# Stepwise functional connectivity reveals altered sensory-multimodal integration in medication-naïve adults with attention deficit hyperactivity disorder

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## Abstract

Neuroimaging studies indicate that children with attention-deficit/hyperactivity disorder (ADHD) present alterations in several functional networks of the sensation-to-cognition spectrum. These alterations include functional over-connectivity within sensory regions and under-connectivity between sensory regions and neural hubs supporting higher-order cognitive functions. Today, it is unknown whether this same pattern of alterations persists in adult patients with ADHD who had never been medicated for their condition. The aim of the present study was to assess whether medication-naïve adults with ADHD presented alterations in functional networks of the sensation-to-cognition spectrum. Thirty-one medication-naïve adults with ADHD and twenty-two healthy adults underwent resting-state functional magnetic resonance imaging (rs-fMRI). Stepwise Functional Connectivity (SFC) was used to characterize the pattern of functional connectivity between sensory seed regions and the rest of the brain at direct, short, intermediate and long functional connectivity distances, thus covering the continuum from the sensory input to the neural hubs supporting higher-order cognitive functions. As compared to controls, adults with ADHD presented increased SFC degree within primary sensory regions and decreased SFC degree between sensory seeds and higher-order integration nodes. In addition, they exhibited decreased connectivity degree between sensory seeds and regions of the default-mode network. Consistently, the higher the score in clinical severity scales the lower connectivity degree between seed regions and the default mode network.



## Keywords

ADHD; adult ADHD; resting-state fMRI; Stepwise functional connectivity; default mode network

## Introduction

Attention-deficit/ hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by excessive levels of inattention, impulsivity and hyperactivity [American Psychiatric Association, 2013]. Approximately 35% of children with ADHD still fulfill DSM-IV diagnostic criteria for ADHD in adult life [Biederman et al., 2010].

Neuroimaging research on ADHD has typically focused on networks supporting higher-order functions, with little attention to findings in primary sensory regions. For instance, several studies report a weaker segregation between cognitive control networks and default mode network both in children and adults with ADHD [Cao et al., 2009; Castellanos et al., 2008; Hoekzema et al., 2014; Lin et al., 2018b; Sun et al., 2012], though only a few studies highlight the need to clarify how sensory regions interact with higher-order association networks in ADHD [Castellanos and Proal, 2012a; Lin et al., 2018a]. In response to this, recently developed analysis tools such as the Stepwise functional connectivity approach (SFC)[Sepulcre et al., 2012] allow evaluating the presence of abnormalities in multi-level information processing systems from early sensory to higher-order cognitive circuits in the brain.

Making use of an SFC protocol, Carmona et al. (2015) provided evidence that the information flow between primary sensory cortices and higher-order association nodes might be disrupted in children with ADHD. Compared with controls, children with ADHD presented increased interconnectivity within primary sensory cortices at initial steps of the sensation to cognition continuum [Carmona et al., 2015]. At the final steps of the sensation to cognition continuum, children presented decreased SFC degree with executive processing areas, and increased SFC degree with DMN areas. These studies indicate atypical connectivity transitions between sensory and higher-order large-scale functional networks, thus potentially compromising the flow of information across the sensation-to-cognition continuum. However, whether this pattern is also present in the adult form of the disorder is still unknown.

The aim of the present study was to test whether medication-naïve adult patients with ADHD show impaired connectivity between primary sensory to attentional and higher-order cognitive circuits. For this purpose, we applied a Stepwise Functional Connectivity (SFC) protocol aimed to detect which parts of the brain were connected with primary sensory regions not only through direct paths (i.e., one-step functional distance, which would be the standard functional connectivity analysis), but also through indirect connections that involve a varying number of link-steps distances or "relay stations". Hence, in contrast to other standard methods such as functional connectivity strength evaluation, SFC allows measuring functional connectivity between any pair of brain locations that are connected by any finite number of relay stations, something that cannot be attained using standard functional connectivity assessments.

Based on the assumption that adult ADHD may share similarities with childhood ADHD in terms of

functional connectivity alterations, we predicted that our sample of medication-naïve adults with ADHD would show increased SFC within sensory regions, as well as decreased connectivity between sensory seeds and networks supporting executive functions, and increased connectivity between sensory seeds and key nodes of the DMN.

## Methods

### Participants

A total of 31 adults with combined ADHD and 22 healthy controls were recruited (see demographics in Table 1). We ensured both sexes were well represented in both groups (12 women in the ADHD group, and 16 women in the HC group). The ADHD patients were selected by a specialized team of psychiatrists and psychologists from *Vall d'Hebron Hospital* in Barcelona (Spain), where they were evaluated. All patients met DSM-V criteria [American Psychiatric Association, 2013] for ADHD combined subtype and were medication-naïve.

Standard ADHD scales were administered to both groups, including the Conners Adult ADHD Rating Scale (CAARS) [Conners, C., Sitarenios, G., Parker, J.D., 1998], the Wender Utah Rating Scale (WURS) [Ward MF, Wender PH, 1993] and the ADHD Rating Scale [DuPaul et al., 1998]. All ADHD scores were significantly higher in the ADHD sample (see demographic data in Table 1).

Exclusion criteria included comorbidity with other psychiatric diseases or personality disorders, assessed by the Structured Clinical Interview for Axis I (SCID-I) [First et al., 1997] and Axis II disorders [First et al., 1994]. Participants with substance abuse disorder, including those who consumed tobacco and cannabis within the last 6 months, were also excluded. Participants with an estimated WAIS-III IQ [Wechsler, 1997] lower than 80 were excluded. The study was approved by the *Hospital de Vall d'Hebron Ethics Committee* and informed consent was obtained from all participants before taking part in the study.

### fMRI image acquisition and preprocessing

Images were acquired using a Philips Achieva 3T scanner. T1-weighted images were obtained using a FSPGR sequence (TR: 8.2 ms, TE: 3.7ms, FA: 88, voxel size: 0.94 x 0.94, slice thickness: 1.00 mm, gap: 0 mm, matrix size: 256 x 256 x 180). An EPI-T2* sequence was used to obtain the resting-state functional volumes in a single run that lasted 5.8 min (116 time points, TR: 3000 ms, TE: 35 ms, FA: 90, in-plane voxel size: 1.80 x 1.80 mm, slice thickness: 3.0 mm, gap: 1.0 mm, matrix size: 128 x 128). Due to a technical problem, 11 participants (evenly distributed between groups; $\chi^2 = 1.753;\ p = 0.186$) were scanned using a

different radiofrequency head coil (16 channels instead of 8 channels), which was considered in the analyses. Participants were instructed to remain still and awake with their eyes open during the functional run.

Functional MRI data were preprocessed with the software packages SPM12 (Welcome Department of Imaging Neuroscience, London, United Kingdom) and AFNI (Scientific and Statistical Computing Core, National Institute of Mental Health, Bethesda, MD). After removing the first 3 volumes, functional images were realigned to the mean image to correct for motion-related artifacts, despiked with 3dDespike AFNI tool (c1=2.5, c2=4), normalized to MNI standard space and spatially smoothed with a 6mm full-width-at-half-maximum Gaussian kernel. All functional images were down-sampled to 4mm voxels to facilitate computational calculations (Sepulcre et al., 2012). Finally, nuisance covariates (6 rigid body realignment parameters, mean white matter, mean cerebrospinal fluid and mean whole brain intensity signals) were regressed out to minimize the effects of movement.

