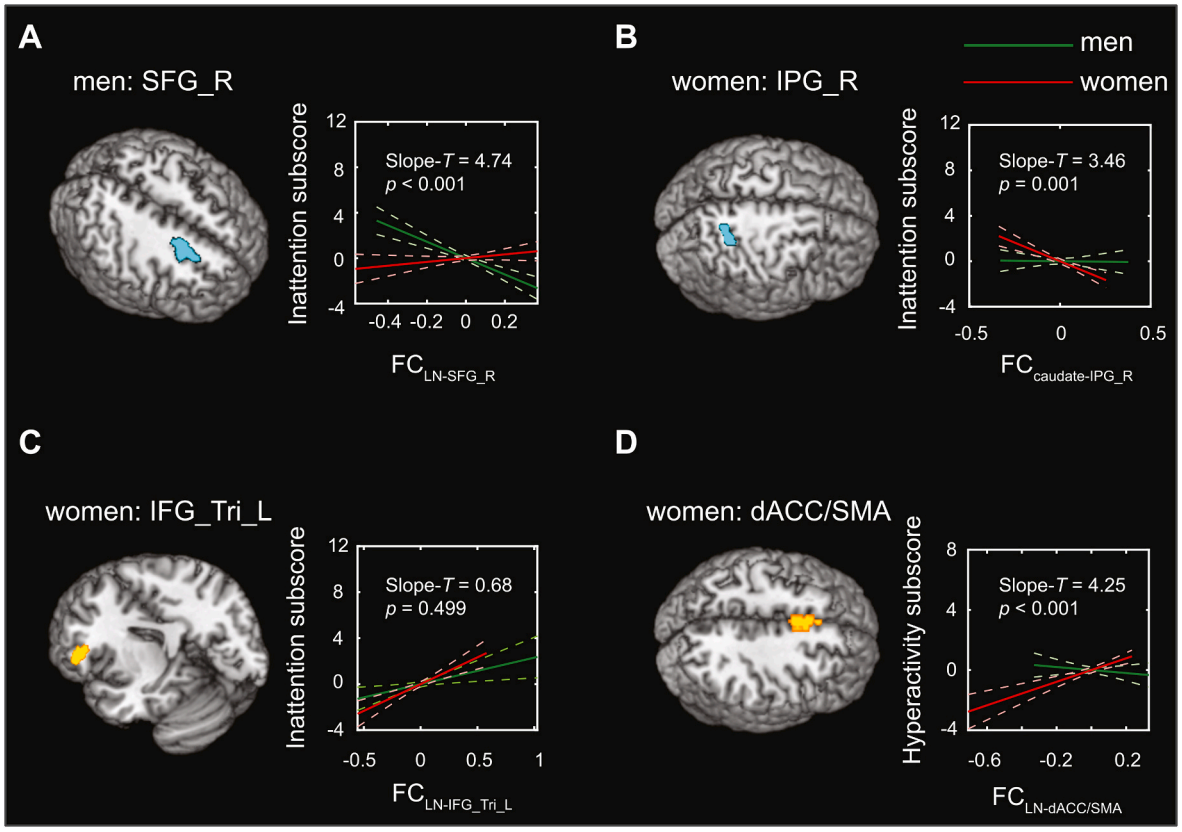

Fig. 2. Brain regions showing caudate or LN connectivity in correlation with inattention or hyperactivity subscore in men or in women alone. (A–D) *Left panels*: Clusters identified in men or in women; SFG: superior frontal gyrus; IPG: inferior parietal gyrus; IFG_Tri: inferior frontal gyrus (pars triangularis); dACC/SMA: dorsal anterior cingulate cortex/supplementary motor area; L: left, R: right. Warm and cold color indicate positive and negative correlation between the FC and ADHD subscore in men or in women, respectively. *Right panels*: Slope tests of sex differences in linear correlation between FC and ADHD scores. Note that the residual scores after controlling for age as a covariate are shown here. Dashed lines represent 95% confidence intervals of the mean regressions (solid lines). See Supplementary Table S2 for statistics.

