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Amygdala reduction in patients with ADHD compared with major depression and healthy volunteers

Frodl T, Stauber J, Schaaff N, Koutsouleris N, Scheuerecker J, Ewers M, Omerovic M, Opgen-Rhein M, Hampel H, Reiser M, Möller H.-J, Meisenzahl E. Amygdala reduction in patients with ADHD compared with major depression and healthy volunteers.

Objective: Results in adult attention deficit hyperactivity disorder (ADHD) on structural brain changes and the clinical relevance are contradictory. The aim of this study was to investigate whether in adult patients with ADHD hippocampal or amygdala volumes differs from that in healthy controls and patients with major depression (MD).
Method: Twenty patients with ADHD, 20 matched patients with MD and 20 healthy controls were studied with high resolution magnetic resonance imaging.
Results: Amygdala volumes in patients with ADHD were bilaterally smaller than in patients with MD and healthy controls. In ADHD, more hyperactivity and less inattention were associated with smaller right amygdala volumes, and more symptoms of depression with larger amygdala volumes.
Conclusion: This study supports findings that the amygdala plays an important role in the systemic brain pathophysiology of ADHD. Whether patients with ADHD and larger amygdala volumes are more vulnerable to affective disorders needs further investigation.

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Key words: attention deficit hyperactivity disorder; major depression; amygdala; hippocampus; magnetic resonance imaging

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Significant outcomes

- Amygdala volumes were smaller in adult patients with attention deficit hyperactivity disorder (ADHD) than in patients with major depression and healthy controls, supporting a role of the amygdala in emotional dysregulation in ADHD.
- More hyperactivity and less inattention were related to smaller right amygdala volumes.
- The presence of more depressive symptoms in ADHD patients was associated with larger amygdala volumes in line with findings that the amygdala increases in size with major depressive disorder.
- Hippocampal volumes were not altered in adult patients with ADHD.

Limitations

- The cross-sectional design does not allow changes in amygdala volume to be assessed.
- The relatively small sample size does not allow generalization of the results, which would first need to be replicated.
- Associations between clinical data and structural volumes are limited to the ADHD group
- Current medication may have confounded the results.

Introduction

Attention deficit hyperactivity disorder (ADHD) has a high prevalence (5–10%) in children (1). Contrary to earlier assumptions, it is no longer considered a disorder exclusive to childhood: about 50% of cases have been found to persist into adulthood. Epidemiological studies indicate that 3–4% of adults suffer from ADHD (2).

Chronic symptoms of ADHD in adults can significantly impair activities of daily living, such as academic, social, occupational and family functioning (3), which over time can exacerbate problems, especially in the absence of adequate coping skills (4). ADHD is associated with significant comorbidity, including mood and anxiety disorders, substance use disorders and personality disorder. Kessler et al. (5) demonstrated that the majority of adults with ADHD have a complicating, clinically significant comorbid disorder, and up to 50% of patients with ADHD have a complicating mood or anxiety disorder. Patients with ADHD are at a higher risk to develop mood disorders, probably not only because of the psychosocial problems that accompany ADHD, but also because of neurobiological changes that may be predictive of depression as well. Despite extensive research in experimental and *in vivo* studies neither the exact underlying neurobiological substrates of ADHD nor the underlying common biological underpinnings of ADHD and mood disorders have been identified.

A number of structural magnetic resonance imaging (MRI) studies have been performed in children with ADHD; they indicated smaller caudate volumes (6–8) and abnormalities in frontal lobe regions (9–13). A study on the hippocampal and amygdala volumes in 51 ADHD children and 63 healthy controls, all aged from 6 to 18 years, found larger hippocampal head volumes, which correlated negatively with clinical symptoms. The amygdala total volume was not significantly altered in this study, whereas surface analyses indicated reduced size bilaterally over the area of the basolateral complex (14). Interestingly, a significant decrease in the left hemispheric amygdala volumes and in the proportions of amygdala to total brain volumes was observed in children with Tourette's syndrome; furthermore, there was a significant negative correlation between amygdala volumes and co-symptoms of ADHD, indicating that amygdala volumes are smaller if ADHD co-symptomatology is more severe (15).