Given the impact of in-scanner motion on functional connectivity analyses [Ciric et al., 2017; Di Martino et al., 2014; Power et al., 2014], participants with a mean Framewise Displacement (FD) over 0.2 mm as measured by the MCFLIRT tool [Jenkinson et al., 2002] were discarded. Additionally, we plotted a resting state functional connectivity quality control index (RSFC-QC;[Power et al., 2014]) to assess the effect of motion in functional connectivity as a function of node distance. The data quality control showed no relationship between functional connectivity estimates and node distance, thus pointing to a reduced effect of head motion artifacts in our data (Supplementary Figure 1).

Stepwise functional connectivity analysis

The SFC analysis allows computing the number of functional paths between previously defined seed regions and every other voxel in the brain at successive numbers of relay stations or "link-step" distances. Intermediate voxels work as relay stations or "link-steps" that range between 0 (direct, one link-step connection) and 6 (seven link-step connections) before stabilizing [Sepulcre et al., 2012] (see Supplementary Figure 2). Based on the number of relay stations, the degree of functional connectivity can be classified as direct (one link-step, and thus zero relay stations), short (two and three link-steps), medium (four and five link-steps), and long (six and seven link-steps).

For each processed brain we computed the whole-brain connectivity matrix by calculating the Pearson's correlation coefficient R for each pair of voxels. From this point onwards, only positive correlations were considered given the challenge of interpreting negative correlations after global signal regression in functional connectivity studies [Van Dijk et al., 2010; Murphy et al., 2009]. Correlation matrices were then filtered to contain only correlations surviving false discovery rate (FDR) correction ($q < 0.001$). The resulting matrix was then binarized. As a result, we obtained an unweighted "one link-step" matrix for each

subject containing 1's for each pair of voxels whose signals were significantly correlated and zeros otherwise.

In parallel, a set of 3 masks including three bilateral sensory seed regions was designed, each encompassing eight voxels (each voxel was 4mm isotropic) forming a cube. Following Sepulcre et al. (2012), the MNI coordinates for the most anterior, lateral and superior voxel of each cube was [8, -76, 10] in the primary visual cortex, [56, -12, 10] in the auditory cortex, and [0, -28, 66] in the somatosensory cortex. To assess the degree of combined SFC of all sensory seeds irrespective of modality, a fourth mask was built combining information from all three primary sensory regions.

Each *n*-step map encoded the number of *n*-step connections (SFC values) between every voxel in the brain and the voxels within the mask including the three bilateral seed regions. At each link step, SFC maps were standardized to Z-scores by subtracting the mean and dividing by its standard deviation to yield SFC values. Henceforth, we refer to these Z-score values as the SFC values. A more detailed description of the SFC method can be found in Sepulcre et al. (2012) and Sepulcre (2014].

Statistical analysis

All the statistical analyses were performed using SPM12. Groups were homogeneous for mean Framewise Displacement (FD), head coil, sex and IQ but differed in age ($t(51) = -2.11$; $p = 0.04$).

For each of the seven SFC maps, general linear models were fit for each group separately. These models included age (mean centered to zero), FD (mean centered to zero) and head coil as covariates of no interest. Statistical inference was performed over the intercept of the models to identify SFC values significantly greater than zero. Since this analysis was performed for exploratory purposes only, we displayed clusters of at least 10 contiguous voxels surviving an uncorrected $p < 0.01$.

General linear models were also fit to compare the seven SFC maps between groups. These models included group as a variable of interest and age, sex, FD and head coil as variables of no interest (age and FD were mean centered to zero). Even though FD, sex and head coil did not differ significantly between groups, they were included as a precaution. For each model we tested the effect of group through a t-test on the value of its estimate.

In addition to group differences, we tested the association between symptom severity --ADHD Rating Scale-- and functional connectivity profiles in each step within the group of ADHD patients. In this correlation analysis we included head coil, FD, sex and age as nuisance covariates.

As supplementary analyses, we explored if group differences were consistent across gender (see Supplementary Figure 3) and across the three main sensory modalities (see Supplementary Figure 4). In addition, we measured the predictive power of the group differences using the software PRoNTo [Schrouff et al., 2013] (see Supplementary Figure 5 and Supplementary Table 1).

To correct for multiple comparisons, we used a Monte-Carlo simulation implemented in the *AFNI 3dClustSim* function [Forman et al., 1995; accessed July 18, 2018]. This method was used to obtain an experiment Family Wise Error (FWE) corrected type 1 error probability of 0.05 ($\alpha^{FWE} = 0.05$). To achieve it, we needed a map FWE corrected type 1 error probability of $0.0071$ (because we have 7 maps and $0.05/7 = 0.0071$). For this purpose, we thresholded the statistical maps with a minimum cluster size of 174 contiguous 4 $mm^3$voxels surviving the uncorrected $p < 0.05$.

Cortical and network visualization

To facilitate interpretation of results in the context of large-scale functional networks, the percentage of significant voxels that overlapped with each of the seven cortical resting-state functional networks described by Yeo et al. (2011] was calculated for each analysis using MATLAB 2019a.

Surface projections of stepwise functional connectivity maps were performed via a Matlab in-house script that uses nearest neighbour (for Yeo's atlas) or linear (for the quantitative maps) interpolation and the surface normals to project cortical voxels onto the surface. The surfaces employed were the left and right "Q1-Q6_R440.#.midthickness.164k_fs_LR.surf.gii" of the software Connectome Workbench [Marcus et al., 2011]. To avoid redundancy, we only present stepwise connectivity profiles of the left hemisphere with uneven step numbers in the main document.

## Results

### SFC maps in patients with ADHD and healthy controls

The combined SFC maps for adult patients with ADHD and healthy controls are shown in Figure 1A and 1B, respectively. As expected, at short link-step distances (one and three link-step maps), both groups exhibited functional connectivity between the sensory seeds and primary sensory regions. At longer link-step distances (five and seven link-step maps), functional connectivity between sensory seed regions and fronto-parietal areas was established in both groups. In turn, healthy controls showed connectivity with medial frontal areas and the precuneus at longer link-step distances, which was not observed in the ADHD group.

**Between-group differences**

Between group comparisons are shown in Table 2 and map projections of between-group differences are presented in Figure 2A. All results were corrected for multiple comparisons (see Methods, Statistical analysis).

The analysis revealed functional connectivity differences starting from the three-step connectivity maps, with ADHD patients exhibiting increased seed region connectivity with the left calcarine sulcus compared to controls. These functional connectivity differences were maintained until the seven link-step maps, which exhibited between-group differences that peaked in the right lingual gyrus.

Patients with ADHD showed decreased functional connectivity in the five link-step distance map in the left medial orbitofrontal gyrus compared to controls. These differences, however, faded in the seven link-step map. Network plots showed that the functional connectivity decreases observed in controls vs. ADHD patients in five-step maps largely overlapped with the DMN (77.84%) and, to a lesser extent, the fronto-parietal network (13.51%) and limbic circuits (8.65%, see Figure 2B).

