Double-dissociation between the mechanism leading to impulsivity and inattention in Attention Deficit Hyperactivity Disorder: A resting state functional connectivity study

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*Title page

Double-Dissociation between the mechanism leading to impulsivity and inattention in Attention Deficit Hyperactivity Disorder.

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***Highlights**

- ADHD showed an increased functional connectivity in the right hemisphere compared to controls.
- A single brain model for ADHD is insufficient
- Hyperactive-impulsive subtype was associated with increased connectivity in cortico-striatal network
- Inattentive subtype was associated with increased connectivity in the right ventral attention network

ABSTRACT

Two core symptoms characterize Attention Deficit Hyperactivity Disorder (ADHD) subtypes: inattentiveness and hyperactivity-impulsivity. While previous brain imaging research investigated ADHD as if it was a homogenous condition, its two core symptoms may originate from different brain mechanisms. We, therefore, hypothesized that the functional connectivity of cortico-striatal and attentional networks would be different between ADHD subtypes. We studied 165 children (mean age 10.93 years; age range, 7-17 year old) diagnosed as having ADHD based on their revised Conner's rating scale score and 170 typical developing individuals (mean age 11.46 years; age range, 7-17 year old) using resting state functional fMRI. Groups were matched for age, IQ and head motion during the MRI acquisition. We fractionated the ADHD group into predominantly inattentive, hyperactive-impulsive and combined subtypes based on their revised Conner's rating scale score. We then analyzed differences in resting state functional connectivity of the cortico-striatal and attentional networks between these subtypes. We found a double dissociation of functional connectivity in the cortico-striatal and ventral attentional networks, reflecting the subtypes of the ADHD participants. Particularly, the hyperactive-impulsive subtype was associated with increased connectivity in cortico-striatal network, whereas the inattentive subtype was associated with increased connectivity in the right ventral attention network. Our study demonstrated for the first time a right lateralized, double dissociation between specific networks associated with hyperactivity-impulsivity and inattentiveness in ADHD children, providing a biological

basis for exploring symptom dimensions and revealing potential targets for more personalized treatments.

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition affecting approximately 8% of school-aged children (Bloom et al. 2011) and 4% of adults (Kessler et al. 2006). Originally described in 1798 (Crichton 1798; reprinted in Crichton 2008) ADHD patients 'incessantly withdrawn from one impression to another' and 'excites such a degree of anger as borders on insanity' (for an historical review see Lange et al. 2010). These two core symptoms are interpreted as inattention and hyperactivity-impulsivity in the DSM5 (American Psychiatric Association 2013) and can be of variable severity. Although these symptoms frequently come together, their expression can be unbalanced leading to the division of ADHD into three clinical subtypes: *predominantly inattentive*, *predominantly hyperactive-impulsive*, and *combined* (American Psychiatric Association 1994). Whether the brain mechanism leading to these subtypes is different remains to be clarified in order to enhance personalised treatment.

The efficacy of current drug treatments is predominantly mediated by their effects on the dopaminergic, and/or noradrenergic systems. They are effective in many patients, but approximately 1/3 fail to respond - predominantly those with the 'inattentive' subtype (Spencer et al. 1995; Weiss et al. 2005; Hazell et al. 2011). This finding suggests that in addition to being clinically heterogeneous (Barkley et al. 2002; Biederman et al. 2006); ADHD subtypes may be modulated by different brain systems with a variable response to pharmacological treatments.

There is increasing evidence that ADHD is associated with abnormalities in specific brain regions; and particularly dorsal anterior midcingulate cortex (daMCC), prefrontal cortex, parietal cortex, striatum, and cerebellum (see Bush 2011; Cortese et al. 2012 for review). The significance of these areas is that they are involved with attention, executive function, motor control, response inhibition, and working memory. However, rather than a mosaic of functionally specialized areas, the human mind is believed to emerge from the coordinated activity of distant but anatomically interconnected regions. Advances in brain imaging have enabled us to study anatomical and functional connectivity within these networks *in vivo*.

One of the most consistent findings from studies of *anatomical* connectivity, in children and adolescents with ADHD, is reduced fractional anisotropy (Hamilton et al. 2008; Makris et al. 2008; Luders et al. 2009; Konrad et al. 2010) of fronto-striatal tracts (within the cortico-striatal network) and fronto-parietal tracts (within the ventral and dorsal attention network). These findings have been supported by some (Dickstein et al. 2006; Rubia 2011; Cubillo et al. 2012) but not all studies of *functional* connectivity (Tian et al. 2006; Uddin et al. 2008).

Studies of *functional* connectivity have employed standard, task-activation, *f*MRI (task-*f*MRI), or resting-state *f*MRI (rs-*f*MRI). A key advantage of rs-*f*MRI is that

participants are not required to focus on an explicit task. This is particularly beneficial in ADHD, where compliance and attention during scanning may be problematic, and confound interpretation of results. The underlying principle of rs-*f*MRI is that functional connectivity between brain regions can be successfully mapped by correlating spontaneous low-frequency (<0.1Hz) fluctuations in blood oxygenation level dependent (BOLD) signal at rest (Fox and Raichle 2007). Previous rs-*f*MRI studies of ADHD have reported both hypo- and hyper-activation of fronto-striatal, fronto-parietal and other networks (see Konrad *et al*. 2010 for review). Also, whole brain voxel-based analyses revealed decreased entropy (Sokunbi et al. 2013) and decreased amplitude of low-frequency fluctuation (Zang et al. 2007; An, Cao, Sui, et al. 2013) in the frontal and the occipital lobes. These inconsistencies are likely to be due to a combination of methodological factors, including the method of analysis employed, micro-movements (Fair et al. 2012), variability in the subtype diagnosis and the age range of subjects. The small size of clinical samples has also been a significant limitation of the majority of imaging studies of ADHD to date. An important consequence of this has been the scarcity of studies with the statistical power to analyse ADHD as a heterogeneous condition. Therefore there has been a need for larger studies, with sufficient power to fractionate ADHD into its clinical subtypes, and that permit a more comprehensive analysis of brain connectivity.

In the present study we accessed a recent, unrestricted public release, dataset of

rs-*f*MRI images from 255 children and adolescents with ADHD (ages: 7-21 years old)[†]. This has provided a valuable opportunity to analyse whether the clinical heterogeneity observed in ADHD is underpinned by differences at a functional brain network level. We focused our analyses on three resting state networks of interest, the dopaminergic circuit (i.e. cortico-striatal circuit Alexander et al. 1986; Nieuwenhuys et al. 2008) for its essential role in impulsivity (Buckholtz et al. 2010), and the dorsal and the ventral fronto-parietal networks (Fox et al. 2006) for their key role in attention (i.e. dorsal and ventral attention networks Corbetta and Shulman 2002).