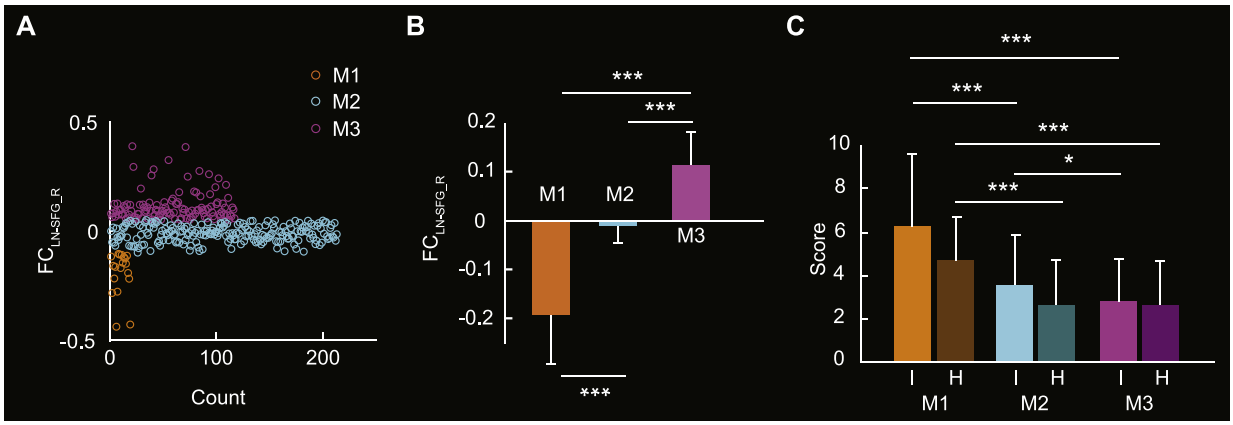

Fig. 3. Clustering of FC and group comparisons of FC and of inattention and hyperactivity subscores in men. (A) Three groups were identified with the *k*-means clustering of $FC_{LN\text{-}SFG\_R}$ (the brain cluster was identified from regression with inattention subscore): M1 (orange), M2 (cyan) and M3 (magenta); (B) Differences in $FC_{LN\text{-}SFG\_R}$ between M1, M2, and M3; (C) Differences in Inattention (left; lighter) and Hyperactivity (right; darker) subscore between M1, M2 and M3; Bars represent mean ± SD; ***$p < 0.001$, **$p < 0.005$, and *$p < 0.05$.