Results from the supplementary analysis indicated that group differences were consistent across gender and sensory modalities (see Supplementary Figures 3 and 4). They also indicated a predictive power of the main group differences of 55.6%, 64.08% and 62.46% for three, five and seven link-steps distances, respectively (see Supplementary Figure 5 and Supplementary Table 1).

**Association with ADHD symptom severity**

Table 3 and Figure 3 show the results of the regression analysis with the symptom severity scales.

As observed in Figure 3, symptom severity was positively associated with the degree of functional connectivity in the left middle frontal gyrus and the right superior temporal gyrus, regions that largely overlapped with the sensory-motor network (56.65% in three link-step, 59.88% in five link-step, and 60.42% in seven link-step maps) and the dorsal attention network (28.24% in three-step, 26.38% in five link-step, and 25.57% in seven link-step maps). With regard to negative correlations, we found that the higher the ADHD rating scale score the less the degree of functional connectivity in the bilateral superior frontal gyrus, clusters that largely overlapped with the DMN (68.15% in three link-step, 64.14% in five link-step, and 62.96% in seven link-step maps) and the fronto-parietal network (21.17% in three link-step, 25.50% in five link-step, and 25.05% in seven link-step maps). The associations between ADHD symptom severity scores and mean SFC values in each significant cluster per link-step distance map are illustrated in Figure 3B and E.

## Discussion

The present study aimed to elucidate how primary sensory regions interact with higher-order association networks in adult ADHD, a disorder that is typically approached with a strong focus on higher-order cognitive functions in neuroimaging research. Hence, we used SFC to assess multi-level information processing between early sensory and higher-order cognitive circuits in the brain of medication-naïve adults with ADHD compared to healthy adults. Our results partially align with a previous stepwise functional connectivity study on children with ADHD [Carmona et al., 2015], suggesting that the increased functional connectivity within sensory regions may persist in adulthood. However, sensorial integration into the DMN was lower in adults with ADHD compared with controls, the reverse pattern of that found in children with ADHD (hyper-connectivity) [Carmona et al., 2015]. Thus, deviations from typical SFC patterns in adult ADHD only partially resembled those observed in children with ADHD in previous studies. The correlations between SFC values and symptom severity in the adult ADHD sample corroborated the between-groups findings. In particular, ADHD rating scale scores were positively associated with increased functional connectivity within the somatosensory-motor network and between seed regions and the dorsal attention network, and inversely associated with functional connectivity between sensory seed regions and the DMN and the fronto-parietal network at short, medium and long functional distances. We discuss each of these findings below.

### 1. INCREASED SFC IN VISUAL CORTICES

Our results indicate increased functional connectivity between primary sensory areas and the visual cortex in adults with ADHD compared to controls. These findings are in line with Carmona et al. (2015) observations in children with ADHD, suggesting a similar pattern of deviations in children and adults with ADHD at intermediate and long functional distances. However, while children with ADHD showed hyperconnectivity within a small area of the lateral occipital cortex at short link-step distances, the differences cover almost all of the bilateral medial occipital cortices in adults with ADHD (including V1, V2, V3, which are part of both the dorsal and the ventral visual circuitry), and are present at short, intermediate and long link-step distances.

We believe that increased connectivity at medium and long functional distances may reflect the general visual network hyperconnectivity frequently described in children with ADHD [Cao et al., 2006; Kessler et al., 2014; Marcos-Vidal et al., 2018; Wang et al., 2009]. Our results suggest that at least part of the sensory information in adults with ADHD keeps reverberating within the visual loops, decreasing the information flow between sensory regions and neural hubs supporting higher-order cognitive functions. In addition, our observations support the notion that existent models of ADHD would benefit from incorporating alterations in primary sensory areas, which are often ignored or taken as a false positive [Castellanos and Proal, 2012b] but may nonetheless significantly alter multi-level information processing in ADHD.

## 2. DECREASED SFC IN DMN REGIONS

While the intra-visual loops were more functionally connected in adults with ADHD compared to controls, the circuits connecting sensory cortices with areas associated with higher-order cognitive functions were weaker. At medium functional distance (five link-step distance) adults with ADHD exhibited reduced degree of functional connectivity with, predominantly, the DMN, and with the frontoparietal and limbic networks to a lesser extent. Such differences do not necessarily imply a less direct connection between sensory regions and the DMN. Since our measurements of between-region functional connections included a number of relay stations (which define functional distance), these differences could be due to: (a) a weaker connection between the sensory cortices and the relay stations, or (b) a weaker connection between the relay stations and areas associated with higher-order cognitive functions. Since the direct functional connectivity between primary sensory cortices and the relay stations was not weaker, the most likely compromised loops are those connecting relay stations (attentional or secondary sensory cortices) with the DMN.

These results are in line with studies pointing at deficits in DMN inter-connectivity in adult ADHD, e.g., decreased functional connectivity between the anterior cingulate cortex and the precuneus/posterior cingulate cortex [Castellanos et al., 2008], decreased network homogeneity in the DMN [Uddin et al., 2008], and distributed hypo-connectivity within the DMN [Sripada et al., 2014]. Additionally, children with ADHD have been found to exhibit decreased short and long-range functional connectivity density in regions of the DMN [Tomasi and Volkow, 2012] and increased local functional connectivity in the boundaries of the DMN [Marcos-Vidal et al., 2018]. In adults with ADHD; weaker segregation has been found between the DMN and the cognitive control networks [Lin et al., 2018b]. Altogether, these results point to a lack of integration in DMN regions and a lack of segregation between DMN and task positive networks.

As part of the DMN, the medial prefrontal cortex (MPFC) was particularly affected in our sample. ADHD-associated alterations in the MPFC have been reported in a wide variety of studies, including altered functional connectivity with other DMN nodes [Castellanos et al., 2008; Uddin et al., 2008], reduced deactivation while completing a task [Peterson et al., 2009], and slower cortical thinning in children with higher symptom severity [Shaw et al., 2011]. Since the MPFC plays a key role within the DMN, the sensory hypo-connectivity with the MPFC observed in the present dataset could be pointing at alterations in DMN-associated functions such as mind-wandering [Fox et al., 2005], which could underlie attentional deficits in ADHD.

Our findings contrast with those in Carmona et al. (2015), which found greater SFC in the DMN in children with ADHD. In general, the DMN undergoes intense maturational changes with age as it transitions from sparse within-network functional connectivity in typically developing children to a more robustly

interconnected network in neurotypical adults [Fair et al., 2008]. On a speculative note, the hypo- and hyper-connectivity profiles observed at long functional distances in adults and children with ADHD, respectively, could be ascribed to altered DMN consolidation in early ages, yielding to abnormal functional connectivity profiles when compared to age-matched controls. However, a longitudinal study would be needed in order to establish conclusions on the evolution of default mode SFC throughout the lifespan of ADHD patients from childhood into adulthood compared to controls.

The discrepancies between our study and the previous study on SFC in children with ADHD [Carmona et al., 2015] could also be related to medication status. Whilst Carmona et al. (2015) analyzed brain activity in a mixed sample of medicated and medication-naïve children, our present study comprised medication-naïve adults. As reported by Carmona et al. (2015), medication status can influence SFC profiles (see Figure 5 in Carmona et al. 2015). Moreover, atomoxetine has been found to strengthen the anti-correlation between the DMN and task-positive networks [Lin et al., 2015] and ADHD medication in general has been proposed to normalize DMN activity [Pereira and de Castro-Manglano, 2017]. All in all, medication status seems a relevant factor to consider in future studies specifically addressing DMN functional connectivity in ADHD across the lifespan.

