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ORIGINAL CONTRIBUTION

The NeuroIMAGE study: a prospective phenotypic, cognitive, genetic and MRI study in children with attention-deficit/hyperactivity disorder. Design and descriptives

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Abstract Attention-deficit/hyperactivity disorder (ADHD) is a persistent neuropsychiatric disorder which is associated with impairments on a variety of cognitive measures and abnormalities in structural and functional brain measures. Genetic factors are thought to play an important role in the etiology of ADHD. The NeuroIMAGE study is a follow-up of the Dutch part of the International Multicenter ADHD Genetics (IMAGE) project. It is a multi-site prospective cohort study designed to investigate the course of ADHD, its genetic and environmental determinants, its cognitive and neurobiological underpinnings, and its consequences in adolescence and adulthood. From the original 365 ADHD families and 148 control (CON) IMAGE families, consisting of 506 participants with an ADHD diagnosis, 350 unaffected siblings, and 283 healthy controls, 79 % participated in the NeuroIMAGE follow-up study. Combined with newly recruited participants the NeuroIMAGE study comprehends an assessment of 1,069 children (751 from ADHD families; 318 from CON families) and 848 parents (582 from ADHD families; 266 from CON families). For most families, data for more than one child (82 %) and both parents (82 %) were available. Collected data include a diagnostic interview, behavioural questionnaires, cognitive measures, structural and functional neuroimaging, and genome-wide genetic information. The NeuroIMAGE dataset allows examining the course of ADHD over adolescence into young adulthood, identifying phenotypic, cognitive, and neural mechanisms associated with the persistence versus remission of ADHD, and studying their genetic and environmental underpinnings. The inclusion of siblings of ADHD probands and controls allows modelling of shared familial influences on the ADHD phenotype.

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neuropsychiatric disorder affecting about 5 % of children and 3–4 % of adults [1, 2]. Its main characteristics are a pervasive pattern of inattention and/or hyperactive-impulsive behaviours that occur early in life and lead to impaired social functioning and educational and occupational achievements [3]. ADHD persists into adulthood in 15–60 % of cases, depending on the definition of remission [4]. Adoption and twin studies have indicated substantial involvement of genetics in the causation of ADHD, with additive heritability estimated around 0.70–0.80 [5]. ADHD is a complex disorder, in which different combinations of genetic and environmental factors contribute to the overall risk of developing the disorder [6]. The genetic model underlying most cases of ADHD is likely one in which multiple genetic factors of small to moderate effect size contribute to disease etiology. In a small number of cases, rare genetic variants with moderate to strong effect size have been identified [7, 8].

Much research has focused on cognitive and neural mechanisms underlying ADHD. One of the most consistent findings in cognitive ADHD research refers to deficient top-down executive functions such as response inhibition deficits [9]. Other cognitive domains involved include reward processing [10] and temporal processing/response variability [11]. ADHD is also associated with various changes in brain structure and function. Structural changes of grey matter consist of a reduction of total brain volume in ADHD, with greatest reductions in frontal regions, the basal ganglia (caudate nucleus), cerebellum, and corpus callosum [12–14]. Changes of white matter, as measured with diffusion tensor imaging (DTI), have most consistently reported alterations in the corona radiata, corpus callosum, internal capsule, and cerebellum [15]. Most functional imaging studies on ADHD have reported changes in fronto-striatal brain circuits, but changes in sensorimotor circuits and the default network have also been documented [16]. Converging evidence suggests that some of these abnormalities normalize due to stimulant medication use [17].

Although various genetic, cognitive, and neural factors have been associated with ADHD, most evidence about these factors and their interplay is inconsistent [18–21]. This may be explained by (1) the substantial clinical and etiological heterogeneity of ADHD; and (2) methodological differences in study design (i.e. instructions, task parameters) and analysis methodologies (e.g. outcome measures in brain imaging data analysis). Large sample sizes could resolve inconsistent findings and segment ADHD into more homogenous subgroups, which may allow dissection of the cognitive, neural, and genetic mechanisms involved in subtypes of ADHD.

Accordingly, several large-scale ADHD projects at the national and international level have been initiated, e.g. the International Multicentre persistent ADHD Genetics CollaboraTion (IMpACT; http://impactadhdgenomics.com/nl/) and ADHD-200 (http://fcon_1000.projects.nitrc.org/indi/adhd200/index.html). One of the first international programs on ADHD is the International Multicenter ADHD Genetics (IMAGE) project that has been designed to identify molecular-genetic factors involved in ADHD [22, 23]. The IMAGE project collected DNA and detailed information on the phenotype of ADHD and relevant comorbidities as well as site-specific cognitive performance of 5,758 subjects from 1,401 ADHD families in eight countries in Europe and Israel between 2003 and 2007. This effort has led to candidate-gene studies [22, 24], linkage [25–27] and genome-wide association analyses [28–30], meta-analyses [31, 32] and several cognitive studies [33–35]. Beyond these efforts the Dutch site of the IMAGE project also collected cognitive measures on unaffected siblings of ADHD probands and of control children that allowed analysing whether dysfunctions in such measures are familial and would qualify as an endophenotype of ADHD. The concept of endophenotype refers to quantitative and objective measures of (psychiatric) disorders that represent heritable vulnerability traits and are intermediate on the pathway from genotype to phenotype [36, 37]. Moreover, because of their assumed heritability, a valid endophenotype should be found at a higher rate in unaffected family members than in the general population [36].

Probands, siblings and healthy control subjects of the Dutch, German and Belgian sites of IMAGE were re-invited to participate in an intermediate follow-up study, focusing on substance-related disorders [38] as well as medication treatment [39]. Approximately 6 years after original study entry at the Dutch site, an additional follow-up has been initiated, the NeuroIMAGE project (http://www.neuroimage.nl/), which is described in the current paper. NeuroIMAGE comprised re-evaluation of the ADHD phenotype and relevant comorbidities, repeated cognitive assessment and acquisition of functional and structural magnetic resonance imaging (MRI) of the brain, as well as phenotypic and cognitive assessments of the parents of affected and healthy participants. Together with all previous measures, the NeuroIMAGE study incorporates longitudinal cognitive and phenotypic data, information about genotype, neural structure and function,

medication history as well as phenotypic family data for probands with childhood ADHD and normal developing children. As a result, the study is an invaluable resource for the examination of the course and consequences of ADHD from childhood over adolescence into adulthood, for the identification of cognitive and neural mechanisms associated with persistence versus remission of ADHD, and for the study of genetic and environmental factors involved. Assessing the phenotype and cognitive performance of parents can enrich our understanding of the risk of ADHD transmission through genes and the familial environment.

Methods

The cohort

Original IMAGE cohort (2003–2006)

Participants for NeuroIMAGE were selected from the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study, conducted between 2003 and 2006 (as described previously [23, 40–42]). In the Dutch part of IMAGE 365, families with at least one child with combined subtype ADHD and at least one biological sibling (regardless of ADHD diagnosis) were recruited, in addition to 148 control families with at least one child, with no formal or suspected ADHD diagnosis in any of the first-degree family members.

Intermediate follow-up (2008–2009)

Here, the intermediate follow-up will be described in short (for a full description of the intermediate recruitment procedures see [38]). During the intermediate follow-up (2008–2009), probands, siblings and healthy control subjects and parents of the Dutch, German and Belgium sites of IMAGE were re-invited to participate on average 4.4 years (SD = 0.71) after original study entry. The complete cohort of the intermediate follow-up comprised 415 ADHD families (1,001 children and 727 parents) and 141 control families (119 children and 253 parents). This resulted in a retention rate of 86.9 % of original families during the intermediate follow-up.

