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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

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3
4 **ABSTRACT**
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6 Two core symptoms characterize Attention Deficit Hyperactivity Disorder (ADHD)
7
8 subtypes: inattentiveness and hyperactivity-impulsivity. While previous brain imaging
9
10 research investigated ADHD as if it was a homogenous condition, its two core symptoms
11
12 may originate from different brain mechanisms. We, therefore, hypothesized that the
13
14 functional connectivity of cortico-striatal and attentional networks would be different
15
16 between ADHD subtypes. We studied 165 children (mean age 10.93 years; age range,
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18 7-17 year old) diagnosed as having ADHD based on their revised Conner's rating scale
19
20 score and 170 typical developing individuals (mean age 11.46 years; age range, 7-17 year
21
22 old) using resting state functional fMRI. Groups were matched for age, IQ and head
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24 motion during the MRI acquisition. We fractionated the ADHD group into predominantly
25
26 inattentive, hyperactive-impulsive and combined subtypes based on their revised
27
28 Conner's rating scale score. We then analyzed differences in resting state functional
29
30 connectivity of the cortico-striatal and attentional **networks** between these subtypes. We
31
32 found a double dissociation of functional connectivity in the cortico-striatal and ventral
33
34 attentional **networks**, reflecting the subtypes of the ADHD participants. Particularly, the
35
36 hyperactive-impulsive subtype was associated with increased connectivity in
37
38 cortico-striatal network, whereas the inattentive subtype was associated with increased
39
40 connectivity in the right ventral attention network. Our study demonstrated for the first
41
42 time a right lateralized, double dissociation between specific networks associated with
43
44 hyperactivity-impulsivity and inattentiveness in ADHD children, providing a biological
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basis for exploring symptom dimensions and revealing potential targets for more personalized treatments.

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3 **INTRODUCTION**
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6 Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental
7
8 condition affecting approximately 8% of school-aged children (Bloom et al. 2011) and
9
10 4% of adults (Kessler et al. 2006). Originally described in 1798 (Crichton 1798; reprinted
11
12 in Crichton 2008) ADHD patients ‘incessantly withdrawn from one impression to
13
14 another’ and ‘excites such a degree of anger as borders on insanity’ (for an historical
15
16 review see Lange et al. 2010). These two core symptoms are interpreted as inattention
17
18 and hyperactivity-impulsivity in the DSM5 (American Psychiatric Association 2013) and
19
20 can be of variable severity. Although these symptoms frequently come together, their
21
22 expression can be unbalanced leading to the division of ADHD into three clinical
23
24 subtypes: *predominantly inattentive*, *predominantly hyperactive-impulsive*, and *combined*
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26 (American Psychiatric Association 1994). Whether the brain mechanism leading to these
27
28 subtypes is different remains to be clarified in order to enhance personalised treatment.
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44 The efficacy of current drug treatments is predominantly mediated by their
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46 effects on the dopaminergic, and/or noradrenergic systems. They are effective in many
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48 patients, but approximately 1/3 fail to respond - predominantly those with the
49
50 ‘inattentive’ subtype (Spencer et al. 1995; Weiss et al. 2005; Hazell et al. 2011). This
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52 finding suggests that in addition to being clinically heterogeneous (Barkley et al. 2002;
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54 Biederman et al. 2006); ADHD subtypes may be modulated by different brain systems
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56 with a variable response to pharmacological treatments.
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6 There is increasing evidence that ADHD is associated with abnormalities in
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9 specific brain regions; and particularly dorsal anterior midcingulate cortex (daMCC),
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11 prefrontal cortex, parietal cortex, striatum, and cerebellum (see Bush 2011; Cortese et al.
12
13 2012 for review). The significance of these areas is that they are involved with attention,
14
15 executive function, motor control, response inhibition, and working memory. However,
16
17 rather than a mosaic of functionally specialized areas, the human mind is believed to
18
19 emerge from the coordinated activity of distant but anatomically interconnected regions.
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21 Advances in brain imaging have enabled us to study anatomical and functional
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23 connectivity within these networks *in vivo*.
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35 One of the most consistent findings from studies of *anatomical* connectivity, in
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37 children and adolescents with ADHD, is reduced fractional anisotropy (Hamilton et al.
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39 2008; Makris et al. 2008; Luders et al. 2009; Konrad et al. 2010) of fronto-striatal tracts
40
41 (within the cortico-striatal network) and fronto-parietal tracts (within the ventral and
42
43 dorsal attention network). These findings have been supported by some (Dickstein et al.
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45 2006; Rubia 2011; Cubillo et al. 2012) but not all studies of *functional* connectivity (Tian
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47 et al. 2006; Uddin et al. 2008).
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58 Studies of *functional* connectivity have employed standard, task-activation,
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60 fMRI (task-fMRI), or resting-state fMRI (rs-fMRI). A key advantage of rs-fMRI is that
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3 participants are not required to focus on an explicit task. This is particularly beneficial in
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6 ADHD, where compliance and attention during scanning may be problematic, and
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9 confound interpretation of results. The underlying principle of rs-fMRI is that functional
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12 connectivity between brain regions can be successfully mapped by correlating
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15 spontaneous low-frequency (<0.1Hz) fluctuations in blood oxygenation level dependent
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18 (BOLD) signal at rest (Fox and Raichle 2007). Previous rs-fMRI studies of ADHD have
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21 reported both hypo- and hyper-activation of fronto-striatal, fronto-parietal and other
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24 networks (see Konrad *et al.* 2010 for review). Also, whole brain voxel-based analyses
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27 revealed decreased entropy (Sokunbi *et al.* 2013) and decreased amplitude of
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30 low-frequency fluctuation (Zang *et al.* 2007; An, Cao, Sui, *et al.* 2013) in the frontal and
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33 the occipital lobes. These inconsistencies are likely to be due to a combination of
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36 methodological factors, including the method of analysis employed, micro-movements
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39 (Fair *et al.* 2012), variability in the subtype diagnosis and the age range of subjects. The
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42 small size of clinical samples has also been a significant limitation of the majority of
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45 imaging studies of ADHD to date. An important consequence of this has been the
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48 scarcity of studies with the statistical power to analyse ADHD as a heterogeneous
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51 condition. Therefore there has been a need for larger studies, with sufficient power to
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54 fractionate ADHD into its clinical subtypes, and that permit a more comprehensive
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57 analysis of brain connectivity.
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61 In the present study we accessed a recent, unrestricted public release, dataset of
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2
3 rs-fMRI images from 255 children and adolescents with ADHD (ages: 7-21 years old)[†].
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6 This has provided a valuable opportunity to analyse whether the clinical heterogeneity
7
8 observed in ADHD is underpinned by differences at a functional brain network level. We
9
10 focused our analyses on three resting state networks of interest, the dopaminergic circuit
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12 (i.e. cortico-striatal circuit Alexander et al. 1986; Nieuwenhuys et al. 2008) for its
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14 essential role in impulsivity (Buckholtz et al. 2010), and the dorsal and the ventral
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16 fronto-parietal networks (Fox et al. 2006) for their key role in attention (i.e. dorsal and
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18 ventral attention networks Corbetta and Shulman 2002).
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33 [†] ADHD-200 Sample; http://fcon_1000.projects.nitrc.org/indi/adhd200
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3 **MATERIAL AND METHODS**
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6 **Dataset**
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9 We selected 165 children out of the 255 children cohort (44 girls, 121 boys; 7-17
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11 year old, 10.93 ± 2.53 years, $FSIQ > 70$) with ADHD. Selection was based on the use of
12
13 the same version of the Conner's Parent Rating Scale-Revised, Long version (CPRS-R).
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16
17 Consequently 90 children were rejected from participating in the study due to the absence
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19 of CPRS-R scores. These children were recruited from two centers: Kennedy Krieger
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21 Institute (KKI) or New York University (NYU). The children were diagnosed based on
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23 evaluations with the Diagnostic Interview for Children and Adolescents, Fourth Edition
24
25 (DICA-IV Reich et al. 1997) or the Schedule of Affective Disorders and Schizophrenia
26
27 for Children-Present and Lifetime Version (KSADS-PL); CPRS-R or ADHD Rating
28
29 Scale-IV (DuPaul and Power 1998). They either had a T-score of 65 or greater on at least
30
31 one ADHD related index of the CPRS-R, or met criteria on the ADHD Rating Scale-IV
32
33 (six out of nine items scored 2 or 3 from Inattention items and/or six out of nine scored 2
34
35 or 3 from the Hyperactivity/Impulsivity items). Consistent with previous studies, children
36
37 taking stimulant medication were instructed to refrain from taking these medications for
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39 at least 24 hours before scanning. Additionally we selected a control group of 170
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41 children matched with our ADHD group (83 girls, 87 boys; 7-17 year old, 11.46 ± 2.76
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43 years, $FSIQ > 70$). Details of the center distribution of the data included in the study are
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45 reported in **Table 1**.
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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-fMRI, participants in both centers (i.e. KKI and NYU) were instructed to relax, think of nothing, and to stay awake. In KKI participants

