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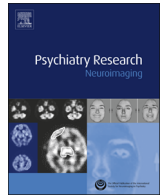
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Disorder-specific functional abnormalities during temporal discounting in youth with Attention Deficit Hyperactivity Disorder (ADHD), Autism and comorbid ADHD and Autism



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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are often comorbid and share cognitive abnormalities in temporal foresight. A key question is whether shared cognitive phenotypes are based on common or different underlying pathophysiologies and whether comorbid patients have additive neurofunctional deficits, resemble one of the disorders or have a different pathophysiology. We compared age- and IQ-matched boys with non-comorbid ADHD (18), non-comorbid ASD (15), comorbid ADHD and ASD (13) and healthy controls (18) using functional magnetic resonance imaging (fMRI) during a temporal discounting task. Only the ASD and the comorbid groups discounted delayed rewards more steeply. The fMRI data showed both shared and disorder-specific abnormalities in the three groups relative to controls in their brain-behaviour associations. The comorbid group showed both unique and more severe brain-discounting associations than controls and the non-comorbid patient groups in temporal discounting areas of ventromedial and lateral prefrontal cortex, ventral striatum and anterior cingulate, suggesting that comorbidity is neither an endophenocopy of the two pure disorders nor an additive pathology.

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1. Introduction

Autism Spectrum Disorders (ASD) are defined by abnormalities in social interaction, communication, and stereotyped/repetitive behaviours (<http://www.dsm5.org>). Attention Deficit Hyperactivity Disorder (ADHD) is defined by age-inappropriate inattention,

impulsiveness and hyperactivity (<http://www.dsm5.org>). About 30% of ASD patients have comorbid ADHD and ASD (Simonoff et al., 2008). Children with the comorbid disorder often have a primary diagnosis of ASD with clinically significant levels of ADHD symptoms, particularly hyperactivity. However, there are also comorbid children with a primary ADHD diagnosis and significant social interaction problems (Kochhar et al., 2011; Mayes et al., 2012; van der Meer et al., 2012). ADHD and ASD share deficits in executive functions (EF), such as planning, decision making, inhibition, and working memory (Rommelse et al., 2011). More recently, patients with ADHD and ASD have been shown to have deficits also in so-called “hot” executive functions involving reward-related decision making as measured by tasks of gambling, reward processing, and temporal discounting, with deficits mainly being observed in the ADHD group during the temporal discounting task (Scheres et al., 2008; Kohls et al., 2011, 2013; Noreika et al., 2013).

Neuroimaging studies have shown that ADHD is characterised by a delay in normal brain structure development and by multisystem structural and functional abnormalities in

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fronto-striato-cerebellar networks that mediate these executive functions (Nakao et al., 2011; Hart et al., 2012, 2013; Shaw et al., 2013; Rubia et al., 2014). ASD is characterised by most prominent abnormalities in fronto-temporo-limbic structures that mediate socio-emotional and affective processes (Di Martino et al., 2009; Minshew and Keller, 2010; Philip et al., 2012). Electrophysiological studies of attention, inhibition and face processing in comorbid ASD-ADHD boys have found combinations of the neurophysiological abnormalities that are observed in pure ADHD and pure ASD (Tye et al., 2013). However, to our knowledge, no functional magnetic resonance imaging (fMRI) study has compared the pure and comorbid disorders.

ADHD patients are particularly impaired in temporal discounting tasks where subjects have to choose between a smaller immediate reward and a larger reward that is given in a future time. Temporal discounting refers to the psychological phenomenon that rewards that are given in the future lose some of their subjective “reward value” relative to immediate rewards, a loss that is proportionate to the time a subject has to wait for the reward. Temporal discounting tasks therefore measure the degree to which a reward is discounted in relation to its temporal delay, i.e., the subjective value of the temporal delay in terms of reward. The task requires the inhibition of the immediate reward and temporal foresight in order to assess the larger future against the smaller immediate gain (Luhmann, 2009; Rubia et al., 2009; Kim and Lee, 2011; Noreika et al., 2013). The ability to wait for a larger reward, and therefore to employ good temporal foresight, is a key aspect of reward-related decision making and known to vary between individuals (Critchfield and Kollins, 2001; Odum, 2011) and to correlate with impulsiveness (Richards et al., 1999). Impulsive individuals find it more difficult to wait for a delayed reward and hence prefer smaller, immediate rewards over larger, delayed rewards (Kalenscher et al., 2006; Peters and Buechel, 2011). Thus, the impact of a delay on the subjective reward value is more pronounced in immature populations such as children and adolescents (Christakou et al., 2011) and in impulsiveness disorders such as ADHD (Scheres et al., 2008; Noreika et al., 2013), although there have also been negative findings (Scheres et al., 2006, 2010). Steeper temporal discounting, where delayed rewards have less subjective value, is thought to reflect an imbalance in the interplay between ventromedial prefrontal cortex (vmPFC) and lateral frontal systems that mediate the evaluation of future rewards and temporal foresight, respectively, and ventral striatal and limbic systems that respond to immediate rewards (Christakou et al., 2011; Peters and Buechel, 2011).