[†] ADHD-200 Sample; http://fcon_1000.projects.nitrc.org/ indi/adhd200

MATERIAL AND METHODS

Dataset

We selected 165 children out of the 255 children cohort (44 girls, 121 boys; 7-17 year old, 10.93±2.53 years, FSIQ > 70) with ADHD. Selection was based on the use of the same version of the Conner's Parent Rating Scale-Revised, Long version (CPRS-R). Consequently 90 children were rejected from participating in the study due to the absence of CPRS-R scores. These children were recruited from two centers: Kennedy Krieger Institute (KKI) or New York University (NYU). The children were diagnosed based on evaluations with the Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV Reich et al. 1997) or the Schedule of Affective Disorders and Schizophrenia for Children-Present and Lifetime Version (KSADS-PL); CPRS-R or ADHD Rating Scale-IV (DuPaul and Power 1998). They either had a T-score of 65 or greater on at least one ADHD related index of the CPRS-R, or met criteria on the ADHD Rating Scale-IV (six out of nine items scored 2 or 3 from Inattention items and/or six out of nine scored 2 or 3 from the Hyperactivity/Impulsivity items). Consistent with previous studies, children taking stimulant medication were instructed to refrain from taking these medications for at least 24 hours before scanning. Additionally we selected a control group of 170 children matched with our ADHD group (83 girls, 87 boys; 7-17 year old, 11.46 ± 2.76 years, FSIQ > 70). Details of the center distribution of the data included in the study are reported in **Table 1**.

Classification

The CPRS-R is a validated and widely used parent questionnaire that assesses hyperactivity–impulsivity and inattention as well as a range of other problem behaviour in children and adolescents. We divided our population into three groups defined by the imbalance between their symptoms. We used K-means cluster analysis (Steinhaus 1957; Forgy 1965; MacQueen 1967; Hartigan and Wong 1979; Lloyd 1982) on the ratio between the hyperactivity–impulsivity and inattention CPRS-R scores to fractionate our sample into three subgroups: predominantly inattentive, predominantly hyperactive and combined. K-means clustering analysis is a commonly used approach to identify relatively homogeneous groups of cases or variables based on selected characteristics (Johansen-Berg et al. 2004; Anwander et al. 2007; Catani et al. 2007; Mars, Jbabdi, et al. 2011; Mars, Sallet, et al. 2011). This identified the following: 53 children with a predominantly *inattentive* CPRS score (32%, 7-17 year old, 11.28 ± 2.75 years, 34 males and 19 females); 44 children (27%, 7-17 year old, 11.36 ± 2.59 years, 34 males and 10 females) with a predominantly *hyperactive-impulsive* CPRS score and 68 children (41%, 7-16 year old, 10.39 ± 2.24 years, 53 males and 15 females) with a *combined* symptom profile. Demographical data are reported in **Table 2**.

Magnetic resonance imaging data acquisition.

During acquisition of the rs-*f*MRI, participants in both centers (i.e. KKI and NYU) were instructed to relax, think of nothing, and to stay awake. In KKI participants

were asked to keep their eyes open, and fixate on a center cross, whereas in NYU participants were instructed to close their eyes. Functional images were obtained using T2-weighted echo-planar imaging (EPI) with blood oxygenation level-dependent (BOLD) contrast using SENSE imaging. In KKI, EPIs (TR/TE = 2500/30 msec) comprised 47 axial slices acquired continuously in ascending order covering the entire cerebrum (voxel size = 2.67 × 2.67 × 3.00 mm^3). In NYU, EPIs (TR/TE = 2000/15 msec) comprised 33 axial slices acquired continuously in interleaved order covering the entire cerebrum (voxel size = 3.0 × 3.0 × 4.0 mm^3).

An axial three-dimensional (3D) magnetization prepared rapid gradient echo (MPRAGE) dataset covering the whole head was also acquired for each participant (200 slices, voxel resolution = 1.00 × 1.00 × 1.00 mm, TE = 3.7 msec, TR = 8.0 msec, flip angle = 8° for KKI; 128 slices, voxel resolution = 1.3 × 1.0 × 1.3 mm, TE = 2530 msec, TR = 3.25 msec, flip angle = 7° for NYU).

rs-*f*MRI independent component analysis Analysis of functional connectivity was carried out using Probabilistic Independent Component Analysis (PICA, Beckmann and Smith 2004; Beckmann 2012) as implemented in Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC) version 3.13, part of FMRIB's Software Library (FSL, www.fmrib.ox.ac.uk/fsl). We chose PICA as it is a robust, operator independent approach(Beckmann and Smith 2004; Beckmann et al.

2005; Beckmann et al. 2009), which provides a very close relationship between the anatomy of the resting networks identified and classical brain functional activations (Smith et al. 2009).

In order to obtain a steady-state signal, the five first volumes of each dataset were discarded from the analyses. Rs-*f*MRI datasets were corrected for head motion by rigid registration to the first volume (Jenkinson et al. 2002), capped with a high pass filter (.01 Hz, Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 sec) and skull-stripped (Smith 2002). Each subject's *f*MRI data was registered to that subject's high-resolution structural image (Jenkinson *et al*. 2002) and then registered again, this time, with the standard MNI152 template using affine (FLIRT) and non-linear registration (FNIRT). All resulting datasets were concatenated in the temporal dimension. This approach is advantageous, as it does not assume that the associated temporal response is consistent across subject but rather looks for common spatial patterns between subjects.

The following data pre-processing was applied to the input data: masking of non-brain voxels; voxel-wise de-meaning of the data; normalisation of the voxel-wise variance; pre-processed data were whitened and projected into a 23-dimensional subspace using probabilistic principal component analysis where the number of dimensions was estimated using the Laplace approximation to the Bayesian evidence of

the model order (Minka 2000; Beckmann and Smith 2004).

We focused our analyses on three resting state networks of interest, the cortico-striatal network(Alexander *et al*. 1986; Nieuwenhuys *et al*. 2008), the dorsal and the ventral attention networks (i.e. DAN and VAN, Corbetta and Shulman 2002; Fox *et al*. 2006).

rs-*f*MRI Dual regressions

In order to assess the presence of group differences in the spatial extent of the RSNs, it is necessary to generate subject-level maps of the components extracted by the group-level ICA. This is achieved in two steps: (1) first, the entire set of 23 group-level spatial components (**Fig. 1**) was regressed against each volume of the preprocessed rs-*f*MRI data using multiple regression in the spatial domain; therefore, the 3D image associated with each time point in the rs-*f*MRI data was modeled as a linear combination of the group-level spatial components. This allowed for the estimation of a subject-specific time course for each group-level component. (2) Afterwards, the whole set of 23 component-specific time courses were used as predictors in a second multiple regression in the temporal domain, against the preprocessed rs-*f*MRI data of each subject. In this way we estimated the correlation of each brain voxel with the characteristic time course of each spatial component, and ultimately obtained maps of the spatial distribution of each subject-specific component. Since this procedure is based on two multiple

regression steps, the first in the spatial domain, the second in the temporal domain, it has been denominated 'dual regression' (Filippini et al. 2009). A visual description of the steps of the dual regression can be found in (Beckmann *et al*. 2009). Importantly, since the full set of components extracted by ICA is used, the dual regression procedure accounts for the potential contamination of the rs-*f*MRI signal by components reflecting structured noise such as motion artifacts and white matter signals. Therefore any variance shared between these components and the rs-*f*MRI networks of interest was regressed out during the estimation of the rs-*f*MRI networks summary time course for each subject. For instance, the white matter signal was modeled as the time course of the IC 8, and subsequently, this component had been estimated in a subject-specific way - by means of the first stage of dual regression. This approach has several benefits with respect to using a standard mask of white matter. The white matter mask is directly estimated from the data: remarkably, this component is among the most reproducible found in different ICA-based resting state investigations (e.g. IC4 in (Biswal et al. 2010); BM20 in (Smith *et al*. 2009); IC31 in (Salimi-Khorshidi et al. 2014)). In addition, the dual regression procedure allows for an estimation of the subject-level component of the white matter component extracted in the group analysis.