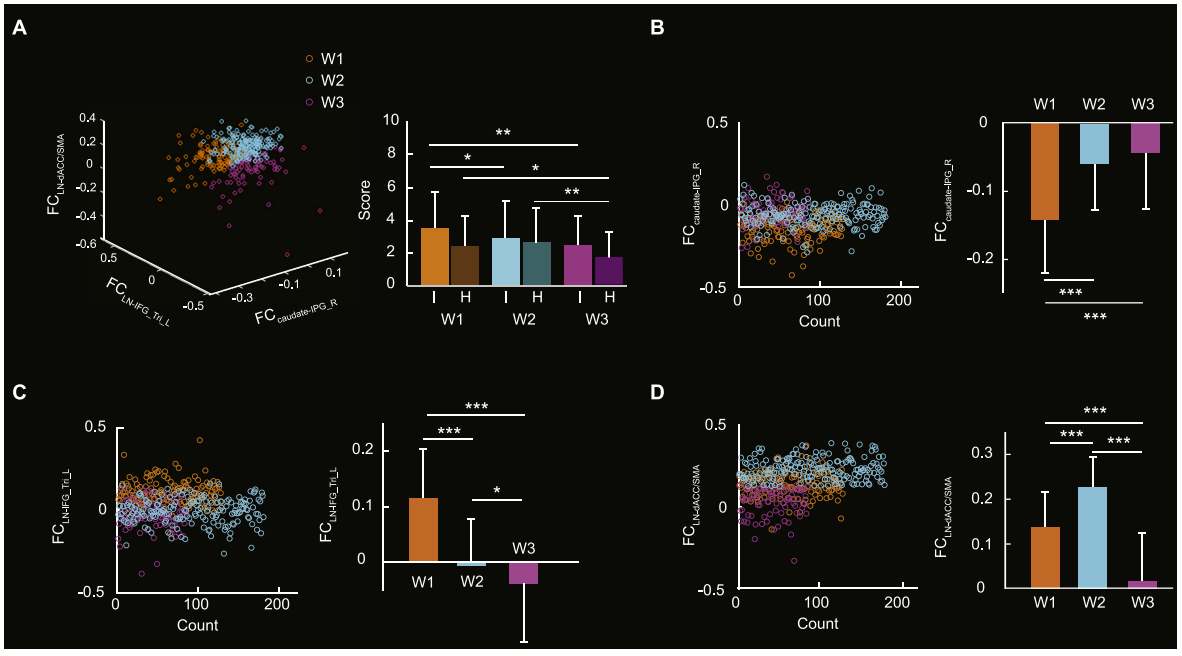

Fig. 4. Clustering of the FC's and group comparisons of the FC's and of inattention and hyperactivity subscore in women. Three groups were identified: W1 (orange), W2 (cyan) and W3 (magenta). (A) *Left panel*: 3D plot of the clusters; X: $FC_{caudate\text{-}IPG\_R}$, Y: $FC_{LN\text{-}IFG\_Tri\_L}$, Z: $FC_{LN\text{-}dACC/SMA}$; the brain clusters were identified from regression with inattention subscore (X and Y) or hyperactivity subscore (Z). *Right panel*: Differences in Inattention (left; lighter) and Hyperactivity (right; darker) subscore between W1, W2 and W3; Bars represent mean ± SD; ***$p < 0.001$ and *$p < 0.05$. (B–D) *Left panel*: Clustering of the subjects for $FC_{caudate\text{-}IPG\_R}$, $FC_{LN\text{-}IFG\_Tri\_L}$ and $FC_{LN\text{-}dACC/SMA}$, respectively; *Right panel*: FC's of W1, W2 and W3; Bars represent mean ± SD; ***$p < 0.001$.

showed significantly higher inattention subscore in group W1 (n = 129, 3.44 ± 2.19) as compared to W2 (n = 181; 2.81 ± 2.31) ($p = 0.030$) and W3 (n = 85, 2.39 ± 1.95) ($p = 0.002$) but no significant difference between W2 and W3 ($p = 0.450$); and significantly lower hyperactivity subscore in W3 (1.67 ± 1.53) as compared to W1 (2.35 ± 1.84) ($p = 0.021$) and W2 (2.55 ± 2.06) ($p = 0.001$) but no significant difference between W1 and W2 ($p = 1.000$).

The FC's are shown in Fig. 4B, C, and 4D. A one-way ANOVA with age as a covariate showed significant group differences in $FC_{caudate\text{-}IPG\text{-}R}$ [$F(2,392) = 62.46$, $p < 0.001$]. Bonferroni post-hoc tests showed a significant difference between group W1 (−0.14 ± 0.08) and both W2 (−0.06 ± 0.07) and W3 (−0.04 ± 0.08) (*p's* < 0.001), but not between W2 and W3 ($p = 0.391$). For $FC_{LN\text{-}IFG\text{-}Tri\text{-}L}$, the ANOVA likewise showed significant group differences [$F(2,392) = 103.50$, $p < 0.001$], with a significant difference between W1 (0.12 ± 0.09) and both W2 (−0.01 ± 0.08) and W3 (−0.04 ± 0.11) (*p's* < 0.001), as well as between W2 and W3 ($p = 0.019$) in post-hoc tests. For $FC_{LN\text{-}dACC/SMA}$, the ANOVA showed significant group differences [$F(2,392) = 202.49$, $p < 0.001$], with W1 (0.14 ± 0.08), W2 (0.23 ± 0.07), and W3 (0.02 ± 0.11) significantly different from each other pair-wise in post-hoc tests (*p's* < 0.001).