NeuroIMAGE (2009–2012)

For NeuroIMAGE, all family members, including those who did not participate in IMAGE, were invited for follow-up measurement and (re)assessed between 2009 and 2012. The follow-up was conducted at two test sites: the VU University Amsterdam/VU University Medical Centre in Amsterdam and the Radboud University Medical Centre in Nijmegen. The time between the IMAGE and NeuroIMAGE measurements ranged between 3.5 and 8.9 years with a significant longer interval between measurements for ADHD families [overall: 5.9 years (SD = 0.74); ADHD: 6.1 years (SD = 0.6); controls: 5.4 years (SD = 0.7); $F(1, 401) = 106$; $p < 0.001$]. Additionally, children with ADHD (foremost girls) and healthy control boys were newly recruited to balance the distribution of gender and age between the ADHD and healthy control groups in NeuroIMAGE. Inclusion criteria were largely consistent with criteria during IMAGE: participants had to be between 5 and 30 years, of European Caucasian descent, have an IQ $\geq$70, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, and known genetic disorders (such as Fragile X syndrome or Down syndrome). Different from the original inclusion criteria used in IMAGE, we allowed inclusion of children with any subtype ADHD in the current study. This was done to closely match the original cohort that included participants with partly remission of ADHD symptoms. The newly recruited patients had significantly more inattentive and hyperactive symptoms than the original cohort [overall: 4.8 inattentive symptoms (SD = 3.1); newly recruited: 6.3 inattentive symptoms (SD = 2.7); original cohort: 4.7 inattentive symptoms (SD = 3.4); $F(1, 555) = 5.5$; $p < 0.02$; overall: 3.9 hyperactive symptoms (SD = 3.2); newly recruited: 5.7 hyperactive symptoms (SD = 2.8); original cohort: 3.8 hyperactive symptoms (SD = 3.2); $F(1, 555) = 10.3$; $p < 0.001$]. Figure 1 provides an overview of the NeuroIMAGE sample composition.

Including the newly recruited families, the complete NeuroIMAGE cohort comprised testing of more than 1,000 children and approximately 850 tested parents. Retention rate from the original IMAGE study was high (79 %) with significantly higher rates for participants from control families compared with participants from ADHD families [84 vs. 77 %, $\text{Chi}^2(df = 1, N = 970) = 6.6$, $p < 0.05$]. The most important reasons for drop-out were being too busy, family problems, and time consumption of the study (for a full measurement the whole family needed to spend an entire day at the test site). Dropped-out participants only differed from followed-up participants on estimated IQ ($M = 99$, SD = 11 vs. 103, $F(1,942) = 7.1$, $p < 0.01$). No differences were present in terms of age, or number of inattentive or hyperactive symptoms (for a more extensive comparison of drop-out and follow-up participants see [43]. For 82 % of the families, we were able to collect data for two or more siblings (87 % ADHD, 72 % controls) and for both parents (85 % ADHD, 76 % controls).

Families

Image I	ADHD	Control	Total
Included families	365	148	513
Retained families	288	119	407
%	79	80	79

NeuroIMAGE	ADHD	Control	Total
	331	**153**	**484**

Newly recruited	ADHD	Control	Total
	43	34	77

Individuals

Children		**ADHD[a]**	**Control[a]**	**Total**
Children from Image I	N	700	270	970
Newly recruited children	N	51	48	99
	Total	**751**	**318**	**1069**
	% male	58	51	56
	Age[b]	17.1 (3.7)	16.7 (3.9)	17.0 (3.7)
	IQ[b]	98 (16)	105 (14)	100 (16)
	SES[bc]	11.4 (2.3)	12.8 (2.7)	11.8 (2.5)

[a]ADHD / Control families
[b]Mean and standard deviation
[c]Average of parents' corrected years of education

Parents		**ADHD[a]**	**Control[a]**	**Total**
Parents from Image I	N	504	208	712
Newly recruited parents	N	78	58	136
	Total	**582**	**266**	**848**
	% male	46	44	46
	Age[b]	47.2 (5.5)	48.7 (4.6)	47.7 (5.3)
	IQ[b]	103 (16)	112 (16)	105 (16)
	SES[bc]	11.5 (2.9)	13.0 (3.3)	12.0 (3.1)

[a]ADHD / Control families
[b]Mean and standard deviation
[c]Average corrected years of education

Fig. 1 Overview of the NeuroIMAGE sample composition. In this figure, an overview of the participating families is displayed (*left*) as well as demographic characteristics of the individual participants (*right*) segregated by family type (ADHD vs CON) and type of family member [child (*above*) vs. parent (*below*)]

Measurements

Measures during intermediate follow-up

Measures at the intermediate follow-up included questionnaires and a structural interview. Questionnaires were used to assess: (a) ADHD symptom severity of both parents and offspring (Conners' Adult ADHD Rating Scale (CAARS R-L [44]); Conners' Parent Rating Scale (CPRS R:L [45]); Conners Wells' Adolescent Self-Report Scale: Short Form (CASS:S [46])), (b) Substance use disorders (SUDs) assessed by self-reported alcohol dependence (Alcohol Use Disorders Identification Test (AUDIT [47])), drug abuse (Drug Abuse Screening Test-20 (DAST-20 [48])), and nicotine dependence (Fagerström Test for Nicotine Dependence (FTND [49])), (c) Alcohol, and tobacco consumption over the past month (Timeline Follow Back Interview (TLFBI [50])), (d) Lifetime alcohol-related problem behaviour (The Michigan Alcohol Screening Test (MAST [51])), (e) Gambling problems (The South Oaks Gambling Screen (SOGS [52])) and (f) Driving behaviour (Driving Behavior Questionnaire (DBQ [53])). Furthermore, parents of participants were interviewed about their children using the SUD module of the Diagnostic Interview Schedule for Children (DISC-IV [54]). A final set of measures was taken to determine patterns of use of prescribed drugs: (1) Medication use (ADHD Medication Use Questionnaire (AMUQ [55])), and (2) The misuse and diversion of ADHD medication (MGH ADHD Medication Misuse and Diversion Assessment (MAMMDA [56])).

Measures during NeuroIMAGE

Assessments for NeuroIMAGE included behavioural questionnaires, a semi-structured clinical interview (Dutch translation of the Schedule for Affective disorders Schizophrenia—present and lifetime version (K-SADS [57])), several cognitive measures, acquisition of saliva and somatic measures obtained in all family members. In addition, all children older than 7 years without contraindication for an MRI measurement (e.g. implanted metal, medical devices, or pregnancy) and willingness to

