Title: Neurobehavioural characterisation and stratification of reinforcement-related behaviour.

Author List:
Tianye Jia Ph.D.[1*]; Alex Ing Ph.D.[2]; Erin Burke Quinlan Ph.D.[2]; Nicole Tay Ph.D.[2]; Qiang Luo Ph.D.[1,3]; Biondo Francesca Ph.D.[2]; Tobias Banaschewski M.D., Ph.D.[4]; Gareth J. Barker Ph.D.[5]; Arun L.W. Bokde Ph.D.[6]; Uli Bromberg Ph.D.[7]; Christian Büchel M.D.[7]; Sylvane Desrivières Ph.D.[2]; Jianfeng Feng Ph.D.[1,8]; Herta Flor Ph.D.[9,10]; Antoine Grigis Ph.D.[11]; Hugh Garavan Ph.D.[12]; Penny Gowland Ph.D.[13]; Andreas Heinz M.D., Ph.D.[14]; Bernd Ittermann Ph.D.[15]; Jean-Luc Martinot M.D., Ph.D.[16]; Marie-Laure Paillère Martinot M.D., Ph.D.[17]; Frauke Nees Ph.D.[4,9]; Dimitri Papadopoulos Orfanos Ph.D.[11]; Tomáš Paus M.D., Ph.D.[18]; Luise Poustka M.D.[19], Juliane H. Fröhner Dipl.-Psych.[20]; Michael N. Smolka M.D.[20]; Henrik Walter M.D., Ph.D.[14]; Robert Whelan Ph.D.[21]; Gunter Schumann M.D., Ph.D.[2,22]*; IMAGEN Consortium‡

[1]Centre for Population Neuroscience and Precision Medicine (PONS), Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, China 200433 and Institute of Psychiatry, Psychology & Neuroscience, SGDP Centre, King's College London, United Kingdom, SE5 8AF; MoE Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence, Fudan University, Shanghai, China, 200433;
[2]Centre for Population Neuroscience and Precision Medicine (PONS), Institute of Psychiatry, Psychology & Neuroscience, SGDP Centre, King's College London, United Kingdom, SE5 8AF;
[3]State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Institutes of Brain Science, Fudan University, China, 200433;
[4]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, 68159 Mannheim, Germany;
[5]Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom;
[6]Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland;
[7]University Medical Centre Hamburg-Eppendorf, Martinistr. 52, Hamburg, Germany;
[8]Department of Computer Science, University of Warwick, Coventry, UK; Collaborative Innovation Center for Brain Science, Fudan University, Shanghai, PR China; Shanghai Center for Mathematical Sciences, Shanghai, PR China;
[9]Institute of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, Mannheim, Germany;
[10]Department of Psychology, School of Social Sciences, University of Mannheim, 68131 Mannheim, Germany;
[11]NeuroSpin, CEA, Université Paris-Saclay, F-91191 Gif-sur-Yvette, France;
[12]Departments of Psychiatry and Psychology, University of Vermont, 05405 Burlington, Vermont, USA;

[13]Sir Peter Mansfield Imaging Centre School of Physics and Astronomy, University of Nottingham, University Park, Nottingham, United Kingdom;
[14]Department of Psychiatry and Psychotherapy CCM, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany;
[15]Physikalisch-Technische Bundesanstalt (PTB), Braunschweig and Berlin, Germany;
[16]Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 "Neuroimaging & Psychiatry", University Paris Saclay, University Paris Descartes; DIgiteo-Labs, F-91191 Gif-sur-Yvette; and Maison de Solenn, Paris, France ;
[17]Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 "Neuroimaging & Psychiatry", University Paris Saclay, University Paris Descartes; DIgiteo-Labs, F-91191 Gif-sur-Yvette; and AP-HP.Sorbonne Université, Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Paris, France;
[18]Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital and Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario, M6A 2E1, Canada;
[19]Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, von-Siebold-Str. 5, 37075, Göttingen, Germany;
[20]Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany;
[21]School of Psychology and Global Brain Health Institute, Trinity College Dublin, Ireland;
[22]PONS Research Group, Dept of Psychiatry and Psychotherapy, Campus Charite Mitte, Humboldt University, Berlin and Leibniz Institute for Neurobiology, Magdeburg, Germany, and Institute for Science and Technology of Brain-inspired Intelligence (ISTBI), Fudan University, Shanghai, P.R. China.

*Corresponding Authors:

Professor Gunter Schumann, M.D., Ph.D. (ORCID: 0000-0002-7740-6469)
Centre for Population Neuroscience and Precision Medicine (PONS), Institute of Psychiatry, Psychology and Neuroscience, King's College London, SGDP-Centre, London SE5 8AF, UK.
Tel. +44-20-7848-5314
Email: gunter.schumann@kcl.ac.uk

and

Dr Tianye Jia, Ph.D. (ORCID: 0000-0001-5399-2953)
Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, 200433, China.
Tel. +86-21-6564-1273
Email: tianyejia@fudan.edu.cn

‡IMAGEN consortium (www.imagen-europe.com) authors and affiliations are listed in the supplementary materials.

Abstract:

Reinforcement-related cognitive processes, such as reward processing, inhibitory control and social-emotional regulation are critical components of externalising and internalising behaviours. It is unclear to what extent the deficit in each of these processes contributes to individual behavioural symptoms, how their neural substrates give rise to distinct behavioural outcomes, and if neural activation profiles across different reinforcement-related processes might differentiate individual behaviours. We created a statistical framework that enabled us to directly compare functional brain activation during reward anticipation, motor inhibition and viewing emotional faces in the European IMAGEN cohort of 2000 14-year-old adolescents. We observe significant correlations and modulation of reward anticipation and motor inhibition networks in hyperactivity, impulsivity, inattentive behaviour and conduct symptoms, and describe neural signatures across cognitive tasks that differentiate these behaviours. We thus characterise shared and distinct functional brain activation patterns underling different externalising symptoms and identify neural stratification markers, while accounting for clinically observed co-morbidity.

Introduction

Reinforcement-related behaviours are commonly implicated in normal behaviour and psychopathology. Symptoms of dysfunctional reinforcement-related cognitive processes may present as hyperactivity, inattention, conduct and emotional problems [1]. These symptoms are manifest in common psychiatric disorders, such as depression, ADHD, addictions, conduct disorder and psychosis [2, 3], and share similar reinforcement-related cognitive processes, including reward processing, inhibitory control and social-emotional regulation [4]. However, while similar cognitive processing deficits are involved in different disorders, there are clear differences in their behavioural presentation in each disorder. It is unclear if and how the reinforcement-related cognitive processes are modulated to achieve the observed behavioural differences among these disorders. Identifying the brain activity patterns related to various manifestations of dysfunctional reinforcement-related behaviour might aid in the characterisation of underlying biological mechanisms, and the identification of targets for therapeutic intervention [5]. Furthermore, clinically relevant psychiatric symptoms typically are characterised by dysfunctions not only in one but often in several reinforcement-related cognitive processes. For example, ADHD symptoms are known to involve dysfunctional inhibitory control [1], as well as dysfunctional reward processing [6]. We were interested in dissecting the contribution of different domains of reinforcement-related cognitive processes to distinct disorder symptoms, and thus characterise a profile of brain activation specific for each disorder.

Whereas animal models have identified networks of multiple cortical and subcortical brain regions involved in reinforcement-related cognitive processes [7], analyses in humans are often based on a few pre-defined regions of interest (ROI). These include the ventral striatum (VS) and orbital frontal cortex (OFC) for reward processing [8], right inferior frontal cortex (rIFC) for inhibitory control [9], and amygdala and superior temporal sulcus (STS) for social-emotional regulation [10, 11]. Often, the underlying assumption is that a cognitive process can be represented by a few key brain regions. However, we [12] and others [13-16] have shown that task-induced brain activity may involve a complex network of cortical and subcortical brain regions. We do not know, however, how activity in these networks relate to observable behaviour.

In this paper we provide a systematic characterisation of brain activity in reinforcement–related behaviour, measuring BOLD-response during tasks targeting reward anticipation, motor inhibition and social-emotional processing. We compare their common and distinct brain activity patterns and assess the modulation of task-specific networks in externalising (e.g. hyperactivity, inattention, impulsivity and conduct symptoms) and internalising (e.g. emotional and anxiety symptoms) behavioural symptoms [17]. We also identify signatures of brain activity across tasks that best characterise symptoms of externalising disorders, as well as helping to distinguish one symptom domain from the other.

Results

Summary of Analysis Strategy

We aim to compare brain activity during functional neuroimaging tasks measuring reward anticipation, motor inhibition and social-emotional processing of 1506 14-year-old adolescents from IMAGEN project [4]. Of the 1506 participants investigated in this study, clinical DAWBA ratings are available from 1190 individuals. Of these individuals 131 have one or more diagnoses. 33 individuals were diagnosed with ADHD, 59 with emotional problems, 12 with anxiety (general + other) and 33 with depression (major + other). We reduced the dimensionality of brain activation by applying a weighted voxel co-activation network analysis (WVCNA) [12, 18], followed by a hierarchical clustering analysis. The combination of both methods could efficiently reduce dimensionality while still preserving localised network features from WVCNA. We then calculated the overall correlation between fMRI clusters and symptoms of externalising or internalising behaviours using ridge-regularised canonical correlation analysis (RCCA) [19], a method to detect multivariate relations between different data types.

First, we tested for an overall significant correlation of externalising or internalising symptoms with brain network activation across all fMRI tasks. In cases where we established an overall correlation, we looked for associations of each fMRI network with externalising or internalising behaviours. Finally, we investigated the sensitivity and specificity of fMRI clusters across different behaviour components. The above workflow was illustrated as Figure 1.

Identification of Reinforcement-related Brain fMRI Networks

We defined brain networks underlying reinforcement-related behaviour by using the Monetary Incentive Delay (MID) task to measure reward processing [20], the Stop Signal Task (SST), to assess motor inhibition [21] and the Emotional Faces Task (EFT) to examine social-emotional processing [22]. In these tasks, we analysed contrasts that are most relevant to the reinforcement-related behaviour and eliciting the largest BOLD-difference, namely the 'large win vs no win' contrast during the reward anticipation phase in the MID task, the 'successful stop vs successful go' contrast in the SST, and the 'angry face vs control' contrast in the EFT.

We applied WVCNA [12, 18], which was established by combining the scale-free network assumption with a dynamic cut of the dendrogram [23], to maximise the resolution of localised brain network features (see Materials and Methods for details). Using this approach, we identified in the MID a brain network consisting of 500 nodes (25130 voxels, Figure 2A); in the SST 487 nodes (24571 voxels, Figure 2B) and in the EFT 79 nodes (3923 voxels, Figure 2C). We further removed redundant information by applying an additional hierarchical clustering on these nodes with a static cut at the 90th percentile, keeping the 10% most distinctive branches (representing clusters) in each dendrogram. This two-step procedure enabled us to efficiently reduce dimensionality while still preserving localised network features from WVCNA (Table S1A-C). Using this approach, we identified 46 clusters in MID, 41 clusters in SST and 9 clusters in EFT (Table S1A-C and Extended Data Figure 1).

