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Hippocampal volume and internalizing behavior problems in adolescence

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Abstract

Adolescence is characterized by dynamic changes in structural brain maturation. At the same time, adolescence is a critical time for the development of affective and anxiety-related disorders. Individual differences in typically developing children and adolescents may prove more valuable for identifying which brain regions correspond with internalizing behavior problems (i.e., anxious/depressive, withdrawal and somatic symptoms) on a continuous scale compared to clinical studies. Participants were 179 (92 males, 87 females) typically developing children and adolescents between ages 8 and 17. Hippocampal and amygdala volumes were measured automatically with FreeSurfer. Internalizing behavior was assessed with the Child Behavior Checklist (CBCL) completed by the parent, and associated with hippocampal and amygdala volumes. Hippocampal volume was inversely related with the total internalizing problems scale of the CBCL, irrespective of gender, age, or informant (mother or father). The effects were most prominent for the withdrawal and anxiety/depression subscales and the left hippocampus: more withdrawal and anxiety/depression was related to smaller left hippocampal volume. No associations were found between internalizing behavior and amygdala volume. This study shows that typically developing children and adolescents with high internalizing behavior share some of the neuroanatomical features of adult depression and anxiety-related disorders.

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1. Introduction

Brain development is a highly dynamic multistep process, which is partly genetically determined, and partly epigenetically directed and environmentally influenced (Tau and Peterson, 2010). In contrast to earlier beliefs, this process continues through childhood and adolescence, the developmental period during which the body and brain emerge from

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an immature state to adulthood (Spear, 2000; Steinberg and Morris, 2001). Although total brain size is approximately 90% of its adult size by age six, the gray and white matter subcomponents of the brain continue to undergo dynamic and region specific changes throughout adolescence (Giedd et al., 1999; Paus, 2005). Concurrent with these brain changes, adolescents show marked changes in cognitive, social and emotional behaviors (Steinberg and Morris, 2001). Thereby, adolescents show a natural tendency to explore their environment; resulting in explorative and daring behavior which is normative for this time of life and which most adolescents navigate relatively well.

At the same time, adolescence is a critical time for the development of internalizing and externalizing symptoms and disorders (Paus et al., 2008; Zahn-Waxler et al., 2008), and therefore heralds a time of vulnerability, which can lead to a myriad of negative health consequences. For example, there is a gender differentiation in vulnerability to mental disorders in adolescence. During puberty, often seen as the start of adolescence, a marked female preponderance (2:1) of mood and anxiety-related disorders emerges, a proportion that persists into adulthood (Zahn-Waxler et al., 2008). Prior research has primarily compared diagnostic groups (i.e., clinical probands vs. typically developing individuals) to identify the neuroanatomical/neural correlates of a psychiatric disorder. Yet, individual differences in non-clinical adolescent samples may provide additional information on which brain regions are associated with clinical symptoms on a continuous scale. One of the most widely-used standardized measures in child psychology and psychiatry for evaluating maladaptive behavioral and emotional problems in (typically developing) individuals between the ages of 4 and 18 is the Child Behavior Checklist (CBCL; (Achenbach and Edelbrock, 1983)). It assesses internalizing (i.e., anxious/depressive, somatic, and withdrawal complaints) and externalizing (i.e., aggressive, hyperactive, noncompliant and delinquent) behaviors. A few studies have been conducted to examine the neuroanatomical correlates of CBCL-sub-scales in childhood and adolescence. Internalizing behavior has been linked to larger pituitary volumes in early and mid-adolescence ($N=155$, ages 11-13; Zipursky et al., 2011). In studies using an adapted version of the CBCL, the Pediatric Behavior Scale (PBS), it was shown that fearfulness was associated with enlarged amygdalar volumes in adolescent girls with and without a family history of depression ($N=116$; ages 7-17; van der Plas et al., 2010); and that aggressive and defiant behavior was associated with decreased right anterior cingulate volumes in boys ($N=117$; ages 7-17; Boes et al., 2008). Finally, Ducharme and colleagues provided evidence for an association between the aggression subscale of the CBCL and a thinner right cingulate cortex, but enlarged striatal volumes ($N=193$; ages 6-18; Ducharme et al., 2011).