## 3. ASSOCIATIONS WITH CLINICAL SCALES

At short, medium and long functional distance, ADHD symptom scores were positively correlated with the degree of functional connectivity between seed regions and regions of the somatosensory-motor and dorsal attention networks. The positive correlation with somatosensory-motor regions is coherent with the increased SFC within sensory cortices in ADHD patients compared to controls. Indeed, children with ADHD also showed increased degree centrality, that is, increased number of direct connections with other nodes in the somatosensory cortex [Di Martino et al., 2013]. Anatomical studies also point to alterations in somatosensory-motor cortices that persist into adulthood [Marcos-Vidal et al., 2018]. For instance, studies in children with ADHD report decreased gray matter volume in the somatosensory, motor and premotor cortices [Carmona et al., 2005], while studies in adults with ADHD found increased cortical thickness in the pre-supplementary motor area and the somatosensory cortex [Duerden et al., 2012].

We also found a positive correlation between ADHD symptom severity and SFC in the dorsal attentional network. This finding dovetails with studies pointing to altered within network connectivity in the dorsal attentional network in adults with ADHD [Sidlauskaite et al., 2016] and increased connectivity between the dorsal attentional network and regions of the DMN in medication-naïve children with ADHD [Lin et al., 2018]. Given the relevance of the dorsal attention network in attentional performance [Vossel et al., 2014], it would be interesting to test whether the increased SFC between seed regions and nodes of the dorsal attention network predicted attentional performance.

Regarding negative correlations, we found that the higher the scores in ADHD symptom severity the lower the degree of connectivity between the seed regions and the DMN and the fronto-parietal network at short, medium and long functional distance (three to seven link-step maps). These findings are aligned with studies pointing to impaired functioning of the fronto-parietal network in ADHD [Castellanos and Proal, 2012b; Dickstein et al., 2006; Lin et al., 2015; Silk et al., 2005; Silk et al., 2008]; but also highlight the relevance of DMN alterations in adult ADHD.

Altogether, our results are consistent with the view that ADHD is associated with altered information flow between sensory and neural nodes supporting higher-order cognitive functions: whereas primary sensory areas seem to be hyper-connected in the first steps, they seem to be under-connected to brain regions supporting higher-order cognitive functions, especially the DMN, at long functional distances [Sepulcre et al., 2012]. Our results also point out that, in terms of SFC, the ADHD brain is highly heterogeneous --as indicated by our limited classification accuracy-- and suggest that part of this variability might be driven by differences in the severity of ADHD symptoms.

## 4. LIMITATIONS

The main limitation of our study is the relatively small sample size with a wide age range. This stems from the difficulty in recruiting ADHD patients who reach adulthood without comorbidity with other disorders (including tobacco and alcohol use in the last 6 months) and, importantly, without previous exposure to ADHD medication.

Also, as our sample exclusively comprised patients with the combined subtype, we could not provide a specific account of what precise ADHD phenotypes are associated with the SFC alterations. The question remains whether impaired sensory-multimodal integration may be affecting attentional control, as well as other symptoms such as hyperactivity and impulsivity. Further research should be able to draw more precise conclusions on what particular phenotypes are linked to which specific SFC alteration.

Regarding methodological concerns, we should specify two. First, computational constraints required us to down-sample data to relatively large voxels ($4\,mm^3$). As computational power continues to increase, the specific details of our results could be re-examined in the original data and in future datasets acquired at even greater temporal and spatial resolutions. Second, stepwise functional connectivity analysis does not provide information on the directionality of the functional connectivity network under study; that is, the alterations observed could be interpreted as affecting sensory-to-cognitive and/or cognitive-to-sensory information processing. If SFC decrease was affecting sensory-to-cognitive functional streams, this would involve a reduced information feed from sensory up to higher-level association nodes; if it was affecting cognitive-to-

sensory functional streams, this would entail lower cognitive control over incoming perceptual information -- thus hindering selective attention--. Hence, although previous studies using SFC analysis trend to interpret their results in the sensory-to-cognitive direction [Carmona et al., 2015; Hong et al., 2019; Sepulcre et al., 2012], the directionality of the observed alterations should be tested in future studies using methods such as Dynamic Causal Modelling [Friston et al., 2011].

## 5. CONCLUSIONS

In this study we characterized how primary sensory regions interact with networks supporting higher-order cognitive functions in adult ADHD by means of an SFC protocol. Furthermore, we ensured that this characterization was biased neither by comorbidities nor by medication. Our results suggest that the brain of adults with ADHD presents an atypical flow of information from short to long functional distances of the sensation to cognition continuum. In particular, SFC in medication-naïve adults with ADHD was characterized by over-connectivity within primary sensory regions followed by under-connectivity between sensory regions and nodes of the DMN. Importantly, this pattern was associated with the severity of ADHD symptoms. These findings highlight the need to draw greater attention to altered multilevel information processing in adult ADHD, with an emphasis on the interaction between primary sensory regions and the DMN.

### Conflict of interest

Dr. Ramos-Quiroga and Dra. Richarte have served on the speakers' bureau and acted as consultant for Eli Lilly and Co., Janssen-Cilag and Shire. Dr. Ramos-Quiroga has also served on the speakers' bureau and acted as consultant for Laboratorios Rubió, Novartis, Lundbeck and Ferrer. Both have received travel awards from Eli Lilly and Co., Janssen-Cilag, and Shire for participating in psychiatric meetings. The ADHD Program has received unrestricted educational and research support from Eli Lilly and Co., Janssen-Cilag, Shire, Rovi, and Laboratorios Rubió in the past two years. The rest of the authors declare no conflict of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

American Psychiatric Association (2013): Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC.

Biederman J, Petty CR, Evans M, Small J, Faraone S V. (2010): How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. Psychiatry Res 177:299–304.