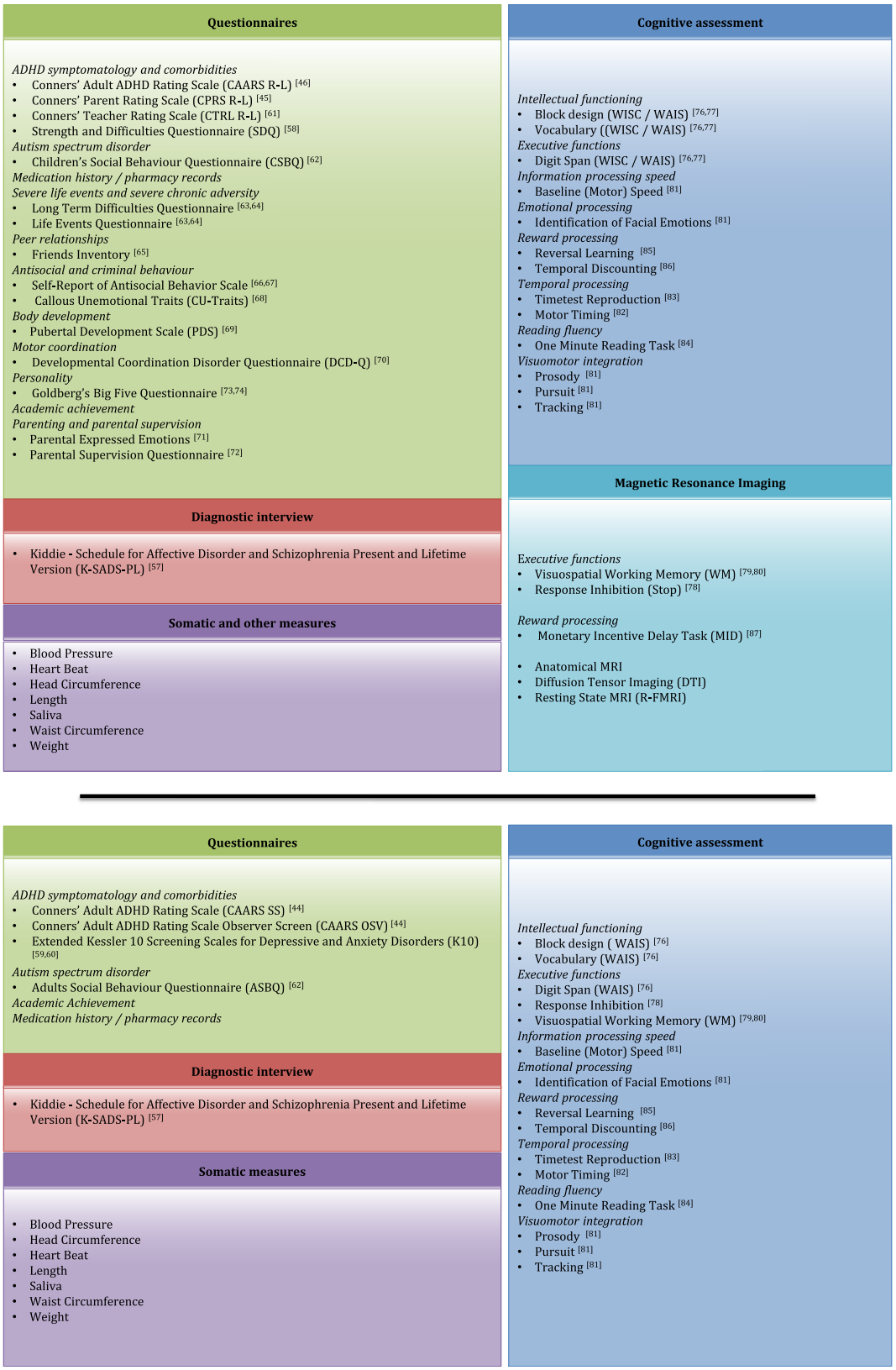

Fig. 2 Assessment protocol NeuroIMAGE. This figure indicates NeuroIMAGE's full assessment protocol for children (*above*) and parents (*below*)

participate underwent an MRI scanning session. Figure 2 outlines all measurements.

Questionnaires Questionnaires assessed several domains of functioning, including: (a) ADHD symptoms and comorbidities including anxiety, depression and oppositional behaviour [44, 45, 58–61], (b) autism spectrum symptoms [62], (c) medication history, (d) severe life events and severe chronic adversity [63, 64], (e) peer relationships [65], (f) antisocial and criminal behaviour [66–68], (g) body development [69], (h) motor coordination [70], (i) academic achievement, (j) parenting and parental supervision [71, 72], and (k) personality traits [73, 74]. For participants using medication, ADHD ratings were collected about the participants' functioning off medication. For children younger than 12 years, their parents or researchers assisted the completion of the self-report questionnaires for the child.

Regarding medication history parents provided detailed information about lifetime use of psychoactive medication for themselves and their children. Additionally, we asked them for written consent to obtain information from the pharmacy records about all delivered psychoactive medications over the last 6 years.

Diagnosis *Diagnostic interview* All participants of NeuroIMAGE were interviewed using the K-SADS. The K-SADS is a semi-structured diagnostic interview and designed to assess current and past episodes of psychopathology in children, adolescents, and adults according to DSM-IV criteria. It provides operational definitions of individual symptoms as well as diagnosis-relevant questions such as symptom onset and impairment. It is separated into screen items, reflecting core symptoms of a disorder, and supplementary modules, consisting of a full assessment of that disorder. Lastly, by interviewing both the parents, and the child, the K-SADS diagnosis is based on different informants. For this study, we included assessments for affective disorders, anxiety disorders, behavioural disorders and tics disorders. The presence of psychiatric disorders within these domains except ADHD [i.e. oppositional defiant disorder (ODD), conduct disorder (CD), chronic or transient motor or vocal tic disorder, Tourette's disorder, major depression (MD), dysthymic disorder, generalized anxiety disorder, social phobia, separation anxiety and panic disorder] was evaluated in all participants using a procedure similar to the ADHD interview. Participants with elevated scores on one or more screen items were administered a full supplement. Final diagnosis was based on DSM-IV criteria for that specific disorder.

Algorithm To determine ADHD diagnosis at the time of participation in NeuroIMAGE, we used a diagnostic algorithm, which combined the diagnostic interview (K-SADS) with the Conners rating scales. The interview served as the fundament for diagnosis. Participants were diagnosed with ADHD provided they (a) had $\geq$6 hyperactive/impulsive and/or inattentive symptoms, (b) met the DSM-IV criteria for pervasiveness and impairment (measures derived from the K-SADS), and (c) showed an age of onset before 12 (following the proposed changes for the DSM-5 [75]). To account for a possible underestimation of ADHD symptomatology in a familial setting, we complemented information from the interview with symptom counts from the Conners' ADHD questionnaires (CTRS-R:L for participants <18 years or CAARS-S:L for participants $\geq$18). To prevent an artificial inflation of ADHD diagnosis, this was only done when at least two symptoms were reported on the questionnaire. When a participant met these criteria, it was checked whether they received a *T* score $\geq$63 on at least one of the DSM-IV ADHD scales on either one of the Conners ADHD questionnaires (DSM inattentive behaviour (scale L of the CTRS-R:L; scale E of the CAARS-S:L), DSM hyperactive/impulsive behaviour (scale M of the CTRS-R:L; scale F of the CAARS-S:L), and DSM total (scale N of the CTRS-R:L; scale G of the CAARS-S:L)) filled out about a period without medication. Cases with inconsistent information [$N = 73$ (7 %)] from these two sources of information were evaluated by a team of experts (psychiatrist JB and 8 psychologists) to derive a consensus (best-estimate) diagnosis.

To be considered unaffected, participants were required to exhibit a $T < 63$ on each of the subscales of each of the Conners questionnaires and to have $\leq$3 symptoms derived from the combined symptom counts of the K-SADS and CTRS-R:L/CAARS-S:L. All participants who did not meet our requirements for either ADHD or unaffected status were classified as subthreshold ADHD and need to be excluded from case–control comparisons.

Criteria were slightly adapted for adults ($\geq$18 years) such that a symptom count of five symptoms was sufficient for a diagnosis [75]. Adults were considered unaffected when they exhibited $\leq$2 ADHD symptoms on the symptom counts. Figure 3 illustrates the steps leading to diagnostic classification. The distribution of diagnostic groups is provided in Table 1.

We were able to determine the diagnostic status for 1,023 (96 %) children who completed the full diagnostic procedure. The remaining cases were not willing to participate in an interview.