Only a few studies have investigated structural brain changes in adult ADHD. One study included eight adult ADHD patients and found smaller volumes in the orbitofrontal cortex for the ADHD group (13). Another study by the same research group investigated 27 patients with ADHD and 27 healthy controls and did not find significant differences in hippocampus and amygdala volumes between the two groups (16); however, the hippocampus and amygdala have been found to be altered in children with ADHD (14). Further studies are therefore necessary to investigate alterations in these brain regions and their possible clinical relevance. An alteration may be expected because the amygdala subserves affective processes such as fear learning, experience of negative emotion, and perception of emotional stimuli (17). Furthermore, unemotional traits have been related to dysfunction in the amygdala and the ventromedial prefrontal cortex (18), and the high incidence of unemotional and impulsive traits in ADHD makes the amygdala a main region of interest (ROI). The hippocampal formation, as a key structural ROI, plays a critical role in the regulation of motivation and emotion, in addition to the well-documented contribution to learning and memory (19).

In contrast to ADHD, in major depression (MD) the hippocampus and amygdala have been studied extensively. When all results on hippocampal mean volumes from studies on MD are considered, it becomes apparent that hippocampal volumes are about 4–5% smaller than in healthy controls (20, 21). However, findings concerning amygdala volumes in MD are inconsistent. It has been reported that, compared with the amygdala in age-matched healthy controls, the amygdala is enlarged in patients with a first depressive episode (22), in young women with MD (23) and in patients with recurrent depression (24). However, two studies failed to find altered amygdala volumes in recurrent depression (25, 26) and one study detected reductions of a subregion of the amygdala, the amygdala core nuclei (27). Thus, in MD, while hippocampal volumes are reduced, the amygdala volumes seem to be enlarged.

Aims of the study

The aims of this study were to investigate whether the amygdala and hippocampus, which are core regions for affect regulation, are smaller in adult patients with ADHD than in age- and gender-matched healthy controls and whether clinical symptoms of ADHD predict these changes. On the basis of previous findings in patients with MD, we also hypothesized that ADHD patients would show smaller amygdala volumes than patients with MD but no differences in hippocampal volumes.

Material and methods

Participants

Twenty patients with adult ADHD and 20 age- and gender-matched patients with MD were recruited from the Department of Psychiatry and Psychotherapy at the Ludwig Maximilians University, Munich, Germany (Table 1). Psychiatric diagnoses were made according to DSM-IV criteria and the structured clinical interview for DSM-IV and were determined by a consensus of at least two psychiatrists. Seven patients with ADHD fulfilled the criteria for previous depressive episodes, but none had a current depressive episode. Clinical variables were documented using the 21-item Hamilton Depression Rating Scale (HDRS) (28). ADHD patients also were rated with the Conners Adult ADHD Scale (CAARS) (rater version) (29) and completed the self-rater versions of the CAARS (29), the Wender Utah Rating Scale (30) and the Beck Depression Inventory (BDI) (31). The Childhood Trauma Questionnaire was used (32) to assess childhood stress.

Table 1. Demographic variables

	ADHD $n = 20$	MD $n = 20$	HC $n = 20$	P-value
Age (years)	33.6 (10.2)	35.6 (9.4)	34.7 (10.7)	n.s.
Gender (m/f)	15/5	15/5	15/5	
Weight (kg)	79.5 (13.9)	74.4 (12.8)	71.8 (13.1)	n.s.
Height (cm)	178.6 (85.0)	175.3 (98.4)	177.1 (80.0)	n.s.
Alcohol consumption (g/month)	8.3 (14.7)	10.4 (17.8)	11.6 (11.6)	n.s.
Smoking (cigarettes/day)	7.2 (14.0)	12.2 (13.8)	4.0 (7.5)	ADHD vs. MD, $P = 0.27$, ADHD vs. HC, $P = 0.37$ MD vs. HC, $P = 0.026$
HDRS	5.8 (5.9)	21.8 (6.0)	n.a.	MD vs. ADHD, $P < 0.001$
CAARS–OR, total	30.5 (9.1)	n.a.	n.a.	
CAARS–OR, inattention	18.2 (4.8)	n.a.	n.a.	
CAARS–OR, hyperactivity	12.3 (5.7)	n.a.	n.a.	
WURS	59.3 (18.5)	n.a.	n.a.	
Emotional abuse	10.9 (3.4)	n.a.	n.a.	
Physical abuse	6.4 (2.5)	n.a.	n.a.	
Sexual abuse	5.0 (no one reported abuse)	n.a.	n.a.	
Emotional neglect	13.3 (5.4)	n.a.	n.a.	
Physical neglect	7.5 (2.3)	n.a.	n.a.	
Total CTQ	54.9 (11.8)	n.a.	n.a.	

