Research Paper
Article de recherche

Hippocampus and amygdala morphology in adults with attention-deficit hyperactivity disorder

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Objective: Attention-deficit hyperactivity disorder (ADHD) in adulthood is a serious health problem with a prevalence of up to 4%. Limbic structures have been implicated in the genesis of ADHD; it has been suggested that they mediate mood and cognitive disturbances in affected individuals. Recently, a large study involving children and adolescents with ADHD reported bilateral enlargement of the hippocampus and indirect evidence of amygdala volume loss in this patient sample. We sought to test the hypothesis that, like in pediatric patients, there might be hippocampus and amygdala volume abnormalities in adult patients with ADHD. **Methods:** We studied 27 adult patients with ADHD and 27 group-matched healthy volunteers using a 1.5 T magnetic resonance imaging scanner. We manually obtained morphometric measurements of the regions mentioned. **Results:** In contrast to previous findings in children and adolescents, we found no significant differences in hippocampus and amygdala volumes among adults with and without the disorder. **Conclusion:** Findings of hippocampus enlargement and amygdala volume loss are not very stable across different samples of patients with ADHD. Contradictory findings may be related to the different locations of alterations along the complex circuits responsible for the different symptoms of ADHD. Further studies involving larger samples of adult patients with ADHD and using multimodal designs are needed.

Objectif : Le trouble d'hyperactivité avec déficit de l'attention (THADA) chez l'adulte est un problème de santé grave dont la prévalence peut atteindre 4 %. On a incriminé les structures limbiques dans la genèse du THADA et laissé entendre qu'elles jouent un rôle dans les troubles de l'humeur et de la cognition chez les individus atteints. Récemment, une étude d'envergure portant sur des enfants et des adolescents atteints de THADA a signalé une hypertrophie bilatérale de l'hippocampe et des preuves indirectes de perte de volume du complexe amygdalien dans cet échantillon de patients. Nous avons cherché à vérifier l'hypothèse selon laquelle il pourrait y avoir chez les patients adultes atteints du THADA des anomalies du volume de l'hippocampe et de l'amygdale, comme chez les patients en pédiatrie. **Méthodes :** Nous avons étudié 27 patients adultes atteints du THADA et 27 volontaires en bonne santé jumelés selon le groupe au moyen d'un appareil d'imagerie par résonance magnétique 1,5 T. Nous avons pris manuellement des mesures morphométriques des régions mentionnées. **Résultats :** Contrairement aux constatations antérieures faites chez les enfants et les adolescents, nous n'avons constaté aucune différence importante au niveau du volume de l'hippocampe et de l'amygdale chez les adultes atteints ou non du trouble. **Conclusion :** Les constatations relatives à l'hypertrophie de l'hippocampe et à la perte de volume de l'amygdale ne sont pas très stables entre différents échantillons de patients atteints du THADA. Les constatations contradictoires peuvent être liées aux lieux différents des altérations dans les circuits complexes responsables des différents symptômes du THADA. D'autres études portant sur des échantillons plus importants de patients adultes atteints du THADA et utilisant des concepts multimodaux s'imposent.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a serious mental dysfunction that begins in childhood and may persist into adult life in a substantial subgroup of patients.[1] It affects adults with an estimated prevalence of up to 4%.[2] Patients

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Medical subject headings: hippocampus; amygdala; attention deficit disorder with hyperactivity.

J Psychiatry Neurosci 2008;33(6):509-15.

