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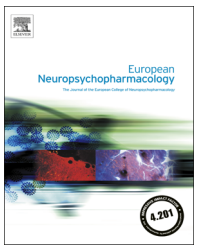

Brain alterations in adult ADHD: Effects of gender, treatment and comorbid depression

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Abstract
Children with attention-deficit/hyperactivity disorder (ADHD) have smaller volumes of total brain matter and subcortical regions, but it is unclear whether these represent delayed maturation or persist into adulthood. We performed a structural MRI study in 119 adult ADHD patients and 107 controls and investigated total gray and white matter and volumes of accumbens, caudate, globus pallidus, putamen, thalamus, amygdala and hippocampus. Additionally, we investigated effects of gender, stimulant treatment and history of major depression (MDD). There was no main effect of ADHD on the volumetric measures, nor was any effect observed in a secondary voxel-based morphometry (VBM) analysis of the entire brain. However, in the volumetric analysis a significant gender by diagnosis interaction was found for caudate volume. Male patients showed reduced right caudate volume compared to male controls, and caudate volume correlated with hyperactive/impulsive symptoms. Furthermore, patients using stimulant treatment had a smaller right hippocampus volume compared to medication-naïve patients and controls. ADHD patients with previous MDD showed smaller hippocampus volume compared to ADHD patients with no MDD. While these data were obtained in a cross-sectional sample and need to be replicated in a longitudinal study, the findings suggest that developmental brain differences in ADHD largely normalize in adulthood. Reduced caudate volume in male patients may point to distinct neurobiological deficits underlying ADHD in the two genders. Smaller hippocampus volume in ADHD patients with previous MDD is consistent with neurobiological alterations observed in MDD.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood and is strongly persistent over time (Polanczyk et al., 2007). At least 15% of affected children still meet full ADHD criteria according to the DSM-IV in adulthood, and 40–60% remit only partially (Faraone et al., 2006). The average prevalence of adult ADHD is estimated to be between 2.5% and 4.9% (Simon et al., 2009).

Magnetic Resonance Imaging (MRI) studies have reported structural abnormalities in several regions of the brain in patients with childhood ADHD compared to controls (see meta-analyses by Ellison-Wright et al. (2008), Frodl and Skokauskas (2012), Nakao et al. (2011), and Valera et al. (2007)). However, there are inconsistencies across studies and it is unclear which brain regions have the strongest reduction of volumes or area compared to controls. An often used strategy to overcome limitations of single studies is to perform a meta-analysis. So far, four meta-analyses of structural MRI studies have been published. The first restricted the analysis to childhood studies and pooled data of 22 region of interest studies comparing 565 ADHD children and 583 controls (Valera et al., 2007). The largest reductions in ADHD compared to controls were found in the cerebellar regions, the splenium of the corpus callosum, total and right cerebral volumes and right caudate nucleus. The second meta-analysis also focused on childhood studies and included seven whole-brain voxel-based morphometry (VBM) studies comparing 114 children with ADHD and 143 comparison subjects; the authors reported that ADHD was associated with gray matter reductions in right putamen and globus pallidus (Ellison-Wright et al., 2008).

An important question is whether brain abnormalities observed in childhood ADHD persist into adulthood. In trying to answer this question, two meta-analyses included pediatric and adult ADHD samples to examine age effects on gray matter volume using VBM. Nakao et al. (2011) included 202 children and adolescents, 176 adults with ADHD and 344 healthy controls, while Frodl and Skokauskas (2012) examined 175 children and adolescents and 145 adult patients with ADHD, plus 288 healthy controls. Both studies confirmed findings from previous meta-analyses that volume reductions of the right globus pallidus and putamen volumes as well as the right and left volumes of the caudate were the most consistent abnormalities in childhood ADHD. Using meta-regression analysis, Nakao and colleagues further showed that differences in gray matter volume in the right putamen disappeared with increasing age suggesting normalization in adulthood. An earlier cross-sectional study in 152 children and adolescents with ADHD and 139 age- and sex-matched controls had also suggested normalization of caudate volume throughout adolescence (Castellanos et al., 2002). Along the same lines, a longitudinal study investigating cortical thickness in 223 ADHD children and 223 normally developing children showed that the peak of cortical thickness maturation was delayed in children with ADHD compared with healthy peers by an average of 3 years, with some regions, including frontal and temporal cortex areas, being delayed in their maturation by up to 5 years (Shaw et al., 2007). A recent longitudinal study in 234 children with ADHD and 231 typically developing children by the same group extended the previous finding by demonstrating that maturation of cortical surface area was delayed in the same way as cortical thickness was (Shaw et al., 2012). However, neither of the longitudinal studies was able to examine whether persistence of ADHD is related with brain maturation, since most of their participants were still under 18 years and adult clinical outcome data were lacking for the majority of subjects. Normalization may still only concern the children/adolescents with ADHD who show recovery in adulthood, because several structural neuroimaging studies in adult ADHD patients did observe differences compared to controls (Table 1). However, sample sizes have been relatively small. So far, 13 studies have been published with sample sizes ranging from 8 (Hesslinger et al., 2002) to 74 ADHD patients (Seidman et al., 2011). Three studies in adult ADHD patients show reductions in the caudate nucleus (Almeida Montes et al., 2010; Proal et al., 2011; Seidman et al., 2011). Additional volumetric reductions are found in putamen (Seidman et al., 2011), right thalamus (Proal et al., 2011), dorso-lateral prefrontal cortex (Biederman et al., 2008; Makris et al., 2007; Seidman et al., 2011, 2006), left fronto-orbital cortex (Hesslinger et al., 2002) and anterior cingulate cortex (Amico et al., 2011; Biederman et al., 2008; Makris et al., 2007), superior and inferior frontal gyrus (Almeida et al., 2010; Depue et al., 2010; Seidman et al., 2006), early visual cortex (Ahrendts et al., 2011), amygdala (Frodl et al., 2010) and cerebellar regions (Biederman et al., 2008; Proal et al., 2011; Seidman et al., 2011).