For participating parents, diagnostic procedures were similar to those applied to children $\geq$18 years old. Parents were administered the K-SADS and, if possible, their partners completed the CAARS-O:SV. A retrospective childhood diagnosis was established in addition to a current diagnosis using the same diagnostic algorithm used for

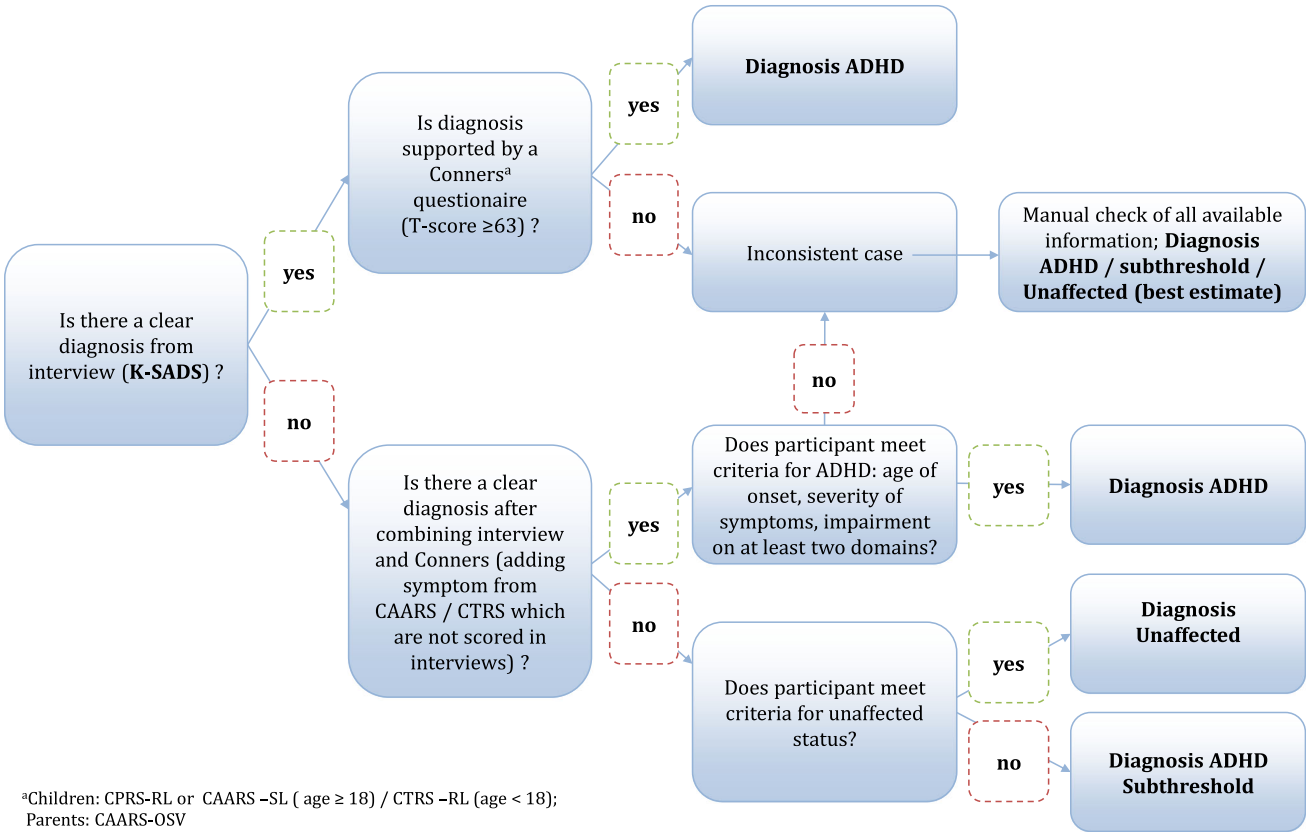

Fig. 3 Flow chart of the diagnostic algorithm for children and parents

Table 1 Demographic information and number of measures in assessed children segregated by diagnosis

Diagnostic groups	ADHD	Unaffected sibs	Controls	Affected controls[d]	Subthreshold[f]	Not diagnosed
N (% of sample)	412 (39)	227 (21)	262 (24)	41 (4)	81 (8)	46 (4)
% male	68	42	49	66	52	52
Age[a]	16.6 (3.4)	17.4 (4.1)	16.6 (3.7)	17.6 (5.3)	18.4 (3.7)	16.9 (2.9)
IQ[a,b]	96 (16)	101 (15)	106 (14)	102 (12)	102 (14)	NA
SES[a,c]	11.4 (2.3)	11.5 (2.4)	12.9 (2.7)	11.8 (2.7)	11.4 (2.2)	11.6 (2.5)
Inattentive symptoms[a,e]	7.3 (1.7)	0.6 (1.4)	0.5 (1.4)	4.6 (2.6)	3.7 (1.4)	NA
Hyperactive symptoms	6.0 (2.4)	0.5 (1.0)	0.4 (1.0)	3.1 (2.4)	2.9 (1.6)	NA
Questionnaires[g]	412 (100)	227 (100)	262 (100)	41 (100)	81 (100)	46 (100)
Neuropsychological data[g]	380 (92)	207 (91)	239 (91)	34 (83)	72 (89)	0 (0)
MRI data[g]	328 (80)	171 (75)	211 (81)	31 (76)	59 (73)	0 (0)
Somatic measures[g]	369 (90)	206 (91)	233 (89)	34 (83)	71 (88)	0 (0)

[a] Mean and standard deviation

[b] Estimated IQ

[c] Corrected years of education

[d] Affected controls are follow-up children that have developed symptoms between IMAGE 1 and NeuroIMAGE

[e] Based on combined symptom count

[f] Probands with less symptoms than needed and healthy controls with more symptoms than allowed

[g] Numbers in each cell represent absolute and relative (within parentheses) amount of available data per diagnostic group

Table 2 Demographic information and number of measures in assessed parents segregated by diagnosis

Diagnostic groups	Persistent	Residual	Remittent	Late onset	Unaffected	Controls	Affected controls[e]	Subthreshold[f]	Not diagnosed
N (% of sample)	101 (12)	40 (5)	9 (1)	22 (3)	319 (38)	224 (26)	19 (2)	56 (7)	58 (7)
% male	56	55	78	32	41	44	37	46	55
Age[a]	47 (5)	47 (5)	45 (4)	47 (5)	47 (5)	49 (5)	49 (5)	47 (6)	49 (6)
IQ[a,b]	104 (16)	99 (13)	114 (25)	106 (18)	103 (15)	112 (16)	113 (16)	104 (16)	NA
SES[a,c]	11.78 (2.97)	11.2 (2.16)	11.79 (3.8)	12 (2.69)	11.55 (3.08)	13.06 (3.33)	11.17 (2.02)	11.33 (2.57)	NA
Inattentive symptoms[a]	5.4 (3.2)	1.6 (2.3)	0.6 (0.9)	3.5 (2.8)	0.4 (1.2)	0.1 (0.4)	1.3 (1.6)	1.7 (1.6)	NA
Hyperactive symptoms[a]	5.2 (3.2)	2 (2.2)	0.6 (0.9)	3.7 (2.8)	0.4 (1.1)	0.2 (0.6)	2.3 (2.1)	2.3 (1.8)	NA
Questionnaires	101 (100)	40 (100)	9 (100)	22 (100)	318 (100)	224 (100)	19 (100)	56 (100)	58 (100)
Neuropsychological data	78 (77)	35 (88)	4 (44)	20 (91)	245 (77)	138 (62)	15 (79)	46 (82)	0 (0)
Somatic measures	77 (76)	34 (85)	4 (44)	17 (77)	241 (76)	136 (61)	15 (79)	46 (82)	1 (2)