Submitted Jun. 21, 2007; Revised Dec. 11, 2007; Jan. 30, Jan. 31, 2008; Accepted Jan. 31, 2008

with ADHD have high levels of impulsivity and inattentiveness, and often high levels of hyperactivity, resulting in important impairment of family, work and social functioning.[1,3,4] Mood and anxiety disorders, disorganized behaviour, emotional dysregulation and substance abuse are common comorbidities of ADHD in adults.[5]

Little is known about the neuroanatomic brain abnormalities in adults with ADHD.[6] Although there are about 30 publications from more than a dozen research groups employing structural neuroimaging in children with ADHD, to our knowledge there are only 2 published structural neuroimaging reports on adults.[6,7]

In the latest meta-analysis of structural imaging findings in children with ADHD, statistically significant differences relative to control participants were reported for cerebellar regions of interest (ROIs); the splenium of the corpus callosum; total and right cerebral volume; right caudate, prefrontal and other frontal lobe ROIs; and deep frontal white matter.[8]

Recently, a very large study by Plessen and colleagues[9] involving children and adolescents with ADHD reported an increased volume of the hippocampus bilaterally in those with the disorder. The hippocampus is known to be involved in attentional processes such as visuospatial working memory[10] and in modulating executive functions.[11] Disturbances in these functional domains belong to core symptoms of ADHD.[9] In the same study, the authors reported indirect evidence of a reduced size of the basolateral amygdala complex in children and adolescents with ADHD.

The finding of altered amygdala and hippocampus volumes in ADHD is of particular interest for adult patients with ADHD because affective symptoms, emotional instability and impulsivity often dominate the clinical picture in this age group compared with hyperactivity and inattentiveness, which often play a minor role. There is evidence of an increased risk of psychiatric comorbidity for almost all affective disorders in patients with ADHD and their family members,[12,13] yet the clinical presentation of such affective syndromes in adults with ADHD is often atypical.[14,15]

Morphometric abnormalities of the hippocampus and the amygdala frequently have been reported in different psychiatric disorders with affective symptoms.[16–21] Thus the hypothesis that amygdala and hippocampus alterations may be a pathogenetic link between the core disorder of ADHD and particular affective symptoms in adult patients with ADHD is intriguing.

To replicate the morphometric brain findings mentioned previously in a population of adults with ADHD, we organized brain investigations based on morphometric magnetic resonance imaging (MRI).

Based on previous findings in children with ADHD described by Plessen and colleagues,[9] we expected to find reduced volumes of the amygdala and enlarged volumes of the hippocampus in adult patients with ADHD compared with healthy controls.

We also sought to test whether the volumes of the amygdala and hippocampus correlate with the severity of ADHD symptoms or subsyndromal depressive symptoms (in the absence of actual comorbidity with major depressive disorders [MDDs]).

Methods

Patients and patient assessment

We obtained approval for this study from the local ethics committee of the Albert-Ludwigs-Universität Freiburg. All patients and healthy control participants provided informed consent before enrolment. The data presented here are part of a larger and ongoing project at the University Hospital of Freiburg in which we are attempting to define the cross-sectional and longitudinal neuroanatomy and neurochemistry in adult patients with ADHD (Freiburg ADHD Imaging Study in Adults [FAISA]). The spectroscopic findings of the FAISA study have been published separately.[22]

We included 27 adult patients (17 male, 10 female) from our ADHD outpatient clinic. Senior consulting psychiatrists diagnosed ADHD based on psychometric investigations and a structured clinical interview (SCID) according to German guidelines[23] that correspond with current criteria of the *Diagnostic and statistical manual of mental disorders*, fourth edition (DSM-IV), adapted for the special needs of adults (as proposed by the German Medical Association, www.bundesaerztekammer.de). For the diagnosis of the combined subtype, we required that participants exhibit 6 of 9 items for inattention and 6 of 9 items for hyperactivity/impulsivity. We excluded patients with comorbid current MDDs, borderline personality disorder, substance abuse/dependency, other axis-I or -II diseases, neurologic brain diseases, learning disabilities or any other medical diagnoses that might affect the brain metabolism (e.g., liver or kidney failure). We took care to include only the patients who were medication-free for at least 6 months and medication-naive for methylphenidate (only 1 patient had been prescribed short-term therapy with methylphenidate during childhood).