https://linkinghub.elsevier.com/retrieve/pii/S0165178109005198.
Cao Q, Zang Y, Sun L, Sui M, Long X, Zou Q, Wang Y (2006): Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study. Neuroreport 17:1033–1036. https://insights.ovid.com/crossref?an=00001756-200607170-00017.
Cao X, Cao Q, Long X, Sun L, Sui M, Zhu C, Zuo X, Zang Y, Wang Y (2009): Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. Brain Res 1303:195–206. https://www.sciencedirect.com/science/article/pii/S0006899309017120.
Carmona S, Vilarroya O, Bielsa a., Trèmols V, Soliva JC, Rovira M, Tomàs J, Raheb C, Gispert JD, Batlle S, Bulbena a. (2005): Global and regional gray matter reductions in ADHD: A voxel-based morphometric study. Neurosci Lett 389:88–93.
Carmona S, Hoekzema E, Castellanos FX, García-García D, Lage-Castellanos A, Van Dijk KR a., Navas-Sánchez FJ, Martínez K, Desco M, Sepulcre J (2015): Sensation-to-cognition cortical streams in attention-deficit/hyperactivity disorder. Hum Brain Mapp 00:n/a-n/a. http://doi.wiley.com/10.1002/hbm.22790.
Castellanos FX, Proal E (2012a): Large-scale brain systems in ADHD: beyond the prefrontal–striatal model. Trends Cogn Sci 16:17–26. http://www.ncbi.nlm.nih.gov/pubmed/22169776.
Castellanos FX, Proal E (2012b): Large-scale brain systems in ADHD: beyond the prefrontal–striatal model. Trends Cogn Sci 16:17–26. https://www.sciencedirect.com/science/article/pii/S1364661311002403.
Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, Shaw D, Shehzad Z, Di Martino A, Biswal B, Sonuga-Barke EJS, Rotrosen J, Adler LA, Milham MP (2008): Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 63:332–7. http://www.ncbi.nlm.nih.gov/pubmed/17888409.
Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, Shinohara RT, Elliott MA, Eickhoff SB, Davatzikos C, Gur RC, Gur RE, Bassett DS, Satterthwaite TD (2017): Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. Neuroimage 154:174–187. http://www.ncbi.nlm.nih.gov/pubmed/28302591.
Conners, C., Sitarenios, G., Parker, J.D. EJN (1998): The revised Conners parent rating scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol 26:257–268. http://acn.oxfordjournals.org/cgi/doi/10.1016/S0887-6177(03)00021-0.
Dickstein SG, Bannon K, Xavier Castellanos F, Milham MP (2006): The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry 47:1051–1062. http://www.ncbi.nlm.nih.gov/pubmed/17073984.
Van Dijk KRA, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL (2010): Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization. J Neurophysiol 103:297–321. http://www.ncbi.nlm.nih.gov/pubmed/19889849.
Duerden EG, Tannock R, Dockstader C (2012): Altered cortical morphology in sensorimotor processing regions in adolescents and adults with attention-deficit/hyperactivity disorder. Brain Res 1445:82–91. https://www.sciencedirect.com/science/article/pii/S0006899312000959.
DuPaul GJ, Power TJ, Anastopoulos AD, Reid R (1998): ADHD rating Scale—IV: Checklists, norms, and clinical interpretation. Ed. New York: Guilford Press.
Fair DA, Cohen AL, Dosenbach NUF, Church JA, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL (2008): The maturing architecture of the brain's default network. Proc Natl Acad Sci U S A 105:4028–32. http://www.ncbi.nlm.nih.gov/pubmed/18322013.
First M, Spitzer R, Gibbon M, Williams J, Benjamin L (1994): Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID II). New York: Biometric Research Department.
First MB, Spitzer RL, Gibbon M, Williams JBW (1997): Structured Clinical Interview for DSM-IV

Axis I disorders (SCID I). New York: Biometric Research Department.
Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med 33:636–47. http://www.ncbi.nlm.nih.gov/pubmed/7596267.
Fox MD, Snyder AZ, Vincent JL, Corbetta M, Essen DC Van, Raichle ME (2005): The human brain is intrinsically organized into dynamic , anticorrelated functional networks.
Friston KJ, Li B, Daunizeau J, Stephan KE (2011): Network discovery with DCM. Neuroimage 56:1202–1221. https://linkinghub.elsevier.com/retrieve/pii/S105381191001623X.
Hoekzema E, Carmona S, Ramos-Quiroga JA, Canals C, Moreno A, Fernández VR, Picado M, Bosch R, Duñó L, Soliva JC, Rovira M, Bulbena A, Tobeña A, Casas M, Vilarroya O (2014): Stimulant drugs trigger transient volumetric changes in the human ventral striatum. Brain Struct Funct 219:23–34.
Hong S-J, Vos de Wael R, Bethlehem RAI, Lariviere S, Paquola C, Valk SL, Milham MP, Di Martino A, Margulies DS, Smallwood J, Bernhardt BC (2019): Atypical functional connectome hierarchy in autism. Nat Commun 10:1022. http://www.nature.com/articles/s41467-019-08944-1.
Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. Neuroimage 17:825–841. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.118.6651&rep=rep1&type=pdf.
Kessler D, Angstadt M, Welsh RC, Sripada C (2014): Modality-spanning deficits in attention-deficit/hyperactivity disorder in functional networks, gray matter, and white matter. J Neurosci 34:16555–66. http://www.ncbi.nlm.nih.gov/pubmed/25505309.
Lin H, Lin Q, Li H, Wang M, Chen H, Liang Y, Bu X, Wang W, Yi Y, Zhao Y, Zhang X, Xie Y, Du S, Yang C, Huang X (2018a): Functional Connectivity of Attention-Related Networks in Drug-Naïve Children With ADHD. J Atten Disord:108705471880201. http://www.ncbi.nlm.nih.gov/pubmed/30259777.
Lin H-Y, Cocchi L, Zalesky A, Lv J, Perry A, Tseng W-YI, Kundu P, Breakspear M, Gau SS-F (2018b): Brain–behavior patterns define a dimensional biotype in medication-naïve adults with attention-deficit hyperactivity disorder. Psychol Med 48:2399–2408. http://www.ncbi.nlm.nih.gov/pubmed/29409566.
Lin H-Y, Tseng W-YI, Lai M-C, Matsuo K, Gau SS-F (2015): Altered Resting-State Frontoparietal Control Network in Children with Attention-Deficit/Hyperactivity Disorder. J Int Neuropsychol Soc 21:271–284. http://www.ncbi.nlm.nih.gov/pubmed/25928822.
Marcos-Vidal L, Martínez-García M, Pretus C, Garcia-Garcia D, Martínez K, Janssen J, Vilarroya O, Castellanos FX, Desco M, Sepulcre J, Carmona S (2018): Local functional connectivity suggests functional immaturity in children with attention-deficit/hyperactivity disorder. Hum Brain Mapp 39:2442–2454. http://doi.wiley.com/10.1002/hbm.24013.
Marcus DS, Harwell J, Olsen T, Hodge M, Glasser MF, Prior F, Jenkinson M, Laumann T, Curtiss SW, Van Essen DC (2011): Informatics and Data Mining Tools and Strategies for the Human Connectome Project. Front Neuroinform 5:4. http://www.ncbi.nlm.nih.gov/pubmed/21743807.
Di Martino A, Yan C-G, Li Q, Denio E, Castellanos FX, Alaerts K, Anderson JS, Assaf M, Bookheimer SY, Dapretto M, Deen B, Delmonte S, Dinstein I, Ertl-Wagner B, Fair DA, Gallagher L, Kennedy DP, Keown CL, Keysers C, Lainhart JE, Lord C, Luna B, Menon V, Minshew NJ, Monk CS, Mueller S, Müller R-A, Nebel MB, Nigg JT, O'Hearn K, Pelphrey KA, Peltier SJ, Rudie JD, Sunaert S, Thioux M, Tyszka JM, Uddin LQ, Verhoeven JS, Wenderoth N, Wiggins JL, Mostofsky SH, Milham MP (2014): The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry 19:659–667. http://www.ncbi.nlm.nih.gov/pubmed/23774715.
Di Martino A, Zuo X-N, Kelly C, Grzadzinski R, Mennes M, Schvarcz A, Rodman J, Lord C,

Castellanos FX, Milham MP (2013): Shared and Distinct Intrinsic Functional Network Centrality in Autism and Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry 74:623–632. http://www.ncbi.nlm.nih.gov/pubmed/23541632.