[a] Mean and standard deviation

[b] Estimated IQ

[c] Corrected years of education

[d] Based on combined symptom count

[e] Affected controls are follow-up parents that have developed (subthreshold) ADHD between IMAGE 1 and NeuroIMAGE

[f] Parents with less symptoms than needed for a diagnosis and healthy controls with more symptoms than allowed

[g] Numbers in each cell represent absolute and relative (within parentheses) amount of available data per diagnostic group

young adults except that for childhood diagnosis a minimum of six symptoms was required. Moreover, the DSM Inattentive, DSM Hyperactive-Impulsive, and DSM Total subscales of the CAARS-O:SV were used to validate the current diagnosis ADHD. Based on the combination of childhood and current diagnosis, different types of ADHD could be differentiated for participating parents. Parents with a childhood diagnosis of ADHD could either be persistent (current diagnosis ADHD), residual (current diagnosis ADHD subthreshold), or remittent (current diagnosis unaffected). For parents without a childhood diagnosis of ADHD, the diagnosis was either ADHD late onset (current diagnosis ADHD) or unaffected. Because there were no participants with a childhood diagnosis subthreshold ADHD, this resulted in seven diagnostic categories which are shown in Table 2.

Cognitive assessment All participants (children and parents) completed a comprehensive protocol of cognitive tasks measuring (a) intellectual functioning [76, 77], (b) executive functions [76–80], (c) information processing speed [81], (d) emotional processing [81], (e) temporal processing [82, 83] (f) reading fluency [84], (g) visuomotor integration [81], and (h) reward processing [85–87]. Except the subtests of the WISC/WAIS and the reading test, all tasks were computerized.

MRI measures Participating children completed a session in a magnetic resonance imaging (MRI) scanner. At the two test sites, comparable 1.5 T MRI scanners were employed (Siemens SONATA and Siemens AVANTO; Siemens, Erlangen, Germany), using identical head coils (8-channel Phase Array Head Coil). A scanning session included two anatomical T1 scans, a diffusion tensor imaging scan (DTI), a resting state functional MRI (R-FMRI) scan, and three functional imaging tasks including a visual working memory task [79, 80], a stop signal reaction task [78] and a monetary incentive delay (MID) task [87]. MRI scanning sequences were closely matched across the two scanning sites (Table 3).

Because of limited time for scanning, we were unable to collect all MRI measurements for each participant. Therefore, we differentiated between four acquisition protocols. All protocols included two anatomical T1 scans. Additionally, three of the four protocols included two of the three functional imaging tasks, the DTI scan, and the R-FMRI measurement (thus dropping one task). The fourth protocol contained all three functional imaging tasks (thus dropping DTI scan and R-FMRI measurement). Following this procedure, we were able to measure brain anatomy for 800 participants (100 %), reward processing for 564 (70 %) participants, response inhibition for 533 (67 %) participants, working memory

Table 3 Scan sequences

Sequence	TR/TE/T1 mm	Field of view mm	Matrix RL/AP/slices	Voxel size (mm)	Gap (%)	GRAPPA factor	*b* value	Directions/ b0′s
T1	2,730/2.95/1,000	256	176/256/256	1.0 × 1.0 × 1.0	50	2	NA	NA
R-FMRI	1,960/40/–	224	64/64/37[a]–38[b]	3.5 × 3.5 × 3.0	17	None	NA	NA
Functional tasks	2,340/40/–	224	64/64/37[a]–38[b]	3.5 × 3.5 × 3.0	17	None	NA	NA
DTI	8,500/97/–	256	128/128/60	2.0 × 2.0 × 2.2	0	2	1,000	60/5

[a] Nijmegen

[b] Amsterdam

for 648 (81 %) participants, R-FMRI for 536 (67 %) participants, and DTI for 591 (74 %) participants. We balanced the order of tasks across protocols and the order of the used protocols was pseudo-randomised across families to achieve an equal distribution of protocols across site and family type.

Genetic determinants *Genetic material and data available for the NeuroIMAGE sample* Participants whose genotypic information was not collected during IMAGE, provided saliva for DNA analysis. We were able to obtain genetic data for almost every participant in the NeuroIMAGE study, except for five participants who did not provide a saliva sample.

DNA isolation An extensive description of DNA extraction and genotyping in IMAGE is provided elsewhere [22]. Briefly, for the IMAGE sample, DNA was extracted from blood samples or immortalized cell lines at Rutgers University Cell and DNA Repository, New Jersey, USA as well the Human Genetics department of the Radboud University Medical Centre in Nijmegen. Additional NeuroIMAGE samples were collected in the form of a saliva sample. DNA was isolated from saliva using Oragene containers (DNA Genotek, Ottawa, Ontario, Canada) according to the protocol supplied by the manufacturer at the Radboud's department of Human Genetics.

Genetic linkage data As described by Asherson et al. [25], a total of 5,545 autosomal single-nucleotide polymorphisms (SNPs) from the Illumina Linkage IVb SNP panel were successfully assayed, with a call rate of 99.6 % and a reproduction rate of 99.994 %. After data cleaning, 5,407 autosomal SNPs with an average resolution of 1.66 SNPs per centimorgan were available for linkage analyses. In total, linkage data were available for 322 subjects with ADHD (144 combined type, 147 with predominantly inattentive type, 31 with predominantly hyperactive-impulsive type), 189 unaffected individuals, 64 subjects subthreshold for ADHD and 28 with unknown status.

Genome-wide genotyping data Genome-wide genotyping of the IMAGE probands ($N = 231$) and their parents ($N = 445$) was performed as part of the GAIN study using the Perlegen genotyping platform of 600,000 tagging single-nucleotide polymorphisms (SNPs) (for details on genotyping, data cleaning, and quality control procedures see [31]). For NeuroIMAGE, genotyping was performed for affected, unaffected and control children who had not been genome-wide genotyped before ($N = 492$); this was done using the HumanCytoSNP-12 genotyping chip with 200,000 tagging SNPs. Quality control steps were performed for the genotype data. SNPs were excluded if the call rate per SNP was <95 %, the minor allele frequency was <1 %, or the SNPs failed the Hardy–Weinberg equilibrium test at a threshold of $p \leq 10 - 6$ (genome-wide). Participants were excluded if the call rate per individual was lower than 95 %. To increase genomic coverage and to harmonize genotyping, imputation was performed in the different datasets using the 1,000 Genomes Reference data. In total, we have genome-wide data available for 331 subjects with ADHD (150 combined type, 143 with predominantly inattentive type, 38 with predominantly hyperactive-impulsive type), 301 unaffected individuals (unaffected siblings and healthy controls), 78 subjects with subthreshold ADHD and 13 not diagnosed.

Somatic and other measures To obtain an estimate of possible unhealthy eating habits, abnormal growth or other physiological abnormalities, we measured body length and weight, head and waist circumference, blood pressure, and heart rate at rest.

Procedures

Ethical approval

This study was approved by the regional ethics committee (Centrale Commissie Mensgebonden Onderzoek: CMO Regio Arnhem Nijmegen; 2008/163; ABR: NL23894.091.08) and the medical ethical committee of the VU University Medical Center. We obtained written informed consent for every participant. For children 12–18 years old, both parents

and children gave consent, for children younger than 12 parents gave consent for their children. In case a participant retracted consent, all data of that participant were removed from the database and withheld from further analysis. Participating families were regularly informed with a newsletter about study progress and resulting publications.