We rated symptoms of ADHD in childhood using the short version of the Wender Utah Rating Scale (WURS;[24] German version[25]), including 25 items on a 5-point Likert scale (presence of symptom rated "not at all" to "severe"). We used the WURS to retrospectively assess ADHD symptoms in childhood. Although this is not an ideal method for the retrospective assessment of ADHD,[26] we used this scale owing to lack of better instruments. Psychometrically, we rated the severity of ADHD symptoms in adulthood on a 3-point Likert scale corresponding to the diagnostic criteria of DSM-IV (ADHD Check List [ADHD-CL]).[27] We assessed depressiveness using the Beck Depression Inventory (BDI);[28] we excluded comorbid axis-I disorders based on the SCID-I and comorbid axis-II disorders based on the SCID-II.[29]

We recruited 27 healthy control participants (15 men, 12 women) via announcements at the university. We carefully matched control participants with respect to age, handedness (only right-handed people were included), sex and years of education. They participated in a clinical interview with 2 senior psychiatric consultants, and we excluded from the study those with relevant psychiatric syndromes; a history of neurologic, psychiatric or psychotherapeutic treatments; or first-degree relatives with known psychiatric disorders.

Imaging and measurements

We obtained the magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy data using a 1.5 T whole-body system (MAGNETOM Sonata; Siemens) with a standard quadrature head coil. To analyze volumetric data, we acquired a high-resolution anatomic 3-dimensional data set using a magnetization-prepared rapid acquisition gradient-echo imaging (MPRAGE) sequence with the following parameters: repetition time (TR) = 1670 ms, echo time (TE) = 3.9 ms, inversion time (TI) = 1100 ms, flip angle = 15°, matrix 256 × 256 pixels, field of view (FOV) = 256 × 256 mm^2. We transferred the images to a Sun workstation via a network (Sun Microsystems). We obtained volumetric measurements using the interactive software program *MRreg* (Epilepsy Research Group, Institute of Neurology, UCL).[30] We outlined the ROIs manually (original magnification × 4) with a mouse-driven cursor, following the established protocol described by Watson and colleagues.[31] We measured the total brain volume by manual delineation of the internal face of the cranium at every 10 slices (original magnification × 2). We calculated the volume of each structure in each slice (the in-slice volume) by multiplying the number of voxels contained within each trace by the voxel volume, 1 × 1 × 1 mm^3, and dividing by the magnification factor. The total volume of each structure was the sum of all in-slice volumes. To correct the substructure volumes for total brain size, we divided the total volume by the intracranial volume, according to the method described by Cendes and colleagues[32] and published in previous works from our group.[33,34] We mixed the images of all patients and healthy control participants, blinding the rater to the identity of the participants. We calculated intrarater reliability figures from repeated measurements of a subset of 20 healthy control participants.

Definition of ROIs

A rater who was blind to the identity of the participants and laterality of the images segmented all ROIs. The delineation of each ROI followed a well established and validated protocol. The rater was allowed to begin with the measurements only after proving a sufficient reliability in a separate subset of 20 images of healthy volunteers who were not otherwise used in this study.

We measured hippocampus and amygdala volumes by manually outlining the boundaries of each structure separately (Fig. 1), following a well established and validated protocol[31,35] that has been used in several other studies by our group.[33,34]

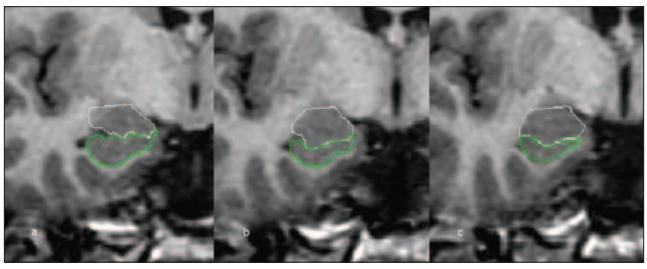

Fig. 1: Example of volumetric segmentation of the amygdala and hippocampus from (left) ventral to (right) caudate segment.