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA (2009): The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44:893–905. http://www.ncbi.nlm.nih.gov/pubmed/18976716.

Pereira V, de Castro-Manglano P (2017): The effects of medication on default mode network (DMN) connectivity in attention deficit/hyperactivity disorder (ADHD): Bibliographic review. Eur Psychiatry 41:S629. https://www.sciencedirect.com/science/article/pii/S0924933817310374.

Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, Plessen KJ, Yu S (2009): An fMRI Study of the Effects of Psychostimulants on Default-Mode Processing During Stroop Task Performance in Youths With ADHD. Am J Psychiatry 166:1286–1294. http://www.ncbi.nlm.nih.gov/pubmed/19755575.

Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE (2014): Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84:320–341. https://www.sciencedirect.com/science/article/pii/S1053811913009117.

Schrouff J, Rosa MJ, Rondina JM, Marquand AF, Chu C, Ashburner J, Phillips C, Richiardi J, Mourão-Miranda J (2013): PRoNTo: Pattern Recognition for Neuroimaging Toolbox. Neuroinformatics 11:319–337. http://www.ncbi.nlm.nih.gov/pubmed/23417655.

Sepulcre J, Sabuncu MR, Yeo TB, Liu H, Johnson KA (2012): Stepwise Connectivity of the Modal Cortex Reveals the Multimodal Organization of the Human Brain. J Neurosci 32:10649–10661. http://www.ncbi.nlm.nih.gov/pubmed/22855814.

Sepulcre J (2014): Integration of visual and motor functional streams in the human brain. Neurosci Lett 567:68–73. http://www.ncbi.nlm.nih.gov/pubmed/24699175.

Shaw P, Gilliam M, Liverpool M, Weddle C, Malek M, Sharp W, Greenstein D, Evans A, Rapoport J, Giedd J (2011): Cortical Development in Typically Developing Children With Symptoms of Hyperactivity and Impulsivity: Support for a Dimensional View of Attention Deficit Hyperactivity Disorder. Am J Psychiatry 168:143–151. http://www.ncbi.nlm.nih.gov/pubmed/21159727.

Sidlauskaite J, Sonuga-Barke E, Roeyers H, Wiersema JR (2016): Altered intrinsic organisation 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 266:349–357. http://www.ncbi.nlm.nih.gov/pubmed/26260900.

Silk T, Vance A, Rinehart N, Egan G, O'Boyle M, Bradshaw JL, Cunnington R (2005): Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: Functional magnetic resonance imaging study. Br J Psychiatry 187:282–283. https://www.cambridge.org/core/product/identifier/S000712500016768 6/type/journal_article.

Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R (2008): Dysfunction in the Fronto-Parietal Network in Attention Deficit Hyperactivity Disorder (ADHD): An fMRI Study. Brain Imaging Behav 2:123–131. http://link.springer.com/10.1007/s11682-008-9021-8.

Sripada C, Kessler D, Fang Y, Welsh RC, Prem Kumar K, Angstadt M, Library WO (2014): Disrupted Network Architecture of the Resting Brain in Attention-Deficit/Hyperactivity Disorder. Hum Brain Mapp 35:4693–4705. http://www.fil.ion.ucl.ac.uk/.

Sun L, Cao Q, Long X, Sui M, Cao X, Zhu C, Zuo X, An L, Song Y, Zang Y, Wang Y (2012): Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. Psychiatry Res 201:120–7. http://www.ncbi.nlm.nih.gov/pubmed/22424873.

Tomasi D, Volkow ND (2012): Abnormal Functional Connectivity in Children with Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry 71:443–450.

http://www.ncbi.nlm.nih.gov/pubmed/22153589.
Uddin LQ, Kelly AMC, Biswal BB, Margulies DS, Shehzad Z, Shaw D, Ghaffari M, Rotrosen J, Adler LA, Castellanos FX, Milham MP (2008): Network homogeneity reveals decreased integrity of default-mode network in ADHD. J Neurosci Methods 169:249–254. http://www.sciencedirect.com/science/article/pii/S0165027007006012.
Vossel S, Geng JJ, Fink GR (2014): Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist 20:150–9. http://www.ncbi.nlm.nih.gov/pubmed/23835449.
Wang L, Zhu C, He Y, Zang Y, Cao Q, Zhang H, Zhong Q, Wang Y (2009): Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Hum Brain Mapp 30:638–649. http://doi.wiley.com/10.1002/hbm.20530.
Ward MF, Wender PH RF (1993): The Wender Utah Rating Scale: An aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. Am J Psychiatry 150:885–890.
Wechsler D (1997): WAIS-III: Wechsler adult intelligence scale. Ed. Psychological Corporation. San Antonio, TX.
Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, Fischl B, Liu H, Buckner RL (2011): The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106:1125–65. http://www.ncbi.nlm.nih.gov/pubmed/21653723.

**Table 1.** Demographic and clinical data of the ADHD and control samples. Three controls did not complete the ADHD Rating Scale. Independent sample t-tests or chi-square were used to compare groups.

| Characteristic | ADHD (N = 31) Mean (sd) | Controls (N = 22) Mean (sd) | Stat (df) | p-value |
|---|---|---|---|---|
| Age (range 19 to 52 ) | 35.4 (9.9) | 30.4 (5.8) | t(51) = -2.11 | .040 |
| ADHD Rating Scale | 32.3 (9.8) | 6.0 (5.8) | t(48) = -11.89 | < .001 |
| Sex (number of women) | 16 | 12 | $\chi2(1) =0$ .044 | n.s. |
| Number scanned with replacement headcoil | 14 | 6 | $\chi2$ (1) = 1.75 | n.s. |
| Framewise Displacement | .054 (.036) | .036 (.030) | t(51)=-1.92 | .061 |

**Table 2.** Results of the stepwise functional connectivity (SFC) analyses, including between-subject comparisons (adult patients with ADHD versus healthy controls) for each SFC map at different functional distances (one-step to seven-steps). Results were corrected for multiple comparisons by means of a Monte-Carlo simulation.

| Between-subject comparison | Peak MNI coordinates | | | No. of voxels | Highest T-score | cluster-level p-value |
|---|---|---|---|---|---|---|
| | x | y | z | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **One-step** | | | | | | |
| **Three-steps** | | | | | | |
| **ADHD > Controls** | | | | | | |
| L calcarine | -4 | -64 | 16 | 248 | 3.25 | <.001 |
| **Five-steps** | | | | | | |
| **Controls > ADHD** | | | | | | |
| L medial orbitofrontal gyrus | -4 | 58 | -17 | 185 | 3.62 | .001 |
| **ADHD > Controls** | | | | | | |
| L calcarine | -4 | -68 | 16 | 398 | 3.47 | <.001 |
| **Seven-steps** | | | | | | |
| **ADHD > Controls** | | | | | | |
| R lingual gyrus | 16 | -61 | -9 | 283 | 3.17 | <.001 |

No. = number; R = right; L = left

**Table 3.** Results of the stepwise functional connectivity (SFC) analyses, including positive and negative associations of the ADHD Rating Scale in adult ADHD patients with each of the SFC maps at different functional distances (one-step to seven-steps). Results were corrected for multiple comparisons by means of a Monte-Carlo simulation.