Assessment

After an initial contact by telephone or through public schools, interested families received an information package including general project information, informed consent forms and questionnaires. Minimal requirement for participation was that a participant was willing to fill out questionnaires. In case of participation, a clinical interview for each family member was done by telephone. During this screening, we asked participants to withhold use of psychoactive drugs or drugs with potential effects on test performance for either 48 hours before the test day or according to the washout period of the drug.

If feasible, we organized a single test day for each family covering all assessments; otherwise, testing spanned several days. For families that were not willing to come to the test sites, we offered a test day without MRI at the family's home, which occurred only in very few cases. In Tables 1 and 2, available data per diagnostic group are indicated. During this day, parents and children older than 12 years were interviewed using the K-SADS; children below the age of 12 were not interviewed. Participants with elevated scores on screen items of the interview (score: 3) were administered the full supplementary module of that disorder. Cognitive tests were administered in a fixed order and due to its length divided in two parts. Across families the administration of both parts was counter-balanced. All children participating in an MRI session were prepared for scanning using a mock scanner. Each testing day ended with a short debriefing. The monetary reward of € 50 was granted to every participating child, and travel cost was reimbursed to parents. Children who completed an MRI session were also offered a copy of the anatomical MRI scan. Moreover, all participants received the monetary reward gained during cognitive assessment and, on demand, a short report of their performance on the IQ test and questionnaire/interview scores. An example of a test day can be found in the supplementary material.

Staff training and supervision

Test staff consisted of PhD students and research assistants. The whole staff carried out cognitive testing, diagnostic interview and MRI scanning was restricted to PhD students who had received training at forehand. The MRI scanning training consisted of practicing to operate the scanner, learning security procedures and monitoring quality of the data (e.g. spike identification). For the diagnostic interview, a PhD student had to attend psychiatric diagnostic intake sessions of ADHD children at local child Psychiatry departments (Karakter, Nijmegen; Accare, Groningen) or interview sessions led by a trained interviewer. Moreover, in practice interviews, PhD students conducted diagnostic interviews under supervision of a clinician or trained professional. For quality control, monthly meetings were held to discuss controversial cases and to maintain agreement about ADHD symptoms. In addition, every interviewer was filmed during an interview and evaluated by other interviewers. By comparing symptom-wise the evaluations of the filmed interviewer with ratings of the other interviewers, we were able to determine the inter-rater reliability (IRR). For ADHD, on average seven raters contributed to each symptom evaluation, for ODD and CD, at least five raters contributed to each evaluation. For ADHD, ODD; and CD, IRR across all raters and interviews was excellent (ADHD: 0.94; ODD: 0.89; CD: 0.95).

To standardize cognitive testing and neuroimaging as much as possible, written standard operating procedures (SOPs) for administration of cognitive tests and MRI assessments were developed. All researchers received training to administer the test battery using the SOPs before they were allowed to test during a test day. The first sessions of research assistance were conducted under supervision of an experienced PhD student.

Data management and quality control

We encoded every participant with an anonymous identifier number to separate personal from scientific data. Data collection was documented with a case report enlisting all available data for that person and notes regarding factors that might have influenced the data acquisition. Moreover, all digital data were securely uploaded to a central storage server which was backed-up to tape daily and archived in at least two different locations. To check data integrity, we compared the presence of the uploaded data with what was expected from the digitized case reports. In addition, we obtained demographic information from multiple sources (e.g. information about gender and age from self-reports and data entry by the researcher during scan session; for gender also from genotypic analysis) to assure that data from different modalities (MRI, genotype, behavioural data, self-reports) were associated with the correct corresponding participant.

The research team digitized all questionnaires. After entering these data, quality checks for a random sample of questionnaires were conducted. When the error rate of a questionnaire was below 1 %, the data were accepted as valid. In case of higher error rates, all data for that specific

questionnaire were checked with the original paper version and corrections were made where needed.

For MRI data, we also implemented several data checks to assess the quality of the collected scans. For every MRI sequences, we calculated the signal-to-noise ratio and the amount of spurious spikes in the signal. For the T1 anatomical scans, two independent raters evaluated quality of both scans on a 4-point scale (1 = good; 2 = useable; 3 = poor; 4 = very poor). Consistency between both raters was sufficient to good (ICC: 0.59) and the evaluated quality of the scans was good: from 1,559 scans, only 105 (6.7 %) were rated other than good or usable by one of the raters, leaving 767 (96 %) participants with at least one useful structural scan.

MRI movement artifacts

Head movement during MRI scans can greatly impact the quality of the data collected [88–90]. Therefore, we undertook several steps to minimize movement during scanning and to assess data quality afterwards. Before the MRI session, all participants were trained in a mock scanner to keep their head still while images were acquired. During the structural scans, participants were offered to watch a short movie or to listen to their favourite music, thereby distracting them from scanning, while helping them to stay still. During functional MRI scans, we monitored participants' movements by performing real-time calculations of the head rotation and translation parameters. When participants moved excessively, we gave feedback and encouraged participants to stay still for the next scan. Finally, given the importance of the anatomical scan for processing the other scan types (i.e., to allow correct normalization to a common space), we administered the T1 anatomical scan twice during the MRI session.

We also made a quantitative between-group comparison of head movement during functional MRI scans. To this end, we calculated the three head rotation (degrees) and three translation parameters (millimetres) using SPM8 software (Wellcome Trust Centre for Neuroimaging, UCL). Rotation parameters were converted to distances (in millimetres). By taking the summed absolute image-to-image displacement per parameter and adding these up, we constructed a summary score of the total movement over the time series per participant. As displayed in Fig. 4, peaks of these distributions are slightly shifted between ADHD cases and controls, suggesting that the ADHD cases moved a bit more during scanning. However, for all sequences, we observed an almost complete overlap of distributions indicating that within-group variance was much larger than between-group variance. This is also illustrated by the computed Cohen's effect sizes that, varying between 0.10 and 0.51, appear to be small to moderate. We concluded from these observations that movement is not very likely to confound our case–control comparisons and we therefore decided to deal with movement in a standard fashion (i.e., statistical correction using realignment parameters in 1st/2nd level analysis, exclusion of extreme movers/outliers, post hoc analysis whether movement does confound a specific analysis).

Site effects

Data acquisition was carried out at the VU University Amsterdam and VU University Medical Centre, or at the Radboud University Medical Centre and Donders Centre for Cognitive Neuroimaging in Nijmegen. This has implications for data analysis, as multi-site data acquisition induces non-specific variability in the data (e.g. differences in test rooms and scanner properties, slight variations in instructions). Several steps were taken to minimize site effects, such as using SOPs, equal (or similar) equipment, standard scan protocols at both sites, training experimenters on cognitive testing and conducting interviews in a standard manner. Table 4 displays an overview of the demographic information of the sample with cognitive data including site information. It is apparent that the number of participants per site, percentage of males, IQ and socio-economic status are not matched across sites, and analyses will need to be adjusted for potential sites effects.