We then tested for statistical differences between the inattentive group and the hyperactive group using FSL's randomise permutation-testing tool. Randomise calculates nonparametric inferences on neuroimaging data. For each voxel of the brain, randomise will test using a permuted general model (Winkler et al. 2014) whether the strength of the

functional connectivity in the cortico-striatal, DAN and VAN networks (i.e. the dependant variables) is different between the 'inattentive' and the 'hyperactive/impulsive' groups (i.e. the independent variables). Results were corrected for multiple comparisons using family-wise error (FWE) (Anderson and Robinson 2001; Nichols and Holmes 2002). 3D rendering of the brain was calculated using the T1 pipeline in Brain VISA (http://brainvisa.info).

Note that recent work revealed that motion can have a substantial effect on the estimation of resting-state functional connectivity (Van Dijk et al. 2012). Removing time points associated with high motion ('scrubbing' Power et al. 2012) represents an effective procedure to reduce the contamination rs-*f*MRI data by residual motion. However, performing 'scrubbing' before temporally-concatenated PICA is not technically feasible and, most importantly, not desirable, as it would lead to heteroschedasticity when performing group-level analysis (i.e., a different number of temporal degrees of freedom for each participant). In addition, a recent work (Jo et al. 2013) revealed that the largest contribution to minimizing head motion was yielded by regressing out from rs-*f*MRI data the mean signal in a white matter mask.

Statistical Analysis

In our analysis, Gaussian distribution of the data for the three groups was confirmed using the Shapiro–Wilk test (Shapiro and Wilk 1965).

Statistical analysis was performed using SPSS 22 software (SPSS, Chicago, IL). Analyses of the differences between the three groups were performed using repeated measure ANOVA for the clinical characteristics. Additionally, repeated measure ANOVA was employed to explore differences in the connectivity strength between the 4 groups in the regions reported as statistically different by the dual regression analysis. Gender, age, centre (KKI or NYU), verbal IQ, performance IQ, full IQ and movement during the rs-*f*MRI (absolute value) were considered as covariates. Note that there were no significant absolute movement differences between the 4 groups. Post-hoc independent sample t-tests were performed, when statistically appropriate, to compare groups individually. Differences significant at $P < 0.0042$ survived Bonferroni correction for multiple comparisons (12 post hoc comparisons for the clinical measures and the functional connectivity as reported in table 3).

RESULTS

The striatum represents an important relay station consisting of a group of parallel circuits connecting the cerebral cortex to the thalamus. Anatomically, it is possible to distinguish two main cortico-striatal loops (Alexander *et al*. 1986; Nieuwenhuys *et al*.

2008). The direct loop includes, in sequence, excitatory corticostriatal, inhibitory striatopallidal (internal pallidum), inhibitory pallidothalamic and excitatory thalamo-cortical connections. The indirect loop sequentially includes the excitatory cortico-striatal, inhibitory striatopallidal (external palidum), inhibitory pallido-subthamalic, excitatory subthalamic-pallidal, inhibitory pallidothalamic and excitatory thalamocortical connections (**Fig. 2**). The overall function of these loops is to facilitate the initiation and execution of movement (Hauber 1998), the selection of purposeful patterns of movement in response to internal and environmental stimuli (Pessiglione et al. 2003), and reward and motivation (Pessiglione et al. 2006).

The cortico-striatal network we identified with rs-*f*MRI (component 5 in **Fig. 1**) mainly involved the frontal, parietal, posterior temporal and to some extent limbic cortices. Subcortically, it involved significantly the striatum, the internal and external pallidum, and the anterior portion of the thalamus. These results are comparable to those obtained in previously task related *f*MRI (Jahanshahi et al. 2015) and rs-*f*MRI connectivity studies (Di Martino et al. 2008; Salomons et al. 2014)

The dorsal attentional network (i.e. DAN) increases its activation during the voluntary orienting of attention involving the frontal eye field, the intraparietal sulcus and superior parietal lobe. Alternatively, the ventral attentional network (i.e. VAN) acts as an alarm for the dorsal network, forcing the automatic reorientation of spatial attention when

unexpected spatial events occur. The VAN classically involves the caudal portion of the inferior and middle frontal gyri and the supramarginal, angular and caudal portion of the superior temporal gyri (Corbetta and Shulman 2002; Shulman et al. 2010) (**Fig. 3**). The DAN we identified with rs-*f*MRI (component 9 in **Fig. 1**) involved mainly the frontal eye field, intraparietal sulcus and the superior parietal lobule. The VAN (component 11 in **Fig. 1**) involved the temporo-parietal junction (caudal superior temporal gyrus, supramarginal and angular gyri) and the posterior portion of the inferior frontal gyrus. These results are similar to those described as in previously task-related *f*MRI studies (Corbetta and Shulman 2002; Shulman *et al*. 2010) and rs-*f*MRI connectivity studies (Fox *et al*. 2006; Shulman et al. 2009; Hacker et al. 2013)

Repeated measures ANOVA revealed a significant interaction between the group and the CPRS scores ($F_{(3,308)}$=206.25; $p < 0.001$). Post-hoc independent-sample t-test are summarized in **table 3** and revealed significant differences between the CPRS scores for the three groups (see **Fig. 4**).

Independent component analysis (ICA) identified the cortico-striatal (**Fig. 5a, Supplementary Material**), dorsal and ventral attention resting state networks (**Fig. 6a, Supplementary Material**). The three networks showed a high inter-individual reproducibility reaching 100% for the core of each networks and each with a different power spectrum (**Fig. 5b and 6b**). Dual regression revealed that compared to the

'inattentive' group, the 'hyperactive' group had stronger connectivity within the cortico-striatal network at the level of the right striatum (MNI coordinates 10,18,0; volume 896 mm^3; peak p = 0.038; situated in the head of the caudate nucleus as shown in **Fig. 5c**). This analysis also revealed that, compared to the 'hyperactive' group, the 'inattentive' group had stronger connectivity within the VAN in the core of its parietal (MNI coordinates 62,-30,40; volume 256 mm^3; peak p = 0.05; **Fig. 6c**) and frontal components (MNI coordinates 58,14,8; volume 384 mm^3; peak p = 0.05; **Fig. 6c**). The connectivity in the DAN, however, did not differ significantly between the 'inattentive' group, the 'hyperactive' group.