4. Discussion

We observed significantly higher ADHD total score in men as compared to women, in line with previous observations (Arnett et al., 2015; Greven et al., 2011). In men, weaker LN FC with the right SFG was associated with higher inattention subscore. In women, weaker caudate FC with the right IPG and stronger LN FC with the left IFG was associated

with higher inattention subscore; and stronger LN FC with the dACC/SMA was associated with higher hyperactivity subscore. Men and women differed in most of these correlations, as confirmed by slope tests, suggesting sex differences in striatal FC in relation to ADHD symptom severity. In addition, *k*-means clustering of the FC features identified 3 groups each in men and in women, with one group showing higher inattention and hyperactivity score and a second group showing only higher inattention and hyperactivity score, in men and in women respectively, than the third group. The results suggest striatal FC features as sex-specific markers of ADHD and potentially clinical subtypes of ADHD. We discussed the main findings in the below.

4.1. Sex differences in the DS FC in relation to ADHD symptom severity

Weaker LN FC with the right SFG is associated with higher inattention subscore in men, consistent with a previous report of diminished connectivity between the left putamen and right SFG in ADHD relative to control children (Cao et al., 2009). The latter work, however, did not specifically examine sex differences. Anatomically and functionally connected (Di Martino et al., 2008; Li et al., 2013), the putamen and SFG both play vital roles in attention, working memory, response inhibition and cognitive control (Hu et al., 2016; Hwang et al., 2015) and have been implicated in the etiological processes of ADHD. For instance, children with ADHD as compared to controls showed smaller GMV in the right SFG and putamen and bilaterally in the GP (Overmeyer et al., 2001). ADHD adults relative to healthy controls displayed greater putamen activation during no-go inhibition in the go/no-go task (Dibbets et al., 2009). Consistent with dual pathway model of ADHD where prefrontal cortical-dorsal striatal circuit dysfunction underlies inattention (Sonuga-Barke, 2005), the current results add to this literature by highlighting potential sex differences in this component mechanism of ADHD symptom severity.

Weaker caudate FC with the right IPG was associated with higher inattention subscore in women. The IPG projects to the striatum in primates; in particular, the caudal portion of the inferior parietal lobule as well as the lower bank of the intraparietal sulcus project predominantly to the caudate nucleus (Yeterian and Pandya, 1993). Diffusion tensor imaging likewise confirmed parietalcortical-dorsal striatal connectivity in humans (Jarbo and Verstynen, 2015). Frontal and parietal cortical projections appeared to converge in distinct patterns in the striatum (Choi et al., 2017). Both the IPG and DS support goal-directed attention (Bayerl et al., 2010; Corbetta and Shulman, 2002; Igelström and Graziano, 2017; Wu et al., 2018). In accord with earlier reports of altered neural metrics of the right IPG and DS (Zhou et al., 2019), the current findings again suggest potential sex differences that need to be considered in the research of neural markers of ADHD.

In contrast, stronger LN FC with the left IFG was associated with greater inattention severity in women (though slope tests failed to demonstrate significant sex differences). This could suggest a role of frontostriatal hyperconnectivity in excessive reorientation to irrelevant distractors in ADHD (Sanefuji et al., 2017) or, alternatively, a compensatory process to support attention and cognitive control (see Rubia, 2018 for a review). IFG dysfunction is known as a pronounced biomarker of ADHD (see Rubia, 2011 for a review). Both children and adults with ADHD showed reduced activation of IFG during motor inhibition, attention and cognitive switching (Booth et al., 2005; Cubillo et al., 2010; Rubia et al., 2008). A previous study suggested that the hyperactive-impulsive subtype was associated with higher cortico-striatal connectivity as compared to typical developing children (Sanefuji et al., 2017). Thus, although it remains premature to interpret the functional significance, the current finding accords broadly with earlier studies implicating fronto-parieto-striatal circuit dysfunction in ADHD (Arnsten and Rubia, 2012; Cao et al., 2013; Tian et al., 2006) and can be considered with structural imaging studies showing smaller LN volumes in women relative to men and sex differences in striatal-frontal cortical structural connectivity (Lei et al., 2016; Rijpkema et al., 2012).