Abnormal activation in ventromedial frontal, limbic and ventral striatal regions has been reported in ADHD patients relative to controls during temporal discounting (Plichta et al., 2009; Rubia et al., 2009; Lemiere et al., 2012) and reward processing (Kohls et al., 2013). Reward-processing tasks in ASD individuals also elicit abnormal activation in ventromedial and frontolimbic brain regions compared with controls (Dichter et al., 2012; Kohls et al., 2013).

Ventromedial and frontolimbic brain regions are crucially involved in temporal discounting (Christakou et al., 2011; Peters and Buechel, 2011) and are abnormal in both ADHD (Plichta et al., 2009; Rubia et al., 2009; Lemiere et al., 2012; Plichta and Scheres, 2014) and ASD individuals during tasks of reward-related decision making (Dichter et al., 2012; Kohls et al., 2013). Despite this, no fMRI study has tested temporal discounting in ASD or compared this function between the two disorders. Only one neuropsychological study has compared temporal discounting performance between ADHD and ASD, and that study found discounting difficulties in the ADHD group, but not the ASD group, relative to controls (Demurie et al., 2012).

It has been debated whether the phenotypically similar behavioural and EF deficits in both disorders are secondary to ASD or a

phenocopy, which had prevented a co-diagnosis in the DSM-IV, or whether they reflect true comorbidity, reflected in the allowance for co-diagnosis in the DSM-V (<http://www.dsm5.org>). Functional imaging could help this debate by elucidating whether executive function deficits in both pure disorders are based on common (“true comorbidity”) or dissociated (“not true comorbidity”) underlying brain dysfunctions and whether the comorbid group is an additive combination of the neurofunctional deficits of both disorders (“true (additive) comorbidity”), more similar to ADHD or ASD (“phenocopy” of either disorder), or a different neurobiological disorder altogether.

To our knowledge, no fMRI study has directly compared the comorbid and the two pure disorders. Only one task-based fMRI study, from our group, has compared pure ADHD and pure ASD patients during a sustained attention task, finding shared frontostriatal dysfunctions with more severe left frontal deficits in ADHD and disorder-specific increased cerebellar activation in ASD (Christakou et al., 2013). However, no comorbid group was included in the study to elucidate whether the comorbidity reflects an additive or distinctive pathophysiology.

The aim of this study was therefore to compare the brain function of age- and IQ-matched boys with non-comorbid ADHD, non-comorbid ASD, and comorbid ADHD and ASD, and healthy controls, while they performed an fMRI temporal discounting task (Rubia et al., 2009; Christakou et al., 2011). We selected the temporal discounting task over other reward-processing tasks, as temporal discounting is a key neuropsychological deficit in ADHD (Rubia et al., 2009; Noreika et al., 2013) and mediated by lateral orbitofrontal and ventromedial fronto-limbic structures that are affected by both ADHD (Plichta et al., 2009; Rubia et al., 2009; Lemiere et al., 2012; Plichta and Scheres, 2014) and ASD individuals during tasks of reward-related decision making (Dichter et al., 2012; Kohls et al., 2013). Given that the key interests of the task are the neural correlates of reward-associated decision making and temporal discounting, which is reflected in the choice of the larger, but delayed reward, we were particularly interested in the group differences in brain correlates underlying the choice of the delayed reward conditions.

We hypothesised that all patient groups relative to controls would be impaired in temporal discounting and their underlying neurofunctional correlates of ventromedial prefrontal and ventral striatal systems, with the most severe impairments in the comorbid group.

2. Methods

2.1. Participants

Participants comprised 64 right-handed (Oldfield, 1971) boys (18 control boys, 18 boys with ADHD but no ASD, 15 boys with ASD and no ADHD and 13 boys with comorbid ASD and ADHD), aged 11–17 years, IQ ≥ 70 (Table 1). ADHD boys met criteria for DSM-IV diagnosis of inattentive/hyperactive-impulsive combined-type ADHD and had to score above clinical thresholds of a raw score of 7 or above for ADHD symptoms on the Strength and Difficulty Questionnaire (SDQ) (Goodman and Scott, 1999), and a T-score of 65 or above on the Conners' Parent Rating Scale-Revised (CPRS-R) (Conners et al., 1998). They also scored below clinical threshold for ASD on the Social Communication Questionnaire (SCQ). ASD diagnosis was made using ICD-10 research diagnostic criteria (World Health Organisation, 1994), and confirmed by the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000). ASD subjects scored above the clinical cut-off for Autism Spectrum Disorders on the SCQ. All ASD participants underwent a structured physical and medical examination to exclude comorbid medical disorders and biochemical, haematological or chromosomal abnormalities associated with ASD. ADHD symptoms were then controlled for in this ASD group to create a pure ASD sub-group and a comorbid ADHD-ASD subgroup. Individuals with pure ASD scored below clinical threshold on either the CPRS-R or the hyperactive/inattentive subscale of the SDQ. Comorbid ASD and ADHD participants scored 65 or above on the CPRS-R and seven or above on the hyperactive/inattentive subscale of the SDQ but had no other comorbid conditions. Patients were recruited through clinical services of the South London and Maudsley

Table 1

Sample characteristics for healthy control boys and patients with ADHD, ASD and comorbid ADHD and ASD.