In all three networks, activated clusters were widely spread across cortical and sub-cortical regions, as well as in the cerebellum (Figure 2 and Extended Data Table 1). Brain regions activated in the three networks were often overlapping (Figure 2D). It is notable that

none of the regions of interest typically associated with reward processing or impulsiveness or social-emotional processing was specific to their corresponding networks. For example, VS and OFC typically linked to reward processing [8] were activated in both MID and SST; rIFC often associated with inhibitory control [9] was activated in both SST and EFT. STS, which is regarded as an essential component of the social brain [11] was also activated in both SST and EFT. The dorsal amygdala, a central node of emotional processing [10], was activated not only in EFT but also in MID. However, some activations were network-specific, for example, distinct activations during the MID in the superior post-central gyrus (i.e. the superior primary somatosensory cortex SPSC), primary auditory cortex (PAC), dorsal striatum and most of the cerebellar vermis; distinct activations in the SST were observed in the frontal operculum and the orbital part of rIFC (rIFC-Orb), inferior primary somatosensory cortex (iPSC) and the lingual part of the cerebellar vermis; and the EFT showed distinct activations in the medial orbitofrontal cortex (mOFC), dorsal posterior cingulate cortex (dPCC), temporal pole and the ventral amygdala (Figure 2D and Extended Data Table 1).

Modulation of Reinforcement-related Brain fMRI Networks in Different Behaviours.

Clinical psychopathology in adolescents is grouped into externalising and internalising disorders [24]. We were interested in examining if externalising and internalising behavioural symptoms correlate with distinct configurations of reinforcement related networks. From the Strength and Difficulties Questionnaire (SDQ) and the Development and Well-Being

Assessment (DAWBA), we selected the entry-level questions, including 44 externalising items (Table 1A) covering symptoms of attentional deficit/hyperactivity disorder (ADHD; 23 items), oppositional defiance disorder (ODD; 11 items) and conduct disorder (CD; 10 items), and 21 internalising items (Table 1B) covering symptoms of depression (12 items) and anxiety (8 items) (see Materials and Methods for more details). To evaluate the overall relationship of behavioural symptoms and patterns of brain activation we carried out ridge-regularised canonical correlation analysis (RCCA) [19]. This method seeks to find subsets of variables in two datasets that best correlate with each other while stabilising the result through penalisation of correlations within each dataset. We first investigated the overall correlation between externalising behaviours and 96 clusters from the three fMRI networks and found a significant canonical correlation (η^2=0.854, 90%CIs=[0.839,0.869], adj-η^2= 0.160, df_{fMRI}=(1506,96), $df_{behaviour}$=(1506,44), P_{perm}<0.001; see Materials and Methods for details; Table 2 and S2). Please note that a predefined scheme of regulation parameters has been evaluated throughout for all RCCAs and highly stable results were obtained as shown in Extended Data Table 2. For simplicity, we only show results with regulation parameter 0.1 in the main text. The number of permutations to calculate p-values in this and all subsequent analyses is 10,000 unless otherwise specified. Also, presented p-values are always corrected for experimental-wise multiple comparisons wherever applicable. We then investigated the RCCA between internalising behaviours and the same 96 fMRI clusters but found no overall significance (η^2=0.574, 90%CIs=[0.547,0.602], adj-η^2=-0.024, df_{fMRI}=(1506,96), $df_{behaviour}$=(1506,20), P_{Perm}=0.786, see Extended Data Table 3 for more results with alternative

parameters). We also did not find significant overall correlations with internalising behaviours when analysing each fMRI network separately (Extended Data Table 3). We, therefore, constrained our subsequent analyses to externalising behaviours only.

Next, we investigated the contribution of each brain network to different behavioural conditions. For the reward anticipation network, we found an overall significant correlation with externalising behaviours (η^2 = 0.579, 90%CIs = [0.551,0.607], adj-η^2 = 0.052, df_{fMRI} = (1506,46), $df_{behaviour}$ = (1506,44), P_{Perm}=0.036, Table 2 and S2). This correlation was then observed significant with ADHD behaviours (η^2 = 0.365, 90%CIs = [0.335,0.394], adj-η^2 = 0.038, df_{fMRI} = (1506,46), $df_{behaviour}$ = (1506,23), P_{Perm}=0.029, Table 2 and S2), but not so with ODD/CD behaviours (η^2 = 0.338, 90%CIs = [0.307,0.370], adj-η^2 = 0.017 df_{fMRI} = (1506,46), $df_{behaviour}$ = (1506,21), P_{Perm}=0.203, Table 2 and S2), indicating that reward anticipation might be important for ADHD symptoms. For the motor inhibition network, we found an overall significant correlation with externalising behaviours (η^2 = 0.573, 90%CIs = [0.543,0.603], adj-η^2 = 0.103, df_{fMRI} = (1506,41), $df_{behaviour}$ = (1506,44), P_{Perm} <0.001, Table 2 and S2). This correlation was then observed significant with ADHD behaviours (η^2 = 0.352, 90%CIs = [0.320,0.384], adj-η^2 = 0.052, df_{fMRI} = (1506,41), $df_{behaviour}$ = (1506,23), P_{Perm}=0.003, Table 2 and S2), as well as with ODD/CD behaviours (η^2 = 0.343 90%CIs = [0.309,0.376], adj-η^2 = 0.054, df_{fMRI} = (1506,41), $df_{behaviour}$ = (1506,21), P_{Perm}=0.003, Table 2 and S2), indicating that motor inhibition might play a role in both ADHD and ODD/CD symptoms. For the social-emotional processing network, we found neither significant correlation with externalising behaviours (η^2 = 0.175, 90%CIs = [0.148,0.203], adj-η^2 = 0.005, df_{fMRI} = (1506,9), $df_{behaviour}$ = (1506,44),

P_{Perm}=0.392, Table 2 and S2), nor with ADHD behaviours (η^2 = 0.089, 90%CIs = [0.068,0.110], adj-η^2 = -0.004, df_{fMRI} = (1506,9), $df_{behaviour}$ = (1506,23),P_{Perm}=0.634, Table 2 and S2) or ODD/CD behaviours (η^2 = 0.092, 90%CIs = [0.071,0.112], adj-η^2 = 0.004, df_{fMRI} = (1506,9), $df_{behaviour}$ = (1506,21), P_{Perm}=0.294, Table 2 and S2) alone. While the above RCCA results provide no indication on the direction of correlation, brain activations during reward anticipation (the MID task) and motor inhibition (the SST) show predominantly negative correlations with externalising behaviours through univariate correlation analyses as shown in the following sections (see Table 3 and Table S2-S4).

Functional brain characterisation of behaviours across different tasks.

While both reward anticipation and motor inhibition networks show significant canonical correlations with ADHD behaviours, neither correlation, between the first components of RCCA (its square is known as Roy's largest root[25]) was significant on its own (R_{Roy} =0.234, Z_{Fisher}=0.237, 90%CIs(Z_{Fisher})=[0.202,0.274], P_{Perm}=0.087 for reward anticipation; R_{Roy}=0.225, Z_{Fisher}=0.229, 90%CIs(Z_{Fisher})=[0.193,0.266], P_{Perm}=0.151 for motor inhibition) and was additional shown to be significantly smaller than a meaningful effect through an equivalence test for inferiority [26] (t=-3.98, p<0.001 for U_Z = 0.324 of reward anticipation; t=-4.06, p<0.001 for U_Z = 0.319 of motor inhibition; L_Z=-∞; the upper bound U_Z was calculated as the estimated inflation of Z_{Fisher} plus a small effect size $\triangle Z$=0.1 [27], see Materials and Methods for more details). These results therefore showed that the overall significant correlation was unlikely to be represented by an individual RCCA component. Therefore, we hypothesised that

distinctive neural bases may underlie different ADHD behaviours and investigated profiles across brain networks that may characterise the ADHD components hyperactivity, inattention or impulsivity (see Materials and Methods). As the factors generated by RCCA are not optimised to detect differences in the brain function underlying these behaviours, we applied a more sensitive multiple linear regression model. Together, reward anticipation and motor inhibition networks were found in significant association with the summed score (i.e. the total score) of ADHD behaviours (R^2=0.085, 90%CIs=[0.063,0.106], adj-R^2=0.029, $F_{(87,1418)}$=1.51, P=0.002, where R^2 is the coefficient of determinant that represents the proportion of behavioural variance explained by the fMRI networks in the multiple linear model), as well as the total scores of ADHD components hyperactivity (R^2=0.089, 90%CIs=[0.067,0.110], adj-R^2=0.033, $F_{(87,1418)}$=1.58, P<0.001), impulsivity (R^2=0.077, 90%CIs=[0.057,0.098], adj-R^2=0.021, $F_{(87,1418)}$=1.37, P=0.017) and inattention (R^2=0.079, 90%CIs=[0.058,0.100], adj-R^2=0.022, $F_{(87,1418)}$=1.40, P=0.011). However, we did not find evidence for identical associations of these ADHD behaviours with reward anticipation and motor inhibition networks: while the motor inhibition network was found in significant association with the total scores of all three ADHD components (R^2=0.045, 90%CIs=[0.028,0.061], adj-R^2=0.018, $F_{(41,1464)}$=1.67, P=0.005 for hyperactivity; R^2=0.051, 90%CIs=[0.033,0.069], adj-R^2=0.024, $F_{(41,1464)}$=1.92, P=<0.001 for impulsivity; R^2=0.042, 90%CIs=[0.026,0.059], adj-R^2=0.016, $F_{(41,1464)}$=1.58, P=0.011 for inattention), the reward anticipation network showed a significant association with the total score of hyperactivity (R^2=0.043, 90%CIs=[0.027,0.059], adj-R^2=0.013, $F_{(46,1459)}$=1.427, P=0.033), however, we found no evidence for an association with impulsivity (R^2=0.027,

90%CIs=[0.014, 0.040], adj-R^2=-0.004, $F_{(46,1459)}$=0.885, P=0.691) and inattention (R^2=0.037, 90%CIs=[0.022, 0.052], adj-R^2=0.006, $F_{(46,1459)}$=1.214, P=0.156).

fMRI signature for hyperactivity

The hyperactivity total score was significantly associated with reduced activation in six out of 46 brain regions in the reward anticipation network: superior parietal lobule (SPL), middle central sulcus (mid-CS), thalamus, primary auditory cortex (PAC), middle cingulate cortex (MCC) and superior frontal junction (SFJ) (Figure 3A, Table 3A and Table S2). We investigated the specificity of the observed associations and found that SPL, mid-CS and thalamus were also associated with inattention, and mid-CS and MCC were associated with ODD/CD behaviours, whereas no significant association was found with impulsivity (Table 3A and Table S2). The brain regions showed no significant difference in association strength with hyperactivity and with inattention (ΔZ_{sum}=-0.142, 95%CIs=[-0.384,0.100], P_{Perm}=0.834), as well as with ODD/CD behaviours (ΔZ_{sum}=-0.128, 95%CIs=[-0.377,0.121], P_{Perm}=1 (Table 4), which were further found significantly smaller than a meaningful effect size with equivalence tests (for inattention: t=3.71, $P_{one\text{-}tailed}$ <0.001 for $L_{\Delta Z}$ = -0.10 and t=6.02, $P_{one\text{-}tailed}$ <0.001 for $U_{\Delta Z}$ = 0.10; for ODD/CD behaviours: t=3.71, $P_{one\text{-}tailed}$ <0.001 for $L_{\Delta Z}$ = -0.10 and t=5.72, $P_{one\text{-}tailed}$ <0.001 for $U_{\Delta Z}$ = 0.10), but significantly weaker in the case of impulsivity (ΔZ_{sum}=-0.308, 95%CIs=[-0.522,-0.094], P_{Perm} =0.017) (Table 4). Thus, our findings suggest a shared specificity of brain activation during reward anticipation in hyperactivity, inattention and ODD/CD behaviours, but not in impulsivity (Figure 3E).