We manually delineated the total brain volume, including the cerebrum, cerebellum and brainstem superior to the pons, following earlier methods used by our group.[32–34] We calculated an intraclass correlation coefficient for the assessment of an intrarater reliability, as suggested by Streiner and Norman.[36] The intraclass correlation coefficient was 0.91 for the right amygdala, 0.96 for the left amygdala, 0.91 for the right hippocampus and 0.95 for the left hippocampus.[33,34]

Statistical analysis

For group comparisons, we used 2-sided *t* tests for parametric variables and χ^2 tests for categorical variables such as sex. To calculate a possible group effect on the volumes of ROIs, we performed a multivariate analysis of covariance (MANCOVA), controlling for age, years of education and sex. In addition, we used the 2-sided *t* test to calculate all morphometric data. We performed correlation analyses using the Pearson correlation coefficient. We deemed results to be statistically significant at $p = 0.05$. For explorative data analysis we used the Bonferroni adjustment. We used SPSS version 13 software (SPSS Inc.) for all statistical calculations.

Results

Comparison of study groups

Table 1 summarizes our demographic and psychometric findings. We were able to include 27 adult patients with ADHD and 27 group-matched healthy control participants. The groups did not differ significantly with regard to age and to sex.

Volumetric findings

Table 2 summarizes our volumetric findings. Results from the multivariate Wilks (lambda) test did not show any sig-

Table 1: Demographic and psychometric comparison of ADHD and control groups

	Group; mean (SD) [range]			
Characteristic	ADHD ($n = 27$)	Controls ($n = 27$)	Statistical test	p value
Age, yr	32.4 (10.6) [19–55]	30.7 (7.8) [22–46]	$t_{52} = 0.66$	0.51
Sex, male: female ratio	17:10	15:12	$\chi^2_1 = 0.30$	0.78
Years of education	12.3 (1.2) [10–13]	12.2 (1.2) [10–13]	$t_{52} = 0.23$	0.82
WURS	59.9 (10.4)	Not tested		
BDI	15.8 (6.5)	Not tested		
ADHD-CL	26.1 (4.5)	Not tested		
Inattention subscore	14.7 (1.8)			

ADHD = attention-deficit hyperactivity disorder; ADHD-CL = ADHD-Check List[27]; BDI = Beck Depression Inventory[28]; SD = standard deviation; WURS = Wender Utah Rating Scale.[24,25]

nificant influence of the factor group (patients with ADHD v. healthy control participants) ($F_{11–40} = 1.30$, $p = 0.26$, with correction for sex and age) on any volumetric finding. Also, when calculating simple 2-sided t tests, the groups did not differ significantly with respect to amygdala, hippocampus or total brain volumes (Table 2).

Correlation analyses

All correlation analyses were exploratory, thus needing Bonferroni adjustment for multiple comparisons. We found a correlation between the BDI value and the volume of the left and right amygdala in the patient group using the Pearson test (left $r_{25} = 0.410$, $p = 0.047$ and right $r_{25} = 0.407$, $p = 0.049$). These results became nonsignificant after Bonferroni adjustment (Fig. 2) and after we performed a Spearman test.

However, when looking at subgroups, we found significant correlation between the volume of the left amygdala and depressiveness, as measured with the BDI, among men with ADHD ($n = 17$, $r_{15} = 0.762$, $p = 0.001$). This result remained significant after Bonferroni adjustment ($p = 0.004$) (Fig. 3). Interestingly, there was no significant correlation between BDI value and the volume of the right amygdala in this group. For women with ADHD ($n = 10$), we found no significant correlations between any psychometric data and volumes of ROIs.

We observed no other correlations between psychometric scales (WURS, ADHD-CL and its subscores for inattention and hyperactivity/impulsivity) or age and volumetric findings.