Repeated measures ANOVA revealed a significant interaction between the group membership and the strength of the connectivity in the areas reported by dual regression analysis as statistically different ($F_{(3,308)}$=14.059; p < 0.001). Post-hoc independent-sample t-test revealed significant differences between the strength of the connectivity for the three groups (see **Fig. 5d, 6d** and **table 2**). Additional analyses of the same regions mirrored in the left hemisphere were not significant ($F_{(3,308)}$=14.059; p < 0.001).

DISCUSSION

Our rs-*f*MRI study revealed, for the first time, a double dissociation between functional brain networks modulating hyperactivity/impulsivity and inattention in

children with ADHD. In children with a predominantly hyperactive-impulsive subtype, we report increased connectivity in the right cortico-striatal network; whereas in those with a predominantly inattentive subtype, we found increased connectivity in the right ventral attention network. Additional analyses did not reveal significant differences in the same regions mirrored in the left hemisphere, further suggesting a right lateralised disturbance of these networks. These findings are consistent with our current understanding of the specific role of these networks and lateralization of specific cognitive function.

Previous neuropsychological, task-*f*MRI and anatomical studies have, for example, reported that attention is dominant in the right hemisphere (Sperry 1974; Mesulam 1999; Shulman *et al*. 2010; Thiebaut de Schotten et al. 2011). Also, the *right hemispheric hypoarousal theory* of ADHD has long suggested that inattention and impulsivity associated with ADHD is due to a lateralised disturbance in frontal lobe network function, mediated by the dysfunction of predominantly right hemispheric frontostriatal (Sheppard et al. 1999) and frontoparietal tracts (Carter et al. 1995). However, most prior studies lacked the statistical power to fractionate the ADHD phenotype further, and analyse the relationship between core symptoms of ADHD and these specific brain networks.

The specificity of our findings is consistent with earlier studies, which have reported that the corticostriatal system (predominantly modulated by dopamine) is central to

hyperactivity and impulse control. For example, in animal studies, mice with neonatal dopamine-depleting lesions demonstrate *hyperactivity* that is reduced by psychostimulants (Avale et al. 2004) and infusions of a D1 antagonist into the prefrontal cortex of monkeys increase impulsivity (Ma et al. 2003; Ma et al. 2005). In children, psychostimulants have been reported to be associated with reduced inferior frontal lobe activation during inhibition related tasks (Pauls et al. 2012). Further, in children with ADHD, increased impulsivity has been reported to be associated with atypical fronto-striatal function (Durston et al. 2003), task related reduced activations (Cubillo et al. 2010), decreased entropy (Sokunbi *et al*. 2013), and increased rs-*f*MRI connectivity (Costa Dias et al. 2013). Therefore the increased connectivity reported in our study may contribute to the overall lack of response control (i.e. hyperactivity and impulsivity) found in ADHD patients. In contrast with our results, fronto-striatal functional connectivity has been reported to be reduced in ADHD during task-related *f*MRI but is 'normalized' with the use of stimulant (Rubia et al. 2009). Methodological differences between the current approach and previous studies may explain this discrepancy; alternatively aberrant connectivity may behave differently during rest or task-related *f*MRI.

Conversely the VAN, predominantly modulated by noradrenaline, has been more closely linked with attention and the control of switching attention from one source to another (Aston-Jones et al. 1984; Corbetta and Shulman 2002; Bouret and Sara 2005). Studies in

monkeys, for example, have reported noradrenergic innervation of the temporo-parietal junction and the frontal lobe by the locus coeruleus/noradrenergic system (Morrison and Foote 1986; Foote and Morrison 1987). Functionally, this serves to reorient an individual to salient or behaviourally relevant visual, auditory or tactile stimuli (Downar et al. 2000). Also, the modulation of inferior frontal gyrus activation with stimulant during presentation of irrelevant distractors covaries with activation within the ventral fronto-parietal network (Pauls *et al*. 2012). Therefore the increased connectivity reported in our study may contribute to the excessive reorientation to irrelevant distracters (i.e. distractibility or inattention) found in ADHD patients(for a review on the noradrenergic system and the ventral attention system see Corbetta et al. 2008). Further, during spatial tasks fronto-parietal functional connectivity has been reported to be reduced in subjects with ADHD (Vloet et al. 2010) again suggesting that aberrant functional connectivity may be different at rest and during a task.

Increased aberrant connectivity within the cortico-striatal and VAN might be related to a delayed synaptic pruning that occurs during brain maturation (Low and Cheng 2006). Preliminary reports show that ADHD children are on a different trajectory of brain maturation (Shaw et al. 2012) that may also have impacted the functional connectivity within the cortico-striatal and ventral fronto-parietal networks. Alternatively, increased functional connectivity may also be related to compensatory mechanisms (for a similar interpretation in posterior cerebral atrophy see Migliaccio et al. 2016).

Although the current study has a number of strengths it also had some limitations. First, in order to increase statistical power, we combined datasets from two different institutes. This approach produced some inhomogeneity in the dataset (e.g., spatial and temporal resolution of rs-*f*MRI and structural MRI, eyes opened/closed during resting state, etc.). However, it is unlikely that this has had a significant effect on our results as the networks identified by rs-*f*MRI are extraordinarily robust across distinct populations and differences in scanner field strength, scanning parameters (Biswal *et al*. 2010), or condition of rest (eyes opened or closed Patriat et al. 2013) and are stable in test-retest designs (Shehzad et al. 2009; Van Dijk et al. 2010). Further the children in the two centres were matched for age, sex and clinical characteristics. A second limitation was the absence of information regarding co-morbid diagnoses (e.g., conduct disorders) and medication status (e.g., medication naïve/not naïve) for many subjects. This effect has been minimized as stimulant drugs were withdrawn at least 24 hours before scanning. However, these factors may still have confounded our findings if they were not randomly distributed between the two groups (Shafritz et al. 2004; An, Cao, Cao, et al. 2013; Zhu et al. 2013). Future studies would benefit from clearer measures of these factors. A third limitation is the hypothetically driven aspect of our study, which purposely focused on the cortico-striatal and attentional networks in order to reduce the number of comparisons. Other studies report strong functional connectivity differences, between ADHD and controls, in the default network, particularly in the anterior cingulate cortex (Tian *et al*.