Taken together, the literature does not provide a clear picture how abnormal childhood brain volumetrics translate into adulthood. Moreover, it remains unclear what the role of gender is in this developmental process. In childhood ADHD, relatively more boys than girls are diagnosed with ADHD, with male-to-female ratios ranging from 3:1 (Arnold, 1996) to as much as 9:1 (Gaub and Carlson, 1997). As an unfortunate consequence, affected girls have been extremely underrepresented in childhood neuroimaging studies (Valera et al., 2007), and the studies that specifically examined gender differences showed inconsistent findings. Castellanos et al. (2002) showed that boys ($n=89$) and girls ($n=63$) have relatively similar structural brain abnormalities. In contrast, Qiu et al. (2009) examined the effects of ADHD, gender and their interaction on basal ganglia volume in 27 boys and 20 girls with ADHD and reported no abnormalities in girls, while boys showed smaller volumes of caudate, putamen and globus pallidus. In the meta-analysis of Frodl and Skokauskas (2012), smaller right putamen volumes in childhood ADHD did not reach significance when gender was a covariate. This indicates that in childhood ADHD gender may indeed play a role. Compared to childhood, the prevalence of ADHD in adults shows a more balanced gender distribution (Biederman et al., 1994, 1993). Most structural neuroimaging studies of adult ADHD included comparable numbers of males and females. Some reported the absence of gender differences (Almeida Montes et al., 2010; Seidman et al., 2011), but most studies may have lacked power to adequately examine such differences because of their limited sample size.

A confounding factor to nearly all ADHD studies is medication use. Stimulants like methylphenidate are currently the

Table 1 Summary of study characteristics and results.

Study	Subjects	Gender (% male)	Age ADHD: range of M (SD)	Analysis method	Findings
Hesslinger et al. (2002)	8 ADHD, 17 HC	100	31.4 (4.4)	Manual defined ROI: orbital frontal cortex	ADHD < HC, left orbital frontal cortex
Seidman et al. (2006)	24 ADHD, 18 HC	50	38.0 (2.2)	Manual parcellation of the neocortex	ADHD < HC, dorsolateral, prefrontal and anterior cingulate cortex
Makris et al. (2007)	24 ADHD, 18 HC	50	38 (2.2)	Cortical thickness	ADHD < HC, right hemisphere: inferior parietal lobule, the dorsolateral prefrontal, and the anterior cingulate cortices
Biederman et al. (2008)	26 ADHD, 23 HC, 18 BPD, 31 ADHD + BPD	50	36.9 (11.1)	Manual parcellation of the neocortex	ADHD < HC, neocortex, overall frontal lobe and superior prefrontal cortex, right anterior cingulate cortex and cerebellum
Perlov et al. (2008)	27 Adult, 27 HC	63	32.4 (10.6)	Manual defined ROI: hippocampus and amygdala	ADHD = HC
Almeida et al. (2010)	21 ADHD children, 18 ADHD adolescents, 20 ADHD adults, 22 HC children, 20 HC adolescents, 20 HC adults	50	28.95 (4.01)	Cortical thickness	Children, adolescents and adult ADHD < HC, regions in the right superior frontal gyrus
Depue et al. (2010)	30 ADHD, 20 HC	61	20.0 (1.7)	VBM. Whole brain, ROI: the superior parietal lobule, right inferior frontal gyrus	ADHD = HC, whole brain. ADHD < HC, right inferior frontal gyrus
Frodl et al. (2010)	20 ADHD, 20 HC, 20 MD	75	33.6 (10.2)	Manual defined ROI: hippocampus and amygdala	ADHD < HC and MD, bilateral amygdala
Montes et al. (2010)	20 ADHD, 20 HC	50	28.95 (4.01)	VBM	ADHD < HC, caudate
Ahrendts et al. (2011)	31 ADHD, 31 HC	65	31.20 (9.70)	VBM	ADHD < HC, visual cortex
Amico et al. (2011)	20 ADHD, 20 HC	75	33.6 (10.2)	VBM. ROI: prefrontal cortex, cingulate cortex, hippocampus and amygdala	ADHD = HC, whole brain. ADHD < HC, anterior cingulate cortex
Proal et al. (2011)	59 Childhood ADHD, 80 HC. 17 persistent ADHD, 26 remitted ADHD	100	41.1 (2.7)	VBM and cortical thickness	ADHD < HC, total cerebral volume, global cortical thickness, right caudate, right thalamus, and bilateral cerebellar hemispheres
Seidman et al. (2011)	74 ADHD, 54 HC	51	37.3 (12.6)	VBM. Whole brain, ROI: dorsolateral prefrontal cortex, anterior cingulate cortex, caudate, putamen, inferior parietal lobule, and cerebellum	ADHD = HC, whole brain. ADHD < HC, dorsolateral prefrontal cortex, anterior cingulate cortex, caudate, putamen, inferior parietal lobule, and cerebellum

most frequently prescribed medications for ADHD (Heal et al., 2009), and are known to alter brain activity (Epstein et al., 2007). Studies examining the effects of stimulants on structural brain measures indicate that psychostimulants may not have a severe effect on the brain. In children with ADHD, no significant differences in brain volumes were found between medicated and treatment-naive children (Castellanos et al., 2002). Other studies reported that chronic stimulant

treatment is associated with normal volumes of brain structures, such as right anterior cingulate and cerebellar vermis (Bledsoe et al., 2009; Pliszka et al., 2006). Moreover, ADHD adolescents not receiving treatment showed more rapid cortical thinning compared with patients taking psychostimulants (Shaw et al., 2009). Two recent meta-regression analyses reported that stimulant use is associated with an absence of reductions of regional gray matter volumes using VBM, suggesting a normalizing effect of treatment on neural abnormalities (Frodl and Skokauskas, 2012; Nakao et al., 2011).

Neuroimaging research addressing the effects of co-morbidity between ADHD and major depressive disorder (MDD) is scarce, even though MDD co-occurs with adult ADHD in up to 50% of cases (McIntosh et al., 2009). There is a strong evidence that MDD is related with structural brain changes in the hippocampus and amygdala. Several meta-analyses demonstrated a reduction in hippocampal volume in patients relative to controls (Arnone et al., 2012; Cole et al., 2011; Du et al., 2012; Kempton et al., 2011; Koolschijn et al., 2009; Videbech and Ravnkilde, 2004). For amygdala volume, a meta-analysis showed that only unmedicated, and not medicated, depressed individuals have decreased amygdala volume relative to healthy controls (Hamilton et al., 2008). However, there is also evidence that amygdala volume may be enlarged in acute first episode MDD (van Eijndhoven et al., 2009). So far, three structural imaging studies examined current depression severity in adult ADHD. Perlov et al. (2008) investigated depression severity in a group of 27 patients and found a correlation between enlarged amygdala volume and depressive symptoms. Frodl et al. (2010) examined amygdala and hippocampal volumes in 20 patients with ADHD, 20 matched patients with MDD and 20 healthy controls. Hippocampal volumes were unaltered in ADHD patients and although patients had smaller amygdala volumes compared with the other groups, they demonstrated that higher rates of depressive symptoms in ADHD patients were related with larger amygdala volumes. Amico et al. (2011) studied depression severity in a sample of 20 ADHD adults, but found no correlation with structural alterations. In sum, the limited literature investigating depressive symptoms in ADHD does not support evidence for smaller hippocampal volume, and two studies suggest that larger amygdala volume is associated with higher current depression scores (Frodl et al., 2010; Perlov et al., 2008).