| ADHD Rating Scale | Peak MNI coordinates | | | No. of voxels | Highest R | cluster-level p-value |
|---|---|---|---|---|---|---|
| | x | y | z | | | |
| **One-step** | | | | | | |
| **Three-steps** | | | | | | |
| **Positive association** | | | | | | |
| L middle frontal gyrus | -36 | 3 | 59 | 556 | 0.68 | <.001 |
| **Negative association** | | | | | | |
| R superior frontal gyrus | 20 | 31 | 53 | 496 | 0.64 | <.001 |
| **Five-steps** | | | | | | |
| **Positive association** | | | | | | |
| R superior temporal gyrus | 56 | -35 | 21 | 1179 | 0.62 | <.001 |
| **Negative association** | | | | | | |
| L superior frontal gyrus | -28 | 65 | 15 | 859 | 0.71 | <.001 |
| R precuneus | 12 | -58 | 35 | 184 | 0.59 | .001 |
| **Seven-steps** | | | | | | |
| **Positive association** | | | | | | |
| R superior temporal gyrus | 56 | -35 | 21 | 1185 | 0.61 | <.001 |
| **Negative association** | | | | | | |
| L middle frontal gyrus | -40 | 23 | 46 | 287 | 0.7 | <.001 |
| R superior frontal gyrus | -28 | 65 | 15 | 441 | 0.65 | <.001 |
| R precuneus | 12 | -58 | 35 | 206 | 0.61 | .001 |

No. = number; R = right; L = left

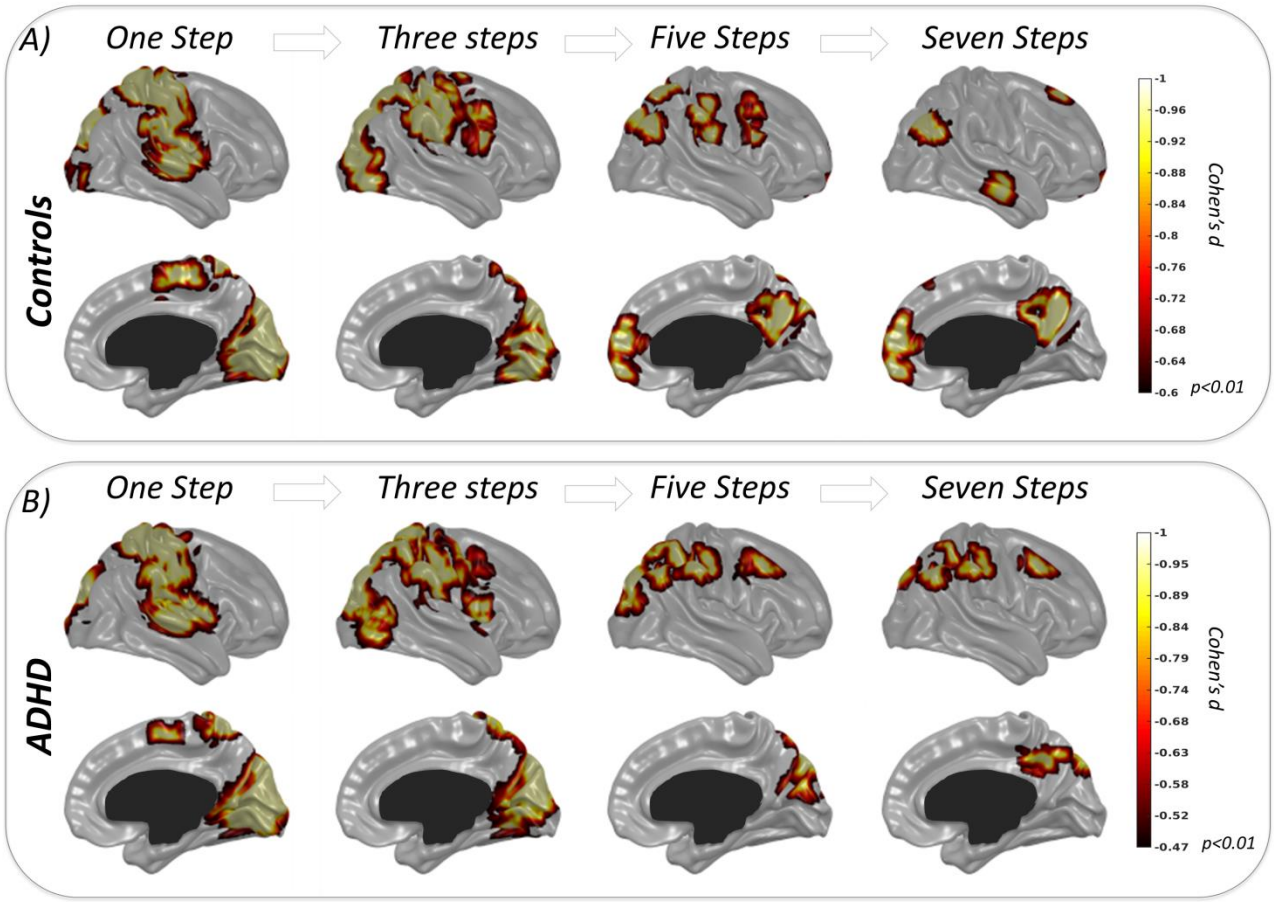


**Figure 1.** Surface projections of the one-sample t-test results of uneven link-step distances for (A) the adult sample of ADHD patients and (B) the control sample of healthy adults. Each image represents Cohen's D ranging from the value that corresponds with a $p<0.01$ (0.6 for the control sample and 0.47 for the ADHD sample) and a value of 1. Cohen's D effect sizes greater than 1 are collapsed to 1. Left hemispheres are displayed.