ADHD, patients with attention deficit hyperactivity disorder; MD, patients with major depression; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; n.a., not available; n.s., not significant; CAARS–OR, Connors Adult ADHD Rating Scale – observer rating; WURS, Wender Utah Rating Scale; CTQ, childhood trauma questionnaire.

Standard deviations values are given in parentheses.

The patients were compared with 20 age- and gender-matched healthy control subjects from the local community. Neither the healthy controls nor their first-degree relatives had a history of neurological or mental illness.

Patients and controls were investigated with structural MRI. Psychopathology and medication history were recorded. On the day of the MRI, medications in the patients with ADHD were as follows: six patients were receiving methylphenidate substances (one also venlafaxine), and one citalopram. One patient had a history of methylphenidate treatment but had stopped taking it. Patients with MD were receiving the following medication: serotonin reuptake inhibitors (8 patients: 2 sertraline, 3 citalopram, 2 fluoxetine and 1 fluvoxamine), tricyclic antidepressants (3 patients: 2 amitriptyline and 1 doxepine), other new antidepressants (5 patients: 1 venlafaxine, 2 reboxetine and 2 mirtazapine); 4 patients were not being treated with an antidepressant at the time of MRI scan.

A structured interview was used to assess medical and medication history, and trauma and other exclusion criteria. Exclusion criteria for all subjects were previous head injury with loss of consciousness, earlier treatment with hydrocortisone, a history of alcohol or substance dependence, and neurological diseases. Patients with comorbid mental illnesses, especially bipolar disorders, or personality disorders were also excluded. None of the subjects had ever been treated with electroconvulsive therapy. Handedness was determined by the Edinburgh inventory (33).

Written informed consent was obtained from patients and controls after they had been given a detailed description of the study. The study was designed in accordance with the ethical standards laid down in the Declaration of Helsinki and was approved by the local ethics committee.

Magnetic resonance imaging procedures

Magnetic resonance images were obtained (1.5 Tesla Magnetom Vision; Siemens, Erlangen, Germany) from patients and controls using a coronal T2- and proton density-weighted Dual-Echo-Sequence [Repetition time (TR) 3710 ms/echo time (TE) 22/90 ms; total acquisition time: 9 min, number of acquisitions: 1; field of view (FOV) 230 mm; matrix 240 × 256, slice thickness: 3 mm] and a 3D magnetization prepared rapid gradient echo sequence (TR/TE 11.6 ms/4.9 ms; total acquisition time: 9 min, number of acquisitions: 1; FOV 230 mm; matrix 512 × 512, slice thickness: 1.5 mm). The commercial software package

Analyze was used (ANALYZE; Biomedical Imaging Resource, Mayo Foundation, Rochester, MN, USA) for further image processing, with size reduction from 16 to 8 bit and transformation to a uniform matrix of 256 × 256 on 192 slices of 1.0 mm slice thickness. All data sets were realigned and resampled three dimensionally in the anterior commissure to posterior commissure line, according to the coordinates of Tailairach, with the software program BRAINS [Brain Research: Analysis of Images, Networks and Systems; developed by Andreasen et al. (34)]. The BRAINS program allowed the ROIs to be controlled on sagittal and transverse sections simultaneously and to be segmented to enable calculation of the intracranial content (ICC) and the grey and white matter volume (cm^3) within the defined ROI. Software and hardware were not changed during the 3-year study period.

Definition of the hippocampal and amygdala formation

A detailed description of the hippocampal and amygdala borders can be found in earlier publications (35). To determine inter-rater reliability, 10 brains were randomly chosen and ROIs were determined by two raters independently. The intraclass correlation was high for both the inter-rater reliability (hippocampus: $r_{ICC} = 0.97$ and amygdala: $r_{ICC} = 0.95$) and the intra-rater reliability (hippocampus: $r_{ICC} = 0.96$ and amygdala: $r_{ICC} = 0.91$). The regions are shown in Fig. 1. The evaluation staffs were blind to subject status (J.S.).