We also found that stronger LN FC with dACC/SMA was related to higher hyperactivity subscore in women but not in men. DS hyperconnectivity with the dACC/SMA has been reported in ADHD (Damiani et al., 2021). In fact, an earlier work specifically showed that the striatum of girls but not boys with ADHD relative to controls showed stronger positive FC with the ACC (Rosch et al., 2018). Further, this and other cortical-subcortical circuits have been investigated in patients with Tourette Syndrome (TS), a condition highly comorbid with ADHD (Bhikram et al., 2020; Martino et al., 2019). For instance, TS patients showed higher fractional anisotropy in SMA-putamen fiber tracts relative to controls and in relation to lower accuracy in motor timing control (Martino et al., 2019). During resting state both putamen and pallidum show positive FC with the dACC/SMA (Di Martino et al., 2008; Zhang et al., 2012), likely to support motor responses to salient and relevant stimuli (Albertini et al., 2020) and behavioral flexibility (Morris et al., 2016). The dACC/SMA and DS, including both putamen and caudate showed higher response to task-switching and incongruency processing in adults with ADHD as compared to controls (Bush et al., 1999; Dibbets et al., 2010; Plichta et al., 2009). Notably, although typically considered part of the motor circuit, the SMA and putamen have been implicated in cognitive deficits in neurological conditions (Luo et al., 2019; Mao et al., 2020; Schönberger et al., 2015). Along with this literature, the current findings suggest a unique and potentially sex-specific role of dACC/SMA putamen circuit dysfunction in manifesting impulsivity and hyperactivity in ADHD.

More broadly, the sex-specific findings of aberrant DS FC with distinct frontoparietal regions may suggest difficulties in the central control process and behavioral implementation each in men and in women with ADHD. Specifically, men with more inattentive symptoms showed diminished DS FC with the SFG, a frontal region central to working memory, information manipulation, and cognitive control (Hu et al., 2016; Li et al., 2021; Li et al., 2013). In contrast, women with more inattentive and hyperactive symptoms showed altered DS FC with the IPG, IFG, dACC/SMA, areas of the ventral attention and saliency circuits and predominantly engaged in attentional re-orientation and prompt execution of goal-directed behavior (Cai et al., 2014; Chikazoe et al., 2007; Desmurget and Sirigu, 2012; Lee et al., 1999; Manza et al., 2016). In support of this proposition, parent ratings of executive function skills were better in distinguishing subjects with ADHD from healthy controls in males than in females (Skogli et al., 2013). Studies combining imaging and behavioral tests to distinguish these functional domains are needed to evaluate the potentially sex-specific neural processes of ADHD.

Additionally, sex differences have also been observed in other comorbidities of ADHD, with men potentially more vulnerable than women to externalizing spectrum and substance use disorders (see Martel, 2013 for a review). A widely investigated model implicates striato-frontal circuit dysfunction in deficits in inhibitory control and decision-making and the pathogenesis of addiction (Hung et al., 2020; Volkow et al., 2011; Wang et al., 2018). Thus, the current findings of sex differences in striato-frontal connectivity in relation to ADHD symptoms may help research of the etiological processes of these comorbidities.

4.2. ADHD subtypes defined by DS FC features

ADHD is known to be heterogeneous in behavioral manifestations and underlying neurobiology (Nigg, 2005). The challenge in differentiating ADHD subtypes results in part from the subjective nature of clinical assessments (Woo and Rey, 2005). For instance, studies showed poor agreement between parents and teachers in structured interviews for ADHD subtypes (Woo and Rey, 2005). Moreover, measures of clinical symptoms provide little knowledge about the underlying neural mechanism of the dimensional nature of ADHD symptoms (Bush, 2009). With *k*-means clustering of Conner's rating scale scores, an earlier study identified three subtypes (ADHD-C, ADHD-I, and ADHD-H), with the ADHD-H showing higher connectivity in the corticostriatal network and the ADHD-I showing higher connectivity in the right ventral attention

network (Sanefuji et al., 2017). Regional anatomical connectivity, as revealed by structural covariance network analysis, could also distinguish ADHD subtypes in children (Saad et al., 2017). In graph theoretical analysis, ADHD-I relative to ADHD-C showed higher nodal degree (i.e., the number of connections that a node has with the rest of the network) of the hippocampus but lower of the ACC, middle frontal gyrus and putamen.