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3 were asked to keep their eyes open, and fixate on a center cross, whereas in NYU
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6 participants were instructed to close their eyes. Functional images were obtained using
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9 T2-weighted echo-planar imaging (EPI) with blood oxygenation level-dependent
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12 (BOLD) contrast using SENSE imaging. In KKI, EPIs (TR/TE = 2500/30 msec)
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14
15 comprised 47 axial slices acquired continuously in ascending order covering the entire
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17
18 cerebrum (voxel size = $2.67 \times 2.67 \times 3.00 \text{ mm}^3$). In NYU, EPIs (TR/TE = 2000/15 msec)
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21 comprised 33 axial slices acquired continuously in interleaved order covering the entire
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24 cerebrum (voxel size = $3.0 \times 3.0 \times 4.0 \text{ mm}^3$).
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29 An axial three-dimensional (3D) magnetization prepared rapid gradient echo
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31 (MPRAGE) dataset covering the whole head was also acquired for each participant (200
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33
34 slices, voxel resolution = $1.00 \times 1.00 \times 1.00 \text{ mm}$, TE = 3.7 msec, TR = 8.0 msec, flip
35
36
37 angle = 8° for KKI; 128 slices, voxel resolution = $1.3 \times 1.0 \times 1.3 \text{ mm}$, TE = 2530 msec,
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40 TR = 3.25 msec, flip angle = 7° for NYU).
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47 rs-fMRI independent component analysis Analysis of functional connectivity
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49 was carried out using Probabilistic Independent Component Analysis (PICA, Beckmann
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52 and Smith 2004; Beckmann 2012) as implemented in Multivariate Exploratory Linear
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54
55 Decomposition into Independent Components (MELODIC) version 3.13, part of
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58 FMRIB's Software Library (FSL, www.fmrib.ox.ac.uk/fsl). We chose PICA as it is a
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61 robust, operator independent approach(Beckmann and Smith 2004; Beckmann et al.
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3 2005; Beckmann et al. 2009), which provides a very close relationship between the
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6 anatomy of the resting networks identified and classical brain functional activations
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9 (Smith et al. 2009).
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14 In order to obtain a steady-state signal, the five first volumes of each dataset
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16 were discarded from the analyses. Rs-fMRI datasets were corrected for head motion by
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18 rigid registration to the first volume (Jenkinson et al. 2002), capped with a high pass filter
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20 (.01 Hz, Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 sec) and
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22 skull-stripped (Smith 2002). Each subject's fMRI data was registered to that subject's
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24 high-resolution structural image (Jenkinson *et al.* 2002) and then registered again, this
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26 time, with the standard MNI152 template using affine (FLIRT) and non-linear
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28 registration (FNIRT). All resulting datasets were concatenated in the temporal dimension.
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30 This approach is advantageous, as it does not assume that the associated temporal
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32 response is consistent across subject but rather looks for common spatial patterns
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34 between subjects.
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49 The following data pre-processing was applied to the input data: masking of
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51 non-brain voxels; voxel-wise de-meaning of the data; normalisation of the voxel-wise
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53 variance; pre-processed data were whitened and projected into a 23-dimensional
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55 subspace using probabilistic principal component analysis where the number of
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57 dimensions was estimated using the Laplace approximation to the Bayesian evidence of
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3 the model order (Minka 2000; Beckmann and Smith 2004).
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9 We focused our analyses on three resting state networks of interest, the
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11 cortico-striatal network (Alexander *et al.* 1986; Nieuwenhuys *et al.* 2008), the dorsal and
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13 the ventral attention networks (i.e. DAN and VAN, Corbetta and Shulman 2002; Fox *et al.*
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17 2006).
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23 **rs-fMRI Dual regressions** 24