In the motor inhibition network, however, despite the overall significant association, none of the six brain regions was significantly associated with hyperactivity (Table S3A), suggesting that the observed overall association was based on multiple fMRI regions of the motor inhibition network, each with a minor contribution.

fMRI signature for impulsivity

The left temporoparietal junction (TPJ) of the motor inhibition network was associated with impulsivity (R=-0.092, 95%CIs=[-0.142,-0.041], t=-3.563, P_{Perm}=0.010) (Figure 3B, Table 3B and Table S3B), and additionally - in exploratory analyses - associated with hyperactivity (R=-0.067, 95%CIs=[-0.117,-0.016], t=-2.59, P_{Perm}=0.025) and ODD/CD behaviours (R=-0.071, 95%CIs=[-0.118,-0.017], t=-2.64, P_{Perm}=0.016), but not so with inattention (R=-0.058, 95%CIs=[-0.109,-0.008], t=-2.270, P=0.062) (Table 3B and Table S3B), where no significant difference in the strength of association was observed (ΔZ_{Hyper}=-0.025, 95%CIs=[-0.073,0.022], P_{Perm}=0.823; ΔZ_{Inatt}=-0.033, 95%CIs=[-0.079,0.012], P_{Perm}=0.456; ΔZ_{ODDCD}=-0.021, 95%CIs=[-0.069,0.027], P_{Perm} =1) (Table 5A), which were further found significantly smaller than a meaningful effect size with equivalence tests (for hyperactivity: t=3.10, $P_{one\text{-}tailed}$ <0.001 for $L_{\Delta Z}$ = -0.10 & t=5.17, $P_{one\text{-}tailed}$ <0.001 for $U_{\Delta Z}$ = 0.10; for inattention: t=2.86, $P_{one\text{-}tailed}$ =0.002 for $L_{\Delta Z}$ = -0.10 & t=5.73, $P_{one\text{-}tailed}$ <0.001 for $U_{\Delta Z}$ = 0.10; for ODD/CD behaviours: t=3.21, $P_{one\text{-}tailed}$ <0.001 for $L_{\Delta Z}$ = -0.10 & t=4.93, $P_{one\text{-}tailed}$ <0.001 for $U_{\Delta Z}$ = 0.10). Together, this suggests a shared specificity across ADHD and ODD/CD behaviours during motor inhibition (Figure 3E).

fMRI signature for inattention

In the motor inhibition network, we found significant association of the right anterior inferior frontal sulcus (aIFS) with inattention (R=-0.087, 95%CIs=[-0.137,-0.037], t=-3.392, P_{Perm}=0.019), as well as - in exploratory analyses - association with ODD/CD behaviours (R=-0.084, 95%CIs=[-0.126,-0.026], t=-2.957, P_{Perm}=0.004), but not with impulsivity (R=-0.056, 95%CIs=[-0.106,-0.006], t=-2.184, P_{Perm}=0.073) and hyperactivity (R=-0.017, 95%CI=[-0.068, 0.033], t=-0.666, P_{Perm}=0.833) (Figure 3C, Table 3C and Table S3C). The strength of association of aIFS with inattention is not significantly different to those with impulsivity (ΔZ=-0.031, 95%CIs=[-0.080,0.018], P_{Perm}=0.562) and ODD/CD behaviours (Δ Z=-0.004, 95%CIs=[-0.052,0.045], P_{Perm}=1) (Table 5B), which were further found significantly smaller than a meaningful effect size with equivalence tests (for impulsivity: t=2.77, $P_{one\text{-}tailed}$ =0.003 for $L_{\Delta Z}$ = -0.10 and t=5.26, $P_{one\text{-}tailed}$ <0.001 for $U_{\Delta Z}$ = 0.10; for ODD/CD: t=3.98, $P_{one\text{-}tailed}$ <0.001 for $L_{\Delta Z}$ = -0.10 and t=4.18, $P_{one\text{-}tailed}$ <0.001 for $U_{\Delta Z}$ = 0.10). However, the strength of association of aIFS with inattention is significantly stronger than that with hyperactivity (ΔZ=-0.070, 95%CIs=[-0.124,-0.017], P_{Perm}=0.017) (Table 5B), suggesting distinct specificities of hyperactivity and inattention during motor inhibition, and shared specificity of inattention with impulsivity and ODD/CD behaviours (Figure 3E).

fMRI signatures for ODD/CD behaviours

ODD/CD behaviours were found only in a significant canonical correlation with the motor inhibition network. Right aIFS (R=-0.084, 95%CIs = [-0.126,-0.026], t=-2.96, P_{Perm}=0.027) and right IFC/anterior insula (R=-0.090, 95%CIs=[-0.133,-0.033], t=-3.25, P_{Perm}=0.011) were associated with the summed score of ODD/CD behaviours (Figure 3D, Table 3D and Table S4). While both regions were also significantly associated with ODD behaviours alone and the right IFC/anterior insula was associated with CD behaviours (Table S4), their association strength with ODD behaviours is significantly stronger than that with CD behaviours (ΔZ_{sum} = -0.090, 95%CIs =[-0.175,-0.006], P_{Perm} = 0.039), suggesting a predominant role of ODD behaviours in the associations with both brain regions. Together ODD/CD prominent regions showed no significant difference in association strength with ODD/CD behaviours and with inattention (ΔZ_{sum}=-0.041, 95%CIs=[-0.122,0.055], P_{Perm}=1), as well as with impulsivity (ΔZ_{sum}=-0.073, 95%CIs=[-0.164,0.019], P_{Perm}=0.274) (Table 5C), which were further found significantly smaller than a meaningful effect size with equivalence tests (for inattention: t=3.68, $P_{one\text{-}tailed}$<0.001 for $L_{\Delta Z}$=-0.10 and t=5.16, $P_{one\text{-}tailed}$<0.001 for $U_{\Delta Z}$=0.10; for impulsivity: t=2.72, $P_{one\text{-}tailed}$=0.003 for $L_{\Delta Z}$=-0.10 and t=5.83, $P_{one\text{-}tailed}$ <0.001 for $U_{\Delta Z}$=0.10), but significantly lower than the association strength with hyperactivity (ΔZ_{sum}=-0.0143, 95%CIs=[-0.237,-0.049], P_{Perm}=0.007) (Figure 3E and Table 5C).

In conclusion of the above results, ADHD and ODD/CD may share several distinctive neural bases during reward anticipation and motor inhibition.

Discussion

Here we characterise clinically relevant behaviours in adolescents by describing brain activation during reinforcement-related cognitive processes. These behaviours include externalising symptoms of hyperactivity, impulsiveness and inattention, oppositional defiance and conduct, and internalising symptoms of anxiety and depression. We have used quantitative measures to assess these behaviours, as empiric evidence shows that psychopathology is generally more dimensional than categorical [28], one of the basic premises of the Research Domain Criteria (RDoC) [29]. We interrogate the neural basis of each of these behaviours by measuring brain activity during reinforcement-related cognitive tasks of reward processing, motor inhibition and social-emotional processing.

We find that activation of similar brain regions is often associated with different tasks (and behaviours). While well-known representative brain areas (e.g. VS and OFC for reward anticipation [8], right-IFC for inhibitory control [9], and amygdala and STS for social-emotional processing [10, 11]) were activated as expected, these activations were not restricted to one task alone (Figure 2D). This might represent the involvement of shared cognitive components in different behaviours that might be less specific to individual tasks. For example, the VS activation during motor inhibition was due to the anticipation of a random event [30], thus sharing the anticipatory component with the reward anticipation network that also activates the same region. In some instances, it may also be caused by brain activation that reflects task presentation (for example, motor cortex activation in the 'active' MID and SST, but not in the passive viewing EFT). Our observation is consistent with the notion of a basic neural function that underlies a complex profile of different behaviours [31].

However, the overlap of brain activation across cognitive tasks might also indicate the presence of different functional or structural domains within a given brain region that relate differentially to each task [32]. This latter hypothesis is supported by the observation of low correlations of the same brain regions across tasks. In contrast, we found high correlations between different brain regions within each task, suggesting network constellations that are specific to each individual cognitive task. This specificity was further suggested by the observation that the variance of hyperactivity explained by reward anticipation and motor inhibition networks are additive (i.e. adj-R^2 were 0.033, 0.013 and 0.018 for both networks, reward anticipation and motor inhibition, respectively), and thus not overlapping. The specificity of cognitive neural networks might thus be defined as much by their internal collaborative structure as by the individual brain regions involved [33].

We also found highly activated regions (Cohen's D>0.30) in the MID task that were normally not expected in the anticipation of a visually presented reward. They included, for instance, the primary auditory cortex (PAC) that we observed to be activated in the absence of any auditory stimulus. As the PAC has been found to predict reward value [16] and is associated with anticipatory motor response [34] upon auditory stimulation, our findings point towards the possibility of the PAC underlying these cognitive processes in a way that is not dependent on the quality of the sensory stimulus. In addition, wide areas within the somatosensory cortex were also activated in the MID task, further suggesting the recruitment of sensory cortices (including the visual cortices) during reward anticipation irrespective of the quality of the signal input [35].

We found a strong overall correlation (adj-η^2 = 0.160, i.e. 16% of variance explained after adjusting for inflation due to the involvement of multiple variables) of neural networks with externalising behaviours (ADHD and ODD/CD), particularly in reward anticipation and motor inhibition, but did not observe a significant correlation with internalising behaviours (adj--η^2 = -0.024). While ADHD behaviours were related to both reward anticipation and motor inhibition networks, we found specific neural signatures that distinguished each of the individual behaviours. While brain activity in the reward anticipation network was correlated with both hyperactivity and inattention (Table 3A), their activation patterns were not significantly different (Figure 3E and Table 4), and in fact equivalent. However, in the motor inhibition network, the correlation with inattention was significantly stronger than that with hyperactivity (Figure 3E, Table 3C and Table 5B), consistent with a greater effort to maintain sustained attention during the task. This interpretation is supported by the strong correlation during successful motor inhibition of inattention with right inferior frontal cortical activity (Figure 3C and Table 3C), a brain region previously implicated in attentional detection, monitoring and motor inhibition [9].