2006; Castellanos et al. 2008; Wolf et al. 2009; Fair et al. 2010) and cortico-cerebellar network (Cao et al. 2006; Tian *et al*. 2006; Zang *et al*. 2007; Rubia *et al*. 2009; Wolf *et al*. 2009). Future research may need to explore further these networks with probabilistic independent component analysis or other approaches such as fractal analysis, entropy and complexity measurements and frequency analysis techniques, which recently provided interesting brain behavior correlations in ADHD (Zang *et al*. 2007; An, Cao, Sui, *et al*. 2013; Sokunbi *et al*. 2013). Finally, it is important to note that our group division suggests that a continuum exists between the different symptoms dimension in ADHD. It is important to note that we use a statistical clustering (k-mean clustering) based on CPRS-R scores rather than the original subtypes classified in the ADHD-200 sample in order to reduce variability in the subtype diagnosis. Our purpose was not to provide a new classification of ADHD but rather to identify the biological mechanisms that lead to profiles that are more hyperactive than inattentive or more inattentive than hyperactive.

In summary our study demonstrated for the first time a right lateralized, double dissociation between specific networks associated with hyperactivity-impulsivity and inattentiveness in children with ADHD. The measure of increased functional connectivity in the cortico-striatal or ventral fronto-parietal networks may assist further studies to fractionate the ADHD phenotype into more homogenous biological subtypes.

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FIGURE LEGENDS

Fig. 1: 23 rs-*f*MRI networks extracted by the independent component analysis. Results

are displayed in radiological convention (left = right).

Fig. 2: Diagram of the direct (cortico-triatal-pallido-thalamo-cortical) and indirect (cortico-striatal-pallido-subthalamic-pallido-thalamo-cortical) loops connecting the cerebral cortex to the basal ganglia and thalamus (Catani and Thiebaut de Schotten 2012).

Fig. 3: The dorsal (in blue) and ventral (in orange) fronto-parietal networks for visuospatial attention as identified by functional neuroimaging (Corbetta and Shulman 2002).

Fig. 4 K-mean clustering of ADHD patients based on inattentiveness and hyperactivity-impulsivity scores in Conner's Parent Rating Scale-Revised, Long version (CPRS-R). Error bars indicate 95% confidence intervals. *p < 0.0042

Fig. 5 Cortico-striatal network. a) group effect of the cortico-striatal network as defined by ICA. b) Power spectrum of the cortico-striatal network according to time frequencies. c) The right striatum shows an increased functional connectivity in the group 'hyperactive/impulsive' when compared to the group 'inattentive' for the cortico-striatal network. Note that coronal sections are displayed in radiological convention (left = right). d) Average functional connectivity in the cluster reported as significant in the striatum.

Error bars indicate 95% confidence intervals. * $p < 0.0042$; SN, substantia nigra; Str, striatum; D1, receptor D_1; D2, receptor D_2; EP, external pallidum; IP, internal pallidum; STN, subthalamic nucleus.

Fig. 6 Dorsal (DAN) and ventral (VAN) attention networks a) group effect of the DAN (blue to light blue) and VAN networks (red to yellow) as defined by ICA. b) Power spectrum of the DAN (blue) and the VAN (orange) according to time frequencies. c) The VAN shows an increased functional connectivity in the group 'inattentive' when compared to the group 'hyperactive/impulsive'. d) Average functional connectivity in the clusters reported as significant in the VAN. Error bars indicate 95% confidence intervals. * $p < 0.0042$. IPs: intraparietal sulcus; SPL: superior parietal lobule, FEF: frontal eye field, TPJ: temporo-parietal junction, IPL: inferior parietal lobule, STg: superior temporal gyrus, VFC: ventral frontal cortex, IFg: inferior frontal gyrus, MFg: middle frontal gyrus.

Table 1: Centers demographics

	N	♂	♀	Age (y)	VIQ	PIQ	FSIQ	>Inatt	>Hyp/imp
Total	165	121	44	11.2 ± 2.8	107.2 ± 14.5	103.8 ± 14.7	105.7 ± 14.3	53	44
KKI (patients)	22	12	10	10.2 ± 1.5	109.3 ± 17.7	109.4 ± 13.8	106.0 ± 14.8	4	7
KKI (controls)	60	33	27	10.2 ± 1.3	114.4 ± 13.3	108.4 ± 11.3	111.5 ± 10.4	–	–
NYU (patients)	143	109	34	11.4 ± 2.6	106.9 ± 13.9	103.0 ± 14.7	105.7 ± 14.2	49	37
NYU (controls)	105	54	51	12.1 ± 3.1	112 ± 13.3	107.5 ± 15	111 ± 10.4	–	–

KKI, Kennedy Krieger Institute; NYU, New York University; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient; FIQ, Full Scale Intelligence Quotient; > Innattentive, Inattentive group; > Hyp/imp, Hyperactive/impulsive group.

Table 2: Groups demographics

	N	♂	♀	Age (y)	VIQ	PIQ	FSIQ	Clinical Diagnostic	Mv
Total	335	208	127	11.2 ± 2.7	110.1 ± 14.2	105.8 ± 14.4	108.5 ± 13.8	–	
Combined	68	53	15	11.46 ± 2.8	107.2 ± 15	104.6 ± 14.5	106.1 ± 13.8	78% / 22% / 0%	.019
Inattentive	53	34	19	11.28 ± 2.7	109.2 ± 12.3	105.4 ± 14.9	108.1 ± 13.5	62% / 38% / 0%	.021
Hyp/imp	44	34	10	11.36 ± 2.6	105 ± 16.1	100.9 ± 14.9	102.7 ± 15.6	82% / 11% / 7%	.023
Controls	170	87	83	11.46 ± 2.8	112.9 ± 13.3	107.8 ± 13.8	111.2 ± 12.9	0% / 0% / 0%	.022

Hyp/imp, Hyperactive/impulsive, VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient; FSIQ, Full Scale Intelligence Quotient; Clinical Diagnostic Combined (%) / Innatentive (%) / Hyperactive/impulsive (%); Mv, Absolute movement.

Table 3: Post-hoc statistics (absolute t values, * indicates $p < 0.0042$)

	Inattentiveness score (light grey) Hyperactivity/impulsivity score (dark grey)				Ventral FP connectivity (light grey) Cortico-striatal connectivity (dark grey)			
	Combined	Inattentive	Hyp/imp	Controls	Combined	Inattentive	Hyp/imp	Controls
Combined	–	5.171*	5.391*	23.581*	–	1.657	3.075*	2.096
Inattentive	3.058*	–	10.273*	13.359*	1.571	–	4.789*	t <1
Hyp/imp	2.236	5.204*	–	33.615*	3.969*	4.888*	–	5.460*
Controls	25.502*	29.573*	20.613*	–	1.874	3.196*	2.05	–