Variables	Controls (18) Mean (S.D.)	ADHD (18) Mean (S.D.)	ASD (15) Mean (S.D.)	Comorbid (13) Mean (S.D.)
Age (months)	183.3 (21.5)	171.7 (24.7)	177.1 (23.2)	168.8 (17.0)
IQ	120 (12.2)	110.0 (10.7)	112 (12.9)	110.8 (16.7)
Handedness	88.8 (14.1)	92.2 (8.8)	93.7 (9.2)	92.8 (9.5)
SDQ hyperactive-impulsive/inattentive subscale	2.1 (1.8)	8.2 (1.3)	4.5 (1.4)	8.5 (1.3)
SDQ – emotional distress Subscale	0.4 (0.6)	4.1 (3.3)	4.3 (2.7)	4.1 (2.8)
SDQ – conduct subscale	0.7 (1.1)	4.8 (2.3)	1.7 (1.8)	4.3 (2.6)
SDQ – peer relations subscale	1.1 (1.4)	3.8 (2.8)	5.4 (2.3)	7.4 (1.9)
SDQ – prosocial behaviour subscale	9.1 (1.2)	5.8 (2.6)	4.7 (2.7)	4.1 (2)
SDQ – total scores	4.2 (3.2)	20.8 (6.5)	15.9 (5)	24.5 (5.6)
SCQ total	2 (1.9)	11.0 (7.5)	25.7 (4.7)	25.5 (5.7)
CPRS-R total T-score	43 (17)	79 (9)	66 (10)	83 (6)
ADOS communication scores	–	–	3.9 (1)	3.8 (1)
ADOS social interaction scores	–	–	9.5 (2)	9.5 (2)
ADOS communication and social scores	–	–	13.3 (3)	13.3 (2)
ADOS stereotyped behaviour scores	–	–	1.7 (2)	1.4 (1)
ADI communication scores	–	–	17 (5)	16 (3)
ADI social interaction scores	–	–	22 (5)	18 (4)
ADI stereotyped behaviour scores	–	–	6 (2)	7 (2)

SDQ: Strength and Difficulties Questionnaire; SCQ: Social Communication Questionnaire; CPRS-R: Conners' Parent Rating Scale-Revised; ADOS: Autism Diagnostic Observation Schedule; and ADI: Autism Diagnostic Interview.

Trust (Table 1). All ASD boys were medication-naïve. Nine ADHD boys (50%) and one comorbid boy (8%) were medicated with psychostimulants, but they were taken off medication for 48 h before the scan. Patients had no comorbidities with other major psychiatric disorders.

Eighteen healthy control boys who were IQ-, handedness-, and age-matched to all other groups were recruited locally by advertisement and scored below clinical thresholds on the SDQ, SCQ, and CPRS (Table 1).

Exclusion criteria for all were neurological disorders, and drug/alcohol dependency. Intellectual ability was measured using the Wechsler Abbreviated Scale of Intelligence-Revised (WASI-R) short form (Wechsler, 1999).

The study was conducted in accordance with the latest version of the Declaration of Helsinki. Ethical approval was obtained from the local Research Ethics Committee. Study details were explained in both written and oral form, and written informed consent and assent was obtained for all participants.

2.2. Temporal discounting fMRI task

In the 12-min task, subjects choose by pressing a left (right index finger) or right button (right middle finger) between a smaller amount of money (between £0 and £100) available immediately, or a larger amount (always £100) available after 1 week, 1 month or 1 year; delay choices are randomly displayed (20 trials for each delay) to the right and left side of the screen for 4 s, followed by a blank screen of at least 8 s (inter-trial-interval: 12 s). The immediate reward is adjusted in an algorithm based on previous choices, which is calculated separately for each of the three different delays, in order to narrow the range of values converging into an indifference value that is considered by the subject as equivalent to the delayed reward for that delay (Richards et al., 1999; Rubia et al., 2009; Christakou et al., 2011). The algorithm ensures equal numbers of immediate and delayed reward choices.

To estimate the steepness of temporal discounting for each participant, we first calculated the indifference value between the immediate amount or the delayed £100 for each delay interval (day, month, or year), calculated as the midpoint value between the lowest immediate reward selected by the subject and the next lowest immediate reward available (i.e., the value of immediate reward offered at which the subject began consistently to select the standard £100 delayed reward) (Richards et al., 1999). The indifference value is equivalent to the individual's subjective value of £100 when it is available after each delay. Reward is typically discounted in a hyperbolic function that depends on amount, delay and a free impulsiveness indicator "k", the main dependent task variable, which is calculated by fitting a hyperbolic function to the indifference values for every delay, i.e., $V=A/(1+kD)$, where V is the subjective value of a reward of amount A, D is the delay, and k is a constant characterising the individual's discounting rate (Richards et al., 1999). Larger k-values are associated with steeper reward devaluation with increasing delay (Richards et al., 1999).