Table 2: Volumetric findings*

Region of the brain	Group	Volume of region, mean (SD) [95% CI], cm^3	t test†	p value
Left amygdala	ADHD	1.87 (0.34) [1.74–1.99]	–0.2	0.87
	Control	1.88 (0.40) [1.74–2.06]		
Right amygdala	ADHD	1.92 (0.25) [1.83–2.01]	–0.8	0.43
	Control	1.97 (0.26) [1.89–2.09]		
Left hippocampus	ADHD	2.68 (0.36) [2.55–2.82]	0.4	0.70
	Control	2.65 (0.20) [2.59–2.74]		
Right hippocampus	ADHD	2.83 (0.29) [2.72–2.94]	0.9	0.36
	Control	2.77 (0.25) [2.67–2.87]		
Total brain volume	ADHD	1284.3 (11.24) [1242–1327]	0.3	0.80
	Control	1275.7 (13.09) [1221–1325]		

ADHD = attention-deficit hyperactivity disorder; CI = confidence interval; SD = standard deviation.
*Multivariate analysis of covariance results were nonsignificant.
†Degrees of freedom were 52 in all cases.

Discussion

To our knowledge, our sample is the largest among studies involving adult patients with ADHD in which morphometric analyses of the amygdala and hippocampus have been performed. We manually traced the ROIs of the hippocampus

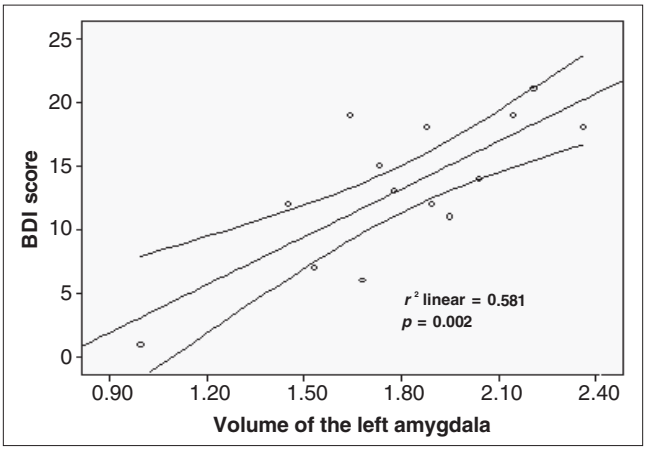

Fig. 3: Correlation between volume of the left amygdala and depressive cognitions (measured with the Beck Depression Inventory[28] [BDI]) in male patients with attention-deficit hyperactivity disorder ($n = 17$).