Fig. 1
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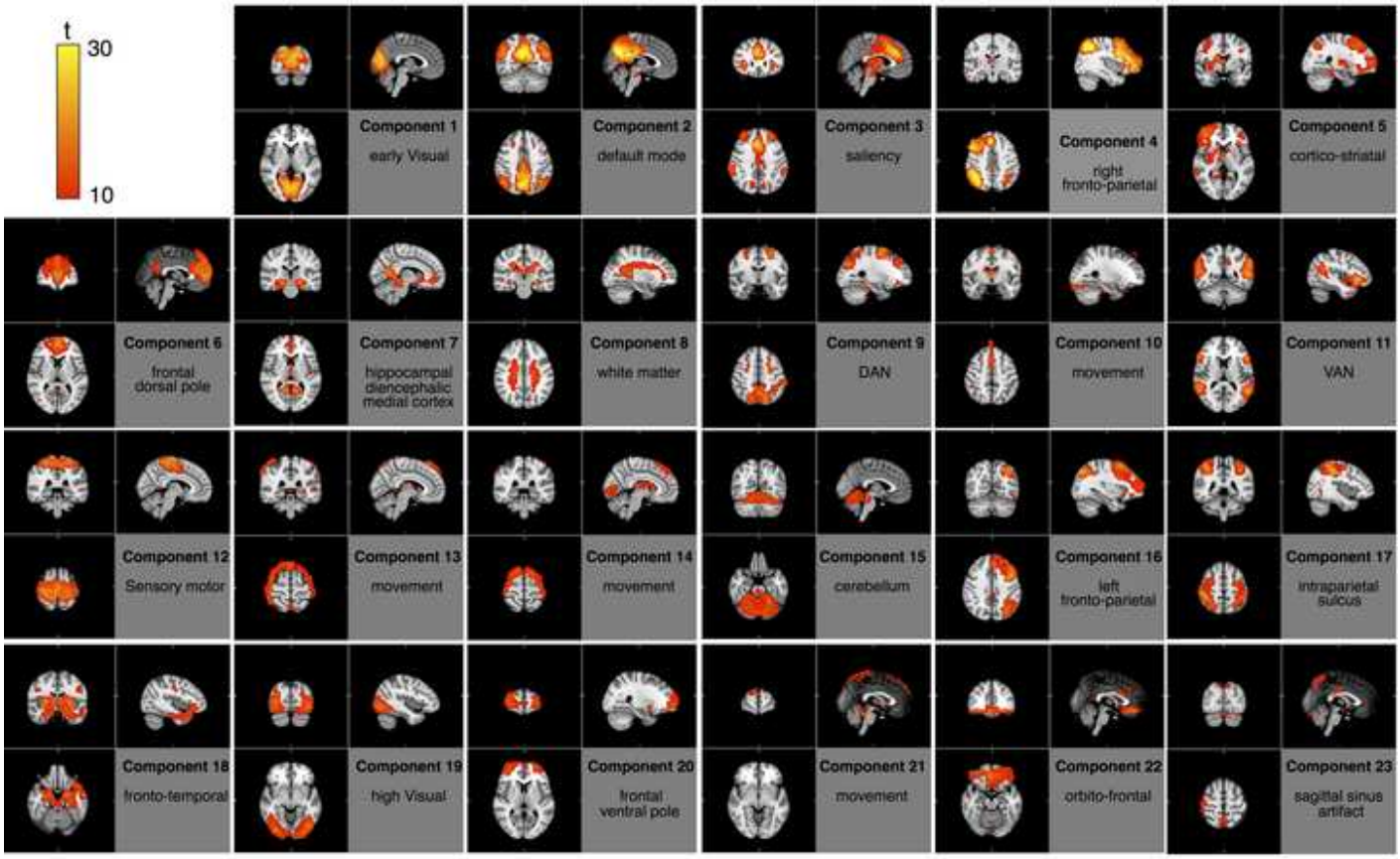

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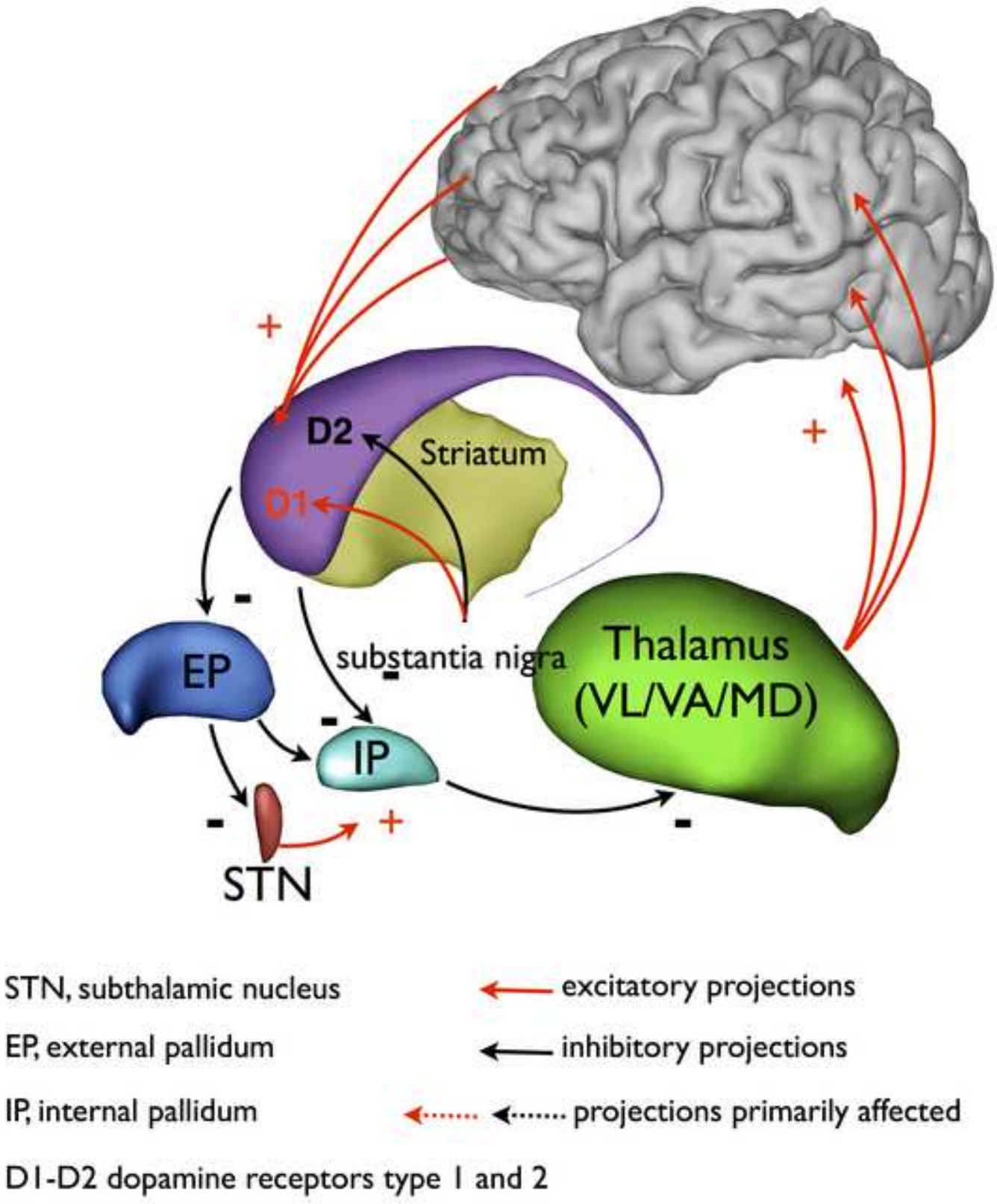