Although we aimed to match imaging protocols between sites, we were unable to completely match the scanner types (Siemens Avanto versus Siemens Sonata). Such difference in hardware can be expected to yield between-site differences imaging quality or parameters. To estimate these differences and assess them in light of between-subject variability, we compared image quality measures and, most importantly, dependent measures of the experimental designs for each scanning modality (T1 anatomical, all functional tasks, R-FMRI, DTI) between gender and age-matched control participants from both sites. Representing image quality, for the T1 anatomical and the DTI scans we calculated the signal-to-noise ratio (SNR), defined as mean imaging signal within the brain divided by the noise level, i.e. the mean standard deviation of the signal in the air divided by 0.655 [91]. For the functional MRI scans, we calculated temporal SNR by the brain averaged ratio of the mean and standard deviation of the signal over time. Temporal SNR was calculated on the raw data after applying realignment to correct for gross head movements. To evaluate potential site effects within our experimental design, we selected one measure of interest for each imaging modality. For the anatomical scan, we selected relative grey matter volume (grey matter divided by the total brain volume as estimated by SPM). For DTI, we calculated the mean FA value within the posterior

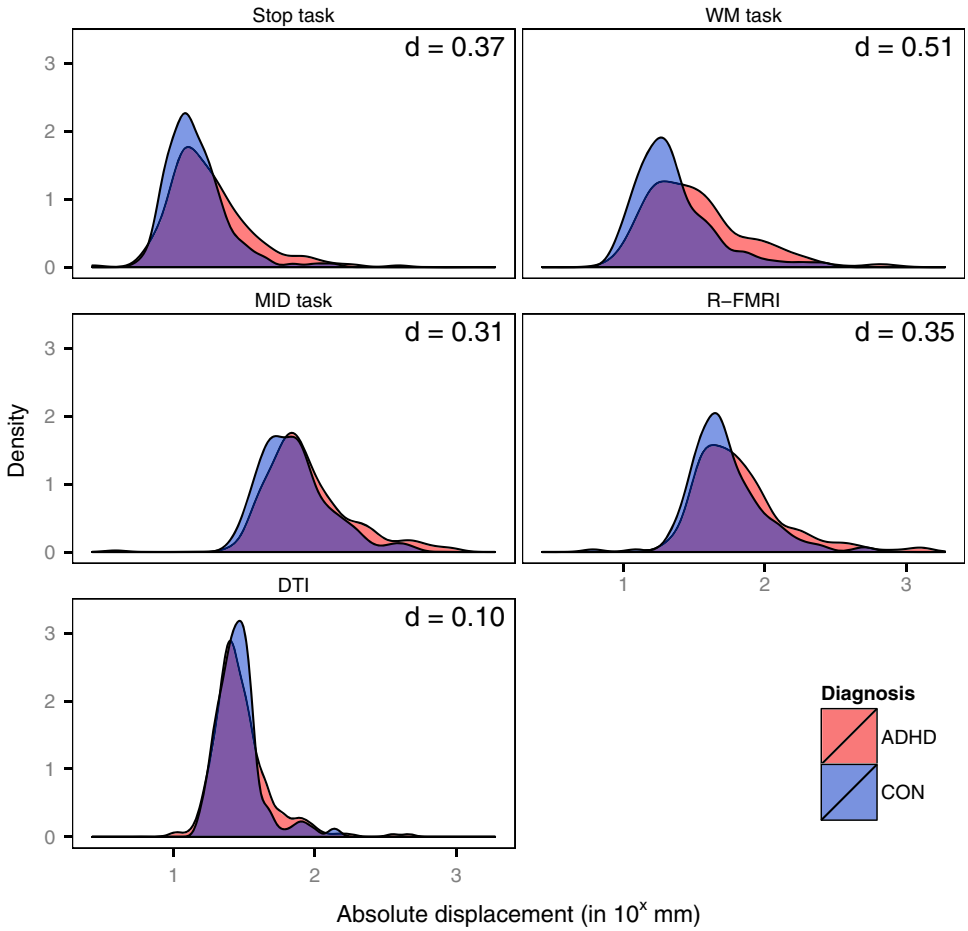

Fig. 4 Movement. This figure displays the distribution of the summarized movement parameters per MRI scan with time series [response inhibition (Stop), reward processing (MID) and visuospatial working memory (WM) task, resting state fMRI (R-FMRI), diffusion tensor imaging (DTI)] stratified by diagnostic group (ADHD vs. CON). The numbers in the upper part of each facet indicate effect sizes (cohen's d) of between-group differences of the mean

Table 4 Sample distribution per measuring site

N Tested	Total				Main effect site	Main effect family	Interaction site × family
	934						
Tested per site	Nijmegen		Amsterdam				
	472 (51 %)		462 (49 %)				
	ADHD	Control	ADHD	Control			
N (%)	379 (80)	93 (20)	280 (61)	180 (39)		$p < 0.001$	$p < 0.001$
% male	53	42	64	57		$p < 0.002$	$p < 0.001$
Age[a]	16.8 (3.7)	16.2 (3.5)	17.3 (3.7)	16.8 (4.1)			
IQ[a]	99 (16)	109 (15)	97 (16)	104 (13)	$p < 0.03$	$p < 0.001$	
SES[a]	11.3 (2.2)	13.8 (2.9)	11.8 (2.4)	12.4 (2.4)	$p < 0.003$	$p < 0.001$	$p < 0.001$
Inattentive symptoms[a,b]	4.8 (3.3)	0.6 (1.4)	4.7 (3.6)	1.3 (2.4)		$p < 0.001$	
Hyperactive symptoms[a,b]	4.2 (3.2)	0.5 (1.3)	3.6 (3.1)	0.8 (1.6)	$p < 0.01$	$p < 0.001$	$p < 0.04$

[a] Mean and standard deviation

[b] Based on combined symptom count

corpus callosum (extracted using the FreeSurfer software package). For each functional task, we assessed task-related activity in a region of interest (ROI). We assessed the ventral striatum during rewarded anticipation (vs. nonrewarded anticipation), right inferior frontal gyrus for successful response inhibition (vs. noninhibited responses) and