Here, we aimed to extend these prior findings by examining the association between CBCL scores for internalizing behavior problems and hippocampal and amygdalar volumes in typically developing children and adolescents. These structures were selected based on their implication in major depressive disorder (MDD; Koolschijn et al., 2009), and anxiety related disorders such as general anxiety disorder (De Bellis et al., 2000; Milham et al., 2005; Schienle et al., 2011) or post-traumatic stress disorder ((Karl et al., 2006) but see (Woon and Hedges, 2008)). Although these brain structures are not

solely responsible for complex behaviors, early life stress, childhood maltreat and genetic variations of the serotonin transporter gene and BDNF genotype have been associated with increased risk for MDD as well as with hippocampal and amygdalar volumes (MacQueen and Frodl, 2010). Moreover, it has been suggested that individuals at risk for MDD have smaller hippocampal volumes compared to healthy controls (Amico et al., 2011; Dedovic et al., 2010). Therefore we predicted that smaller hippocampal and amygdalar volumes would be associated with higher internalizing scores derived from the CBCL. We also explored associations of the CBCL internalizing sub-scales for somatic, anxiety/depression, and withdrawal symptoms with hippocampal and amygdalar volumes to examine which dimensions of internalizing behavior are most strongly related to brain volume.

2. Experimental procedures

2.1. Participants

We combined data from several different neuroimaging studies performed at the Brain and Development Lab, Leiden University, between 2006 and 2010. The same scanner and scanner-protocols were utilized to create a large dataset of typically developing participants. One hundred seventy-nine (92 males; 87 females) typically developing children were included. The age range was between 8 and 17 years with an about equal distribution across age cohorts (see Table 1 for subgroups). There was no difference in age between males ($M=12.90$, $SD=2.52$) and females ($M=13.29$, $SD=2.48$; $p=0.30$), and no differences in gender across age distribution at time of scan ($p=0.34$).

Participants had no self-reported history of neurological or psychiatric disorders, chronic illness, learning disabilities, or use of medicines known to affect nervous system functioning. They were required to be right handed and to have no MRI contraindications. Participants and their primary caregivers gave informed consent for the studies and received fixed payment for participation. All studies and procedures were approved by the Medical Ethics Committee of the Leiden University Medical Center.

2.2. Data acquisition

All participants were scanned with the same standard whole-head coil on the same 3-Tesla Philips Achieva MRI system (Best, The Netherlands). High-resolution T1-weighted anatomical scan were obtained: 3D-T1-weighted scan: TR=9.717 ms; TE=4.59 ms, flip angle=8 degrees, 140 slices, $0.875 \times 875 \times 1.2 \text{ mm}^3$, FOV=224.000 \times 168.000 \times 177.333. All anatomical scans were reviewed and cleared by a radiologist. No anomalous findings were reported.

Table 1 Distribution of gender across age.

Age	Females	Males	Total*
8-9	13	14	27
10-11	15	23	38
12-13	21	24	45
14-15	26	16	42
16-17	12	15	27
Total	87	92	179

*There were no differences in distribution of gender across age: $\chi^2=4.50$, $p=0.34$.

2.3. Hippocampal and amygdalar volumes

Volumetric segmentation was measured automatically using the software FreeSurfer version 5.0 (<http://www.surfer.nmr.mgh.harvard.edu/>) (Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000). Until recently, manual tracing of brain regions by experts in neuroanatomy has been the accepted standard. However, as the size of the MRI datasets has increased, the time and cost required for the labor-intensive process of manual tracing has become prohibitive. It has been demonstrated that FreeSurfer is sufficiently reliable and valid particularly in the context of larger sample sizes to detect associations with clinical or demographic variables (e.g. Cherbuin et al., 2009; Dewey et al., 2010; Doring et al., 2011).