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26 In order to assess the presence of group differences in the spatial extent of the
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28 RSNs, it is necessary to generate subject-level maps of the components extracted by the
29
30 group-level ICA. This is achieved in two steps: (1) first, the entire set of 23 group-level
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32 spatial components (**Fig. 1**) was regressed against each volume of the preprocessed
33
34 rs-fMRI data using multiple regression in the spatial domain; therefore, the 3D image
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36 associated with each time point in the rs-fMRI data was modeled as a linear combination
37
38 of the group-level spatial components. This allowed for the estimation of a
39
40 subject-specific time course for each group-level component. (2) Afterwards, the whole
41
42 set of 23 component-specific time courses were used as predictors in a second multiple
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44 regression in the temporal domain, against the preprocessed rs-fMRI data of each subject.
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46 In this way we estimated the correlation of each brain voxel with the characteristic time
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48 course of each spatial component, and ultimately obtained maps of the spatial distribution
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50 of each subject-specific component. Since this procedure is based on two multiple
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3 regression steps, the first in the spatial domain, the second in the temporal domain, it has
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5
6 been denominated 'dual regression' (Filippini et al. 2009). A visual description of the
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9 steps of the dual regression can be found in (Beckmann *et al.* 2009). Importantly, since
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11
12 the full set of components extracted by ICA is used, the dual regression procedure
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14
15 accounts for the potential contamination of the rs-fMRI signal by components reflecting
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17
18 structured noise such as motion artifacts and white matter signals. Therefore any variance
19
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21 shared between these components and the rs-fMRI networks of interest was regressed out
22
23
24 during the estimation of the rs-fMRI networks summary time course for each subject. For
25
26
27 instance, the white matter signal was modeled as the time course of the IC 8, and
28
29
30 subsequently, this component had been estimated in a subject-specific way - by means of
31
32
33 the first stage of dual regression. This approach has several benefits with respect to using
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35
36 a standard mask of white matter. The white matter mask is directly estimated from the
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39 data: remarkably, this component is among the most reproducible found in different
40
41
42 ICA-based resting state investigations (e.g. IC4 in (Biswal et al. 2010); BM20 in (Smith
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44
45 *et al.* 2009); IC31 in (Salimi-Khorshidi et al. 2014)). In addition, the dual regression
46
47
48 procedure allows for an estimation of the subject-level component of the white matter
49
50
51 component extracted in the group analysis.

52
53 We then tested for statistical differences between the inattentive group and the
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55
56 hyperactive group using FSL's randomise permutation-testing tool. Randomise calculates
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58
59 nonparametric inferences on neuroimaging data. For each voxel of the brain, randomise
60
61
62 will test using a permuted general model (Winkler et al. 2014) whether the strength of the
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3 functional connectivity in the cortico-striatal, DAN and VAN networks (i.e. the
4
5
6 dependant variables) is different between the ‘inattentive’ and the ‘hyperactive/impulsive’
7
8
9 groups (i.e. the independent variables). Results were corrected for multiple comparisons
10
11 using family-wise error (FWE) (Anderson and Robinson 2001; Nichols and Holmes
12
13 2002). 3D rendering of the brain was calculated using the T1 pipeline in Brain VISA
14
15 (<http://brainvisa.info>).
16
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20
21 Note that recent work revealed that motion can have a substantial effect on the
22
23 estimation of resting-state functional connectivity (Van Dijk et al. 2012). Removing time
24
25 points associated with high motion (‘scrubbing’ Power et al. 2012) represents an effective
26
27 procedure to reduce the contamination rs-fMRI data by residual motion. However,
28
29 performing ‘scrubbing’ before temporally-concatenated PICA is not technically feasible
30
31 and, most importantly, not desirable, as it would lead to heteroschedasticity when
32
33 performing group-level analysis (i.e., a different number of temporal degrees of freedom
34
35 for each participant). In addition, a recent work (Jo et al. 2013) revealed that the largest
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37 contribution to minimizing head motion was yielded by regressing out from rs-fMRI data
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39 the mean signal in a white matter mask.
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3 **Statistical Analysis**
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6 In our analysis, Gaussian distribution of the data for the three groups was
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8 confirmed using the Shapiro–Wilk test (Shapiro and Wilk 1965).
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14 Statistical analysis was performed using SPSS 22 software (SPSS, Chicago, IL).
15
16 Analyses of the differences between the three groups were performed using repeated
17
18 measure ANOVA for the clinical characteristics. Additionally, repeated measure ANOVA
19
20 was employed to explore differences in the connectivity strength between the 4 groups in
21
22
23 the regions reported as statistically different by the dual regression analysis. Gender, age,
24
25
26 centre (KKI or NYU), verbal IQ, performance IQ, full IQ and movement during the
27
28
29 rs-fMRI (absolute value) were considered as covariates. Note that there were no
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32 significant absolute movement differences between the 4 groups. Post-hoc independent
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35 sample t-tests were performed, when statistically appropriate, to compare groups
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38 individually. Differences significant at $P < 0.0042$ survived Bonferroni correction for
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41 multiple comparisons (12 post hoc comparisons for the clinical measures and the
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44 functional connectivity as reported in table 3).
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52 **RESULTS**
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54 The striatum represents an important relay station consisting of a group of parallel
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58 circuits connecting the cerebral cortex to the thalamus. Anatomically, it is possible to
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61 distinguish two main cortico-striatal loops (Alexander *et al.* 1986; Nieuwenhuys *et al.*
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3 2008). The direct loop includes, in sequence, excitatory corticostriatal, inhibitory
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5
6 striatopallidal (internal pallidum), inhibitory pallidothalamic and excitatory
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8 thalamo-cortical connections. The indirect loop sequentially includes the excitatory
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10 cortico-striatal, inhibitory striatopallidal (external pallidum), inhibitory
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12 pallido-subthalamic, excitatory subthalamic-pallidal, inhibitory pallidothalamic and
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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-fMRI (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 fMRI (Jahanshahi et al. 2015) and rs-fMRI 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

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3 unexpected spatial events occur. The VAN classically involves the caudal portion of the
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6 inferior and middle frontal gyri and the supramarginal, angular and caudal portion of the
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9 superior temporal gyri (Corbetta and Shulman 2002; Shulman et al. 2010) (**Fig. 3**).

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11 The DAN we identified with rs-fMRI (component 9 in **Fig. 1**) involved mainly the
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14 frontal eye field, intraparietal sulcus and the superior parietal lobule. The VAN
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17 (component 11 in **Fig. 1**) involved the temporo-parietal junction (caudal superior
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20 temporal gyrus, supramarginal and angular gyri) and the posterior portion of the inferior
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23 frontal gyrus. These results are similar to those described as in previously task-related
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26 fMRI studies (Corbetta and Shulman 2002; Shulman *et al.* 2010) and rs-fMRI
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29 connectivity studies (Fox *et al.* 2006; Shulman et al. 2009; Hacker et al. 2013)
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34 Repeated measures ANOVA revealed a significant interaction between the group and the
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37 CPRS scores ($F_{(3,308)}=206.25$; $p < 0.001$). Post-hoc independent-sample t-test are
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40 summarized in **table 3** and revealed significant differences between the CPRS scores for
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43 the three groups (see **Fig. 4**).