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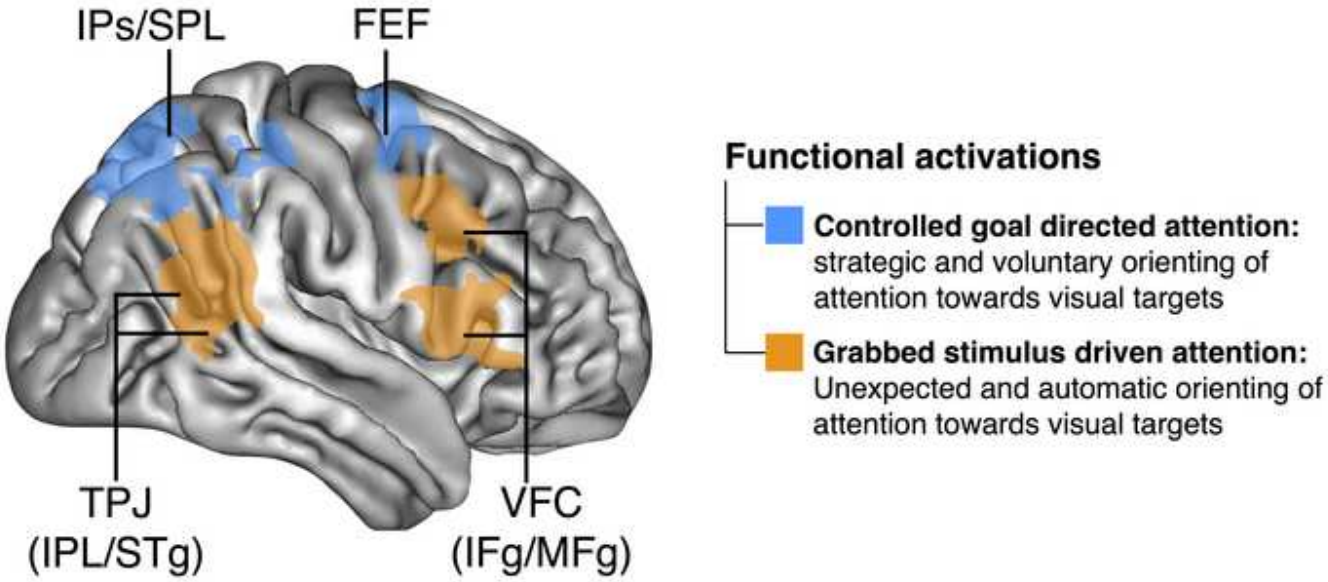

Fig. 4
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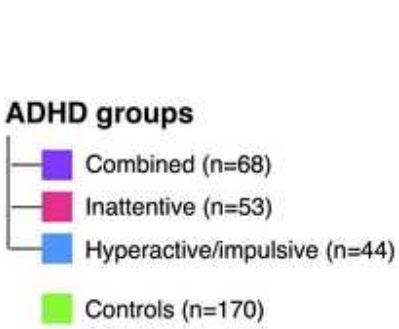