Briefly, processing consisted of removal of non-brain tissue (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and hippocampus and amygdala (Fischl et al., 2002), intensity normalization (Sled et al., 1998) and tessellation of the gray matter white matter boundary (Fischl et al., 2001; Segonne et al., 2007). All processing was done in native space. The procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set. The segmentation is carried out as follows. First, the image is rigid body registered to a probabilistic brain atlas, followed by non-linear morphing to the atlas. Manually segmented images were previously used to create statistics about how likely a particular label is at any given location in the brain. This serves as a Bayesian prior for estimating the label of a given voxel in a given brain image based on the maximum a posteriori probability. The segmentation uses three pieces of information to disambiguate labels: (1) the prior probability of a given tissue class occurring at a specific atlas location, (2) the likelihood of the image intensity given that tissue class, and (3) the probability of the local spatial configuration of labels given the tissue class. The technique has previously been shown to be comparable in accuracy to manual labeling (Fischl et al., 2002). However, all segmentations were visually inspected for accuracy prior to inclusion in the group analysis. In no case were errors in segmentation identified by visual inspection. Total hippocampal and amygdalar volumes were calculated by summing the left and right volumes.

2.4. Child Behavior Checklist (CBCL) for internalizing behaviors

Parents of the participants completed the Child Behavior Checklist (Achenbach and Rescorla, 2001). The CBCL is a widely used and

carefully validated questionnaire on child's behavior problems as observed in the previous two months (Crijnen et al., 1999). Each item is scored as 0=not true, 1=somewhat or sometimes true, and 2=very true or often true. Here we focused on the broad-band internalizing problems scale with 31 items ($M=5.16$, $SD=4.88$, range 0-21, alpha reliability=0.84), and three empirically based internalizing syndrome scales: anxious/depressed (14 items, $M=2.49$, $SD=2.74$, range 0-12, alpha reliability=0.80), somatic (9 items, $M=1.10$, $SD=1.55$, range 0-7, alpha reliability=0.66), and withdrawal symptoms (9 items, $M=1.71$, $SD=2.04$, range 0-9, alpha reliability=0.70). We used the raw CBCL scores because age of participants was included as a covariate or predictor in the analyses (see also Ducharme et al., 2011). Higher scores indicate more internalizing problems (Crijnen et al., 1999).

2.5. Statistics

The volumes of the intracranium, hippocampus and amygdala were calculated by FreeSurfer as described in the previous section. Since (sub-)cortical brain volumes scale with head size, hippocampal and amygdalar volumes were corrected for total intracranial volume as an estimate of head size. In a preliminary analysis we computed bivariate Pearson correlations between brain volumes and the CBCL broadband and syndrome scales. Some studies have found non-linear relationships with age and hippocampal or amygdalar volumes during adolescence. Therefore, *F*-tests were used to determine whether a linear, quadratic or cubic model significantly best fit the data (Thomas et al., 2009). In the current study, a non-linear fit was not significantly better compared to a linear fit ($p=0.65$). In a set of multivariate analyses, we conducted analyses of covariance, including an effect size measure η^2 , for the CBCL broadband and syndrome scales with corrected hippocampal and amygdala volumes as predictors controlling for age, gender and informant (mother or father). In case of significant findings, the analyses were repeated for left and right volumes separately.

3. Results

In Table 2 means and standard deviations for hippocampal and amygdala volumes (residualized for total intracranial volume), for CBCL total internalizing behavior problems, and for the CBCL sub-scales for anxiety/depression, somatic, and withdrawal issues are presented, separately for male and female participants. Gender differences were absent.

Table 2 Amygdala and hippocampal volumes, and CBCL internalizing scores for males and females.