In contrast, in impulsivity we found no significant correlation with the reward anticipation network. In the motor inhibition network, its strongest correlation was with activation of the left temporal-parietal junction (TPJ) (Figure 3B and Table 3B), but there were no significant differences and in practical equivalence of the activation patterns of both hyperactivity and inattention (Figure 3E and Table 5B). This observation is in line with the previous finding of reduced bilateral TPJ activity in ADHD patients [36].

We, thus, identify neural signatures that distinguish hyperactivity, inattention and impulsivity on the basis of brain activation patterns during reward anticipation and motor inhibition. These signatures enable a more refined characterisation of ADHD behaviour than the currently used distinction between motivational vs motor inhibitory processes [37].

ODD/CD behaviours were only related to the motor inhibition network, but not reward anticipation, which is in line with previous findings [38, 39]. Activation patterns for ODD and CD behaviours in the motor inhibition network were similar, although dominated by ODD behaviours, suggesting a shared neural basis (Table S4) [40]. Surprisingly, we were not able to distinguish activation patterns in the motor inhibition network in conduct and inattention symptoms (Figure 3 C-E, Table 3 C&D, Table 5 B&C), which were also found practically equivalent. While this may indicate in part a shared neural basis, the phenotypic differences between these behaviours also suggest the presence of a distinguishing cognitive domain, which we have not captured in our tasks. Nevertheless, the shared neural signatures between ODD/CD and ADHD symptoms indicate a shared neural basis underlying the high comorbidity between ODD/CD and ADHD [41, 42], supporting the idea of unifying ADHD and ODD/CD into a single spectrum disorder [43].

It is a limitation of this work, and indeed of all task-based fMRI studies that none of the tasks selected represents all aspects of the behavioural domain interrogated. For example, the 'Research Domain Criteria' (RDoC) divide reward processing into three different constructs and nine sub-constructs. The MID interrogates only two sub-constructs, reward anticipation and early response to reward. Nonetheless, it is well established that MID, SST

and EFT capture important and clinically relevant aspects of reward processing [12], impulsiveness (and in particular response inhibition) [44] and social-emotional processing [10], respectively. While we showed distinctive patterns in neural networks that stratify ADHD subtypes/components during reward anticipation (i.e. the motivational pathway) and motor inhibition, the explained variance from individual regions of these neural networks is low (R^2<1%), which might be partly due to a task-dependent, incomplete representation of neural pathways underlying ADHD. However, given that together the neural networks could explain up to 16% variance of externalising behaviours (i.e. adj-η^2=0.160 for RCCA after adjusting for the number of variables; also note this effect could be even larger should the ridge restriction not be applied), the observed small effect size in the univariate analyses might be due to two additional factors: first, the current behavioural constructs, for example hyperactivity, impulsivity and inattention of ADHD, might themselves hide heterogeneity leading to reduced explanation of variance; second, neural networks might not be homogenous, for example, despite a significant overall association of the motor inhibition network with hyperactivity across all 40 brain clusters (adj-R^2=0.018), no cluster survived correction for multiple comparisons (Table S3A). This is in striking contrast to the greater homogeneity of the reward anticipation network, where 6 out of 46 brain clusters were in significant association with hyperactivity (Table 3A and Table S2), despite a smaller overall explained variance (adj-R^2 = 0.013). Thus, the reduced effect size may highlight the heterogeneity of behavioural components as well as neural networks.

Our approach provides a unified framework to investigate brain activity in reinforcement-related behaviour enabling the characterisation of shared and distinct functional brain activation patterns that underlie different externalising symptoms. It also results in the identification of neural signatures that may help to stratify these symptoms, while accounting for clinically observed co-morbidity.

Materials and Methods

Ethical Approval

The IMAGEN study was approved by local ethics research committees at each research site: King's College London, University of Nottingham, Trinity College Dublin, University of Heidelberg, Technische Universität Dresden, Commissariat à l'Energie Atomique et aux Energies Alternatives, and University Medical Center. Informed consent was sought from all participants and a parent/guardian of each participant.

Participants

One thousand five hundred and six adolescents (mean age = 14.44 y old; SD = 0.42; range = 12.88–16.44 y old, female-male ratio=783/723) from the baseline assessment of the IMAGEN sample with complete data in fMRI and behavioural measurements were included in the analyses. Of the 1506 participants investigated in this study, clinical DAWBA ratings are available from 1190 individuals. Of these individuals 131 have one or more diagnoses: 33 individuals were diagnosed with ADHD, 59 with emotional problems, 12 with anxiety (general + other) and 33 with depression (major + other). Detailed descriptions of this study have previously been published [4]. Gender, handedness and imaging sites were regressed out before conducting canonical correlation analyses and henceforward in all rest analyses.

Strength Difficulty Questionnaire (SDQ) and DAWBA

The Strength and Difficulties Questionnaire (SDQ) [45] is a brief 25-item behavioural screening tool probing hyperactivity, emotional symptoms, conduct problems, peer problems and prosocial behaviour for 3-16 years old. In the current study, we chose parent-rated hyperactivity (5 items) and conduct problem (5 items) to present externalising problems (Table 1A), and child-rated emotional problem (5 items) to represent internalising problems (Table 1B). Such a choice is based on findings that externalising problems scores from parents is more reliable than those from children themselves, and vice versa [46].

In DAWBA [47], similar to SDQ, parents-rated ADHD and ODD/CD items (Table 1A), and child-rated special phobia, social phobia, general anxiety, fear and depressions items (Table 1B) are included in the analyses.

fMRI Data Acquisition and Analysis

Structural and functional MRI data were acquired at eight IMAGEN assessment sites with 3T MRI scanners of different manufacturers (Siemens, Philips, General Electric, Bruker). The scanning variables were specifically chosen to be compatible with all scanners. The same scanning protocol was used in all sites. In brief, high-resolution T1-weighted 3D structural images were acquired for anatomical localization and co-registration with the functional time-series. Blood-oxygen-level-dependent (BOLD) functional images were acquired with gradient-echo, echo-planar imaging (EPI) sequence. For all tasks, 300 volumes were acquired for each participant, and each volume consisted of 40 slices aligned to the anterior commission/posterior commission line (2.4 mm slice thickness, 1 mm gap). The echo-time

(TE) was optimized (TE=30 ms, repetition time (TR)=2,200 ms) to provide reliable imaging of subcortical areas.

Functional MRI data were analysed with SPM8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). Spatial preprocessing included: slice time correction to adjust for time differences due to multi-slice imaging acquisition, realignment to the first volume in line, non-linearly warping to the MNI space (based on a custom EPI template (53x63x46 voxels) created out of an average of the mean images of 400 adolescents), resampling at a resolution of $3x3x3mm^3$ and smoothing with an isotropic Gaussian kernel of 5 mm full-width at half-maximum.

At the first level of analysis, changes in the BOLD response for each subject were assessed by linear combinations at the individual subject level, for each experimental condition (e.g. reward anticipation high gain of Monetary Incentive Delay (MID) task), each trial was convolved with the hemodynamic response function to form regressors that account for potential noise variance, e.g. head movement, associated with the processing of reward anticipation. Estimated movement parameters were added to the design matrix in the form of 18 additional columns (three translations, three rotations, three quadratic and three cubic translations, and every three translations with a shift of ±1 TR).

For the MID anticipation phase we contrasted brain activation during 'anticipation of high win [here signaled by a circle] vs anticipation of no-win [here signaled by a triangle]'; For the emotional faces task (EFT) we contrasted brain activation during 'viewing Angry Face vs viewing Control [circles]'; For the stop signal task (SST) we contrasted brain activation during

'successful stop vs successful go'. The single-subject contrast images were then taken to the population-based weighted co-activation network analysis.

The Monetary Incentive Delay Task for fMRI

Participants performed a modified version of the Monetary Incentive Delay (MID) task to examine neural responses to reward anticipation and reward outcome [20]. The task consisted of 66 10-second trials. In each trial, participants were presented with one of three cue shapes (cue, 250 ms) denoting whether a target (white square) would subsequently appear on the left or right side of the screen and whether 0, 2 or 10 points could be won in that trial. After a variable delay (4,000-4,500 ms) of fixation on a white crosshair, participants were instructed to respond with left/right button-press as soon as the target appeared. Feedback on whether and how many points were won during the trial was presented for 1,450 ms after the response (Extended Data Figure 2[6]). Using a tracking algorithm, task difficulty (i.e. target duration varied between 100 and 300 ms) was individually adjusted such that each participant successfully responded on ~66% of trials. Participants had first completed a practice session outside the scanner (~5 minutes), during which they were instructed that for each 5 points won they would receive one food snack in the form of small chocolate candies.

Based on prior research suggesting reliable associations between ADHD-symptoms and fMRI BOLD responses measured during reward anticipation, the current study used the contrast 'anticipation of high-win vs anticipation of no-win'. Only successfully 'hit' trials were included here.

The Emotional Reactivity fMRI Paradigm (Emotional Faces Task)

This task was adapted from [22]. Participants watched 18-second blocks of either a face movie (depicting anger or neutrality) or a control stimulus. Each face movie showed black and white video clips (200-500ms) of male or female faces. Five blocks each of angry and neutral expressions were interleaved with nine blocks of the control stimulus. Each block contained eight trials of 6 face identities (3 female). The same identities were used for the angry and neutral blocks. The control stimuli were black and white concentric circles expanding and contracting at various speeds that roughly matched the contrast and motion characteristics of the face clips (Extended Data Figure 3).

The neutral blocks contained emotional expressions that were not attributable to any particular emotion (e.g. nose twitching); however previous research has suggested that neutral stimuli are not always interpreted as such. Functional imaging studies have found significant activation of the amygdala in response to the presentation of neutral faces in healthy adult males [48], social anxiety patients and matched control participants [49], adolescents with conduct disorder problems [50] and young men with violent behaviour problems [51]. This suggests that neutral faces may be interpreted as emotionally ambiguous. This study focused specifically on the effects of viewing angry faces (vs control) to eliminate this ambiguity so that any significant relationships between behaviour and brain could be interpreted as the consequence of viewing negative social stimuli (anger).

The Stop Signal Task for fMRI

Participants performed an event-related stop signal task (SST) task designed to study neural responses to successful and unsuccessful inhibitory control [21]. The task was composed of Go trials and Stop trials. During Go trials (83%; 480 trials) participants were presented with arrows pointing either to the left or to the right. During these trials, subjects were instructed to make a button response with their left or right index finger corresponding to the direction of the arrow. In the unpredictable Stop trials (17%; 80 trials), the arrows pointing left or right were followed (on average 300 ms later) by arrows pointing upwards; participants were instructed to inhibit their motor responses during these trials (Extended Data Figure 4[52]). A tracking algorithm changes the time interval between Go signal and Stop signal onsets according to each subject's performance on previous trials (average percentage of inhibition over previous Stop trials, recalculated after each Stop trial), resulting in 50% successful and 50% unsuccessful inhibition trials. The inter-trial interval was 1,800 ms. The tracking algorithm of the task ensured that subjects were successful on 50% of Stop trials and worked at the edge of their own inhibitory capacity.