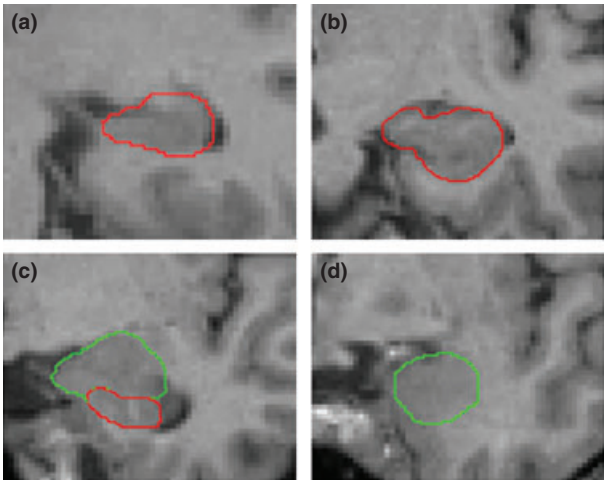

Fig. 1. Example of hippocampal and amygdala measurement. Depicted are coronal MRI slices that run in occipito-rostral direction: (a) hippocampal body, (b) anterior part of the hippocampus, (c) posterior-medial part of the amygdala and (d) anterior-medial part of the amygdala. The whole volumes of the amygdala and hippocampus were determined by performing this procedure in all MRI slices in which the amygdala and hippocampus was visible.

The hippocampus and the amygdala were outlined manually using a mouse-driven cursor.

Statistical analyses

All statistical tests were considered to be significant if $P < 0.05$. Morphometric measurements were tested for normality using the Kolmogorov–Smirnov test and for homogeneity of variance. Hippocampal and amygdala volumes were subjected to a 2 (hemisphere) × 3 (group) analysis of covariance (ANCOVA), with total brain volume as the covariate, to assess the main and interaction effects of the within-subjects factor hemisphere (left and right), and the between-subjects factor diagnosis (ADHD, MD and healthy control).

Regression analysis was used to explore the variance of amygdala or hippocampal volumes that was explained by ADHD, depression symptomatology or early life stress. Spearman correlation coefficients were used to calculate the relationship between amygdala volumes and depression severity (Fig. 3).

Results

Morphometric data did not differ from a normal distribution (left amygdala: $P = 0.77$; right amygdala: $P = 0.52$; left hippocampus: $P = 0.90$; and right hippocampus: $P = 0.98$). Patients with ADHD or MD and healthy controls did not differ in age, gender, alcohol consumption, height or weight (Table 1). Furthermore, there was no significant difference in total brain volumes between the patient groups and controls ($F = 0.57$, $df = 2, 57$, $P = 0.57$).

Main hypothesis

The main ANCOVA found a significant main effect on the amygdala volume for diagnosis ($F = 5.3$, $df = 2, 56$, $P = 0.008$). *Post hoc* ANCOVA of the groups revealed that patients with ADHD had significantly smaller amygdala volumes than healthy controls ($F = 7.1$, $df = 1, 37$, $P = 0.012$) and patients with MD ($F = 8.0$, $df = 1, 37$, $P = 0.007$). Amygdala volumes did not differ between patients with MD and healthy controls ($F = 0.12$, $df = 1, 37$, $P = 0.73$) (Fig. 2).

No significant differences in hippocampal volumes were found between diagnostic groups ($F = 1.7$, $df = 2, 56$, $P = 0.18$). There was no significant effect of hemisphere ($F = 0.08$, $df = 2, 56$, $P = 0.78$) and no significant interaction between hemisphere and diagnosis ($F = 0.64$, $df = 2, 56$, $P = 0.53$).

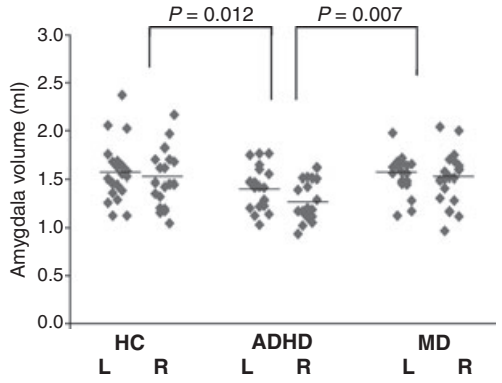

Fig. 2. Scatter plot of the individual amygdala volumes [ml] for the patients with ADHD or major depression and the healthy controls. Mean values are indicated by horizontal lines. Amygdala volumes were significantly smaller in patients with ADHD than in patients with major depression and healthy controls. There were no significant effect of hemisphere and no significant interaction between hemisphere and diagnosis. (L = left and R = right).