To shed more light on the issues discussed above, we investigated a large sample of 119 adult ADHD patients and 107 healthy comparison subjects. We were particularly interested in subcortical gray matter structures, which have been consistently found to be altered in persistent ADHD. This is in line with the hypothesis of Halperin and Schulz (2006), which provides a neurodevelopmental model for ADHD persistence proposing that the disorder is caused by non-cortical neural dysfunction that is present early in life and remains relatively stable throughout the lifetime, potentially compensated by prefrontal cortex function in remitting forms of ADHD. We used the automated FSL FIRST subcortical segmentation tool to compare regional volumetric data for a range of deep gray matter structures. A reduced caudate nucleus volume is one of the most consistent findings in childhood literature (Frodl and Skokauskas, 2012; Nakao et al., 2011; Valera et al., 2007), and while some studies suggest that this volume difference may disappear during adolescence (Ahrendts et al., 2011; Amico et al., 2011; Carmona et al., 2005; Castellanos et al., 2002; Depue et al., 2010), several studies still find reduced caudate volume in adult ADHD patients (Almeida Montes et al., 2010; Proal et al., 2011; Seidman et al., 2011). Moreover, caudate volume was found to be significantly smaller in patients in the largest MRI study performed in adult ADHD to this date ($n=74$). The results from Proal et al. (2011) nicely support the hypothesis by Halperin and Schulz by showing that caudate volume differences were present independent of whether ADHD persisted or remitted. Based on this evidence, we hypothesized that caudate volume differences are still present in adults with ADHD. In addition, we explored other brain structures for differences between patients and controls and the role of gender herein, expecting structural differences to be less pronounced in females than in males (Frodl and Skokauskas, 2012; Qiu et al., 2009). For differences observed, we explored their clinical relevance for symptom severity in ADHD. To test for additional regions of altered gray matter volume between patients and controls not captured by FSL FIRST, we also performed a voxel-based morphometry (VBM) analysis of the entire brain. We subsequently examined stimulant treatment effects on the subcortical brain volumes expecting to find that treatment-naive patients show smaller brain volumes as compared to patients taking medication (Frodl and Skokauskas, 2012; Nakao et al., 2011). Lastly, effects of a history of MDD in ADHD were investigated, since our sample contained enough ADHD patients diagnosed with previous MDD to reach an adequate sample size. Here, we focused on hippocampal and amygdala volumes for their known importance in depression. We expected smaller hippocampal volume in patients with a history of MDD (Arnone et al., 2012; Cole et al., 2011; Du et al., 2012; Kempton et al., 2011; Koolschijn et al., 2009; Videbech and Ravnkilde, 2004). Since we collected no information on current depression, we tested amygdala volume differences in an exploratory fashion.

2. Experimental procedures

2.1. Participants

228 Individuals (119 adult ADHD patients, 107 healthy comparison subjects) from the Dutch cohort of the International Multicentre persistent ADHD CollaboraTion, IMpACT (Franke et al., 2010a), participated in this study. The ADHD patients and the age-, gender-, and IQ-comparable group of healthy comparison subjects were recruited from the department of Psychiatry of the Radboud University Nijmegen Medical Centre and through advertisements. For the analyses of stimulant treatment effects, we split the ADHD group into a group of medication naive patients and a group of patients receiving stimulant treatment. Eight ADHD subjects receiving atomoxetine and 13 patients who had previously received medication and had stopped medication well before testing were excluded from this part of the analysis.

Patients were included if they met DSM-IV-TR criteria for ADHD in childhood as well as adulthood. All participants were assessed using the Diagnostic Interview for Adult ADHD (DIVA) (Kooij, 2010). This interview focuses on the 18 DSM-IV symptoms of ADHD and uses concrete and realistic examples to thoroughly investigate whether a symptom is currently present or was present in childhood. In order to

obtain information about ADHD symptoms and impairment in childhood, additional information was acquired from parent and school reports, whenever possible. The Structured Clinical Interview for DSM-IV (SCID-I & SCID-II) (Groenestijn et al., 1999; Weertman et al., 2000) was used for comorbidity assessment. Assessments were carried out by trained professionals (psychiatrists or psychologists). In addition, a quantitative measure of clinical symptoms was obtained using the ADHD-DSM-IV Self-Rating scale (Kooij et al., 2005).

Exclusion criteria for participants were psychosis, alcohol or substance use disorder in the last 6 months, current major depression, full-scale IQ estimate <70 (prorated from Block Design and Vocabulary of the Wechsler Adult Intelligence Scale-III), neurological disorders, sensorimotor disabilities, non-Caucasian ethnicity, and medication use other than psychostimulants or atomoxetine. An additional exclusion criterion for the healthy comparison subjects was a current neurological or psychiatric disorder according to SCID-I. This study was approved by the regional ethics committee. Written informed consent was obtained from all participants.

2.2. MRI acquisition and data processing

T1-weighted images were acquired using a 1.5 T MRI scanner (Sonata Siemens, Munich, Germany) at the Donders Centre for Cognitive Neuroscience. All scans covered the entire brain and had a voxel size of $1 \times 1 \times 1$ mm^3, TR 2730 ms, TI 1000 ms, TE 2.95 ms, 176 sagittal slices, field of view 256 mm.