2.3. Analysis of performance data

An analysis of variance (ANOVA) was conducted with group as independent measure and k as dependent measures to test for group differences in performance.

2.4. fMRI image acquisition

The fMRI images were acquired at the King's College London's Centre for Neuroimaging Sciences, on a 3T General Electric Signa HDx TwinSpeed (Milwaukee, WI, USA) MRI scanner using a quadrature birdcage headcoil. In each of 22 non-contiguous planes parallel to the anterior–posterior commissure, 480 T2*-weighted MR images depicting BOLD (blood oxygen level dependent) contrast covering the whole brain were acquired with echo time (TE)=30 ms, repetition time (TR)=1.5 s, flip angle=60°, in-plane voxel size=3.75 mm, slice thickness=5.0 mm, slice skip=0.5 mm). A whole-brain high resolution structural scan (inversion recovery gradient echo planar image) used for standard space normalisation was also acquired in the inter-commissural plane with TE=40 ms, TR=3 s, flip angle=90°, number of slices: 43, slice thickness=3.0 mm, slice skip=0.3 mm, in-plane voxel size=1.875 mm, providing complete brain coverage.

2.5. fMRI image analysis

Event-related activation data were acquired in randomized trial presentation, and analysed using non-parametric analysis software developed at the Institute of Psychiatry, King's College London (XBAM) (Brammer et al., 1997; Bullmore et al., 1999). Data were first processed (Bullmore et al., 1999) to minimize motion-related artifacts. A 3D volume consisting of the average intensity at each voxel over the whole experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the x, y and z axes) and translations (in x, y and z) that maximised the correlation between the image intensities of the volume in question and the template. Following realignment, data were then smoothed using a Gaussian filter (full width at half-maximum (FWHM) 2.354 * in-plane fMRI voxel size mm) to improve the signal-to-noise characteristics of the images (Bullmore et al., 1999). Then, time series analysis for each individual subject was conducted based on a previously published wavelet-based resampling method for functional MRI data (Bullmore et al., 1999, 2001). The individual maps were then registered into Talairach standard space using a two-step process (Talairach and Tournoux, 1988).

Given that the key focus of the analysis was to understand the neural underpinnings of temporal discounting underlying delayed choices, we conducted linear brain-behaviour correlational analyses between the steepness of temporal discounting in the variable k and brain activation during the delayed choices – resting baseline. For this purpose, the Kendall non-parametric correlation coefficient was first computed at each voxel in standard space between the impulsiveness measure k and signal change in each group during the delayed choice condition. The correlation coefficients were recalculated after randomly permuting the subjects' k (but not the fMRI data). Repeating the second step many times (1000 times per voxel) gives the distribution of correlation coefficients under the null hypothesis that there is no association between k and specific BOLD effects. This null distribution can then be used to assess the probability of any particular correlation coefficient under the null hypothesis. The critical value of the correlation coefficient at any desired type I error level in the original (non-permuted) data can be determined by reference to this distribution. Statistical analysis was extended to the 3D cluster level as described before (Bullmore et al., 1999). The

cluster probability under the null hypothesis was chosen to set the level of expected type I error clusters to less than 1 error cluster per whole brain. In this analysis less than one error cluster was observed at a p -value of $p < 0.05$ at the voxel level and of $p < 0.01$ at the cluster level.

This led to the production of a specific brain-behaviour activation map (BBAM) for each group.

3. Results

3.1. Subject characteristics

Univariate ANOVAs showed no group differences for age ($F=1.3$; $d.f.=3, 63$; $p < 0.3$), IQ ($F=2.1$; $d.f.=3, 63$; $p < 0.11$), or handedness ($F=0.7$; $d.f.=3, 63$; $p < n.s.$).

As expected, multivariate ANOVAs showed significant group effects for all clinical measures (Table 1). As expected, groups significantly differed in measures of the SDQ ($F=7.7$; $d.f.=3, 63$; $p < 0.0001$), with post hoc testing (corrected for multiple testing using least significance difference (LSD)) showing that all patient groups scored higher than controls ($p < 0.05$) with the exception of conduct problems, which were not impaired in ASD participants relative to controls. Both the ADHD and the comorbid groups scored significantly higher on the SDQ conduct and hyperactive-impulsive/inattentive scores than ASD patients ($p < 0.05$). All groups differed significantly between each other in peer relationships, which was significantly lower in the comorbid group compared with the other three groups ($p < 0.05$), followed by ASD compared with ADHD ($p < 0.04$). In the prosocial scale, the comorbid group scored lower than the ADHD group ($p < 0.03$) and the ASD group scored at a trend-level lower than the ADHD group ($p < 0.1$). In the CPRS, significant group differences were observed ($F=43$; $d.f.=3, 63$; $p < 0.0001$), due to all patients scoring higher than controls ($p < 0.0001$) and the ADHD group scoring higher than controls and the ASD group ($p < 0.01$) but not the comorbid group ($p < 0.3$) and the comorbid group scoring higher than the ASD group ($p < 0.0001$).