Population-based Weighted Voxel Co-Activation Network Analysis

The weighted voxel co-activation network analysis (WVCNA) [12, 18] was applied to parcellate those highly co-activated voxels in all three fMRI contrasts, e.g. large win vs no win contrast anticipation phase of MID task, angry face vs control contrast of face task and successful stop vs successful go contrast of SST. Such a parcellation procedure could

effectively reduce the dimensionality without losing too much information. The procedure is summarised as below:

Pre-processing. For all three tasks, the initial pre-processing steps involved removing null voxels (including the removal of out-brain voxels based on Automated Anatomical Labelling (AAL) template) and potential participant outliers from contrast data based on low inter-sample correlations. The activation maps of pre-processed data were then generated and only those positive activations with at least a medium effect size, i.e. Cohen's D>0.3 (see the following section for more details), will be included in the following analyses.

Parameter Selection. To minimize the arbitrary choice of parameters, we took the default and suggested settings of R package 'WGCNA' [53], except for the soft-thresholds of adjacency matrices, which were determined as 7 for the MID, 8 for the EFT and 7 for the SST based on the fitness of scale free topology criteria (Extended Data Figure 5). The above adjacency matrices will then be used to generate the topology overlapping matrices (TOMs), which capture both the direct and indirect connections among voxels. The hierarchical clustering will then be applied on the distance matrices, as 1-TOMs, and together with the dynamic cut tree function, the fMRI modules will be generated as functional ROIs. The first principle component of each module will be included in the following analysis to represent the brain activation (or BOLD response). No merge of modules will be conducted after the hierarchical clustering to avoid using an arbitrary threshold.

The Effect Size Threshold for Brain Activation

Cohen's D is defined as $\frac{\beta_1-\beta_2}{\sigma_{\text{pooled}}}$, and Cohen proposed (although reluctantly) to use Cohen's D=0.5 for a two-sample t-test, as well as an alternative option of using correlation coefficient r=0.3, as the threshold for a median effect size [27]. As pointed out by Cohen, these two effect sizes (i.e. D and r) could be mutually transformed (i.e. a two-sample t-test could be alternatively understood as testing for a correlation between the group label and the pooled sample) that (in case the variances are equal in both groups and the total sample is N):

$$\frac{\mathrm{t}}{\sqrt{\mathrm{N}}} = \frac{\mathrm{D}_{2-\mathrm{sample}}}{\mathrm{k}} = \frac{\mathrm{r}}{\sqrt{1-\mathrm{r}^2}}$$

, where t is the t-statistic and k is determined by the percentage of each group in the full sample (i.e. p and q respectively) as $\sqrt{1/pq}$, of which the minimum value 2 is acquired when the sample sizes are equal in both groups, i.e. p=q. A clear difference between D and r in a two-sample t-test could therefore be readily understood as while the achieved statistical power depends on the exact sample size in each group for Cohen's D, the achieved statistical power of r (i.e. the correlation coefficient) only depends on the full sample size. Therefore, the proposed thresholds for median effect size (i.e. D=0.5 and r=0.3) are not equivalent, and r=0.3 is more stringent than D=0.5 (equivalent to or less than r=0.243 depends on the exact sample size in each group). This highlights the fact that the choice of a threshold for effect size is of certain flexibilities if not completely arbitrary.

In the case of a one-sample t-test, however, with the same definition of D, the relationship between the t-statistic and effect size D now changes to $\frac{\mathrm{t}}{\sqrt{\mathrm{N}}} = \mathrm{D}_{1-\mathrm{sample}}$. Therefore, Cohen's D in a one-sample t-test shares a similar relationship to the achieved statistical power with the correlation coefficient r in a two-sample t-test that only the total

sample size matters. Therefore, to achieve the same statistical power as of r=0.30 (i.e. the threshold of median effect size) with the same sample size, the equivalent Cohen's D of a one-sample t-test could be calculated as 0.32.

In addition, Cohen [27] also discussed the differences of Cohen's D in the cases of two-sample and one-sample t-tests (Case 3 in Chapter 2), where he suggested of using the transformation $\mathrm{D}_{1-\mathrm{sample}} = {\mathrm{D}_{2-\mathrm{sample}}}/{\sqrt{2}}$ to re-calculate the critical values for the one-sample t-test, of which the corresponding threshold of median effect size is therefore D = 0.35. This transformation, however, aims to achieve an equal statistical power between the one-sample and two-sample t-tests on the condition that the sample size in the one-sample t-test is half of that in the two-sample t-test with balanced sample sizes in both groups.

Nevertheless, despite alternative strategies in calculation, both thresholds are indeed similar, and therefore we propose to use Cohen's D=0.30 as the threshold of median effect size for a one-sample t-test, agreeable with both calculations when keeping one decimal.

Regularised Canonical Correlation Analysis (RCCA)

CCA has been widely used to investigate the overall correlation between two sets of variables [54]. However, in our case, due to high intra-correlations in both brain fMRI networks and behavioural items, multicollinearity is a potential risk factor that could jeopardise the validity of following statistical inference. Therefore, we will adopt the ridge regularised canonical correlation proposed by [19], where two ridge regulation parameters, λ_x and λ_y, will be added to the diagonals of corresponding covariance matrices to avoid the singularity.

As our purposes are not to maximise the power of prediction, instead of estimating the optimal regulation parameters [55], we will fix the regulation parameters across all analyses. Although multiple pre-defined regulation parameters have been experimented, i.e. 0.1, 0.2, 0.3, 0.4 and 0.5 for both λ, the significance of major results are consistent throughout all settings (Extended Data Table 2), and therefore we will simply report the P-values as well as relevant statistics based on regulation parameter 0.1. It is also noteworthy that the optimisation of regulation parameter will almost surely invalid any attempt of calculating internalised P-values through permutation test unless the optimisation procedure is also permuted, which is very difficult, if not impossible, due to the extremely high computational demanding of optimisation at each iteration. It should also be noted that current optimisation procedures of CCA related approaches focus on maximising the prediction power for the first component and therefore is not a 'real' optimum for our purpose of evaluating the overall correlation described below.

RCCA was then applied on two sets of standardized variables to investigate their overall correlation, of which the P-value or significance level will be determined through permutation tests, where individual IDs of behaviour items will be randomly shuffled at each iteration to generate the null distribution of statistics of interest. Particularly, we use the eta square (η^2) to represent the proportion of mutually explained variance between the two sets of variables, analogue to the R^2 (i.e. the coefficient of determinant) in a multiple linear model. η^2 is defined as $1-\lambda_{Wilks}$, where λ_{Wilks} (Wilks's Lambda) is a commonly used effect size in CCA [56] and could be calculated as the multiplication of unexplained variance for the correlation of each pair of

components:

$$\lambda_{Wilks} = \prod_{i=1}^{k}(1 - \rho_i^2)$$

, where ρ_i^2 denotes the squared correlation (i.e. mutually explained variance) between the *i*th pair of RCCA components, and *k* denotes the total number of CCA components for each set of variables. Please note that η^2, similar to R^2, will increase when more variables were included in the CCA even if all these variables were completely irrelevant. Therefore, we further included an adjusted-η^2 (analogue to the adjusted-R^2) that corrects for the inflation in η^2 caused by the increased number of variables as:

$$\eta_{adj}^2 = 1 - \frac{1 - \eta^2}{1 - \eta_0^2}$$

, where η_0^2 presents the expected η^2 under the null hypothesis that there is no relationship between the two sets of variables, i.e. a measure of inflation in η^2, and could be directly estimated through the permutation test. Clearly, η_{adj}^2 is a monotonic increasing function of η^2, where η_{adj}^2 tends to 0 when $\eta^2 \to \eta_0^2$, and 1 when $\eta^2 \to 1$.

The standard error (SE) of η^2 was then estimated using Jackknife [57, 58], and the corresponding 90% confidence intervals were then calculated as $[Z_{5\%}xSE_{\eta 2}+\eta^2, Z_{95\%}xSE_{\eta 2}+\eta^2]$, where $Z_{x\%}$ denotes the Z-score at the x% quantile of a standardised normal distribution.

Comparison of Related Associations/Correlations through Permutation

To compare two correlations, a fisher's transformation is normally applied to first normalise the distributions of correlations. The transformed correlations, now follow the

normal distribution, could then be directly compared, and the corresponding difference should also follow a normal distribution [59]. However, estimation for the variance of such a difference should properly count in the relationship of variables involved in calculating the correlations. For example, in the present paper, we are interested in the difference between two correlations that share one variable in common, i.e. in the form of cor(A,B) vs cor(A,C). While the analytical solution of the variance estimation for the above case has been extensively investigated in the past [60-62], we will additionally implement the permutation process to empirically investigate the variance, which not only is known to be robust even if the normality assumption has been violated, but also enable us to investigate multiple comparisons altogether, where the variance of summed absolute differences under the null hypothesis could be directly estimated through the permutation process.

In the present paper, we directly calculate the P-value (which is determined by the underlying variance) of the observed summed absolute difference through a permutation process as the chance of randomly observing (i.e. at each permutation iteration) a summed absolute difference larger than the original observation. For the comparison purpose, we also include the results from Steiger's test [61] in relevant tables, which are highly similar to results using the permutation test.

Equivalence Test

Whenever a null result was observed from a statistical test, no meaningful statistical inference could be drawn unless a proper test was conducted to show that the observed non-

significant effect size is indeed smaller than a meaningful threshold. In the present study, we adopted the equivalence test through a "two one-sided tests" (TOST) procedure [26] that the observed effect size was tested against a lower equivalence bound (noted as L) with a null hypothesis that the observed effect size is lower than this lower bound and an upper equivalence bound (noted as U) with a null hypothesis that the observed effect size is larger than this upper bound. If both tests are significant, we could then conclude that the observed effect size has been statistically found smaller than a meaningful one, hence in that sense equivalent to zero. In case that we are only interested in a one-tailed test (e.g. we are only interested in a positive correlation or R^2, i.e. the coefficient of determinant), "it is also possible to test for inferiority, or the hypothesis that the effect is smaller than an upper equivalence bound, by setting the lower equivalence bound to ∞" [26]. This strategy is generally applicable even without the knowledge of the exact distribution of the observed effect size (like RCCA) of which the confidence interval could be established based on variance estimated through methods like bootstrap or jackknife.

The equivalence test for the first eigenvalue of RCCA: Due to the fact that correlations between RCCA components are forced non-negative, a test for the first eigenvalue is equivalent to that for the correlation, of which the square is also known as Roy's largest root, between the first pair of components in the RCCA. We therefore only test for inferiority in the corresponding equivalence test, i.e. where the lower equivalence bound (L_Z) was set as -∞, and the upper equivalence bound (U_Z) of Z-score (i.e. Z_{Fisher}, Fisher's r-to-z transformed correlation) was calculated as the inflated $Z_{Fisher0}$ between the first components of RCCA under

the null hypothesis (estimated through permutation) plus a small effect size q=0.1 suggested by Cohen (i.e. the difference between two Fisher-transformed correlations, known as Cohen's q [27]). The standard deviation (σ_z) of the observed Z_{Fisher} could be estimated through jackknife [57, 58], and the corresponding *t*-statistic for the one-tailed test could be calculated as $t = (Z_{Fisher} - 0.1 - Z_{Fisher0})/\sigma_Z$.