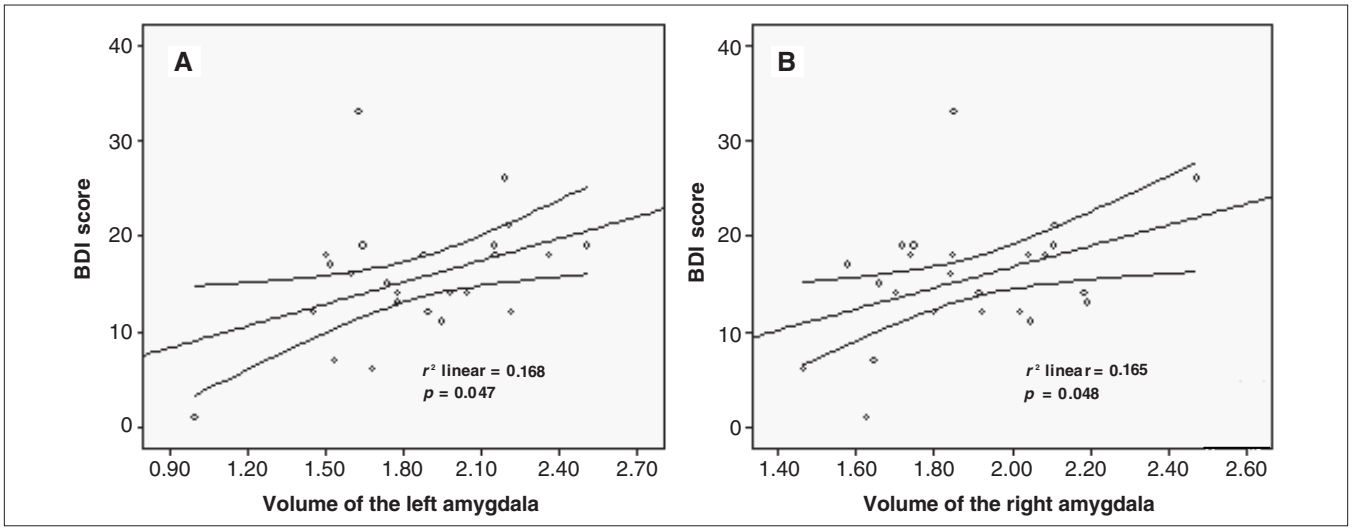

Fig. 2: Correlation between volume of (**A**) the left and (**B**) the right amygdala and depressive cognitions (measured with the Beck Depression Inventory [BDI][28]) in patients with attention-deficit hyperactivity disorder.

and the amygdala according to established and validated protocols. Contrary to our expectations and published findings from earlier studies involving children with ADHD,[9] we did not find any significant between-group differences in the volumes of the left and right hippocampus and amygdala. However, we found a significant correlation between amygdala volumes and BDI scores, particularly in men.

Limitations

There are some limitations to our study that affect the power of this investigation and that should be considered. Although the participants in the ADHD and control groups were matched for relevant demographic variables, there were slight differences among participants in mean age and sex. The mean age (and standard deviation [SD]) was 30.7 (7.8) years in the control group compared with 32.4 (10.6) years in the ADHD group. There were 15 men and 12 women in the control group compared with 17 men and 10 women in the ADHD group. To control for a possible confounding effect of these variables, we used these factors as covariates in our MANCOVA calculation.

Furthermore, it is almost impossible to find adult patients with ADHD who are medication-naive to participate in studies. To minimize the influence of medication, we included only patients who were medication-free for at least 6 months, and all patients but 1 were naive for methylphenidate therapy, which has been shown to influence volumetric findings in children with ADHD.[37] We also excluded patients with a history of substance abuse in the 6 months before the study.

We used the method of manual volumetry, which offers a more precise individual approach, particularly for subcortical brain volumes such as that of the amygdala and hippocampus. The disadvantage of this method is that it is a rater-based method. However, we ensured good intrarater reliability before obtaining the measurements. We minimized the influence of the individual total brain volumes by applying a widely used and generally accepted correction method.[32]

Another limitation of this study, which particularly reduces the comparability of our findings with those of Plessen and colleagues,[9] is that we did not perform surface analyses of the ROIs. Unfortunately, this method is not yet established in our research group.

In addition, the mean total score on the ADHD-CL was 26 of a possible 36 points, which was not very high. The same was true for the mean inattention subscore (14.4 of a possible 18 points). Thus our patient sample was only moderately impaired, which may be wholly or partly responsible for our negative result.

Finally, we estimated the intelligence quotient equality indirectly, using years of education as a surrogate marker. Also, we did not obtain BDI, WURS and ADHD-CL scores from control participants. Although the expected variance of the scores between the groups was low, because none of the participants had psychiatric syndromes we should have assessed these variables to better comment on unexpected findings such as the correlation between amygdala volumes and BDI scores.

Volumetric findings

With respect to total brain volumes, our finding is in line with the only other large morphometric study involving adults with ADHD, conducted by Seidman and colleagues.[6] Similar to Seidman and colleagues, we did not find significant differences in total brain volume. In addition, Seidman and colleagues reported smaller cortical grey matter but larger white matter volumes with normal overall brain volumes in 24 adult patients with ADHD. Since we included grey and white matter in our ROIs, our findings are essentially similar. A putative reduction of total brain volume in patients with ADHD has been widely discussed in the literature. Studies by Mostofsky and colleagues,[38] Hill and colleagues[39] and Castellanos and colleagues[40–42] reported a significant reduction of total brain volume in patients with ADHD (for a review see Valera and colleagues[8]). Conversely, other groups did not report (significant) differences in total brain volume[7,43–45] (for a review see Valera and colleagues[8]). Thus loss in total brain volume cannot be regarded as a stable finding across ADHD samples.