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47 Independent component analysis (ICA) identified the cortico-striatal (**Fig. 5a**,
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50 **Supplementary Material**), dorsal and ventral attention resting state networks (**Fig. 6a**,
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53 **Supplementary Material**). The three networks showed a high inter-individual
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56 reproducibility reaching 100% for the core of each networks and each with a different
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59 power spectrum (**Fig. 5b and 6b**). Dual regression revealed that compared to the
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3 'inattentive' group, the 'hyperactive' group had stronger connectivity within the
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6 cortico-striatal network at the level of the right striatum (MNI coordinates 10,18,0;
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9 volume 896 mm³; peak p = 0.038; situated in the head of the caudate nucleus as shown in
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11 **Fig. 5c**). This analysis also revealed that, compared to the 'hyperactive' group, the
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14 'inattentive' group had stronger connectivity within the VAN in the core of its parietal
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17 (MNI coordinates 62,-30,40; volume 256 mm³; peak p = 0.05; **Fig. 6c**) and frontal
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20 components (MNI coordinates 58,14,8; volume 384 mm³; peak p = 0.05; **Fig. 6c**). The
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23 connectivity in the DAN, however, did not differ significantly between the 'inattentive'
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26 group, the 'hyperactive' group.

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32 Repeated measures ANOVA revealed a significant interaction between the group
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35 membership and the strength of the connectivity in the areas reported by dual regression
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38 analysis as statistically different ($F_{(3,308)}=14.059$; $p < 0.001$). Post-hoc
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41 independent-sample t-test revealed significant differences between the strength of the
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44 connectivity for the three groups (see **Fig. 5d, 6d** and **table 2**). Additional analyses of the
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47 same regions mirrored in the left hemisphere were not significant ($F_{(3,308)}=14.059$; $p <$
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49 **0.001**).

50 51 52 53 54 55 **DISCUSSION**

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

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3 children with ADHD. In children with a predominantly hyperactive-impulsive subtype,
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6 we report increased connectivity in the right cortico-striatal network; whereas in those
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9 with a predominantly inattentive subtype, we found increased connectivity in the right
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11 ventral attention network. Additional analyses did not reveal significant differences in the
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13 same regions mirrored in the left hemisphere, further suggesting a right lateralised
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16 disturbance of these networks. These findings are consistent with our current
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20 understanding of the specific role of these networks and lateralization of specific
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23 cognitive function.
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29 Previous neuropsychological, task-fMRI and anatomical studies have, for example,
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31 reported that attention is dominant in the right hemisphere (Sperry 1974; Mesulam 1999;
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33 Shulman *et al.* 2010; Thiebaut de Schotten *et al.* 2011). Also, the *right hemispheric*
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36 *hypoarousal theory* of ADHD has long suggested that inattention and impulsivity
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38 associated with ADHD is due to a lateralised disturbance in frontal lobe network function,
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41 mediated by the dysfunction of predominantly right hemispheric frontostriatal (Sheppard
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44 *et al.* 1999) and frontoparietal tracts (Carter *et al.* 1995). However, most prior studies
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47 lacked the statistical power to fractionate the ADHD phenotype further, and analyse the
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50 relationship between core symptoms of ADHD and these specific brain networks.
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58 The specificity of our findings is consistent with earlier studies, which have reported that
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61 the corticostriatal system (predominantly modulated by dopamine) is central to
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3 hyperactivity and impulse control. For example, in animal studies, mice with neonatal
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5 dopamine-depleting lesions demonstrate *hyperactivity* that is reduced by
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8 psychostimulants (Avale et al. 2004) and infusions of a D1 antagonist into the prefrontal
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10 cortex of monkeys increase impulsivity (Ma et al. 2003; Ma et al. 2005). In children,
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12 psychostimulants have been reported to be associated with reduced inferior frontal lobe
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14 activation during inhibition related tasks (Pauls et al. 2012). Further, in children with
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16 ADHD, increased impulsivity has been reported to be associated with atypical
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18 fronto-striatal function (Durstun et al. 2003), task related reduced activations (Cubillo et
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20 al. 2010), decreased entropy (Sokunbi *et al.* 2013), and increased rs-fMRI connectivity
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22 (Costa Dias et al. 2013). Therefore the increased connectivity reported in our study may
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24 contribute to the overall lack of response control (i.e. hyperactivity and impulsivity)
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26 found in ADHD patients. In contrast with our results, fronto-striatal functional
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28 connectivity has been reported to be reduced in ADHD during task-related fMRI but is
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30 ‘normalized’ with the use of stimulant (Rubia et al. 2009). Methodological differences
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32 between the current approach and previous studies may explain this discrepancy;
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34 alternatively aberrant connectivity may behave differently during rest or task-related
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36 fMRI.