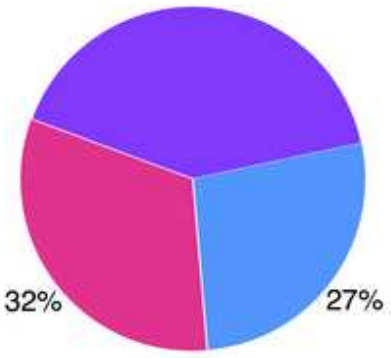

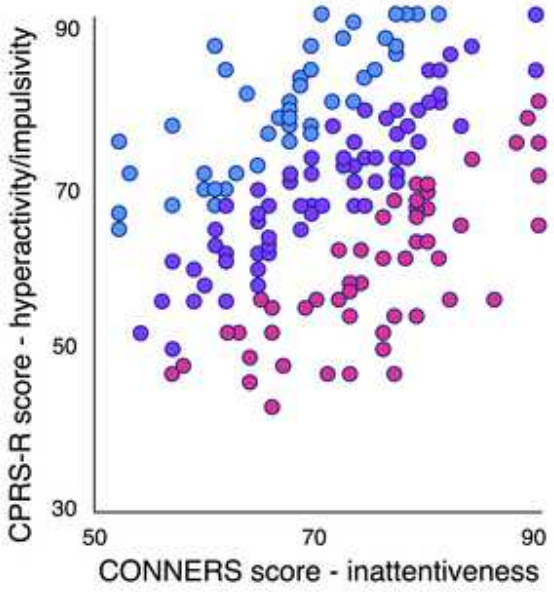

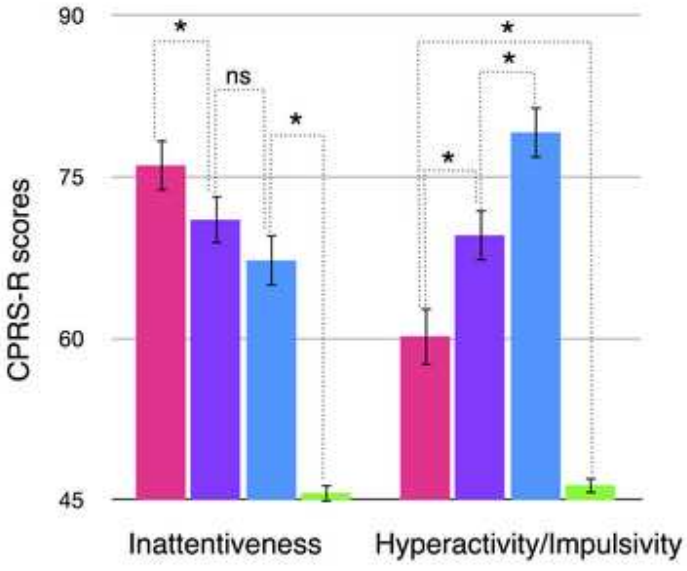

Fig. 5
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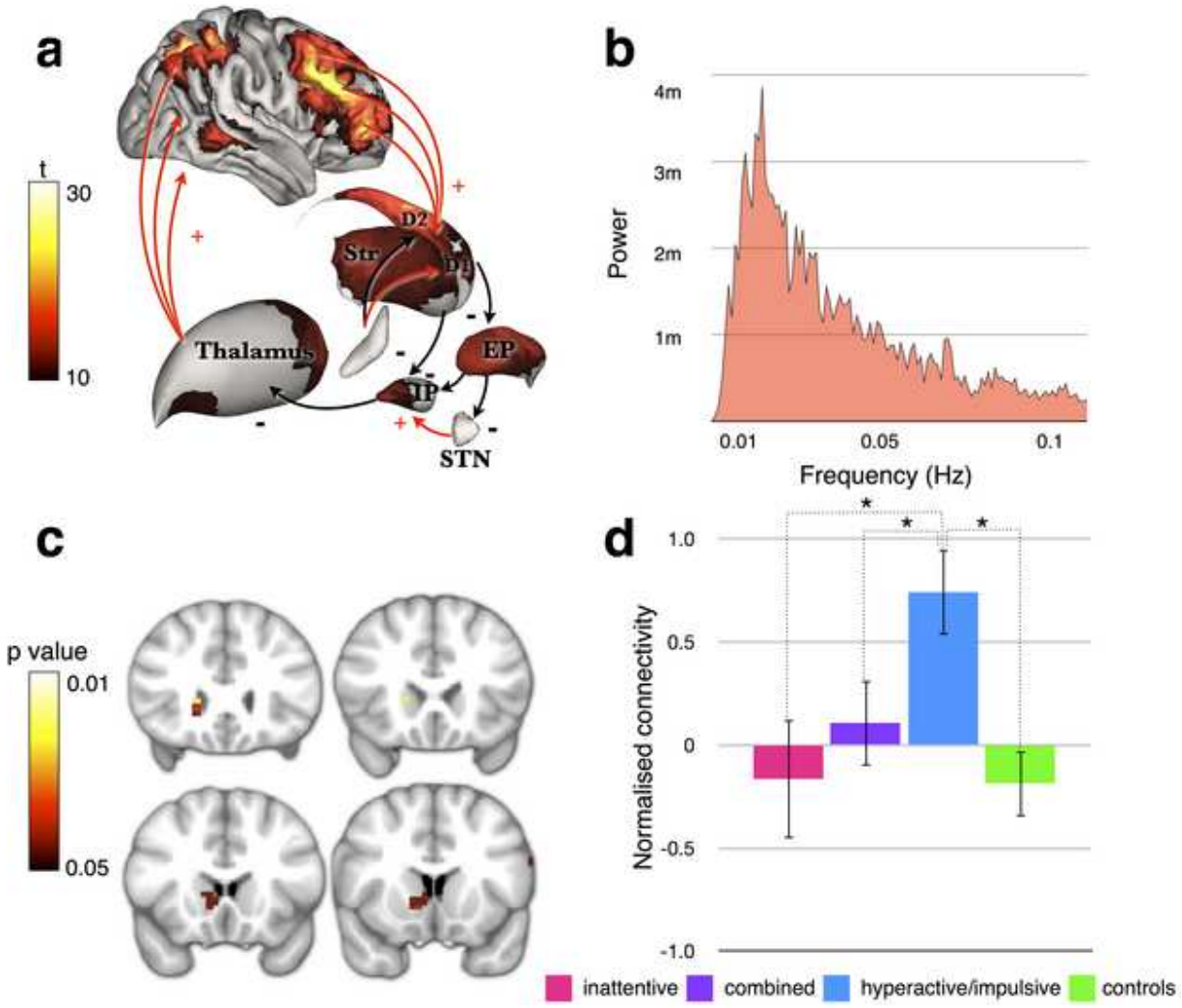

Fig. 6
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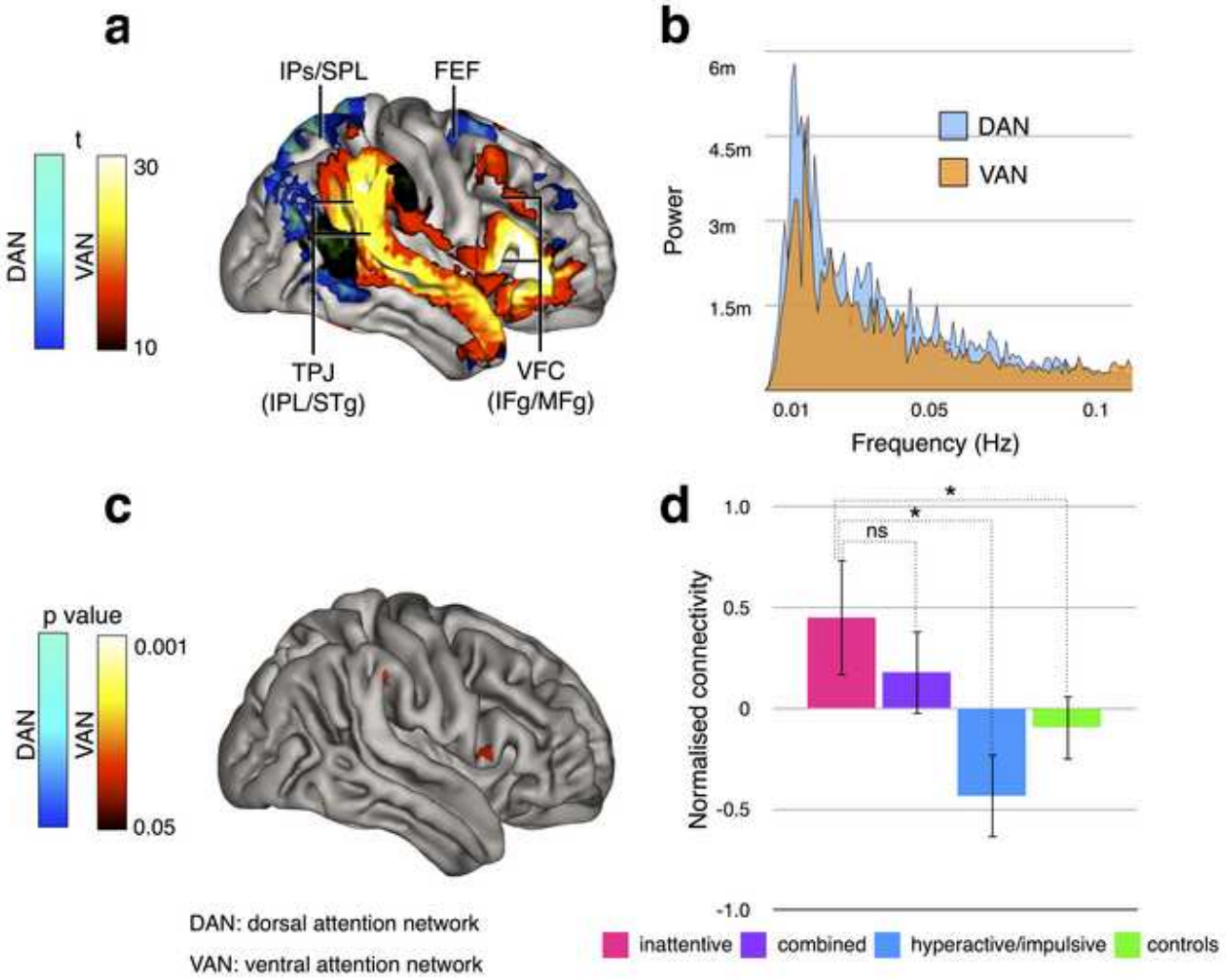

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