3.2. Performance

ANOVA showed a trend toward a significant group effect for the temporal discounting variable k ($F=2$; $d.f.=3, 63$; $p < 0.1$) (mean k (SD): controls: 0.02 (0.01); ADHD: 0.04 (0.03); ASD: 0.07 (0.08); comorbid: 0.06 (0.1)). Post hoc t -tests (LSD corrected for multiple comparison) showed that the ASD group had a significantly larger mean k -value compared with controls ($p < 0.02$) and the comorbid group had a trend-level higher k -value compared with controls ($p=0.07$) (effect size=0.5), indicating that the ASD and comorbid groups discounted rewards more steeply than controls as a function of delay (Fig. 1). The analysis was repeated using the area under the curve (AUC). The trend finding remained similar for AUC ($F=2$; $d.f.=3, 63$; $p < 0.1$). Post hoc analyses (LSD corrected for multiple comparisons) showed that the ASD group had a significantly smaller AUC than the controls ($p < 0.03$), while none of the other groups differed from controls.

3.3. Movement

Multivariate ANOVA (MANOVA) or multiple ANOVAs showed no significant group differences in mean, median or maximum rotation and translation movement parameters in the three-dimensional Euclidean space ($F=0.8$; $d.f.=3, 63$; $p=n.s.$).

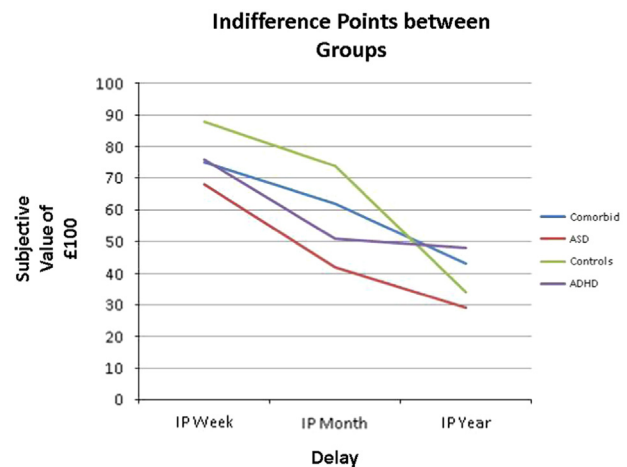


Fig. 1. Graph showing the subjective indifference value for the delayed value of £100 for each delay for each group. ADHD=Attention Deficit Hyperactivity Disorder; ASD=Autism Spectrum Disorder; comorbid: group with both ADHD and ASD. The subjective value of £100 decreases as a function of delay, more steeply in ASD and at a trend-level in the comorbid group relative to controls.

3.4. Correlation between delay discounting and brain activation during delayed choices within each group

In controls, decreased temporal discounting (as expressed by k) was associated with activation during delayed choices in left vmPFC/ACC/ventral striatum, right superior frontal cortex, supplementary motor area (SMA), left anterior cingulate cortex (ACC)/caudate, bilateral pre- and postcentral gyri, bilateral superior temporal lobe/insula reaching into left inferior frontal lobe, left midbrain and right superior cerebellar hemisphere (Table 2(A), Fig. 2A).

In the ADHD group, decreased k was associated with activation during delayed choices in right inferior frontal (IFC)/premotor cortex, bilateral occipital and inferior cerebellar areas (Table 2(B), Fig. 2B).

In the ASD group, decreased k was associated with activation during delayed choices in left inferior parietal lobe reaching into pre- and post-central gyri and in right superior cerebellum (Table 2(C), Fig. 2C).

In the comorbid group, decreased k was associated with activation during delayed choices in right middle temporal and occipital lobes (Table 2(D), Fig. 2D).

3.5. Group differences in brain-behaviour correlations

Given that the main focus of this study was to understand the differential activation between groups in neural response associated with better (less steep) temporal discounting, we selected brain areas that were correlated with lower k in any of the four groups. For this purpose, a conjunction analysis was conducted of all brain regions that were correlated with k across any of the four groups during delayed choices. This resulted in 14 brain regions: left vmPFC/ACC/ventral striatum, right superior frontal cortex, right IFC, SMA, left ACC/caudate, bilateral pre- and post-central gyri, bilateral superior temporal lobe, left midbrain, left inferior parietal lobe, right superior and left inferior cerebellum and bilateral occipital lobe (Fig. 3, Table 3). All resulting areas were used as regions of interest (ROIs) and the BOLD responses were extracted in each of these regions for each study participant. T -tests were then conducted to test for differences in brain-behaviour correlations in each cluster between the different groups using Bonferroni correction for multiple comparisons (14 regions by six tests=0.05/84; $p < 0.00059$) (Fig. 3, Table 3).

Table 2

Brain activation clusters that correlated negatively with temporal discounting in each of the 4 groups.