The equivalence test for comparison of related correlations: similar to above, the corresponding lower and upper equivalence bounds ($L_{\Delta Z}$ and $U_{\Delta Z}$) of Fisher's r-to-z transformed correlation Z_{Fisher} were set as -0.1 and 0.1 to represent a tiny effect size Cohen's D =0.1. The variance (σ_Z^2) of the observed Z_{Fisher} was estimated through jackknife, and the corresponding *t*-statistics of one-tailed tests for the lower and upper bounds could be given as $(0.1 + Z_{Fisher})/\sigma_Z$ and $(Z_{Fisher} - 0.1)/\sigma_Z$, respectively.

Data Availability

IMAGEN data are available from a dedicated database: https://imagen2.cea.fr.

Code Availability

Custom code that supports the findings of this study is available from the corresponding author upon request.

Reference

1. Castellanos, F.X., Sonuga-Barke, E.J., Milham, M.P. & Tannock, R. Characterizing cognition in ADHD: beyond executive dysfunction. *Trends Cogn Sci* **10**, 117-123 (2006).
2. Blanken, L.M.*, et al.* Cognitive functioning in children with internalising, externalising and dysregulation problems: a population-based study. *Eur Child Adolesc Psychiatry* **26**, 445-456 (2017).
3. Shakoor, S., McGuire, P., Cardno, A.G., Freeman, D. & Ronald, A. A twin study exploring the association between childhood emotional and behaviour problems and specific psychotic experiences in a community sample of adolescents. *J Child Psychol Psychiatry* **59**, 565-573 (2018).
4. Schumann, G.*, et al.* The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. *Mol Psychiatry* **15**, 1128-1139 (2010).
5. Chen, J.E. & Glover, G.H. Erratum to: Functional Magnetic Resonance Imaging Methods. *Neuropsychol Rev* **25**, 314 (2015).
6. Nymberg, C.*, et al.* Neural mechanisms of attention-deficit/hyperactivity disorder symptoms are stratified by MAOA genotype. *Biol Psychiatry* **74**, 607-614 (2013).
7. Dalley, J.W. & Robbins, T.W. Fractionating impulsivity: neuropsychiatric implications. *Nat Rev Neurosci* **18**, 158-171 (2017).
8. Schultz, W. Neuronal Reward and Decision Signals: From Theories to Data. *Physiol Rev* **95**, 853-951 (2015).
9. Aron, A.R., Robbins, T.W. & Poldrack, R.A. Inhibition and the right inferior frontal cortex: one decade on. *Trends in Cognitive Sciences* **18**, 177-185 (2014).
10. Quinlan, E.B.*, et al.* Psychosocial Stress and Brain Function in Adolescent Psychopathology. *Am J Psychiatry* **174**, 785-794 (2017).
11. Adolphs, R. Cognitive neuroscience of human social behaviour. *Nat Rev Neurosci* **4**, 165-178 (2003).
12. Jia, T.*, et al.* Neural basis of reward anticipation and its genetic determinants. *Proc Natl Acad Sci U S A* **113**, 3879-3884 (2016).

13. Gerdes, A.B., *et al.* Emotional sounds modulate early neural processing of emotional pictures. *Front Psychol* **4**, 741 (2013).

14. Serences, J.T. Value-based modulations in human visual cortex. *Neuron* **60**, 1169-1181 (2008).

15. Pleger, B., Blankenburg, F., Ruff, C.C., Driver, J. & Dolan, R.J. Reward facilitates tactile judgments and modulates hemodynamic responses in human primary somatosensory cortex. *J Neurosci* **28**, 8161-8168 (2008).

16. Salimpoor, V.N., *et al.* Interactions between the nucleus accumbens and auditory cortices predict music reward value. *Science* **340**, 216-219 (2013).

17. Goodman, A., Lamping, D.L. & Ploubidis, G.B. When to Use Broader Internalising and Externalising Subscales Instead of the Hypothesised Five Subscales on the Strengths and Difficulties Questionnaire (SDQ): Data from British Parents, Teachers and Children. *Journal of Abnormal Child Psychology* **38**, 1179-1191 (2010).

18. Mumford, J.A., *et al.* Detecting network modules in fMRI time series: A weighted network analysis approach. *Neuroimage* **52**, 1465-1476 (2010).

19. Vinod, H.D. Canonical ridge and econometrics of joint production. *Journal of Econometrics* **4**, 147-166 (1976).

20. Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L. & Hommer, D. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* **12**, 3683-3687 (2001).

21. Bari, A. & Robbins, T.W. Inhibition and impulsivity: behavioral and neural basis of response control. *Prog Neurobiol* **108**, 44-79 (2013).

22. Grosbras, M.H. & Paus, T. Brain networks involved in viewing angry hands or faces. *Cereb Cortex* **16**, 1087-1096 (2006).

23. Langfelder, P., Zhang, B. & Horvath, S. Defining clusters from a hierarchical cluster tree: the Dynamic Tree Cut package for R. *Bioinformatics* **24**, 719-720 (2008).

24. Bartels, M., *et al.* Childhood aggression and the co-occurrence of behavioural and emotional problems: results across ages 3-16 years from multiple raters in six cohorts in the EU-ACTION project. *Eur Child Adolesc Psychiatry* **27**, 1105-1121 (2018).

25. Kuhfeld, W.F. A note on Roy's largest root. *Psychometrika* **51**, 479-481 (1986).

26. Lakens, D. Equivalence Tests: A Practical Primer for t Tests, Correlations, and Meta-Analyses. *Soc Psychol Personal Sci* **8**, 355-362 (2017).

27. Cohen, J. *Statistical power analysis for the behavioral sciences* (L. Erlbaum Associates, Hillsdale, N.J., 1988).

28. Krueger, R.F.*, et al.* Progress in achieving quantitative classification of psychopathology. *World Psychiatry* **17**, 282-293 (2018).

29. Cuthbert, B.N. & Insel, T.R. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med* **11**, 126 (2013).

30. Pas, P., van den Munkhof, H.E., du Plessis, S. & Vink, M. Striatal activity during reactive inhibition is related to the expectation of stop-signals. *Neuroscience* **361**, 192-198 (2017).

31. Fox, P.T. & Friston, K.J. Distributed processing; distributed functions? *Neuroimage* **61**, 407-426 (2012).

32. Robinson, J.L., Laird, A.R., Glahn, D.C., Lovallo, W.R. & Fox, P.T. Metaanalytic connectivity modeling: delineating the functional connectivity of the human amygdala. *Hum Brain Mapp* **31**, 173-184 (2010).

33. Logothetis, N.K. What we can do and what we cannot do with fMRI. *Nature* **453**, 869 (2008).

34. Li, J.*, et al.* Primary Auditory Cortex is Required for Anticipatory Motor Response. *Cereb Cortex* **27**, 3254-3271 (2017).

35. Mountcastle, V.B., Lynch, J.C., Georgopoulos, A., Sakata, H. & Acuna, C. Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *J Neurophysiol* **38**, 871-908 (1975).

36. Rubia, K., Smith, A.B., Brammer, M.J. & Taylor, E. Temporal lobe dysfunction in medication-naive boys with attention-deficit/hyperactivity disorder during attention allocation and its relation to response variability. *Biol Psychiatry* **62**, 999-1006 (2007).

37. Swanson, J.M.*, et al.* Etiologic subtypes of attention-deficit/hyperactivity disorder: brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. *Neuropsychol Rev* **17**, 39-59 (2007).

38. Hobson, C.W., Scott, S. & Rubia, K. Investigation of cool and hot executive function in ODD/CD independently of ADHD. *J Child Psychol Psychiatry* **52**, 1035-1043 (2011).

39. Scheres, A., Oosterlaan, J. & Sergeant, J.A. Response inhibition in children with DSM-IV subtypes of AD/HD and related disruptive disorders: the role of reward. *Child Neuropsychol* **7**, 172-189 (2001).

40. Burke, J.D., Waldman, I. & Lahey, B.B. Predictive validity of childhood oppositional defiant disorder and conduct disorder: implications for the DSM-V. *J Abnorm Psychol* **119**, 739-751 (2010).

41. Spencer, T., Biederman, J. & Wilens, T. Attention-deficit/hyperactivity disorder and comorbidity. *Pediatr Clin North Am* **46**, 915-927, vii (1999).

42. Jensen, P.S., Martin, D. & Cantwell, D.P. Comorbidity in ADHD: implications for research, practice, and DSM-V. *J Am Acad Child Adolesc Psychiatry* **36**, 1065-1079 (1997).

43. Heidbreder, R. ADHD symptomatology is best conceptualized as a spectrum: a dimensional versus unitary approach to diagnosis. *Atten Defic Hyperact Disord* **7**, 249-269 (2015).

44. Whelan, R.*, et al.* Adolescent impulsivity phenotypes characterized by distinct brain networks. *Nat Neurosci* **15**, 920-925 (2012).

45. Goodman, R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry* **40**, 1337-1345 (2001).

46. Herjanic, B. & Reich, W. Development of a structured psychiatric interview for children: agreement between child and parent on individual symptoms. *J Abnorm Child Psychol* **25**, 21-31 (1997).

47. Goodman, R., Ford, T., Richards, H., Gatward, R. & Meltzer, H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry* **41**, 645-655 (2000).

48. Ernst, M.*, et al.* Choice selection and reward anticipation: an fMRI study. *Neuropsychologia* **42**, 1585-1597 (2004).

49. Cooney, R.E., Atlas, L.Y., Joormann, J., Eugene, F. & Gotlib, I.H. Amygdala activation in the processing of neutral faces in social anxiety disorder: is neutral really neutral? *Psychiatry Res* **148**, 55-59 (2006).

50. Passamonti, L.*, et al.* Neural abnormalities in early-onset and adolescence-onset conduct disorder. *Arch Gen Psychiatry* **67**, 729-738 (2010).

51. Pardini, D.A. & Phillips, M. Neural responses to emotional and neutral facial expressions in chronically violent men. *Journal of psychiatry & neuroscience : JPN* **35**, 390-398 (2010).

52. Gan, G.*, et al.* Alcohol-Induced Impairment of Inhibitory Control Is Linked to Attenuated Brain Responses in Right Fronto-Temporal Cortex. *Biol Psychiat* **76**, 698-707 (2014).

53. Langfelder, P. & Horvath, S. WGCNA: an R package for weighted correlation network analysis. *Bmc Bioinformatics* **9** (2008).

54. Combes, S.*, et al.* Relationships between sensory and physicochemical measurements in meat of rabbit from three different breeding systems using canonical correlation analysis. *Meat Sci* **80**, 835-841 (2008).

55. Leurgans, S.E., Moyeed, R.A. & Silverman, B.W. Canonical Correlation-Analysis When the Data Are Curves. *J Roy Stat Soc B Met* **55**, 725-740 (1993).

56. Sherry, A. & Henson, R.K. Conducting and interpreting canonical correlation analysis in personality research: a user-friendly primer. *J Pers Assess* **84**, 37-48 (2005).

57. Efron, B. & Stein, C. The jackknife estimate of variance. *The Annals of Statistics*, 586-596 (1981).

58. Bulik-Sullivan, B.*, et al.* An atlas of genetic correlations across human diseases and traits. *Nat Genet* **47**, 1236-1241 (2015).