For automatic segmentation of subcortical brain structures, the FIRST module (version 1.2) of FSL (version 4.1) was used (www.fmrib.ox.ac.uk/fsl/first/index.html). This method is based on Bayesian statistical models of shape and appearance for 17 subcortical structures from 317 manually labeled T1-weighted MR images. To fit the models, the probability of the shape given the observed intensities was used (Smith et al., 2004). In addition, to model intensity at the structural boundary, automatic boundary correction was applied. The scan-rescan reliability of FSL derived volumes is about 0.9 or higher for large structures such as the thalamus and caudate, but is smaller (0.6) for smaller structures such as the accumbens, pallidum and amygdala (Morey et al., 2010; Narayana et al., 1988). After automatic segmentation, volume determination of the subcortical structures was calculated using a script in Matlab7.2 (MathWorks, USA). In this script the volumes of the regional structures of interest were calculated by multiplying the number of voxels with the voxel volume (1 mm^3). Inspection of the segmented subcortical structures projected onto the T1-weighted MRI scans was performed using the software MRIcroN Version Beta 7 (www.mricro.com/mricron) to detect obvious seg mentation errors.

Whole brain segmentation of gray matter, white matter and cerebrospinal fluid (CSF) was performed using the VBM8 toolbox in SPM8. Total volume of gray and white matter was calculated by adding the resulting tissue probability maps. Total brain volume was defined as the sum of white and gray matter volume.

A post-hoc VBM analysis was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and Matlab7.2 (MathWorks, USA). Images were segmented into gray matter, white matter and CSF using the standard unified segmentation model in SPM8 (Ashburner and Friston, 2005). Gray matter population templates were generated from the entire image dataset using the diffeomorphic anatomical registration using exponentiated Lie algebra (DARTEL) technique (Ashburner, 2007). After an initial affine registration of the gray matter DARTEL templates to the tissue probability maps in Montreal Neurological Institute (MNI) space (http://www.mni.mcgill.ca/), non-linear warping of gray matter images was then performed to the DARTEL gray matter template in MNI space. Subsequently images were modulated to ensure that relative volumes of gray matter were preserved following the spatial normalization proce dure. Lastly, images were smoothed with an 8 mm full width at half maximum Gaussian kernel. After spatial pre-processing, the smoothed, modulated, normalized gray matter datasets were used for statistical analysis (absolute threshold: 0.2).

2.3. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS, Inc., Chicago, IL). Differences for total gray and white matter were tested with separate general linear models (GLM) with diagnosis and gender as fixed factors. Age and total white matter volume (when correcting for gray matter) and total gray matter volume (when correcting for white matter) were included in the model as co-variates. To compare volumetric data of our regions of interests (left and right nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidus, putamen and thalamus), a GLM was used in which the volumes were included as dependent factors. Diagnosis (healthy comparison subjects vs. ADHD patients), treatment (healthy comparison subjects vs. ADHD naive vs. ADHD stimulant-medicated) and depression history (ADHD patients with no history of depressive episodes vs. ADHD patients with one or more episodes in the past) were added as between subject factors. For each between-subject factor, a separate GLM analysis was used. For all the GLM analyses, age and total brain volume were included in the model as co-variates and gender was added as fixed factor to investigate interaction effects. Whenever this interaction term was significant at $\alpha=0.05$, we analyzed the results separately by gender. The relation between total number of self-reported ADHD symptoms and right caudate volume in male patients was studied using linear regression analysis adjusting for age and total brain volume. To explore effects of the distinct ADHD symptom domains, a similar analysis was performed including either inattentive symptom count or hyperactivity/impulsivity symptom count as an independent variable. Significance between subject findings was explored using linear regression analysis to investigate the relation between volume and duration of medication use (in months) adjusting for age and total brain volume. Because data for the rating scale scores and duration of medication use were highly positively skewed, prior to the regression analyses, a logarithmic transformation was conducted because data for the rating scale scores and duration of medication use were highly positively skewed. All statistical tests were two-sided, unless stated otherwise. As we hypothesized smaller caudate nucleus volume in ADHD and smaller hippocampus volume in former depressed ADHD patients, we performed a one-sided test and did not correct for multiple testing for these structures. All other tests were corrected for multiple testing. This correction consisted of adjusting p-values based on the false discovery rate (FDR) controlling procedure with a p-value of less than 0.05 (Benjamini and Hochberg, 1995).

For the post-hoc VBM analysis, group differences in absolute gray matter volume were assessed using a full-factorial ANCOVA with diagnosis and gender included as factors and participants' age and total brain volume added to the model as covariates. The FDR correction for multiple comparisons was used with a p-value of less than 0.05. The extent threshold was set at 10 voxels, to eliminate very small clusters.

3. Results

A total of 119 adult ADHD patients and 107 healthy comparison subjects were included in the analysis. The demographics for this sample are summarized in Table 2. There were no significant differences in age and estimated IQ between patients and controls ($p>0.05$), and sex ratio did not significantly differ between the two groups ($\chi^2=0.25$, $p=0.68$). Group-by-sex ANOVAs showed group

Table 2 Demographic characteristics of ADHD patients and healthy comparison subjects.

Variable	Total group		Males		Females	
	HC (n=107)	ADHD (n=119)	HC (n=45)	ADHD (n=46)	HC (n=62)	ADHD (n=73)
Age	36.92±11.54	36.29±10.90	36.02±11.06	37.72±10.47	37.56±11.92	35.40±11.14
Esitmated IQ[a]	110.21±15.35	107.49±14.69	112.11±14.68	106.57±14.11	108.84±15.79	108.07±15.11
Inattentive symptoms[b]	0.62±1.12	6.43±2.06	1.02±1.39	6.87±2.06	0.32±0.76	6.15±2.03
Hyperactive/impulsive symptoms[b]	0.82±1.29	5.60±2.24	1.11±1.56	5.63±2.09	0.61±1.01	5.58±2.35
	N	N	N	N	N	N
One or more depressive episode (remitted)[c]	11 (10%)	55 (46%)	6 (13%)	17 (37%)	5 (9%)	38 (52%)
Bipolar (remitted)[c]	0	8 (7%)	0	3 (7%)	0	5 (7%)
Anxiety disorder (remitted)[c]	7	27 (23%)	4 (9%)	7 (15%)	3 (5%)	20 (27%)
Substance abuse (remitted)[c]	8	22 (18%)	7 (16%)	17 (36%)	1 (2%)	5 (7%)
Borderline[c]	0	10 (8%)	0	2 (4%)	0	8 (11%)
Antisocial[c]	0	3 (3%)	0	2 (4%)	0	1 (1%)
Medication-naive	-	16 (13%)	-	9 (20%)	-	7 (10%)
On stimulant medication	-	82 (69%)	-	29 (61%)	-	53 (74%)
Medication in the past	-	13 (11%)	-	6 (13%)	-	7 (10%)
On atomoxetine	-	8 (7%)	-	2 (4%)	-	6 (8%)