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55 Conversely the VAN, predominantly modulated by noradrenaline, has been more closely
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57 linked with attention and the control of switching attention from one source to another
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59 (Aston-Jones et al. 1984; Corbetta and Shulman 2002; Bouret and Sara 2005). Studies in
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3 monkeys, for example, have reported noradrenergic innervation of the temporo-parietal
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6 junction and the frontal lobe by the locus coeruleus/noradrenergic system (Morrison and
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9 Foote 1986; Foote and Morrison 1987). Functionally, this serves to reorient an individual
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12 to salient or behaviourally relevant visual, auditory or tactile stimuli (Downar et al. 2000).
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14 Also, the modulation of inferior frontal gyrus activation with stimulant during
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17 presentation of irrelevant distractors covaries with activation within the ventral
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20 fronto-parietal network (Pauls *et al.* 2012). Therefore the increased connectivity reported
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23 in our study may contribute to the excessive reorientation to irrelevant distracters (i.e.
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26 distractibility or inattention) found in ADHD patients(for a review on the noradrenergic
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29 system and the ventral attention system see Corbetta et al. 2008). Further, during spatial
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32 tasks fronto-parietal functional connectivity has been reported to be reduced in subjects
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35 with ADHD (Vloet et al. 2010) again suggesting that aberrant functional connectivity
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38 may be different at rest and during a task.
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43 Increased aberrant connectivity within the cortico-striatal and VAN might be related to a
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46 delayed synaptic pruning that occurs during brain maturation (Low and Cheng 2006).
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49 Preliminary reports show that ADHD children are on a different trajectory of brain
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52 maturation (Shaw et al. 2012) that may also have impacted the functional connectivity
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55 within the cortico-striatal and ventral fronto-parietal networks. Alternatively, increased
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58 functional connectivity may also be related to compensatory mechanisms (for a similar
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61 interpretation in posterior cerebral atrophy see Migliaccio et al. 2016).
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6 Although the current study has a number of strengths it also had some limitations. First,
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9 in order to increase statistical power, we combined datasets from two different institutes.
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11 This approach produced some inhomogeneity in the dataset (e.g., spatial and temporal
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13 resolution of rs-fMRI and structural MRI, eyes opened/closed during resting state, etc.).
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16 However, it is unlikely that this has had a significant effect on our results as the networks
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18 identified by rs-fMRI are extraordinarily robust across distinct populations and
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21 differences in scanner field strength, scanning parameters (Biswal *et al.* 2010), or
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23 condition of rest (eyes opened or closed Patriat *et al.* 2013) and are stable in test-retest
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26 designs (Shehzad *et al.* 2009; Van Dijk *et al.* 2010). Further the children in the two
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29 centres were matched for age, sex and clinical characteristics. A second limitation was
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32 the absence of information regarding co-morbid diagnoses (e.g., conduct disorders) and
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35 medication status (e.g., medication naïve/not naïve) for many subjects. This effect has
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38 been minimized as stimulant drugs were withdrawn at least 24 hours before scanning.
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41 However, these factors may still have confounded our findings if they were not randomly
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44 distributed between the two groups (Shafritz *et al.* 2004; An, Cao, Cao, *et al.* 2013; Zhu
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47 *et al.* 2013). Future studies would benefit from clearer measures of these factors. A third
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49
50 limitation is the hypothetically driven aspect of our study, which purposely focused on
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52
53 the cortico-striatal and attentional networks in order to reduce the number of comparisons.
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56 Other studies report strong functional connectivity differences, between ADHD and
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59 controls, in the default network, particularly in the anterior cingulate cortex (Tian *et al.*
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3 2006; Castellanos et al. 2008; Wolf et al. 2009; Fair et al. 2010) and cortico-cerebellar
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6 network (Cao et al. 2006; Tian *et al.* 2006; Zang *et al.* 2007; Rubia *et al.* 2009; Wolf *et al.*
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9 2009). Future research may need to explore further these networks with probabilistic
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11 independent component analysis or other approaches such as fractal analysis, entropy and
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13 complexity measurements and frequency analysis techniques, which recently provided
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15 interesting brain behavior correlations in ADHD (Zang *et al.* 2007; An, Cao, Sui, *et al.*
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17 2013; Sokunbi *et al.* 2013). Finally, it is important to note that our group division
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19 suggests that a continuum exists between the different symptoms dimension in ADHD. It
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21 is important to note that we use a statistical clustering (k-mean clustering) based on
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23 CPRS-R scores rather than the original subtypes classified in the ADHD-200 sample in
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25 order to reduce variability in the subtype diagnosis. Our purpose was not to provide a
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27 new classification of ADHD but rather to identify the biological mechanisms that lead to
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29 profiles that are more hyperactive than inattentive or more inattentive than hyperactive.
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44 In summary our study demonstrated for the first time a right lateralized, double
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46 dissociation between specific networks associated with hyperactivity-impulsivity and
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48 inattentiveness in children with ADHD. The measure of increased functional connectivity
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50 in the cortico-striatal or ventral fronto-parietal networks may assist further studies to
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52 fractionate the ADHD phenotype into more homogenous biological subtypes.
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58 **FIGURE LEGENDS**

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

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3 are displayed in radiological convention (left = right).
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9 **Fig. 2:** Diagram of the direct (cortico-striatal-pallido-thalamo-cortical) and indirect
10 (cortico-striatal-pallido-subthalamic-pallido-thalamo-cortical) loops connecting the
11 cerebral cortex to the basal ganglia and thalamus (Catani and Thiebaut de Schotten
12 2012).
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23 **Fig. 3:** The dorsal (in blue) and ventral (in orange) fronto-parietal networks for
24 visuospatial attention as identified by functional neuroimaging (Corbetta and Shulman
25 2002).
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35 **Fig. 4** K-mean clustering of ADHD patients based on inattentiveness and
36 hyperactivity-impulsivity scores in Conner's Parent Rating Scale-Revised, Long version
37 (CPRS-R). Error bars indicate 95% confidence intervals. * $p < 0.0042$
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47 **Fig. 5** Cortico-striatal network. a) group effect of the cortico-striatal network as defined
48 by ICA. b) Power spectrum of the cortico-striatal network according to time frequencies.
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52 c) The right striatum shows an increased functional connectivity in the group
53 'hyperactive/impulsive' when compared to the group 'inattentive' for the cortico-striatal
54 network. Note that coronal sections are displayed in radiological convention (left = right).
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61 d) Average functional connectivity in the cluster reported as significant in the striatum.
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3 Error bars indicate 95% confidence intervals. * $p < 0.0042$; SN, substantia nigra; Str,
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5 striatum; D1, receptor D₁; D2, receptor D₂; EP, external pallidum; IP, internal pallidum;
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9 STN, subthalamic nucleus.

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14 **Fig. 6** Dorsal (DAN) and ventral (VAN) attention networks a) group effect of the DAN
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16 (blue to light blue) and VAN networks (red to yellow) as defined by ICA. b) Power
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18 spectrum of the DAN (blue) and the VAN (orange) according to time frequencies. c) The
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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; FSIQ, Full Scale Intelligence Quotient; > Innattentive, Inattentive group; > Hyp/imp, Hyperactive/impulsive group.