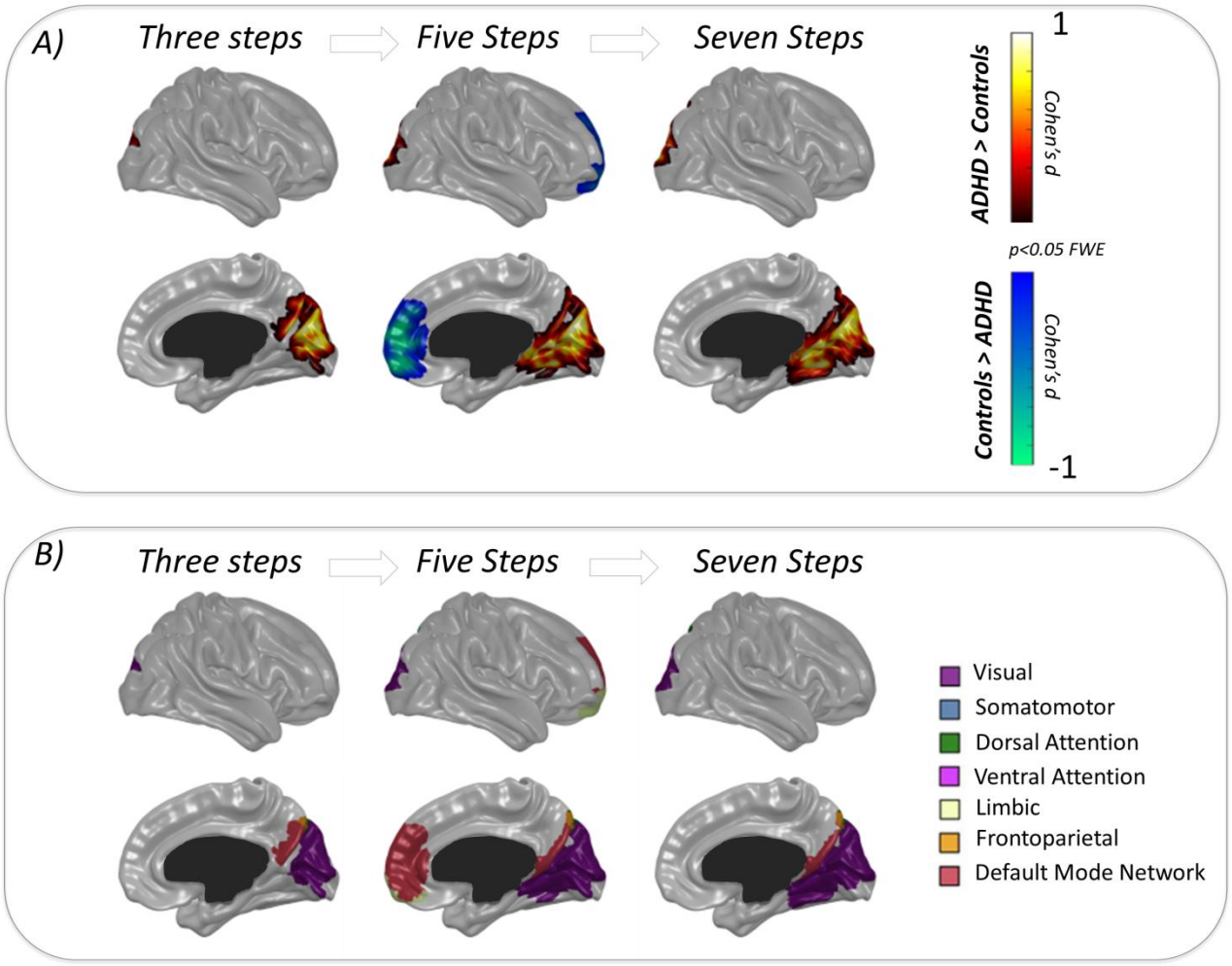


**Figure 2.** (A) Surface projections of the two-sample t-test results of uneven link-step distances for the between-groups' contrast between adult ADHD patients and the control sample. Images display Cohen's D effect sizes, and the positive (hot) and negative (winter) color maps range from the absolute value corresponding to an uncorrected $p<0.05$ to an absolute value of 1. Values greater than 1 and lower than -1 are collapsed to 1 and -1, respectively. Subplot (B) indicates to which large-scale resting-state functional networks the significant voxels belong according to the parcellation of Yeo et al. (2011). Left hemispheres are displayed.

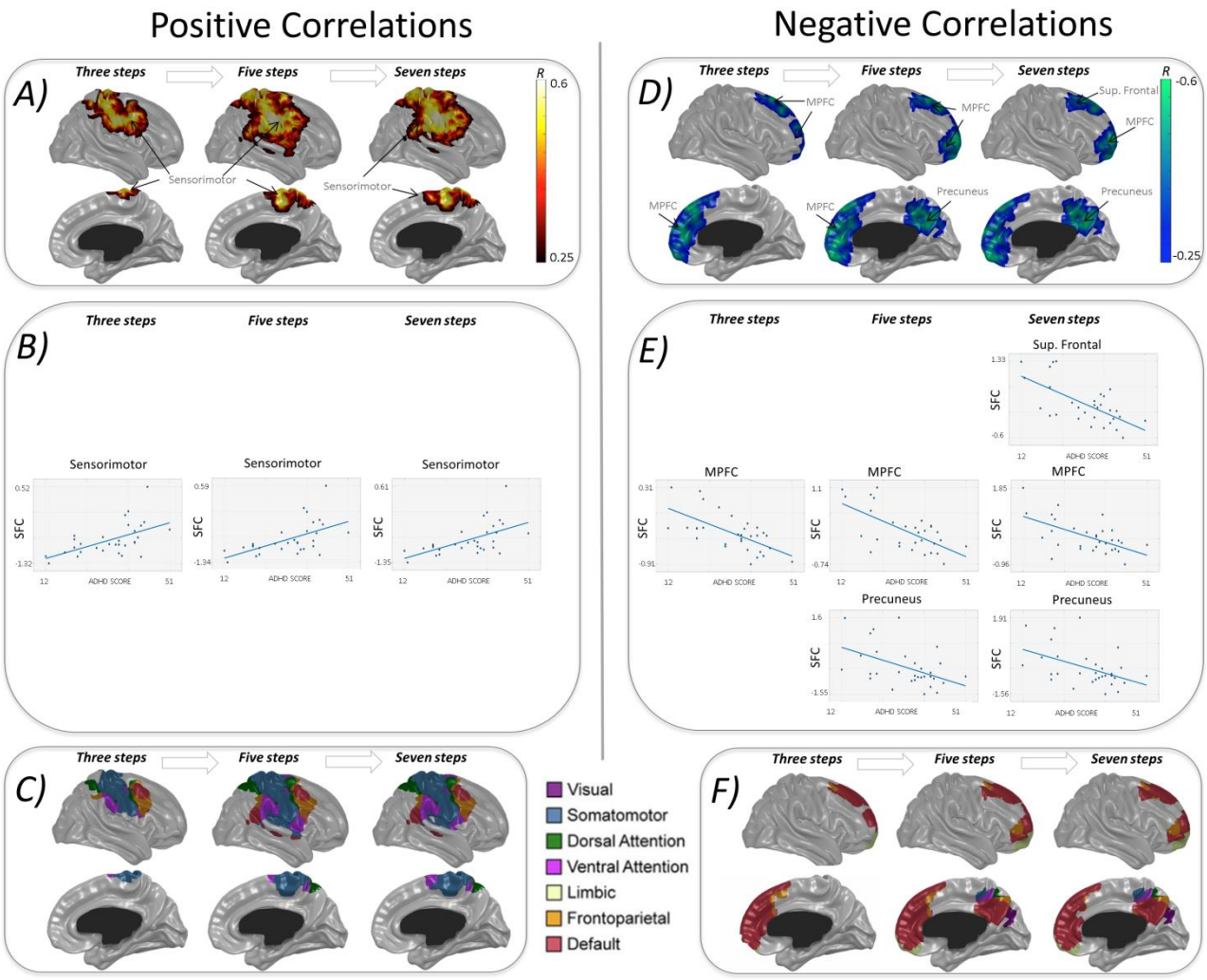


**Figure 3.** Results of the regression analysis using the ADHD rating scale score as predictor of stepwise functional connectivity. Subplots A), B) and C) depict positive correlations and subplots D), E) and F) depict negative correlations. Top surface images show the correlation coefficient R at three, five and seven link-step distances, and the color maps range from r= 0.25 absolute value (which corresponds to the minimum (bilateral) significant correlation at $p<0.05$) to r= 0.6 absolute value. Subplots B) and E) show the scatter plots for the positive and negative correlations, respectively. Bottom surface images (C and F) indicate to which large-scale resting-state functional networks the significant voxels belong according to the parcellation of Yeo et al. (2011). Left hemispheres are displayed.