Table 2. Regression analysis of ADHD symptoms derived from CAARS and amygdala volumes

	Right amygdala			Left amygdala		
	Beta	t	*P*	Beta	t	*P*
Inattention	0.58	2.70	0.016	0.36	1.38	0.19
Hyperactivity	−0.54	−2.49	0.024	−0.04	−0.16	0.88
Impulsivity/emotional instability	0.15	0.74	0.48	0.01	0.06	0.95
	Right hippocampus			Left hippocampus		
Inattention	−0.016	0.06	0.95	−0.29	−1.23	0.24
Hyperactivity	0.27	0.56	0.31	0.44	1.90	0.08
Impulsivity/emotional instability	−0.26	−1.12	0.28	−0.35	−1.64	0.12

ADHD, attention deficit hyperactivity disorder; CARRS, Conners Adult ADHD Scale.

Further exploratory analysis

ADHD symptomatology. Regression analysis revealed that the right amygdala volume of ADHD patients was predicted by inattention and hyperactivity ($F = 3.37$, d$f = 3, 19$, $P = 0.045$), whereas the left amygdala volume was not significantly related to ADHD symptomatology. Patients with more hyperactivity and fewer inattention symptoms had smaller right amygdala volumes (Table 2). The subscale impulsivity was not related to amygdala volumes. The regression analysis of hippocampal volumes did not reveal any significant effects of ADHD symptoms.

Depression symptomatology. In the regression analysis, left amygdala volumes were significantly associated with depression severity ($\beta = 0.48$, $t = 2.29$, $P = 0.034$, $r = 0.63$, $P = 0.003$; Fig. 3). Right amygdala volumes were not significantly predicted by depression severity ($\beta = 0.253$, $t = 1.01$, $P = 0.323$). No significant effects were detected for HDRS depression scores. The ROI volumes did not differ significantly between patients with ADHD and previous depressive episodes ($n = 7$) and those without depression in their medical history (amygdala: t = 0.81, df = 18, $P = 0.54$; hippocampus: t = 0.81, df = 18, $P = 0.43$).

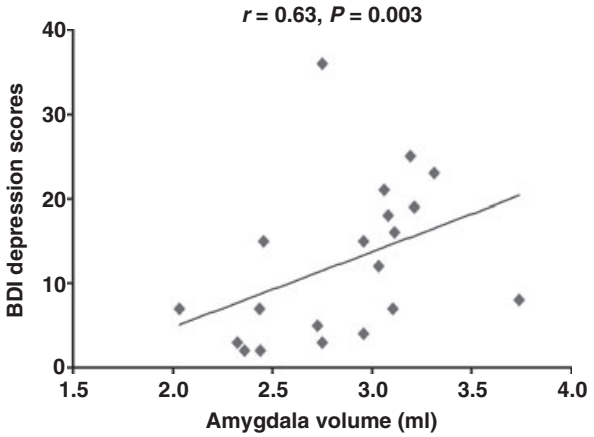

Fig. 3. Association between mean amygdala volumes (left + right) [ml] and depression severity as measured by BDI scores in patients with ADHD.

Effects of early life stress. Early life stress subscores did not significantly explain the variance of the left, right amygdala or hippocampal volumes, as revealed by the regression analysis.

Previous treatment with stimulants. Amygdala volumes did not differ significantly between patients with ADHD who had been treated previously with stimulants and those who had never been treated (left amygdala: t = 0.24, $P = 0.82$ and right amygdala: t = 0.03, $P = 0.98$). Left hippocampal volumes were significantly smaller in patients previously treated with stimulants than in those who had never received them (t = 2.2, $P = 0.042$), whereas right hippocampal volumes did not show any significant differences (t = 1.0, $P = 0.32$).

Discussion

The hypothesis that in adult patients with ADHD amygdala volumes are smaller than in healthy controls and patients with MD was confirmed. This is the first study that directly compared adult patients with ADHD and patients with MD.

Our findings of smaller amygdala volumes in adults with ADHD than in healthy controls are

supported by earlier studies that found that, compared with healthy controls, children with ADHD showed a bilateral reduction of the area of the basolateral complex (14). Moreover, in patients with Tourette's syndrome the amygdala volumes correlated negatively with symptoms of ADHD (15). Reduced volumes of the amygdala can be taken to indicate a reduced number of neurons in the amygdala: a study with MRI and histological examinations of postmortem brains showed that brain volume and neuron number is highly associated (36).