Table 2**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 (%) / Inattentive (%) / 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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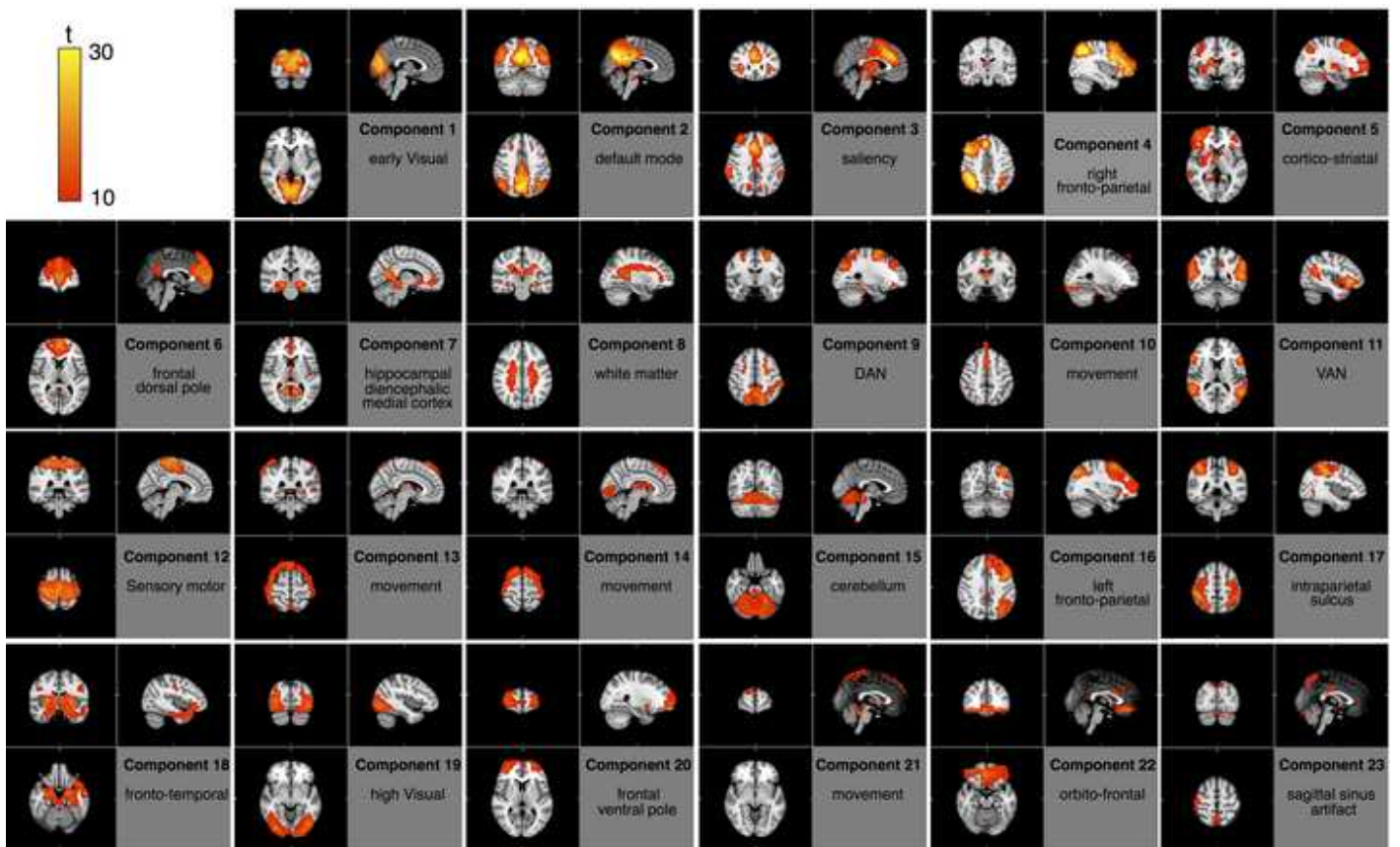
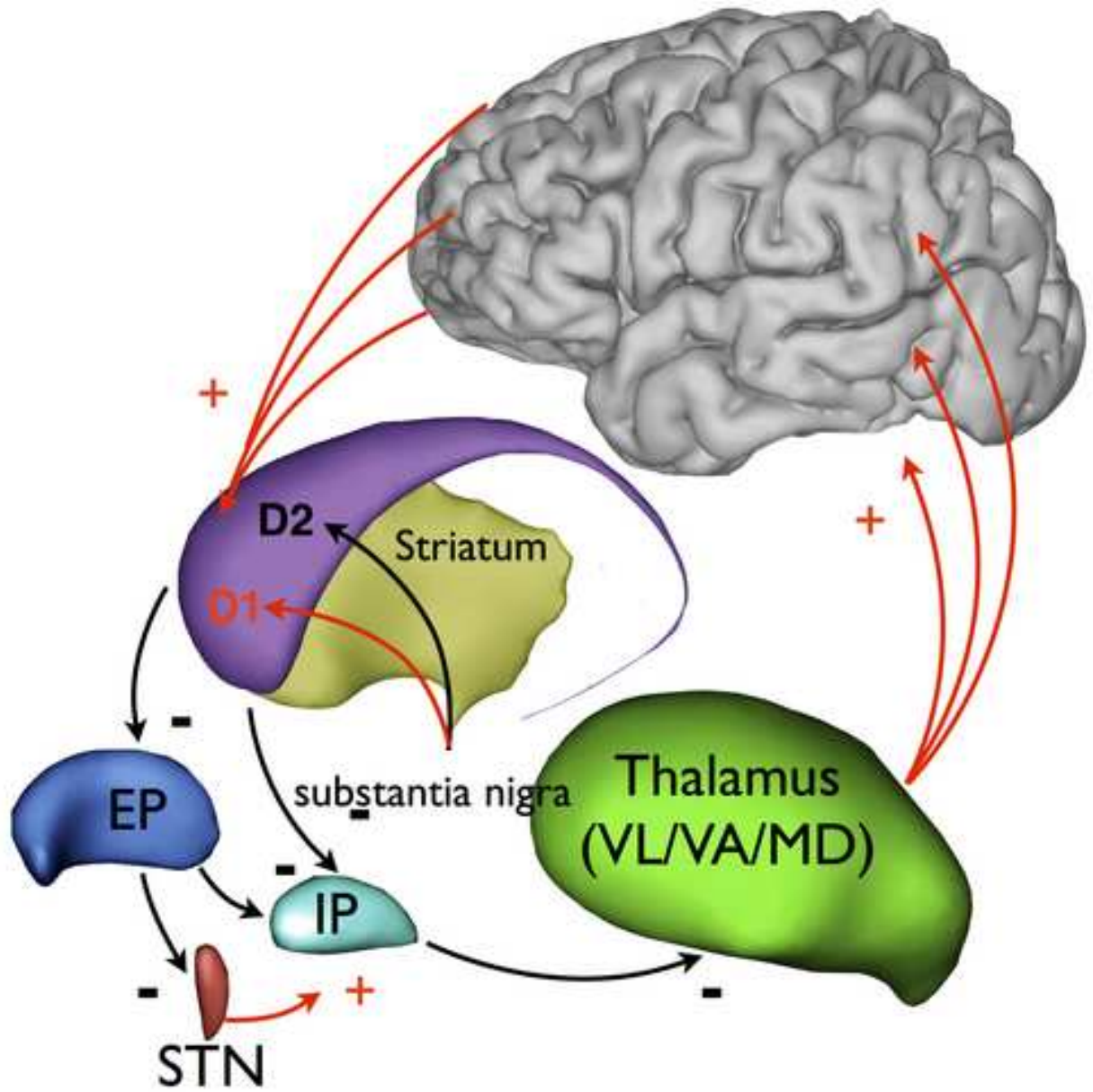


Fig. 2
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STN, subthalamic nucleus