Brain regions of activation	Brodmann area (BA)	Talairach coordinates (x;y;z)	Voxels	Cluster p-value
A. CONTROLS				
L ventromedial OFC/ACC/ventral striatum	11/32/25	−4;26;−18	12	0.00005
R superior frontal cortex	10	25;52;−18	27	0.00005
Supplementary Motor Area (SMA)	6	4;4;53	37	0.00005
R pre/postcentral	4/3/2/1	51;−11;53	59	0.00005
L pre/postcentral	4/3/2/1	−29;−7;48	59	0.00005
Superior temporal/insula	42	47;−19;9	49	0.001
ACC/caudate	24/32/6	−7;19;26	75	0.004
L superior temporal/insula	42	−40;−7;9	13	0.005
L superior temporal/inferior frontal	21/45	−58;7;−18	68	0.00005
L midbrain		−11;−22;−35	19	0.00005
R superior cerebellum (hemisphere)		22;−37;−29	14	0.00005
B. ADHD				
R inferior frontal/premotor cortex	44/6	61;7;15	51	0.00005
L lingual gyrus	18/19	−11;−70;−7	39	0.00005
L inferior cerebellum (hemisphere)		−58;−67;−29	15	0.00005
R inferior cerebellum/occipital	19/18	43;−56;−35	227	0.00005
C. ASD				
L inferior parietal/postcentral/precentral	40/2/1/3/4/6	−43;−15;42	155	0.00005
R superior cerebellum (hemisphere)	20/37	33;−30;−29	20	0.00005
D. Comorbid ADHD and ASD				
R middle temporal lobe	20	29;−7;−40	10	0.00005
R occipital	19	33;−74;9	18	0.00005

Note: ACC=anterior cingulate cortex and OFC=orbitofrontal cortex.

Brain-behaviour correlation analyses were conducted at voxel-wise $p < 0.05$ and cluster-wise $p < 0.01$.

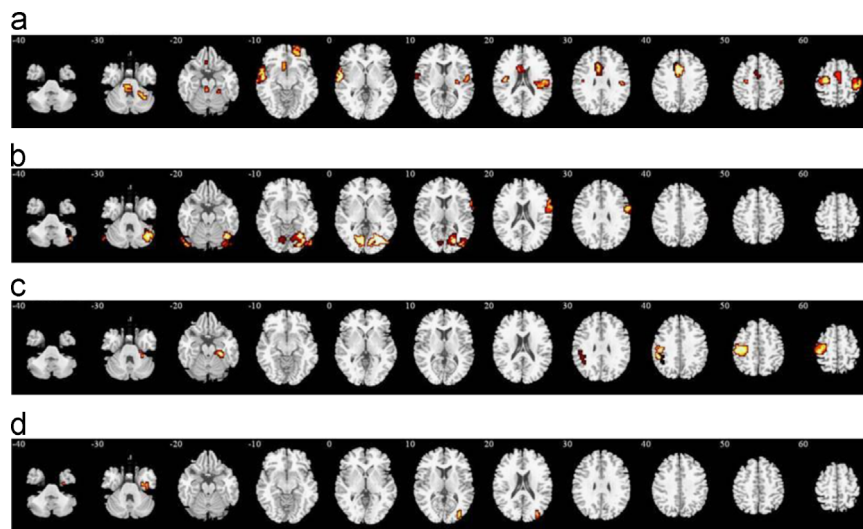


Fig. 2. Horizontal slices showing brain regions that correlated with temporal discounting during delayed choices for each group. (A) Healthy controls, (B) ADHD, (C) ASD and (D) Comorbid ADHD and ASD. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

3.6. Shared abnormalities in brain-discounting associations relative to controls

In SMA, pre- and post-central gyri and midbrain, controls had significantly stronger brain-discounting relationships than all the patient groups, who did not differ from each other (Table 3A).

3.7. Disorder-specific abnormalities in brain-discounting associations

The comorbid group had significantly weaker brain-behaviour associations than all other groups in the vmPFC extending into the

ACC and ventral striatum. In a dorsal ACC/caudate cluster, they differed from all groups except the ASD group.

In right superior frontal cortex and left superior temporal lobe/IFC, the comorbid group showed significantly weaker brain-behaviour associations than the other two groups, who, however, shared weaker associations in these regions relative to controls.

The ADHD and comorbid groups showed weaker brain-behaviour associations in the right lateral superior cerebellum relative to controls, while ASD participants and controls did not differ from each other.

The ASD boys showed weaker brain-behaviour associations than all other groups in right superior temporal lobe/insula, which

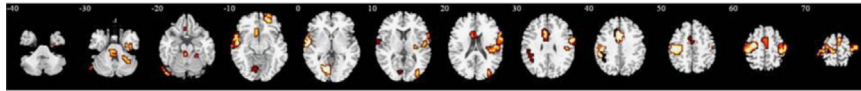


Fig. 3. Conjunction analysis. Axial slices show brain areas that correlated with temporal discounting during delayed choices in any of the 4 groups. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

Table 3

Significant group differences in the correlations between brain activation and the temporal discounting variable k in the 14 regions of interest.

