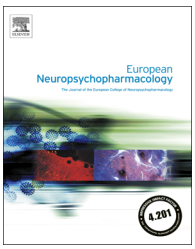
European Neuropsychopharmacology (2013) 23, 622–628



www.elsevier.com/locate/euroneuro

Hippocampal volume and internalizing behavior problems in adolescence

P. Cédric M.P. Koolschijn[a,b,*], Marinus H. van IJzendoorn[b,d], Marian J. Bakermans-Kranenburg[b,d], Eveline A. Crone[a,b,c]

[a]Institute of Psychology, Leiden University, Leiden, The Netherlands
[b]Leiden Institute for Brain and Cognition, Leiden, The Netherlands
[c]Department of Developmental Psychology, University of Amsterdam, Amsterdam, The Netherlands
[d]Centre for Child and Family Studies, Leiden University, Leiden, The Netherlands

Received 18 November 2011; received in revised form 20 March 2012; accepted 4 July 2012

KEYWORDS
Adolescence;
CBCL;
Hippocampus;
Anxiety;
Depression;
MRI

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.

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

*Correspondence to: Institute of Psychology, Brain and Development Lab, Leiden University, 3B33.A, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands.
E-mail address: koolschijnpcmp@fsw.leidenuniv.nl (P. Cédric M.P. Koolschijn).

0924-977X/$ - see front matter © 2012 Elsevier B.V. and ECNP. All rights reserved.
http://dx.doi.org/10.1016/j.euroneuro.2012.07.001

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-subscales 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 contra-indications. 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, $0.875 \times 875 \times 1.2\ mm^3$, 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: χ^2=4.50, p=0.34.