59. Fisher, R.A. On the probable error of a coefficient of correlation deduced from a small sample. *Metron* **1**, 3-32 (1921).

60. Dunn, O.J. & Clark, V. Correlation Coefficients Measured on the Same Individuals. *Journal of the American Statistical Association* **64**, 366-377 (1969).

61. Steiger, J.H. Tests for Comparing Elements of a Correlation Matrix. *Psychol Bull* **87**, 245-251 (1980).

62. Meng, X.-L., Rosenthal, R. & Rubin, D.B. Comparing correlated correlation coefficients. *Psychol Bull* **111**, 172 (1992).

Acknowledgements

This work received support from the following sources: National Natural Science Foundation of China (81801773), the Shanghai Pujiang Project (18PJ1400900), the European Union-funded FP6 Integrated Project IMAGEN (Reinforcement-related behaviour in normal brain function and psychopathology) (LSHM-CT- 2007-037286), the Horizon 2020 funded ERC Advanced Grant 'STRATIFY' (Brain network based stratification of reinforcement-related disorders) (695313), ERANID (Understanding the Interplay between Cultural, Biological and Subjective Factors in Drug Use Pathways) (PR-ST-0416-10004), BRIDGET (JPND: BRain Imaging, cognition Dementia and next generation GEnomics) (MR/N027558/1), Human Brain Project (HBP SGA 2, 785907), the FP7 project MATRICS (603016), the Medical Research Council Grant 'c-VEDA' (Consortium on Vulnerability to Externalizing Disorders and Addictions) (MR/N000390/1), the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, the Bundesministerium für Bildung und Forschung (BMBF grants 01GS08152; 01EV0711; Forschungsnetz AERIAL 01EE1406A, 01EE1406B), the Deutsche Forschungsgemeinschaft (DFG grants SM 80/7-2, SFB 940, TRR 265, NE 1383/14-1), the Medical Research Foundation and Medical Research Council (grants MR/R00465X/1 and MR/S020306/1), the National Institutes of Health (NIH) funded ENIGMA (grants 5U54EB020403-05 and 1R56AG058854-01), the Human Brain Project (HBP SGA 2). Further support was provided by grants from: ANR (project AF12-NEUR0008-01 - WM2NA, and ANR-12-SAMA-0004), the Fondation de France, the Fondation pour la Recherche Médicale, the Mission Interministérielle de Lutte-contre-les-Drogues-et-les-Conduites-Addictives (MILDECA), the Assistance-Publique-Hôpitaux-de-Paris and INSERM (interface grant), Paris Sud University IDEX 2012; the National Institutes of Health, Science Foundation Ireland (16/ERCD/3797), U.S.A. (Axon, Testosterone and Mental Health during Adolescence; RO1 MH085772-01A1), and by NIH Consortium grant U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centres of Excellence; the 111 Project (B18015), the National Key Research and Development Program of China (2018YFC0910503, 2018YFC1312900), the NSFC (81873909, 81930095, 91630314), The Key Project of Shanghai Science and Technology Innovation Plan (16JC1420402), the Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZHANGJIANG LAB. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Author Contributions

Design of Study: G.S. and T.J.
Manuscript Writing and Editing: T.J. and G.S. wrote the manuscript; A.I., E.B.Q, N.T., Q.L. and B.F. edited the first draft; all authors critically reviewed the manuscript

Study Principal Investigators: T.B., G.B., A.L.W.B., U.B., C.B., S.D., J.F., H.F., A.G., H.G., P.G., A.H., B.I., J-L.M., M-L.P.M., F.N., T.P., L.P., J.H.F., M.N.S., H.W., R.W., G.S.
Data acquisition: E.B.Q., T.B., G.B., A.L.W.B., U.B., C.B., H.F., A.G., H.G., P.G., A.H., B.I., J-L.M., M-L.P.M., F.N., D.P.O., T.P., L.P., J.H.F., M.N.S., H.W., R.W., G.S.
Data analysis: T.J. and A.I.

Competing Interests Statement

Dr. Banaschewski served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships. Dr. Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses. The other authors declare no competing interests.

Figure Legends:

Figure 1. The workflow of the Analyses. We included the monetary incentive delay task (MID) as a measure of reward processing, the stop signal task (SST) as a measure of impulsivity (motor inhibition), and the emotional face task (EFT) as a measure of social-emotional processing. Only strong brain activation (with effect size Cohen's D>0.30) was included in the analyses. The weighted voxel co-activation network analysis (WVCNA) in combination with a further hierarchical clustering was implemented to establish the brain fMRI networks. The ridge-restricted canonical correlation analysis (RCCA) was adopted to evaluate the overall correlation between the brain networks and reinforcement-related behaviours. Based on the RCCA results, we have identified the neural signatures across three brain fMRI networks for each reinforcement-related behaviour.

Figure 2. The Activation map of MID (A), SST (B), EFT (C) and their overlay (D). In all figures, MID, SST and EFT were represented by red, blue and green. The activation levels were measured as the -log10 transformation of P-value and only voxels with P-value < $1.0x10^{-34}$ (i.e. Effect Size Cohen's D>0.3) were illustrated.

Figure 3. A. Reward anticipation network underlying Hyperactivity (Red: Thalamus, Superior Parietal Lobule, middle Central Sulcus, Primary Auditory Cortex, Middle Cingulate Cortex and Superior Frontal Junction); **B. Motor inhibition network underlying Impulsivity** (Blue: left middle Temporal-Parietal Junction); **C. Motor inhibition network underlying Inattention** (Green: right anterior Inferior Frontal Sulcus); **D. Motor inhibition network underlying ODD/CD behaviours** (Yellow: right Inferior Frontal Gyrus + anterior Insula and right anterior Inferior Frontal Sulcus); **E. Neural signatures of ADHD and ODD/CD behaviours.** For each neural network identified in A-D, its correlations with the corresponding primary behaviour and the rest ADHD or ODD/CD behaviours were compared that the corresponding relative strength of correlations were plotted (Red: Hyperactivity; Blue: Impulsivity; Green: Inattention; Yellow: ODD/CD behaviours). P-values for pairwise significant differences after correction for multiple testing were provided .

Formatted: Highlight

Tables

Table 1. List of (A) Externalising Items from parents-rated SDQ and DAWBA, and (B) Internalising Items from child-rated SDQ and DAWBA.

(A)

Hyperactivity	Restless (SDQ_Parent)
	Fidgety (SDQ_Parent)
	Adhd.fidgets (DAWBA_Parent).
	Adhd.cant.remain.seated (DAWBA_Parent)
	Adhd.runs.or.climbs.when.shouldnt (DAWBA_Parent)
	Adhd.cant.play.quietly (DAWBA_Parent)
	Adhd.cant.calm.down (DAWBA_Parent)
Inattention	Easily Distracted (SDQ_Parent)
	Attentiveness (SDQ_Parent)
	Adhd.careless.mistakes.inattentive (DAWBA_Parent)
	Adhd.loses.interest (DAWBA_Parent)
	Adhd.doesnt.listen (DAWBA_Parent)
	Adhd.doesnt.finish (DAWBA_Parent)
	Adhd.poor.self.organisation (DAWBA_Parent)
	Adhd.avoids.tasks.needing.thought (DAWBA_Parent)
	Adhd.loses.things (DAWBA_Parent)
	Adhd.distractible (DAWBA_Parent)
	Adhd.forgetful (DAWBA_Parent)
Impulsivity	Think before action (SDQ_Parent)
	Adhd.blurts.out.answers (DAWBA_Parent).
	Adhd.cant.wait.for.a.turn (DAWBA_Parent)
	Adhd.butts.into.conversations.or.games (DAWBA_Parent)

	Adhd.unstoppable.talk (DAWBA_Parent)
ODD	Tantrum (SDQ_Parent)
	Generally obedient (SDQ_Parent)
	Odd.temper.outbursts.parent1 (DAWBA_Parent)
	Odd.argues.with.adults.parent1 (DAWBA_Parent)
	Odd.ignores.rules.disobedient (DAWBA_Parent)
	Odd.deliberately.annoys.others (DAWBA_Parent)
	Odd.blames.others.for.own.acts (DAWBA_Parent)
	Odd.easily.annoyed (DAWBA_Parent)
	Odd.angry.and.resentful (DAWBA_Parent)
	Odd.spiteful (DAWBA_Parent)
	Odd.vindictive (DAWBA_Parent)
CD	Fight or bully others (SDQ_Parent)
	Often lie (SDQ_Parent)
	Steal (SDQ_Parent)
	Cd.lies (DAWBA_Parent)
	Cd.fights (DAWBA_Parent)
	Cd.bullies (DAWBA_Parent)
	Cd.stays.out (DAWBA_Parent)
	Cd.steals (DAWBA_Parent)
	Cd.runs.away (DAWBA_Parent)
	Cd.cannot.find.at.school (DAWBA_Parent)

(B)

Anxiety	Sepa.any.concerns.about.separations (DAWBA_Self)
	Soph.any.concerns (DAWBA_Self)
	Panic.attacks.in.last.4.weeks (DAWBA_Self)
	Fear.or.avoidance.of.crowds (DAWBA_Self)
	Fear.or.avoidance.of.public.places (DAWBA_Self)
	Fear.or.avoidance.of.travelling.alone (DAWBA_Self)
	Fear.or.avoidance.of.being.far.from.home (DAWBA_Self)
	Gena.ever.worries (DAWBA_Self)
	Gena.specific.or.generalised (DAWBA_Self)
	Gena.excessive.worry (DAWBA_Self)
	Many worries (SDQ_Self)
	Many fears (SDQ_Self)
	Anxious in new situations (SDQ_Self)
Depression	Dep.sad (DAWBA_Self)
	Dep.irritable (DAWBA_Self)
	Dep.loss.of.interest (DAWBA_Self)
	Dep.recent.talk.of.dsh (DAWBA_Self)
	Dep.dsh.recently (DAWBA_Self)
	Dep.dsh.ever (DAWBA_Self)
	Headache/stomach ache (SDQ_Self)
	Unhappy (SDQ_Self)

Table 2. Regularised CCA P-values based on 10000 Permutation with penalty λ=0.1 for both fMRI and externalising behaviour items. Similar results have been achieved with a pre-defined scheme of penalty settings as shown in Extended Data Table 2. η^2 denotes the proportion of behaviour variance explained by the fMRI and is analogue to the R^2 in the multiple linear regression model.