While these findings highlighted the neural markers of the heterogeneity of ADHD diagnoses, studies of neurotypical populations can inform dimensional variation in ADHD traits and the biological bases of the dimensional variances (Fair et al., 2012). Here, focusing solely on DS FC of largely typically developing individuals, we showed that men and women can each be distinguished in three groups, with one (ADHD-C) significantly higher in both inattention and hyperactivity both in men and women, and another significantly higher only in inattention (ADHD-I) and hyperactivity (ADHD-H) subscore in men and women, respectively, as compared to a third group. Specifically, FC features identified in relation to inattention subscore distinguished male ADHD-C and ADHD-I from a third, lowest-scored group. In contrast, FC features of both inattention and hyperactivity distinguished female ADHD-C and that of hyperactivity (i.e., LN connectivity with the dACC/SMA) specifically distinguished female ADHD-H from the third, lowest-scored group. That is, these striatal FC features did not identify a unique group of ADHD-H males or ADHD-I females. It is very likely that DS FC alone does not provide sufficient information to identify these ADHD subtypes. Further, it should be noted that these findings are not necessarily inconsistent with the observation that females with ADHD tend not to exhibit impulsivity or hyperactivity (Slobodin and Davidovitch, 2019); behavioral features that can be modified by environmental factors, including social norms (Young et al., 2020). A more comprehensive study to include multiple neural markers, including other seed-based FCs, task-related activations and/or regional GMV would perhaps represent a fruitful approach to addressing this issue. In the spirit of Research Domain Criteria research (see Hyman, 2007 for a review), studies of the striato-frontal circuits would help refining the diagnoses of ADHD.

4.3. Limitations of the study and conclusions

The current study has a number of limitations. First, the HCP aimed to recruit individuals that broadly reflect the general populations as long as the participants do not receive treatment for the mental condition. Thus, the current findings reflect the symptom severity rather than clinical diagnosis of ADHD. Second, we did not form specific hypotheses regarding sex differences in the relationships between DS FC and ADHD subscores; the study should be considered as exploratory, and the findings need to be verified. Further, we did not consider other clinical variables, including anxiety, depression and substance use, frequent comorbidities of ADHD, in data analyses. Thus, the findings would need to be verified in clinical populations of ADHD. Third, the current study utilized one of the two sessions of the HCP data (REST1). Earlier studies showed that the test-retest reliability of FC metrics across REST1 and REST2 varied from 0.44 to 0.54. Details in analytics as well as within-subject variation in arousal and emotion states may account for the moderate correlation. This suggests the need of more and perhaps larger-scale studies to fully understand the stability of FC metrics. Besides, we focused solely on resting state FC. Future work combining multi-modal imaging data and/or employing different connectivity metrics (Park and Park, 2016) may shed light on the neural markers and sex differences in the neural markers of ADHD subtypes. Further, although the identification of subpopulations offers an alternative approach toward characterizing the heterogeneity of ADHD (Feczko et al., 2019), the current findings fall short of providing a neural basis for classification of individual ADHD traits (Lange et al., 2014). Finally, whole-brain connectomics identified primarily cortical connectivities in the classification of sex (Weis et al., 2020), suggesting the need to extend beyond the subcortical circuits in investigating sex-specific subtypes of ADHD symptoms.

In conclusion, we confirmed sex differences in ADHD symptom severity and its relationship to DS FC in young adults. These findings add to the growing imaging literature on the neural features of ADHD, support the utility of FC-based neural markers to characterize ADHD pathophysiology, and suggest the critical importance in considering sex differences in neurobiological studies of ADHD.

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.

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Appendix A. Supplementary data

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