Demographic information representing mean±standard deviations or percentage per group. HC=healthy comparison subject.
[a]Prorated from Block Design and Vocabulary of WAIS-III-R.
[b]As measured with the ADHD-DSM-IV Self-Rating scale (Kooij et al., 2005).
[c]As measured by the Structured Clinical Interview for DSM-IV for axis I (Groenestijn et al., 1999) and axis II (Weertman et al., 2000) disorders.

effects for number of self-reported symptoms for inattention (F(1, 222)=673.33, p>0.001) and hyperactivity/impulsivity symptoms (F(1, 222)=354.17, p>0.001) and sex effect for number of symptoms for inattention (F(1, 222)=9.94, p=0.002) but no interactions. The subjects with ADHD had higher number of self-reported symptom of inattention and hyperactivity/impulsivity and the women had higher number of self-reported symptoms for inattention. There were no significant differences in sex ratio and age and estimated IQ was not different between healthy comparison subjects, ADHD naive and ADHD stimulant-medicated patients (p>0.05). The groups differed on symptoms for inattention and hyperactivity/impulsivity symptoms (F(2, 199)=344.26, p>0.001; F(2, 199)=192.51, p>0.001). On both scales, healthy comparison subjects, showed lower number of symptoms than ADHD naive and ADHD stimulant-medicated. There were no significant differences in age, estimated IQ between and number of symptoms for inattention and hyperactivity/impulsivity symptoms between ADHD patients with one or more episode in the past and no history of depressive episodes (p>0.05). The group ADHD patients with one or more episode in the past contained more females than the group ADHD patient with no history of depressive episodes (χ^2=3.94, p=0.047).

Comparison of the volumes of caudate nucleus between patients and controls showed no main effect of diagnosis on volume (Table 3). However, when probing caudate volumes for interaction effects of ADHD diagnosis and gender, right caudate volume showed a significant interaction effect (F(1, 220)=5.84, p=0.016, partial eta squared=0.026). Separate post-hoc analyses for both genders indicated that right caudate volume was significantly smaller in male ADHD patients (F(1, 87)=7.14, $p_{one\text{-}sided}$=0.005, partial eta squared=0.076), while this was not the case in females (F(1, 131)=0.55, $p_{one\text{-}sided}$=0.23, partial eta squared=0.004). Results for the analysis of the volumes of nucleus accumbens, amygdala, hippocampus, globus pallidus, thalamus, and total white and gray matter are summarized in Table 3. No differences between ADHD patients and healthy subjects were observed for total brain volume, gray matter or white matter volume. In addition, none of the other subcortical brain volumes nor hippocampus volume differed significantly. Taking gender into account did not change these results. A post-hoc, whole-brain, voxel-by-voxel examination comparing the subjects and controls did not reveal any areas with significant gray matter differences, nor was there no significant effect of diagnosis × gender interaction (p<0.05, FDR corrected).

In the male ADHD patients, a linear regression analysis showed right caudate volumes were significantly associated with the total number of ADHD symptoms (β=−0.35, p=0.011). Post-hoc analysis indicated that the association in the right caudate was primarily due to an effect on hyperactive/impulsive (β=−0.42, p=0.002) rather than inattentive (β=−0.15, p=0.30) symptoms. In Figure 1, the relationship between right caudate volume and symptom rates is shown.

In a more exploratory design, we tested the effect of stimulant treatment. As shown in Table 4, stimulant treatment was associated with volumes of the right amygdala (F(2, 197)

Table 3 Bilateral and total volumes (ml) ± standard error for ADHD patients (ADHD) and healthy comparison subjects (HC) based on the estimated marginal means and controlled for age, gender and total brain volume. Volumes are also shown for males (M) and females (F), separately.

	HC (n=107)	HC M (n=45)	HC F (n=62)	ADHD (n=119)	ADHD M (n=46)	ADHD F (n=73)
L CDN	2.60 ± 0.03	2.74 ± 0.04	2.51 ± 0.03	2.57 ± 0.02	2.65 ± 0.04	2.51 ± 0.03
R CDN	2.69 ± 0.03	**2.88 ± 0.04**	2.56 ± 0.03	2.65 ± 0.02	**2.74 ± 0.04**	2.59 ± 0.03
L ACC	0.34 ± 0.01	0.37 ± 0.01	0.33 ± 0.01	0.34 ± 0.01	0.37 ± 0.01	0.33 ± 0.01
R ACC	0.37 ± 0.01	0.40 ± 0.01	0.36 ± 0.01	0.36 ± 0.01	0.38 ± 0.01	0.35 ± 0.01
L AMY	1.11 ± 0.01	1.19 ± 0.02	1.06 ± 0.02	1.10 ± 0.01	1.20 ± 0.02	1.04 ± 0.02
R AMY	1.09 ± 0.01	1.18 ± 0.02	1.02 ± 0.02	1.10 ± 0.01	1.21 ± 0.02	1.04 ± 0.02
L HIPP	2.76 ± 0.03	2.97 ± 0.04	2.62 ± 0.03	2.77 ± 0.02	2.92 ± 0.04	2.66 ± 0.03
R HIPP	2.69 ± 0.02	2.85 ± 0.04	2.57 ± 0.03	2.66 ± 0.02	2.80 ± 0.04	2.57 ± 0.03
R GP	0.92 ± 0.01	1.00 ± 0.01	0.86 ± 0.01	0.92 ± 0.01	0.99 ± 0.01	0.88 ± 0.01
L GP	0.96 ± 0.01	1.02 ± 0.01	0.91 ± 0.01	0.96 ± 0.01	1.03 ± 0.01	0.91 ± 0.01
L PUT	3.01 ± 0.03	3.25 ± 0.04	2.84 ± 0.04	3.02 ± 0.03	3.22 ± 0.04	2.88 ± 0.03
R PUT	3.06 ± 0.03	3.31 ± 0.05	2.88 ± 0.04	3.01 ± 0.03	3.21 ± 0.04	2.89 ± 0.04
L THA	5.43 ± 0.03	5.70 ± 0.05	5.25 ± 0.04	5.43 ± 0.03	5.70 ± 0.05	5.25 ± 0.04
R THA	5.77 ± 0.03	6.06 ± 0.05	5.56 ± 0.04	5.71 ± 0.03	5.97 ± 0.05	5.54 ± 0.07
GRAY	732.61 ± 5.25	774.12 ± 8.40	705.02 ± 6.75	737.53 ± 4.98	771.31 ± 8.31	714.08 ± 6.22
WHITE	504.17 ± 4.19	537.35 ± 7.02	482.00 ± 5.19	508.93 ± 3.97	536.32 ± 6.94	490.06 ± 4.78