	ADHD		**ODD/CD**		**All Behaviours**	
	P-value	**η^2 [90% CIs]**	**P-value**	**η^2 [90% CIs]**	**P-value**	**η^2 [90% CIs]**
MID	0.029	0.356 [0.328,0.385]	0.203	0.331 [0.301,0.361]	0.036	0.565 [0.530,0.587]
SST	0.003	0.344 [0.314,0.374]	0.003	0.334 [0.303,0.366]	<0.001	0.558 [0.530,0.587]
EFT	0.634	0.087 [0.067,0.108]	0.294	0.091 [0.071,0.110]	0.392	0.171 [0.145,0.197]
All fMRI					<0.001	0.836 [0.820,0.851]

Table 3. Prominent clusters of brain networks for (A) hyperactivity, (B) impulsivity, (C) inattention and (D) ODD/CD behaviours. For each behaviour component, the prominent clusters in each brain network were identified if their univariate correlations with the sum of corresponding behaviour items (i.e. column 'Primary Behaviour') were significant after correction for multiple comparisons through 10000-permutation (column $P_{corrected}$). For all prominent clusters identified in the first step, we further explored their univariate correlations with the remaining behaviour components (i.e. column 'Exploratory Analyses). ‡ these P-values were evaluated based on 10000-permutation to correct for multiple comparisons in the corresponding exploratory tests. See Table S2-S4 for the complete results.

A

MID Regions	Primary Behaviour		Exploratory Analyses					
	Hyperactivity		Impulsivity		Inattention		ODD/CD	
	R [95%CIs]	$P_{corrected}$ (t-statistics)	R [95%CIs]	P‡ (t-statistics)	R [95%CIs]	P‡ (t-statistics)	R [95%CIs]	P‡ (t-statistics)
Thalamus	-0.091 [-0.141,-0.041]	0.011 (-3.539)	-0.032 [-0.089,0.012]	0.726 (-1.511)	-0.074 [-0.125,-0.025]	0.040 (-2.918)	-0.065 [-0.109,-0.008]	0.118 (-2.276)
SFJ	-0.084 [-0.134,-0.033]	0.029 (-3.255)	-0.014 [-0.073,0.028]	0.992 (-0.873)	-0.066 [-0.117,-0.016]	0.105 [-2.584]	-0.052 [-0.073,0.028]	0.332 [-1.975]
PAC	-0.085 [-0.135,-0.035]	0.025 (-3.309)	-0.025 [-0.088,0.013]	0.771 (-1.442)	-0.051 [-0.098,0.002]	0.445 (-1.871)	-0.063 [-0.110,-0.010]	0.134 (-2.340)
SPL	-0.094 [-0.144,-0.044]	0.007 (-3.666)	-0.045 [-0.103,-0.002]	0.324 (-2.055)	-0.077 [-0.127,-0.027]	0.031 (-3.000)	-0.068 [-0.113,-0.012]	0.091 (-2.436)
mid-CS	-0.091 [-0.141,-0.041]	0.011 (-3.552)	-0.040 [-0.098,-0.003]	0.452 (-1.860)	-0.075 [-0.124,-0.024]	0.044 (-2.888)	-0.074 [-0.117,-0.017]	0.044 (-2.613)
MCC	-0.084 [-0.134,-0.034]	0.027 (-3.269)	-0.017 [-0.073,0.028]	0.991 (-0.882)	-0.046 [-0.097,0.004]	0.500 (-1.802)	-0.078 [-0.129,-0.028]	0.028 (-3.059)

B

SST Regions	Primary Behaviour		Exploratory Analyses					
	Impulsivity		Hyperactivity		Inattention		ODD/CD	
	R [95%CIs]	$P_{corrected}$ (t-statistics)	R [95%CIs]	P‡ (t-statistics)	R [95%CIs]	P‡ (t-statistics)	R [95%CIs]	P‡ (t-statistics)
Left TPJ	-0.092 [-0.142,-0.041]	0.009 (-3.570)	-0.067 [-0.117,-0.016]	0.025 (-2.594)	-0.058 [-0.109,-0.008]	0.062 (-2.270)	-0.071 [-0.118,-0.017]	0.016 (-2.639)

C

SST Regions	Primary Behaviour		Exploratory Analyses					
	Inattention		Hyperactivity		Impulsivity		ODD/CD	
	R [95%CIs]	$P_{corrected}$ (t-statistics)	R [95%CIs]	P‡ (t-statistics)	R [95%CIs]	P‡ (t-statistics)	R [95%CIs]	P‡ (t-statistics)
Right aIFS	-0.087 [-0.137,-0.037]	0.019 (-3.392)	-0.017 [-0.068,0.033]	0.833 (-0.666)	-0.056 [-0.106,-006]	0.073 (-2.184)	-0.084 [-0.126,-0.026]	0.004 (-2.957)

D

SST Regions	Primary Behaviour		Exploratory Analyses					
	ODD/CD		Hyperactivity		Impulsivity		Inattention	
	R [95%CIs]	$P_{corrected}$ (t-statistics)	R [95%CIs]	P‡ (t-statistics)	R [95%CIs]	P‡ (t-statistics)	R [95%CIs]	P‡ (t-statistics)
Right IFC + aInsula	-0.090 [-0.133,-0.033]	0.011 (-3.246)	-0.014 [-0.065,0.036]	0.980 (-0.546)	-0.045 [-0.095,0.005]	0.295 (-1.754)	-0.053 [-0.109,-0.003]	0.158 (-2.070)
Right aIFS	-0.084 [-0.126,-0.026]	0.027 (-2.957)	-0.017 [-0.068,0.033]	0.954 (-0.666)	-0.056 [-0.106,-0.006]	0.125 (-2.184)	-0.087 [-0.137,-0.037]	0.005 (-3.392)

Table 4. Evaluating the Specificity of Prominent Brain Regions for Hyperactivity during Reward Anticipation. The specificity of prominent brain regions for hyperactivity was evaluated by comparing their correlations/associations to those with the rest behaviours, i.e. ADHD constructs impulsivity and inattention, and ODD/CD behaviours. For each brain region, its correlations with all behaviours were firstly transformed into normal distributed Z-scores (columns Z_{Hyper}, Z_{Impul}, Z_{Inatt} and $Z_{ODD/CD}$ respectively) through the Fisher transformation, and the pairwise differences (column ΔZ) were then tested against null using both Steiger's test (columns Steiger's Z-statistic and $P_{steiger}$) and Permutation test (column P_{Perm}), both of which provided very similar results. The overall significance throughout all brain regions was then evaluated based on the summed ΔZ across all brain regions using a Permutation test. The number of permutations was set as 10000. All P-values presented in the table were based on two-tailed tests without correction for multiple testing.

					Hyper-Impul				Hyper-Inatt				Hyper-ODD/CD			
	Z_{Hyper}	Z_{Impul}	Z_{Inatt}	$Z_{ODD/CD}$	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}
Thalamus	-0.091	-0.039	-0.075	-0.065	-0.052 [-0.100,-0.005]	-2.270	0.023	0.024	-0.016 [-0.070,0.036]	-0.634	0.526	0.526	-0.026 [-0.080,0.029]	-0.955	0.340	0.342
SFJ	-0.084	-0.023	-0.067	-0.053	-0.061 [-0.111,-0.011]	-2.670	0.008	0.008	-0.017 [-0.070,0.035]	-0.686	0.493	0.491	-0.031 [-0.090,0.028]	-1.156	0.248	0.247
PAC	-0.085	-0.037	-0.048	-0.064	-0.048 [-0.089,-0.007]	-2.091	0.037	0.036	-0.037 [-0.086,0.012]	-1.472	0.141	0.139	-0.021 [-0.071,0.028]	-0.787	0.431	0.431
SPL	-0.094	-0.053	-0.077	-0.068	-0.041 [-0.088,0.002]	-1.801	0.072	0.070	-0.017 [-0.065,0.031]	-0.681	0.496	0.496	-0.026 [-0.080,0.028]	-0.976	0.329	0.328
mid-CS	-0.092	-0.048	-0.074	-0.075	-0.044 [-0.107,0.001]	-1.893	0.058	0.058	-0.017 [-0.066,0.031]	-0.678	0.498	0.496	-0.017 [-0.072,0.038]	-0.627	0.531	0.529
MCC	-0.084	-0.023	-0.046	-0.078	-0.062 [-0.107,-0.016]	-2.676	0.008	0.008	-0.038 [-0.088,0.013]	-1.503	0.133	0.133	-0.006 [-0.057,0.045]	-0.225	0.822	0.822
Sum	-0.530	-0.222	-0.388	-0.402	-0.308 [-0.522,-0.094]			0.006	-0.142 [-0.384,0.100]			0.278	-0.128 [-0.377,0.121]			0.411

Table 5. Evaluating the Specificity of Prominent Brain Regions for (A) Impulsivity, (B) Inattention and (C) ODD/CD during Motor Inhibition. The specificity of prominent brain regions for the corresponding behaviours was evaluated by comparing their correlations/associations to those with the rest behaviours from ADHD constructs and ODD/CD behaviours. For each brain region, its correlations with all behaviours were firstly transformed into normal distributed Z-scores (columns Z_{Hyper}, Z_{Impul}, Z_{Inatt} and $Z_{ODD/CD}$ respectively) through the Fisher transformation, and the pairwise differences (column ΔZ) were then tested using both Steiger's test (columns Steiger's Z-statistic and $P_{Steiger}$) and Permutation test (column P_{Perm}), both of which provided very similar results. When there are multiple prominent regions, their overall significance was then evaluated based on the summed absolute ΔZ across all brain regions using a Permutation test. The number of permutations was set as 10000. All P-values presented in the table were based on two-tailed tests without correction for multiple testing.

A

					Impul- Hyper				Impul-Inatt				Impul-ODD/CD			
	Z_{Impul}	Z_{Hyper}	Z_{Inatt}	$Z_{ODD/CD}$	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}
Left TPJ	-0.092	-0.067	-0.059	-0.071	-0.025 [-0.073,0.022]	-1.090	0.276	0.274	-0.033 [-0.079,0.012]	-1.429	0.153	0.152	-0.021 [-0.069,0.027]	-0.886	0.375	0.375

B

					Inatt-Hyper				Inatt-Impul				Inatt-ODD/CD			
	Z_{Inatt}	Z_{Hyper}	Z_{Impul}	$Z_{ODD/CD}$	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}
Right aIFS	-0.087	-0.017	-0.056	-0.084	-0.070 [-0.124,-0.017]	-2.795	0.005	0.006	-0.031 [-0.080,0.018]	-1.330	0.184	0.187	-0.004 [-0.052,0.045]	-0.146	0.884	0.884

C

	$Z_{ODD/CD}$	Z_{Hyper}	Z_{Impul}	Z_{Inatt}	ODD/CD-Hyper				ODD/CD-Impul				ODD/CD-Inatt			
					ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}	ΔZ [95%CIs]	Steiger's Z-statistic	$P_{Steiger}$	P_{Perm}
Right IFC + aInsula	-0.090	-0.014	-0.045	-0.053	-0.076 [-0.128,-0.024]	-2.821	0.005	0.004	-0.045 [-0.096,0.005]	-1.896	0.058	0.058	-0.037 [-0.086,0.012]	-1.530	0.129	0.131
Right aIFS	-0.084	-0.017	-0.056	-0.087	-0.067 [-0.118,-0.015]	-2.465	0.013	0.013	-0.028 [-0.077,0.022]	-1.156	0.248	0.251	0.004 [-0.045,0.052]	0.146	0.884	0.884
Sum	-0.174	-0.031	-0.102	-0.141	-0.143 [-0.237,-0.049]			0.002	-0.073 [-0.164,0.019]			0.091	0.041 [-0.122,0.055]			0.390