	Males ($n=92$)		Females ($n=87$)		<i>t</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Hippocampal volume <i>total</i> ^a (ml)	0.019	1.080	-0.047	0.934	-0.44
Hippocampal volume <i>left</i> ^a (ml)	0.064	1.059	-0.085	0.928	-1.00
Hippocampal volume <i>right</i> ^a (ml)	-0.035	1.074	0.004	0.951	0.26
Amygdala volume <i>total</i> ^a (ml)	0.062	1.047	-0.064	0.949	-0.84
Amygdala volume <i>left</i> ^a (ml)	0.032	1.058	-0.031	0.926	-0.43
Amygdala volume <i>right</i> ^a (ml)	0.079	1.053	-0.085	0.953	-1.09
CBCL internalizing	4.82	4.41	5.38	5.12	0.79
CBCL somatic	1.04	1.42	1.10	1.66	0.26
CBCL anxiety/depression	2.36	2.39	2.55	2.92	0.49
CBCL withdrawal	1.55	1.92	1.86	2.16	1.03

^aResidualized for Total Intracranial Volume.

Bivariate Pearson correlations showed that smaller total hippocampal volume was related to more withdrawal problems (see Table 3). Smaller left hippocampal volume was associated with more internalizing behavior problems and with more withdrawal behaviors. Interestingly, older participants showed smaller hippocampal volumes (relative to total intracranial volume), and older participants showed more withdrawal. Gender of the informant was significantly associated with CBCL scores, with fathers reporting less internalizing behavior problems, except for withdrawal. Therefore we controlled for age and gender of informant (parent) in the multivariate analyses.

In Table 4 the results of the analyses of covariance for the CBCL (sub-)scales with corrected hippocampal and amygdala volumes as predictors controlling for age, gender and informant (mother or father) are presented. Smaller total hippocampal volume predicted more internalizing behavior problems ($F_{(1, 173)}=4.96$, $p=0.027$, $\eta^2=0.028$). In particular,

total hippocampal volume was significantly associated with the CBCL sub-scale for withdrawal ($F_{(1, 173)}=6.25$, $p=0.013$, $\eta^2=0.035$). Left hippocampal volume seemed most important in predicting total internalizing, anxious/depressive and withdrawal behavior problems. Figure 1 shows that the association between left hippocampal volume and total internalizing behavior problems was not dependent on a few outlying cases. Amygdala volumes were not associated with CBCL internalizing behavior problems. Results remained basically the same in the sub-sample of 138 mother-reported CBCL scores, showing similar effect sizes.

4. Discussion

We examined brain-behavior correlations in 8- to 17-year-old typically developing children and adolescents based on internalizing behavior scores of the CBCL and hippocampal

Table 3 Bivariate correlations between age, CBCL informant, hippocampal and amygdala volumes, and CBCL scores.

	Age	CBCL internalizing	CBCL somatic	CBCL anxiety/depression	CBCL withdrawal
Age	-	0.05	0.09	-0.07	0.15*
Parent	-0.16*	0.22**	0.25**	0.20**	0.07
Hippocampal volume <i>total</i> ^a (ml)	-0.26**	-0.13	-0.10	-0.07	-0.17*
Hippocampal volume <i>left</i> ^a (ml)	-0.29**	-0.16*	-0.09	-0.10	-0.20**
Hippocampal volume <i>right</i> ^a (ml)	-0.18*	-0.08	-0.09	-0.02	-0.11
Amygdala volume <i>total</i> ^a (ml)	-0.08	0.02	0.00	-0.01	0.05
Amygdala volume <i>left</i> ^a (ml)	-0.09	0.01	0.00	0.02	0.01
Amygdala volume <i>right</i> ^a (ml)	-0.04	0.02	0.01	-0.03	0.08

* $p < 0.05$.

** $p < 0.01$; ($N=179$).

^aResidualized for Total Intracranial Volume.

Table 4 Analyses of covariance of CBCL internalizing scores with age, hippocampal volume, and amygdala volume as predictors.