HC: healthy controles; ADHD: ADHD patients; M: males; F: females; L: left; R: right; CDN: caudate; ACC: accumbens; AMY: amygdala; HIPP: hippocampus; GP: globus pallidus; PUT: putamen; THA: thalamus; T BRAIN: total of white and gray matter; GRAY: volume of gray matter; WHITE: volume of white matter. Bold indicates results at $p<0.05$.

=3.81, p=0.024, p_{adj}=0.096, partial eta squared=0.037), left and right caudate (left: F(2, 197)=3.28, p=0.040, p_{adj}=0.128, partial eta squared=0.031; right: F(2, 197) =3.13, p=0.046, p_{adj}=0.122, partial eta squared =0.031), left globus pallidus (F(2, 197)=3.84, p=0.023, p_{adj}=0.122, partial eta squared=0.037), right putamen (F(2, 197)=4.28, p=0.015, p_{adj}=0.120, partial eta squared=0.041) and right hippocampus (F(2, 197)=6.31, p=0.002, p_{adj}=0.042, partial eta squared= 0.060). The effect on right hippocampus volume survived multiple comparisons correction. Post-hoc tests revealed that patients using stimulant treatment had a smaller right hippocampus volume compared to medication-naïve patients (p=0.001) and controls (p=0.016). A linear regression showed that right hippocampus volume was not associated with duration of stimulant use (β=0.09, p=0.333).

As shown in Table 1, 46% of the ADHD patients had had one or more depressive episodes in the past. A comparison between ADHD patients with and without a history of MDD revealed significantly smaller left hippocampus volume in ADHD patients with at least one past depressive episode (F(1, 108)=5.21, $p_{one\text{-}sided}$=0.012, partial eta squared=0.043), but no effects on amygdala volumes (Table 5).

4. Discussion

In the present study, we investigated total, subcortical and hippocampal brain volumes in a sample of 119 adult ADHD patients and 107 healthy comparison subjects. The analyses of regional brain volumes were all adjusted for total brain volume. Our hypothesis of smaller caudate volume in adult ADHD was confirmed, though the right caudate volume was only smaller (relative to brain size) in male patients. This gender effect was consistent with our hypothesis that structural differences are less pronounced in females than in males. We demonstrated in addition, that the reduction in the caudate was correlated with severity of the illness, with a smaller caudate being associated with more ADHD symptoms (primarily hyperactive/impulsive symptoms). We found no reduction of total gray or white matter volume in patients compared to healthy comparison subjects, nor were any of the other subcortical brain volumes or hippocampus volume affected. In the VBM analysis, no additional differences in cortical gray matter volume were observed between adult patients and controls either. Patients using stimulant treatment had a smaller right hippocampus volume compared to medication-naïve patients and controls. ADHD patients with a lifetime history of MDD showed a smaller volume of left hippocampus compared with ADHD patients having no earlier episodes of MDD. Effect sizes (given as partial eta-squared) for the observed effects ranged from 0.043 (for hippocampus volume in depression) to 0.06 (for hippocampus volume in stimulant users) and 0.076 (for caudate nucleus finding in ADHD males), which means that the effect sizes were small to modest.

The fact that only few differences between adult patients and controls were found is in line with hypotheses of developmental delay and normalization of brain structure in adulthood (Shaw et al., 2007, 2012). Our finding of an absence of total brain (sum of gray and white matter)