EP, external pallidum

IP, internal pallidum

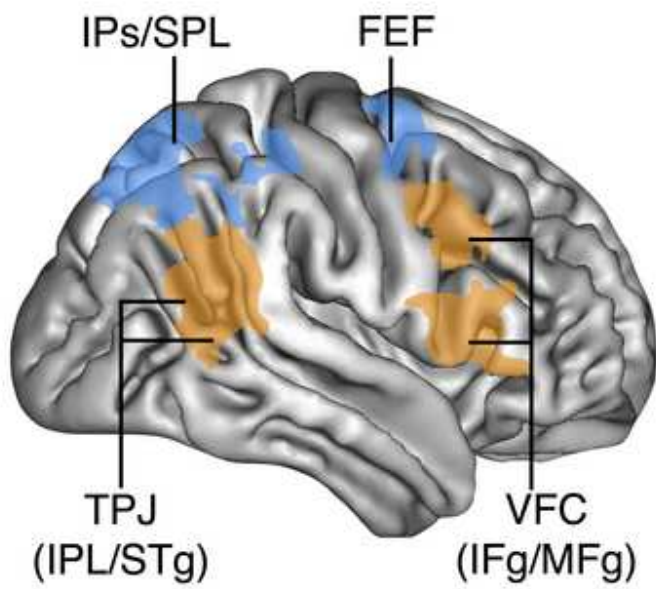
D1-D2 dopamine receptors type 1 and 2

← excitatory projections

← inhibitory projections

←..... projections primarily affected

Fig. 3
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Functional activations

- Controlled goal directed attention:**
strategic and voluntary orienting of attention towards visual targets
- Grabbed stimulus driven attention:**
Unexpected and automatic orienting of attention towards visual targets

Fig. 4
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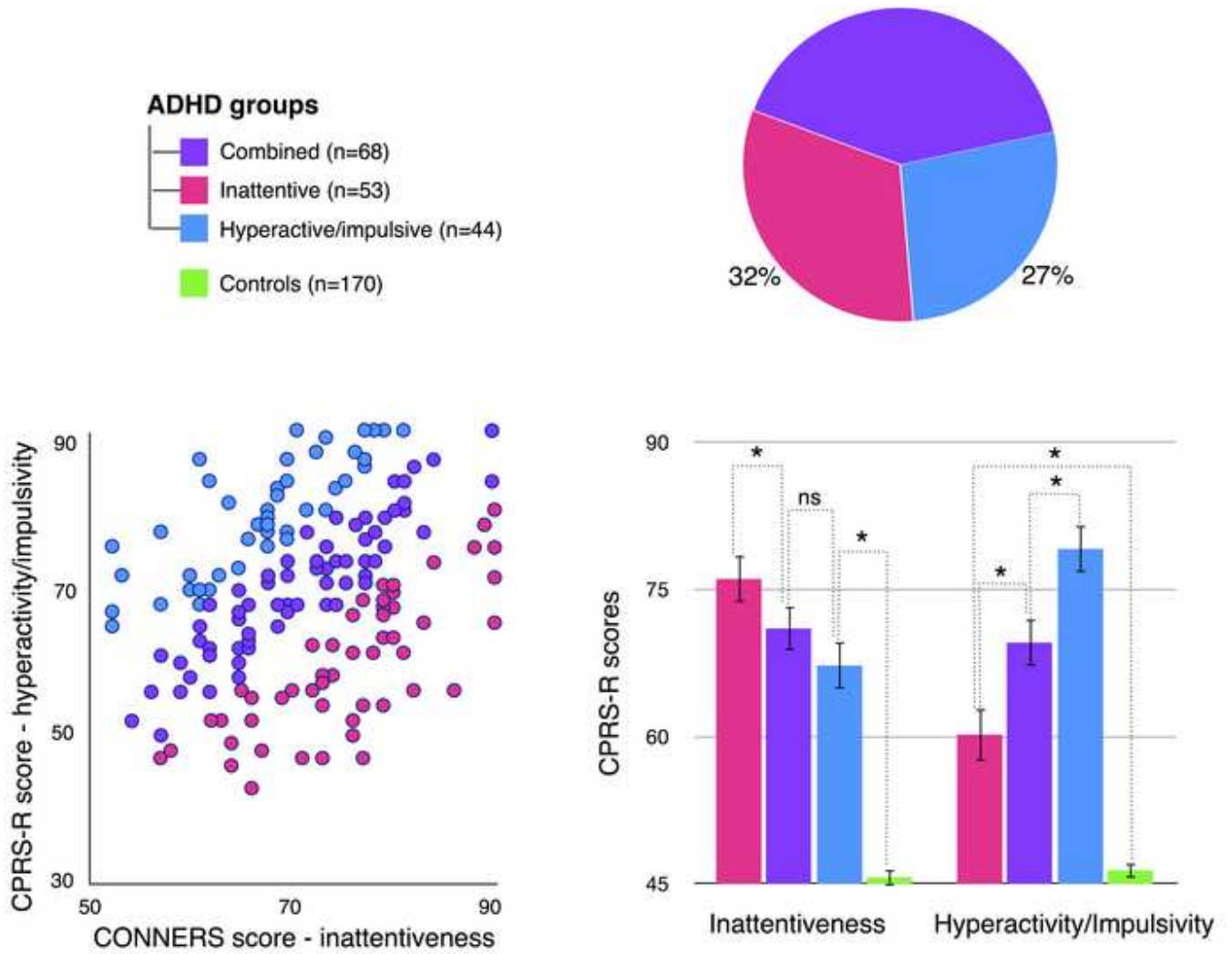