	CBCL internalizing		CBCL somatic		CBCL anxiety/depression		CBCL withdrawal	
	<i>F</i>	<i>eta</i> ²	<i>F</i>	<i>eta</i> ²	<i>F</i>	<i>eta</i> ²	<i>F</i>	<i>eta</i> ²
Age	0.26	0.00	2.04	0.01	0.88	0.00	2.58	0.02
Gender	1.14	0.01	0.23	0.00	0.65	0.00	1.08	0.01
Parent	11.07**	0.06	14.79**	0.08	6.91**	0.04	2.08	0.01
Hippocampal volume <i>total</i> ^a (ml)	4.96*	0.03	1.99	0.01	1.92	0.01	6.25**	0.04
Amygdala volume <i>total</i> ^a (ml)	1.57	0.01	0.64	0.00	0.26	0.00	3.49	0.02
Age	0.09	0.00	1.94	0.01	1.26	0.01	1.84	0.01
Gender	0.78	0.01	0.23	0.00	0.30	0.00	0.86	0.01
Parent	11.75**	0.06	14.61**	0.08	7.43**	0.04	2.47	0.01
Hippocampal volume <i>left</i> ^a (ml)	5.44*	0.03	0.42	0.00	4.73*	0.03	5.38*	0.03
Hippocampal volume <i>right</i> ^a (ml)	0.22	0.00	0.28	0.00	1.05	0.01	0.04	0.00
Amygdala volume <i>left</i> ^a (ml)	0.21	0.00	0.06	0.00	0.56	0.00	0.00	0.00
Amygdala volume <i>right</i> ^a (ml)	0.71	0.00	0.29	0.00	0.04	0.00	3.63	0.02

* $p < 0.05$.

** $p < 0.01$; ($N=179$).

^aResidualized for Total Intracranial Volume.

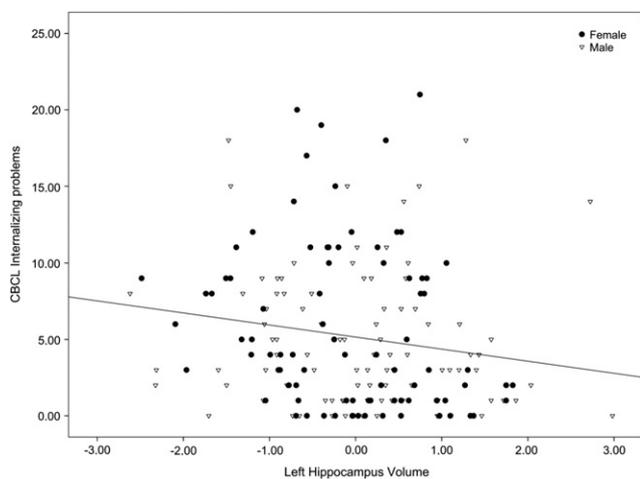


Figure 1 The association between left hippocampal volume and total internalizing behavior problems.

and amygdalar volumes. We found that higher scores on internalizing behavior were associated with smaller hippocampal volumes, irrespective of age and informant. More specifically, the effect was driven by higher scores on the withdrawal and anxiety/depression syndrome scales and smaller volume in the left hippocampus. No associations between amygdala volumes and internalizing behavior and no gender differences were found.

Our findings of smaller hippocampal volumes in relation to higher scores on internalizing behavior contribute to the notion of hippocampal involvement in individuals at risk for depression and anxiety. Smaller hippocampal volumes have also been reported in adolescent girls at elevated risk for depression (Chen et al., 2010), and smaller left (posterior) hippocampal volume in healthy adult twins at risk for depression and anxiety (de Geus et al., 2007). In contrast, in a nonclinical sample of early adolescents, there was no relationship between adolescent depressive symptoms and hippocampal and amygdalar volumes (Yap et al., 2008). However, a prior meta-analysis on the relation between hippocampal volume and childhood onset depression came to the conclusion that there was large heterogeneity between studies demonstrating both smaller volumes as well as null findings (Kempton et al., 2011).

Several meta-analyses on hippocampal volume loss in depression interpreted hippocampal volume reduction as a result of the disease representing a burden of illness (Campbell et al., 2004; McKinnon et al., 2009; Videbech and Ravnkilde, 2004). However, studies investigating hippocampal volume in patients with first-episode MDD reported findings that contrast this view. For example, it was shown that patients diagnosed with a first episode of depression and thus a short lifetime duration of the illness already have smaller hippocampal volumes, pointing to smaller hippocampal volume as a risk factor for, rather than a consequence of, the illness (Frodl et al., 2002; Kronmuller et al., 2008, 2009; MacMaster and Kusumakar, 2004). In addition, lower levels of N-acetyl-aspartate have been reported in the left hippocampus in medication naïve depressed adolescents, which may reflect reduced neuronal viability in the hippocampus (MacMaster et al., 2008). Our findings suggest that even levels of internalizing symptoms that are

below the threshold for a clinical diagnosis are negatively associated with hippocampal volumes.