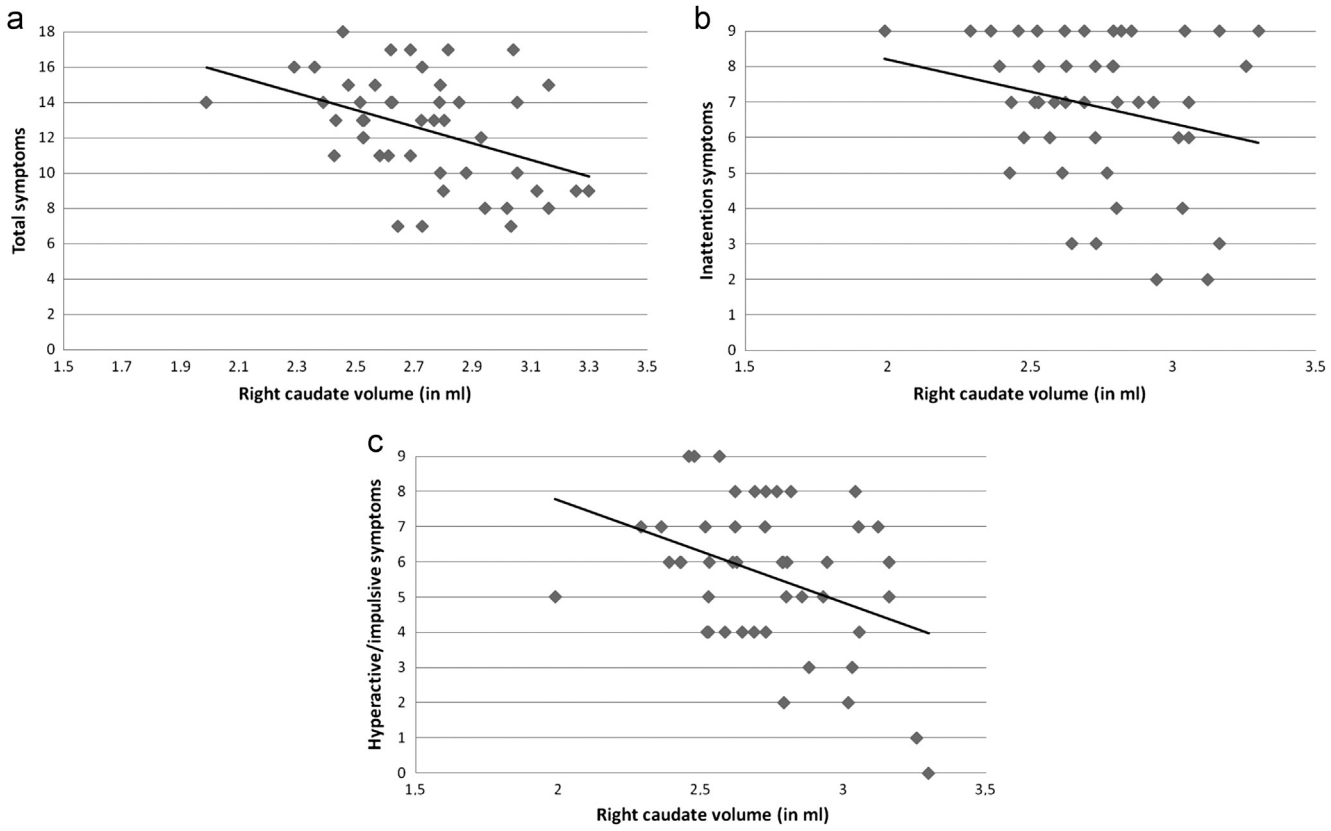

Figure 1 (A–C) Association between the volume of the right caudate in male ADHD patients and number of total, inattentive and hyperactive/impulsive symptoms on the ADHD-DSM-IV Self-Rating scale. The dots represent individual volumes and the solid line represents the linear fit.

volume differences is a common finding in ADHD (Biederman et al., 2008; Hesslinger et al., 2002; Perlov et al., 2008; Seidman et al., 2006). The absence of total brain volume in our sample was not reflected by an imbalance between white and gray matter as found by Seidman et al. (2006), nor was it related to an effect of stimulant treatment as reported by Castellanos et al. (2002).

Whereas cortical brain volume seems to normalize, we confirm prior evidence that smaller caudate volume is persistent in ADHD (Almeida Montes et al., 2010; Proal et al., 2011; Seidman et al., 2011). Moreover, the current results extend these studies by showing that caudate volume phenotype might be a gender-specific effect only observed in males with ADHD. This is in line with a study in children showing smaller basal ganglia volumes only in ADHD boys (Qiu et al., 2009). In addition, our study shows that caudate volume reduction in male patients is associated with ADHD symptoms, with higher hyperactive/impulsive ratings linked to smaller volume in the right caudate. The association with hyperactive/impulsive ratings with caudate volume is consistent with the literature that the caudate is part of the extrapyramidal motor system and plays an important role in locomotor control (Ferris, 1972; Rebec, 2006). Furthermore, a study in ADHD children showed that task performance on a response inhibition task is positively associated with caudate volume (Casey et al., 1997). While there seems to be a link with symptom levels, the link with disease persistence is less clear. The normalization of caudate volume in ADHD by late adolescence as shown in the longitudinal study of Castellanos et al. (2002) seems parallel to the reported reduction of overt hyperactivity during adolescence (Biederman et al., 2000; Hill and Schoener, 1996). Indeed, we also find that the reduction of caudate volume is correlated with impulsive/hyperactive symptoms in male adult patients, which suggests that persistence of overt hyperactivity might be related to persistent volume reductions of the caudate. On the other hand, Proal et al. (2011) investigated structural differences between ADHD remitters and persisters and found that, among other regions, a reduced right caudate volume was present in patients independent of whether they had persistent ADHD or had remitted. This finding is in line with the hypothesis of Halperin and Schulz (2006) that subcortical dysfunction that manifests early in life, remains static throughout the lifetime, and is not associated with the remission of symptomatology.

Although male and female adults with ADHD have similar phenotypic features in terms of symptom ratings and comorbidity patterns (Biederman et al., 2004), the gender-specific finding for caudate nucleus volume suggests that partially distinct neurobiological deficits underlie ADHD in males and females. At the neurocognitive level, there is evidence that adolescent males with ADHD show more impaired inhibition than female patients (Rucklidge, 2006). Interestingly, the caudate nucleus is involved in impulse inhibition in a sex-specific manner, as shown by a recent study in healthy subjects (Liu et al., 2012). During a

Table 4 Bilateral and total volumes (ml) ± standard error for healthy comparison subjects (HC), stimulant-naive ADHD patients (ADHD naive: medication for ≤1 month) and stimulant-medicated patients (ADHD medicated: stimulant treatment for >1 month) based on estimated marginal means and controlled for age, gender and total brain volume.

	HC (n=107)	ADHD naïve (n=16)	ADHD stimulant-medicated (n=82)
L ACC	0.35 ± 0.01	0.37 ± 0.01	0.34 ± 0.01
R ACC	0.37 ± 0.01	0.37 ± 0.01	0.36 ± 0.01
L AMY	1.12 ± 0.01	1.14 ± 0.04	1.12 ± 0.02
R AMY	**1.10 ± 0.01**	**1.20 ± 0.04**	**1.10 ± 0.02**
L CDN	**2.61 ± 0.03**	**2.69 ± 0.07**	**2.53 ± 0.03**
R CDN	**2.71 ± 0.03**	2.75 ± 0.07	**2.62 ± 0.03**
L HIPP	2.78 ± 0.03	2.82 ± 0.07	2.75 ± 0.03
R HIPP	**2.70 ± 0.02**[a]	**2.83 ± 0.06**[a]	**2.61 ± 0.03**[a]
L GP	**0.96 ± 0.01**	**1.01 ± 0.02**	**0.95 ± 0.01**
R GP	0.93 ± 0.01	0.96 ± 0.02	0.92 ± 0.01
L PUT	3.03 ± 0.03	3.14 ± 0.07	2.99 ± 0.03
R PUT	**3.09 ± 0.03**	**3.17 ± 0.08**	**2.97 ± 0.04**
L THA	5.45 ± 0.03	5.55 ± 0.08	5.44 ± 0.04
R THA	5.78 ± 0.03	5.90 ± 0.09	5.69 ± 0.04
GRAY	738.13 ± 4.17	744.08 ± 10.75	741.14 ± 4.9
WHITE	508.42 ± 3.29	509.17 ± 8.49	510.79 ± 3.90

HC: healthy controls; ADHD: ADHD patients; L: left; R: right; ACC: accumbens; AMY: amygdala; CDN: caudate; HIPP: hippocampus; GP: globus pallidus; PUT: putamen; THA: thalamus; T BRAIN: total of white and gray matter; GRAY: volume of gray matter; WHITE: volume of white matter. Bold indicates results at $p<0.05$.