Correlation between brain activation and k	Brain regions of activation	Brodmann area (BA)	Talairach coordinates (x;y;z)	Voxels	Cluster p -value
A. Shared differences in brain-discounting associations relative to controls					
C > ADHD, ASD, CM	R SMA	6	7; -15; 53	37	0.00001
C > ADHD, ASD, CM	R pre/postcentral	4/3/2/1	51; -15; 42	59	0.00001
C > ADHD, ASD, CM	R midbrain		4; -33; -35	19	0.00001
B. Disorder-specific differences in brain-discounting associations					
C, ADHD, ASD > CM	Ventromedial OFC/ACC/ventral striatum	11/32/25	-4; 30; -24	12	0.00001
C > ADHD, ASD > CM	R superior frontal cortex	10	29; 48; -18	27	0.00001
C, ADHD > CM	R and L ACC/caudate	24/32/6	-7; 15; 9	71	0.00001
C > ADHD; ASD > CM	L superior temporal/inferior frontal	21/45	-65; -11; -18	68	0.00001
C > ADHD, CM	R superior cerebellum (hemisphere)		36; -52; -35	14	0.00001
ADHD > C, CM > ASD	R inferior frontal/premotor cortex	44/6	65; 4; 4	51	0.00001
C > ADHD, CM > ASD	R superior temporal/insula/putamen	42	33; -15; 4	49	0.00001
C. Alternative brain-discounting associations in patients					
CM > ADHD, ASD > C	R occipital	19	36; -78; -2	18	0.00001
ASD > C, ADHD, CM	L inferior parietal/postcentral/precentral	40/2/1/3/4/6	-36; -48; 26	194	0.00001
ADHD > C, ASD, CM	L lingual	18/19	-7; -74; -13	39	0.00001
ADHD > C	L inferior cerebellum		-58; -67; -35	15	0.00001

Note: SMA, supplementary motor area; OFC, orbitofrontal cortex; and ACC, anterior cingulate cortex.

was, however, also weaker in ADHD and comorbid patients relative to controls (Table 3B).

3.8. Stronger brain-discounting associations

The ADHD group had significantly stronger brain-behaviour correlations in right IFC and lingual gyrus relative to all other groups and in left inferior cerebellum relative to controls but not the other patient groups. The ASD group had a significantly stronger brain-behaviour correlation in left inferior parietal lobe than all other groups. The comorbid group had the strongest brain-behaviour correlation in the occipital lobe relative to all other groups, which also applied to both pure patient groups relative to controls (Table 3C).

4. Discussion

We investigated differences in temporal discounting and the underlying brain-behaviour correlations between healthy controls and patients with ADHD, ASD and comorbid conditions. We found that only the ASD group showed significantly steeper (worse) discounting relative to controls, followed by a trend toward significantly steeper discounting in the comorbid group. The fMRI analysis showed shared as well as disorder-specific abnormalities in the three patient groups in their brain-behaviour associations. As expected, the comorbid group had the most pronounced abnormalities in their brain-behaviour associations in key regions of temporal discounting, including the vmPFC, ACC, and caudate as well as the superior frontal and temporal cortices relative to the other two groups. The ASD group had the weakest brain-behaviour association in the right IFC, superior temporal lobe, and insula relative to all other groups. The ADHD patients shared weak brain-behaviour associations in the right cerebellum with the comorbid group and in the right superior frontal and left inferior frontal and superior temporal cortices with ASD. The findings of both qualitatively (disorder-specific) and quantitatively (shared but more

severe) more deviant brain-behaviour association in the comorbid group relative to healthy controls and the other two pure patient groups suggests that comorbid ADHD and ASD is characterised by a different underlying neurofunctional pathology than the two pure disorders and is not simply a phenocopy or an additive combined pathology of the two pure disorders.

4.1. Performance differences

The finding of no impairments in temporal discounting in ADHD patients is not in line with previous evidence for temporal discounting deficits in ADHD (Scheres et al., 2008; Noreika et al., 2013), but with negative findings from other studies (Scheres et al., 2006, 2010), in particular in task versions with variable rather than fixed delays (Scheres et al., 2006) and with hypothetical versus real rewards (Scheres et al., 2010). As our study used hypothetical rewards, this may have accounted for the negative findings. Also, our sample was older than the younger paediatric samples tested in neuropsychological studies, and not all prior studies have carefully excluded ASD symptoms in ADHD. The findings of performance deficits only in the ASD and (at a trend level) in the comorbid groups parallel disorder-specific deficit findings in the related function of planning in ASD relative to ADHD (Geurts et al., 2004). The trend-level significance for steeper discounting in the comorbid group was likely underpowered as shown in an effect size of 0.5 and may have reached significance with larger numbers. This may also apply to the findings in ADHD boys who had non-significantly, but nominally higher k -values than controls. While subject numbers of 15–20 are sufficiently powered for fMRI analyses (Thirion et al., 2007), they are underpowered for performance effects, and negative findings need to be interpreted with caution.