The most important finding in this study was that amygdala volumes were smaller in patients with ADHD than in patients with MD. This is not surprising considering the role that the amygdala plays in emotion regulation and the fact that ADHD patients have problems in regulating their affects and emotions. This finding, therefore, may indicate that smaller amygdala volumes are associated with frequent changes in emotional states and with deficits in emotion regulation. Such a hypothesis is supported by some studies that investigated the role of the amygdala in emotion processing: deficits, including callous-unemotional traits, were observed after amygdala lesions, which supports an association between callous-unemotional traits and amygdala dysfunction (37). Using functional MRI, other groups have also related callous-unemotional traits to dysfunction in the amygdala and the ventromedial prefrontal cortex (18, 38).

Interestingly, patients with MD seem to have no changes in amygdala volumes as demonstrated in our study or by others (25, 26) or even seem to have enlarged amygdala volumes in some studies (22–24). The results of this study clearly show differences between patients with ADHD compared with patients with MD with bilaterally smaller amygdala volumes in the ADHD group. Therefore, larger amygdala volumes seem to be related to depressive symptomatology as shown also in our study, because of the significant association between larger depression scores and larger amygdala volumes. Smaller amygdala volumes seem to be specific for the patients with ADHD, which is supported by the relationship between clinical data and amygdala volumes.

This was the second important finding of the study: The impulsivity/emotional instability subscore of the CAARS did not explain the variance of the amygdala volumes. Instead, the patients with less inattention and more hyperactivity had smaller right amygdala volumes. Therefore, structural changes in the amygdala may be most pronounced in patients with the hyperactive or combined subtype. The finding, however, has to be kept considered with caution because we found the effect only for the right and not for the left amygdala. Further studies are therefore necessary to replicate the results and to show in longitudinal evaluations whether patients with marked structural changes, e.g. of the amygdala, have a different clinical outcome or respond differently to treatment.

The third important result was that amygdala volumes were larger in those ADHD patients with more depressive symptoms. This result may indicate that in depressed patients the amygdala volume and, therefore, also the number of neurons increase, perhaps because of neuroplastic changes. A relationship between larger amygdala volumes and depression is supported by studies that found larger amygdala volumes in patients with MD (22–24) and in patients with bipolar disorder (20). One limitation of this study, however, is that we found the positive correlation between amygdala volumes in the ADHD group and depression severity when the latter was measured with the self-rating BDI but not when the observer scale HDRS was used; therefore, this finding needs further exploration.

No significant differences in hippocampal volumes were detected between patients with ADHD and healthy controls, which is in line with a recent study (16). In contrast, one study in children with ADHD found increased volumes of the hippocampus (14). Moreover, in our study hippocampal volumes did not differ significantly between patients with MD and healthy controls, in contrast to earlier studies that found smaller hippocampal volumes (20, 39) in patients with MD. One possible reason may be that hippocampal volume is only reduced by a relatively small extent – about 4–5% on average – in patients with MD, a change that may remain undetected in studies with a relatively small sample size because of insufficient statistical power; small sample size is also a limitation in our study.

Smaller left hippocampal volumes were found in patients with previous or current stimulant treatment, or both. This result should be treated with caution because the study was not intended to show effects of stimulants on brain structures. Such a question would have needed a follow-up design with investigations before and after treatment. A recent study found that stimulant treatment resulted in an enhanced dopamine neuron drive, which was expressed as an increased neuronal population activity (40). However, these effects may result in larger rather than smaller hippocampal volumes.

Another overall limitation of our study is that patients with depression were receiving antidepressant medications. Data on the influence of antidepressants on brain volume are limited; one study in post traumatic stress disorder showed an increase of hippocampal volumes with antidepressant treatment (41), while another study in patients with MD found no significant changes (42). It would have been worthwhile to provide the ADHD ratings also in the sample of patients with MD and the healthy controls; however, these subjects had no ADHD symptoms and ratings would have shown only minor variance, which would not be able to explain structural changes.

In conclusion, we found that amygdala volumes were smaller in adult patients with ADHD than in healthy controls and patients with MD. Reduced amygdala volumes may be related to hyperactivity and fewer inattention symptoms; however, further studies need to replicate this finding. The amygdala alterations seem not to result from depressive comorbidity because the more depressive symptoms the patients had, the larger the amygdala volumes were. Investigations of patients with comorbid ADHD and mood disorders are warranted, because patients with comorbid ADHD have a worse clinical outcome with more frequent affective episodes and more interpersonal violence (43). Further studies are needed to investigate potential structural, functional, and effective connectivity changes in the neural networks underlying emotion and affect, as well as the functional basis and consequences of reduced amygdala volumes.

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Declaration of interest

None.

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