[a]Indicated significance after multiple testing.

Table 5 Bilateral and total hippocampus volumes (ml) ± standard error for ADHD patients with no MDD history (ADHD −) and ADHD patients remitted from one or more episodes of MDD (ADHD +) based on estimated marginal means and controlled for age, gender and total brain volume.

	ADHD depression − (n=54)	ADHD depression + (n=53)
L HIPP	**2.81 ± 0.03**	**2.71 ± 0.04**
R HIPP	2.70 ± 0.03	2.62 ± 0.04
L AMYG	1.12 ± 0.02	1.10 ± 0.02
R AMYG	1.13 ± 0.02	1.09 ± 0.02

ADHD depression −: ADHD patients with no MDD history; ADHD depression +: ADHD patients remitted from one or more MDD; L: left, R: right; HIPP: hippocampus. Bold indicates results at $p<0.05$.

stop task, activation of the caudate nucleus and putamen in males was positively correlated with task performance. Females showed a positive correlation in the right inferior temporal gyrus, while activation of the precuneus was negatively correlated with task performance. A better understanding of sex differences in brain anatomy and activity would improve our understanding of the basis for different neurocognitive profiles (such as impulse inhibition) in males and females with ADHD. In that respect, an fMRI study in ADHD looking specifically at gender differences reported that ADHD males, but not ADHD females, showed significantly altered patterns of neural activity during a verbal working memory task (Valera et al., 2010). Importantly, the results from MRI studies in childhood ADHD, which mostly included boys, need to be considered with caution since findings may not generalize to both genders.

The VBM analysis did not pick up the gender-specific effect on right caudate found with FSL FIRST. This is likely due to the fact that the reduction is dispersed across the entire caudate nucleus, with small effects, below detection limit, on individual voxels measured in VBM.

Patients using stimulant treatment had a smaller right hippocampus volume compared to medication-naïve patients and controls. This unexpected finding is not in line with a meta-analysis suggesting that untreated children have additional structural reductions compared with children receiving treatment (Frodl and Skokauskas, 2012). There was no effect of duration of stimulant medication use on the right hippocampus volume, which makes it difficult to draw firm conclusions regarding the effect of long term use of stimulants in adult ADHD.

In the present study we also investigated the effects of the most frequent co-morbidity of adult ADHD, i.e. MDD, on brain structure. Observing smaller volumes of total and left hippocampus in ADHD subjects with a history of MDD is in

line with well-studied reductions in hippocampal volume in patients with current and recurrent depression (Arnone et al., 2012; Cole et al., 2011; Du et al., 2012; Kempton et al., 2011; Koolschijn et al., 2009; Videbech and Ravnkilde, 2004). Previous findings suggested that depression severity in ADHD adults had no effect on hippocampal volumes (Frodl et al., 2010). In this previous study, depression severity had been measured using a self-report measure of current MDD symptoms, whereas we used a clinical retrospective diagnosis of past MDD episodes. This is a possible explanation for the conflicting results, while there are indications that hippocampal volume may decrease at the greatest rate early after MDD onset (MacQueen et al., 2003). Further studies are clearly needed to fully elucidate the link between MDD and structural brain changes in ADHD.

The results of this study should be considered in the context of some strengths and limitations. Our MRI study sample is the largest one published to date for clinically diagnosed adult ADHD, a clear strength of this work. Because our main hypotheses were based on caudate nucleus and hippocampus volumes, we chose to use FSL FIRST, which is known to be a reliable tool for the automated segmentation of subcortical structures (Morey et al., 2010; Narayana et al., 1988) and is successfully used in other studies (De Jong et al., 2008; Franke et al., 2010b; Narayana et al., 1988; Rijpkema et al., 2012; Seror et al., 2010). Certain localized changes in subcortical structures can also be detected using voxel-based morphometry (VBM), but is more sensitive to inaccuracies of tissue-type classification and arbitrary smoothing extents (Patenaude et al., 2011). Due to the poor and variable intensity contrast, VBM might be more prone to registration artifacts in the deep gray matter (Bookstein, 2001). Additionally, Frodl and Skokauskas (2012) suggested that changes in smaller regions like the amygdala and hippocampus might be more difficult to detect with VBM when large cluster threshold corrections for the whole brain are used. Although, besides the volumes of subcortical structures, we were interested in cortical gray matter volume. We therefore performed a whole brain VBM which is not biased towards a priori hypothesized regions (Friston et al., 2006) which additionally increases comparability with previous research.

This study was not initially designed to study stimulant medication effects, therefore we were not able to study the effects of different doses of treatment. In addition, treatment histories of patients were solely based on self-report, which may be vulnerable to biases.

In conclusion, the results presented here provide support for the hypothesis that alterations in right caudate volume persist into adulthood in ADHD in males. This gender difference advocates for gender to be taken into account in future neuroimaging studies. Caudate volume correlated with behavioral measures of hyperactivity/impulsivity in the male patients, which may point to different ADHD pathophysiology in men and women. Depression in ADHD was related to hippocampal volume reduction, but it has to be clarified whether effects of current depressive symptoms also exist. Finally, as brain alterations in children and adults with ADHD seem not to be restricted to isolated brain regions in most cases, further studies should also investigate structural and functional connectivity in neural networks in ADHD.

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Contributors

Onnink, Zwiers, Hoogman, Kan, Buitelaar and Franke participated in the design of the study. Onnink, Zwiers, Buitelaar and Franke wrote the manuscript. Onnink, Hoogman, Mostert and Kan collected the data. Onnink performed statistical analysis. All authors contributed and have approved the final manuscript.

Conflict of interest

All authors report to have no conflict of interest. Kan was a paid member of the European Adult ADHD Advisory Board of Eli Lilly in 2011 and 2012. Buitelaar has served as a consultant, advisory board member, or speaker for Bristol-Myers Squibb, Janssen Cilag BV, Eli Lilly, Novartis, Schering-Plough, Shire, Servier, and UCB. He is not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. The other authors report no financial relationships with commercial interests.

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