Like Seidman and colleagues,[6] we did not find any significant differences in hippocampus and amygdala volumes between patients with ADHD and control participants. These findings are in line with data reported in 2 studies involving children with ADHD[40,46] (for a review see Valera and colleagues[8]). Conversely, bilateral hippocampus enlargement has recently been reported in a sample including pediatric patients with ADHD.[9] Thus the results with respect to these substructures also seem to be inconclusive.

Correlations between amygdala volume and depressiveness

In explorative post-hoc Pearson correlation analysis, we found correlations between amygdala volumes and BDI scores. After Bonferroni adjustment, this correlation remained significant only for the subgroup of men with ADHD. However, the subgroup analyses were also limited by the small sample, particularly the small number of women with ADHD ($n = 10$). The high variance of BDI scores in patients with ADHD can be explained by the emotional instability of the patients, including frequent depressive mood swings.

An association between increased amygdala volumes and depressed mood has been previously reported in different psychiatric and neurologic disorders such as borderline personality disorder, bipolar disorder, temporal lobe epilepsy and dysthymia, and in young women with a first episode of major depression.[20,47–50] To our knowledge, ours is the first report of such a correlation in patients with ADHD. The causal pathophysiologic relation between amygdala enlargement and depressive symptoms is open to discussion. It remains unclear whether an increased processing of negative emotional information in depression leads to amygdala enlargement or whether the pre-existing enlarged amygdala renders individuals more sensitive to the development of depressive symptoms. Frodl and colleagues[51] reported enlarged amygdala volumes in patients with a first episode of depression compared with patients with recurrent depression. They

found putative higher neuronal activity in patients with a first episode of depression and long-term exposure to antidepressants than in patients with recurrent depression. Zetzsche and colleagues[52] found a positive correlation between the severity of depressive symptoms and the volume of the left amygdala in patients with borderline personality disorder. They discussed amygdala enlargement as either being a vulnerability factor for the development of depressive symptoms or a state marker of long-term depression. One longitudinal prospective study involving patients with depression did not show any changes in amygdala volumes over a period of 1 year. The authors concluded that the duration of 1 year was too short to show that kind of morphometric transformation.[53] Longitudinal studies with longer observation periods could possibly help to answer this question.

In summary, we present manual morphometric data for a relatively large sample of adult patients with ADHD. Based on earlier reports involving children, we hypothesized that amygdala volumes would decrease and that hippocampus volumes would increase in adult patients with ADHD. However, we did not find any significant difference in brain substructure volume. As in other studies involving patients with epilepsy or borderline personality disorder, we found a correlation between an enlarged amygdala and depressive symptoms, particularly in men with ADHD. Therefore, one might speculate that the extent of additional comorbid psychopathologic symptoms such as subsyndromal depression might affect the morphometric findings of different cerebral substructures. Such an assumption could explain the heterogeneity of MRI findings in ADHD research.

We conclude that the findings of interest (i.e., hippocampus enlargement and amygdala volume loss) are not very stable across different samples of patients with ADHD and that the different and contradictory findings may be related to the different locations of alterations along the complex circuits responsible for the different symptoms of ADHD. Further studies involving larger samples of adult patients with ADHD and using multimodal designs are needed. Further studies should combine categorical definitions of patient samples based on diagnostic criteria with a dimensional assessment of the different ADHD symptoms and comorbidities to disentangle the contradictory and unreplicated findings.

Competing interests: None declared.

Contributors: Drs. Perlov, Philipsen, Tebartz van Elst and Hesslinger designed the study. Drs. Perlov and Henning and Mr. Maier acquired the data, which Drs. Perlov, Tebartz van Elst, Ebert, Henning, Bubl and Hesslinger analyzed. Drs. Perlov, Tebartz van Elst and Hesslinger wrote the article, which Drs. Philipsen, Tebartz van Elst, Ebert, Henning, Bubl and Hesslinger and Mr. Maier reviewed. All authors provided approval for publication.

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