Fig. 5
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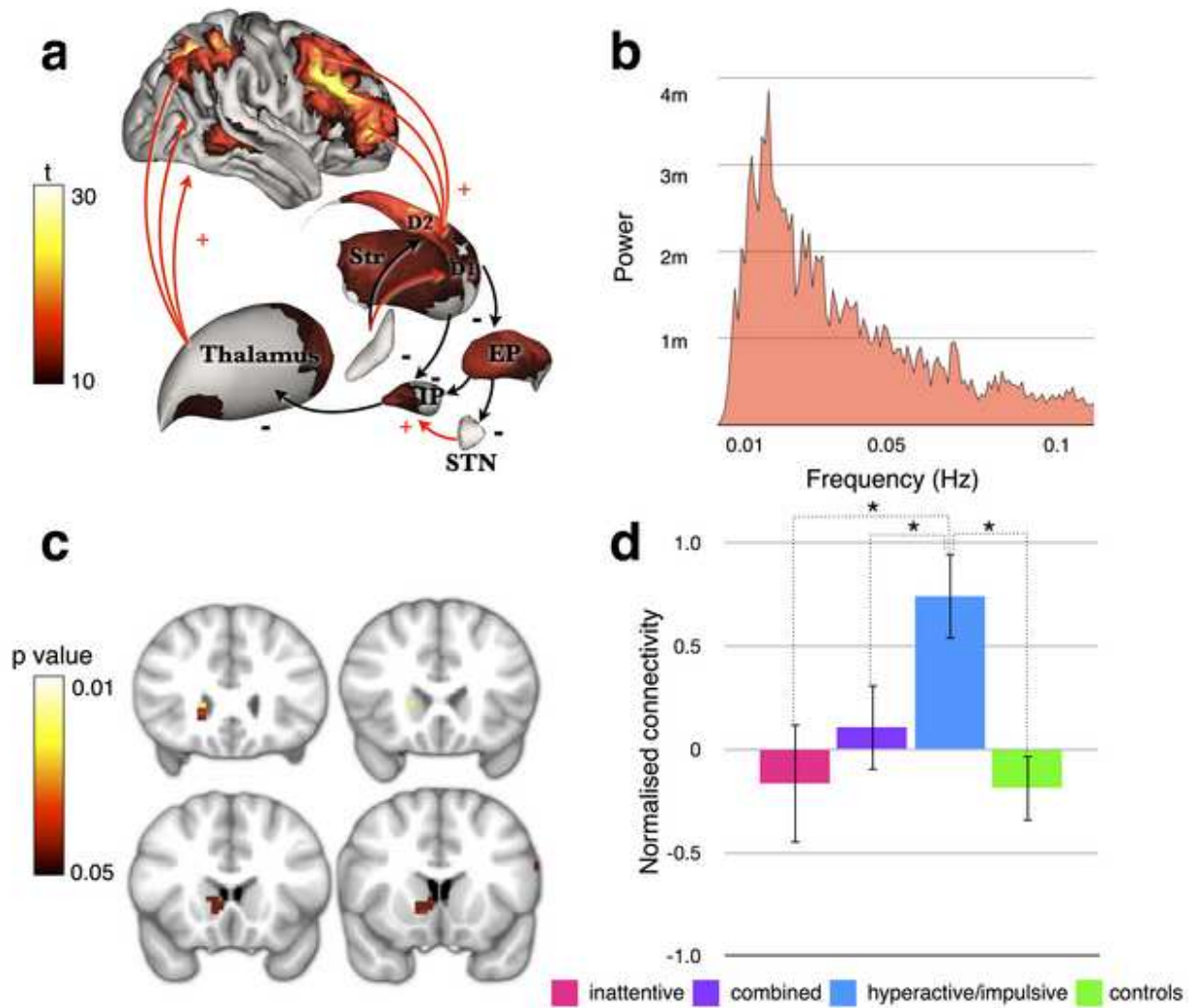
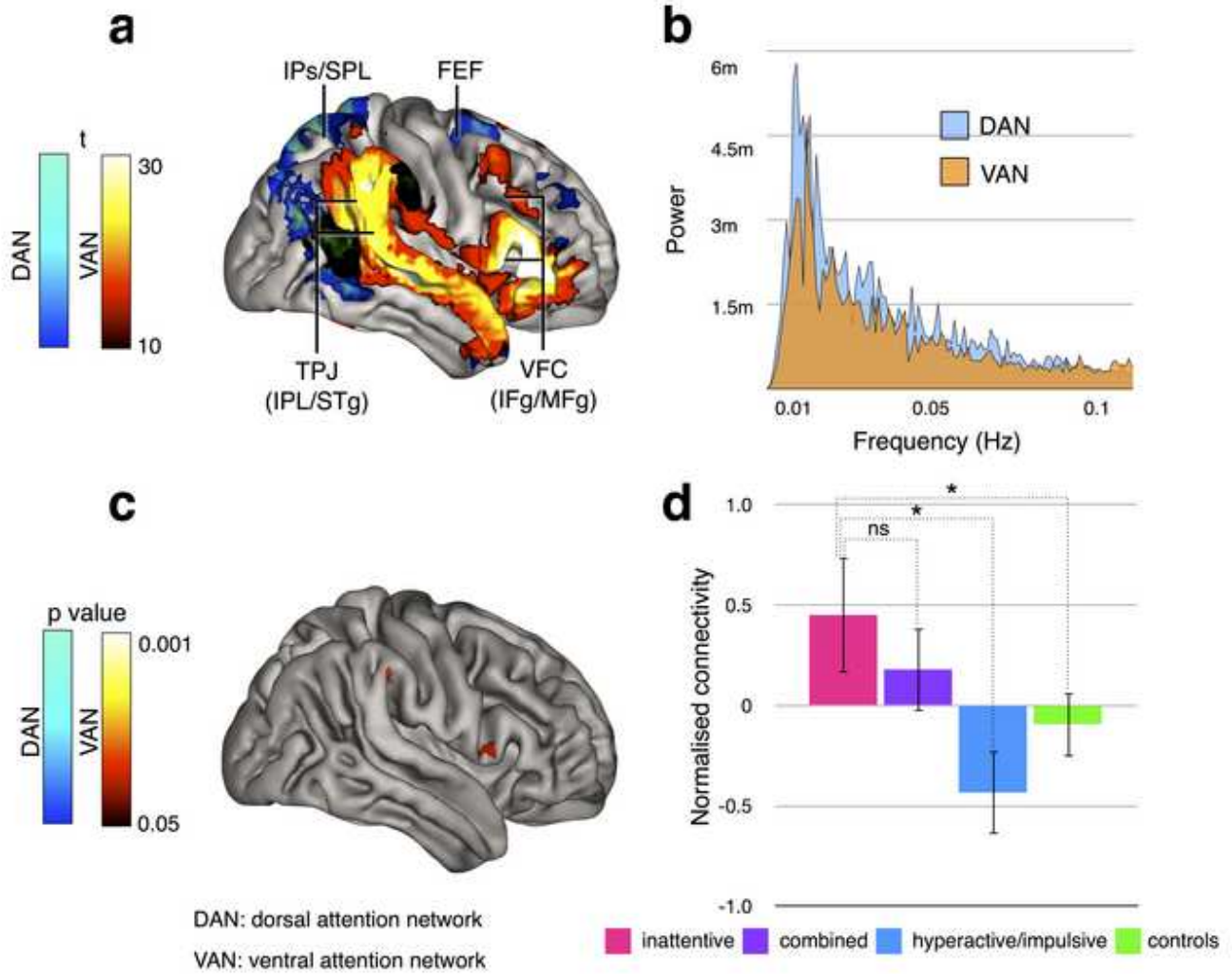


Fig. 6
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