4.2. fMRI results

In fMRI analyses, the comorbid group exhibited the weakest brain-behaviour correlations relative to all other groups in key

regions of temporal discounting, in vmPFC, ACC, ventral striatum, right superior frontal cortex and left IFC/superior temporal lobe (Christakou et al., 2011; Peters and Buechel, 2011). This suggests that the comorbid group is the group with the most pronounced brain function abnormalities. The vmPFC mediates the assessment of the subjective reward value (Peters and Buechel, 2011), while the ACC and SMA are vital for decision making and cognitive control, exerted during delayed gratification (Bush et al., 2002; Cardinal, 2006; Peters and Buechel, 2011). The lateral prefrontal cortex, caudate and insula have a crucial role in timing, in particular temporal foresight and future reward prediction (Cardinal, 2006; Wittmann et al., 2007; Christakou et al., 2011; Peters and Buechel, 2011). Furthermore, in particular, the vmPFC and lateral/inferior PFC are progressively more recruited in association with progressively reduced steepness of discounting during development from childhood to adulthood. This suggests that the comorbid group had the most immature brain-behaviour correlation (Christakou et al., 2011), possibly reflecting a delay in functional development.

The findings of both disorder-specific brain-behaviour abnormalities (vmPFC/ACC/ventral striatum) as well as shared but quantitatively more severe abnormalities (inferior and superior frontal and temporal lobes) in the comorbid group relative to the other groups in key discounting areas suggest that this group has a different underlying pathophysiology compared with that of either of the two non-comorbid patient groups, suggesting it is neither a phenocopy of either disorder nor an additive pathology but a different neurofunctional pathology altogether.

Although the pure ASD group showed the steepest temporal discounting, they showed relatively little disorder-specific brain-behaviour deviance compared with the other groups. ASD patients exhibited the weakest brain-behaviour association in the right superior temporal lobe/insula and IFC compared with all other groups, but shared deficits in left IFC and superior temporal lobe with ADHD. The insula plays an integral part in temporal coding and selection of rewards (Cardinal, 2006; Wittmann et al., 2007; Christakou et al., 2011), while the IFC mediates temporal foresight (Wittmann et al., 2007; Christakou et al., 2011). The significantly weaker brain-discounting correlation in ASD compared with the other groups in these two brain regions that mediate temporal foresight could suggest that problems with forward planning underlie poor temporal discounting in ASD, which would be in line with consistent evidence for planning deficits in ASD relative to controls (Hill, 2004) and ADHD patients (Geurts et al., 2004).

The ADHD group had no disorder-specific but only shared abnormalities in the SMA and the pre- and post-central gyri with all other patient groups, in right superior cerebellum with the comorbid group and in left IFC/superior temporal lobe with the ASD group. Furthermore, ADHD patients showed stronger brain-behaviour correlations compared with all other groups in the right IFC and left posterior cerebellum, both important regions for temporal foresight (Wittmann et al., 2007; Christakou et al., 2011), which may have been a compensation for reduced correlation with frontal decision-making areas in the SMA (Bush et al., 2002; Cardinal, 2006; Peters and Buechel, 2011) and with the left IFC and right superior cerebellum, important timing regions (Wittmann et al., 2007; Christakou et al., 2011). This compensation may have protected the ADHD group from poor task performance. Abnormalities in the SMA have consistently been observed in ADHD patients during tasks of cognitive control (Hart et al., 2013) and in the left IFC and right superior cerebellum during timing tasks (Hart et al., 2012). A compensatory over-activation of the left posterior cerebellum in combination with frontal deficits has previously been observed in ADHD during attention functions (Rubia et al., 2009; Cubillo et al., 2012; Hart et al., 2013). The spared performance and relatively minor brain-behaviour differences between ADHD and controls suggest that, while ADHD

patients share deficits with the other groups in some areas that are important for timing and decision making (left IFC and SMA), they are more similar to controls in their underlying neurofunctional substrates of temporal discounting than the comorbid ADHD/ASD and the ASD groups.

A limitation is the relatively small subject numbers, in particular of the comorbid group. Also, only males were investigated to increase homogeneity, but limiting generalisability of findings. A strength of the study is the robust diagnostic characterisation of IQ-matched, non-comorbid patient groups and the medication-naïveté of all ASD patients and the majority of ADHD patients, given long-term effects of psychotropic medication on brain structure and function (Nakao et al., 2011). However, a limitation is that the diagnosis of ADHD was not confirmed by a semi-structured assessment and the comorbidity between ADHD and ASD was not confirmed by clinical interview.

In conclusion, to our knowledge, this is the first comparative fMRI study between patients with ADHD, ASD and comorbid ADHD and ASD. We demonstrate that during temporal discounting, ADHD, ASD and the comorbid conditions are associated with both shared and disorder-specific abnormalities in their brain-behaviour associations, with the comorbid group showing the most pronounced differences in their brain-behaviour associations relative to controls and relative to the “pure” disorders, suggesting they are neither a phenocopy of the two pure disorders nor an additive pathology but a different neuro-functional pathology altogether.

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