We did not find significant relations between amygdalar volumes and internalizing behavior. This is in line with a previous study in healthy adolescents reporting no significant association between depressive symptoms and amygdala volumes, despite the fact that boys with smaller amygdala volumes reported more depressive symptoms (Yap et al., 2008). On the other hand, work by Van der Plas and colleagues showed that fearfulness in healthy adolescent girls was associated with larger amygdala volumes, most pronounced in girls at risk for depression (van der Plas et al., 2010). Several explanations may account for the lack of significant associations with amygdalar volume in our sample. First, the amygdala may be affected only in clinical cases in which higher symptomatology is related to volume differences. Second, the lack of an association with internalizing behavior may be associated with heterogeneity and inconsistent findings in clinical studies. For example, pediatric generalized anxiety disorder has been associated with larger (De Bellis et al., 2000), but also smaller left amygdala volumes (Milham et al., 2005). In adolescent onset depression larger (MacMillan et al., 2003), smaller (Rosso et al., 2005) and no differences were found in amygdala volumes between patients and healthy controls (Caetano et al., 2007; MacMaster et al., 2007). Inconsistencies in amygdala volumes were also reported in adults with major depressive disorder (Koolschijn et al., 2009). It has been suggested that the clinical profile (i.e. number of depressive episodes, depression subtype, current depressed vs. remission, depression duration) and antidepressant and psychotropic medication use may contribute to the inconclusive findings (Hamilton et al., 2008; Koolschijn et al., 2009). Future research should investigate these hypotheses in more detail.

A strength of the current study is that we were able to measure a large sample of typically developing children and adolescents with the same MRI scanner and protocols, so that our results are not confounded by differences in acquisition factors. Because of the typical, non-clinical sample our findings are also not confounded by potential co-morbidity or medication in individuals with a clinical anxiety or depression disorder. However, some potential limitations should be noted. First, we had only a single but well-established measure to assess internalizing behavior. Independent psychiatric symptom assessment might have given a more distinct pattern of symptom severity within our sample. Second, there was no information available on familial history of psychiatric disorders. From adult and adolescent studies it is known that familial history of a psychiatric disorder can influence brain anatomy and behavior in offspring and siblings (MDD: (Amico et al., 2011; Baaré et al., 2010; Rao et al., 2010); Schizophrenia/Bipolar Disorder: (Boos et al., 2007; Kempton et al., 2009; Mondelli et al., 2008), but see (Hajek et al., 2008, 2009)).

In conclusion, we showed that smaller hippocampal volume may be considered a risk factor for the development of internalizing symptoms, and maybe, in the long run, anxiety and depression. The CBCL assessment of internalizing problems used in myriads of clinical and non-clinical studies seems rooted in the brain anatomy. We do not yet know whether the emergence of internalizing symptoms causes changes in volumes of critical brain areas, or

whether (epi-)genetically based hippocampal volume increases the individual's vulnerability to develop internalizing symptoms. This study shows that typically developing children and adolescents with high internalizing behavior share some (but not all) of the neuroanatomical features of adult depression and anxiety-related disorders. This implies that samples with typically developing children and adolescents may contribute to the ongoing effort to elucidate the biological underpinnings of internalizing behavior. In future research, this approach can prove valuable in longitudinal assessments of changes in clinical symptoms and possible predictors of the onset of depression and anxiety.

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Contributors

Authors PCK, MIJ, MBK, and EAC designed the study. PCK processed the MRI data and MIJ and MBK undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

No authors of this manuscript have fees and grants from, employment by, consultancy for, shared ownership in, or any close relationship with, an organization whose interests, financial or otherwise, may be affected by the publication of the paper.

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