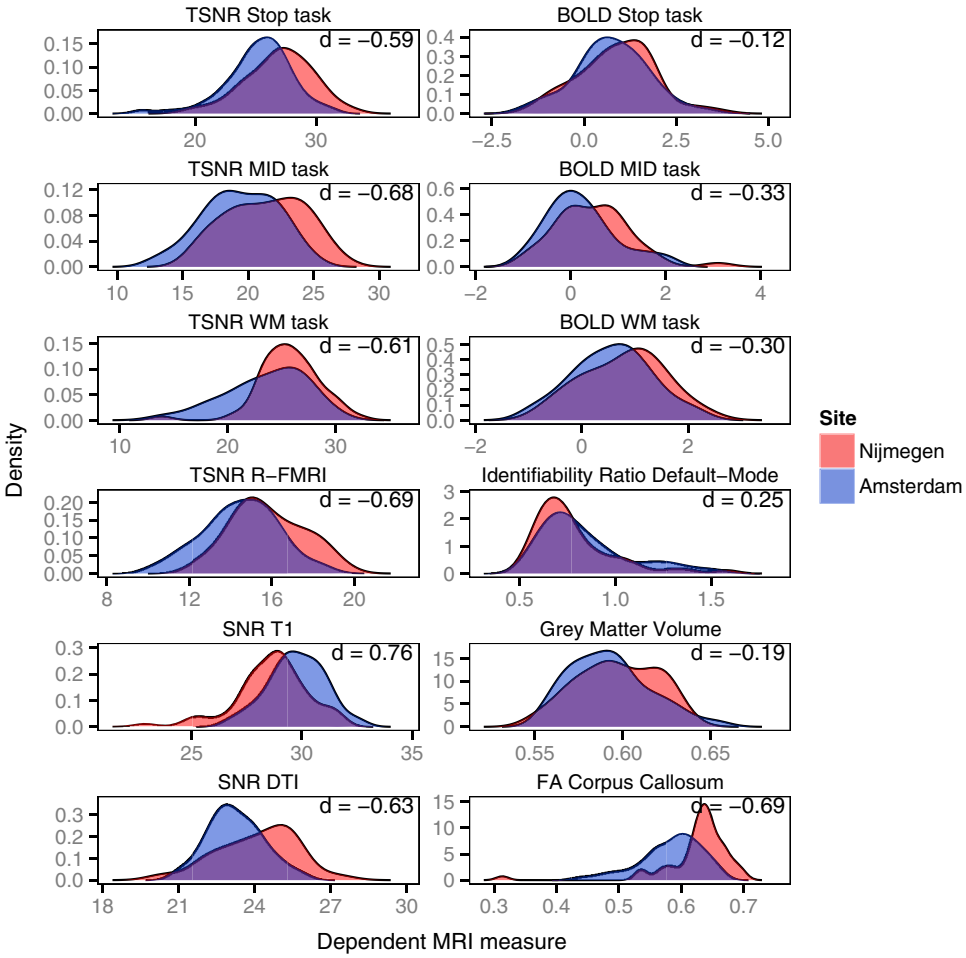

Fig. 5 Distribution of dependent MRI measures stratified by scan site. This figure shows the density plots of all MRI measures for a global (*left*) and specific (*right*) dependent measure. Measures comprise signal-to-noise ratios (SNR) of the anatomical T1 and DTI scan, temporal signal-to-noise ratios (TSNR), blood oxygen-level dependent (BOLD) responses for all functional tasks [response inhibition (Stop), reward processing (MID) and working memory (WM)], identifiability measure (log10 transformed) of a R-FMRI default network, relative grey matter volume, and the mean fractional anisotropy (FA) value of the corpus callosum. Effect sizes (cohen's d) of between-group differences are indicated in the *upper* part of each facet

inferior frontal gyrus for working memory demanding periods (vs. baseline). For each region, we extracted mean activity from the normalized contrast maps of the first-level parameter estimates for the specified contrast. For the R-FMRI scan, we quantified the identifiability of the default network by calculating the ratio between the connectivity strength within a default-mode mask and connectivity strength outside this mask. Connectivity measures were obtained by dual regression using ten well-defined networks [92]. The distribution of each measure per imaging site is plotted in Fig. 5. As expected, differences between sites could be observed in the distribution of all measurements. However, all measures exhibited large overlap [Cohen's d was in the range between (±) 0.12 and 0.76, with a mean around 0.50] between sites, suggesting that between-subject variability within site outweighed any systematic between-site differences. Importantly, compared to the effect on raw image quality, site had a considerably smaller effect on most derived measures indicating that in our study site effects are likely to play a less important role when answering experimental questions.

Age- and gender-specific templates For MRI analyses

Each participant's brain is different in size and structure. Accordingly, between-subject comparisons necessitate transformation of each participant's MRI data to a common analysis space. This allows making inferences about group differences in specific brain structures or functions, based on the assumption that the transformation has aligned similar brain structures across participants. A typically used transformation is the alignment of a participant's brain to a template from the Montreal Neurological Institute (MNI152). This template represents the average healthy adult brain and is used in most MRI studies. This approach has the advantage that brain regions described in one study can be compared to brain regions described in another. However, given the wide age-range of the NeuroIMAGE sample (8–30 years) and the developmental phase in which our participants fall, a possible transformation bias may exist in that brains of older participants will need less transformation to match the MNI152 template compared to brains from younger participants. Similarly, it is possible that structural brain differences

between ADHD and controls translate into functional differences detected with fMRI. This could be due to differences in transformation to the MNI152 space caused by the underlying structural differences between ADHD and controls. To counteract such biases, we developed a transformation procedure that ultimately transforms participants' brains to a 'neutral midspace'. Such a midspace is determined by the participants included in a specific analysis. For instance, when conducting a case–control comparison for a certain task all participants with ADHD and all healthy participants who performed that task are used to calculate a neutral midspace. In short, the midspace was obtained through as stepwise normalization of each participant's brain to (1) MNI152 space, (2) a study template based on the average of all participant's brains in MNI152 space, (3) a specific subtemplate (e.g. based on all participants with ADHD, or all males). Transformation of a participant's brain to the desired midspace was then accomplished by concatenating the transformation of the participant's brain to the study template with a weighted transformation of the study template to a combination of subtemplates. As an example, in case of 60 controls and 40 patients with ADHD, bringing a participant to a diagnosis neutral midspace would entail transformation of that participant's brain using a concatenation of the participant to study template transformation with (0.6 × transformation of study template to control template) + (0.4 × transformation of study template to ADHD template). Because the midspace accounts for demographic characteristics of the analysed population, transformation of imaging data to that space minimizes possible confounders as gender, age and diagnosis. Importantly, the midspace and templates are aligned with the MNI152 template space. Thus, coordinates of results obtained with this procedure are comparable to coordinates obtained using the traditional transformation to MNI152 space.

Conclusion: anticipated outcome and opportunities of NeuroIMAGE

The NeuroIMAGE database offers the opportunity to study several key aspects of ADHD in a large family-based sample: (1) the course of ADHD, (2) its neurocognitive and genetic underpinning, and (3) its heterogeneity. By assessing cognitive systems during the critical period from childhood to adulthood, we can investigate which cognitive and associated neural systems are stable and which undergo developmental changes. Finding a profile of cognitive, neural and/or genetic markers linked to remitting or persistent ADHD would significantly deepen our understanding of the biological mechanisms involved in the course of ADHD. Very importantly, on a clinical level, it would provide a means of identifying children with ADHD who are at risk for a persistent course into adulthood and poor clinical outcome. In turn, this should provide a basis for the development of more powerful treatment approaches for this group of patients and monitoring treatments more effectively.

ADHD is likely to be a combination of multiple etiologically distinct subtypes with overlapping symptom presentations. By bringing together diverse measures, we may be able to identify specific subtypes on the basis of cognitive and/or brain measures, where behavioural measures alone might have been unsuccessful. Furthermore, NeuroIMAGE encompasses a comprehensive assessment of other psychopathological domains (e.g. ODD/CD, ASD), which allows exploring the specificity of genetic, cognitive and neural correlates of ADHD. Detailed medication use data enables the study of brain correlates associated of long-term medication use. Using empirical modelling techniques like latent class analysis (LCA) and recent extensions of these techniques, one may identify groups of participants who have very similar patterning of scores on cognitive and brain measures reflecting biologically relevant, distinct etiological pathways towards disease [93, 94].

While being too small for gene-finding studies, the NeuroIMAGE database forms an excellent resource for mapping biological pathways from gene to disease. For gene-finding studies, for which even larger samples are needed, NeuroIMAGE contributed its data to meta- and mega-analyses in international initiatives like those of the Psychiatric Genomics Consortium (PGC; https://pgc.unc.edu/) and the ENIGMA consortium (Enhancing NeuroImaging Genetics through meta-analysis, see enigma.Ioni.ucla.edu). In addition to that, the NeuroIMAGE database forms an international scientific resource which may be accessed by other researchers in the field (for requests regarding access to the NeuroIMAGE data see http://www.neuroimage.nl).

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Conflict of interest Jan Buitelaar has been in the past 3 years a consultant to/member of advisory board of/speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis and Servier. He is not an employee of any of these

companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents and royalties. Jaap Oosterlaan has been on the advisory board of Shire and UCB Pharmaceuticals. He has received an unrestricted grant from Shire. Pieter Hoekstra has received honoraria for advice from Eli Lilly and Shire. In the past year, Stephen V. Faraone received consulting income and/or research support from Shire, Otsuka and Alcobra and research support from the National Institutes of Health (NIH). In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. SVF receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health* and Oxford University Press: *Schizophrenia: The Facts*. The other authors have no potentially competing interests.

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