Developmental Cognitive Neuroscience 5 (2013) 106–118

Contents lists available at SciVerse ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

Sex differences and structural brain maturation from childhood to early adulthood

P. Cédric M.P. Koolschijn[a,b,*], Eveline A. Crone[a,b,c]

[a] Institute of Psychology, Brain and Development Lab, Leiden University, P.O. Box 9555, 2300 RB Leiden, The Netherlands
[b] Leiden Institute for Brain and Cognition, P.O. Box 9600, 2300 RC Leiden, The Netherlands
[c] Department of Developmental Psychology, University of Amsterdam, Weesperplein 4 1018 XA Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 15 September 2012
Received in revised form 11 February 2013
Accepted 13 February 2013

Keywords:
Adolescence
Brain volumes
Cortical thickness
Surface area
Sex differences

ABSTRACT

Recent advances in structural brain imaging have demonstrated that brain development continues through childhood and adolescence. In the present cross-sectional study, structural MRI data from 442 typically developing individuals (range 8–30) were analyzed to examine and replicate the relationship between age, sex, brain volumes, cortical thickness and surface area. Our findings show differential patterns for subcortical and cortical areas. Analysis of subcortical volumes showed that putamen volume decreased with age and thalamus volume increased with age. Independent of age, males demonstrated larger amygdala and thalamus volumes compared to females. Cerebral white matter increased linearly with age, at a faster pace for females than males. Gray matter showed nonlinear decreases with age. Sex-by-age interactions were primarily found in lobar surface area measurements, with males demonstrating a larger cortical surface up to age 15, while cortical surface in females remained relatively stable with increasing age. The current findings replicate some, but not all prior reports on structural brain development, which calls for more studies with large samples, replications, and specific tests for brain structural changes. In addition, the results point toward an important role for sex differences in brain development, specifically during the heterogeneous developmental phase of puberty.

1. Introduction

Brain development is an organized and highly dynamic multistep process, which is genetically determined, epigenetically directed and environmentally influenced (Tau and Peterson, 2010). This process continues both through childhood and adolescence, the developmental period during which the body and brain emerge from 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, it is now well known that the gray and white matter subcomponents of the brain continue to undergo dynamic changes throughout adolescence (Giedd et al., 1999; Paus, 2005).

1.1. Age differences in brain structures

There is increasing consensus on the overall pattern of gray matter development over the course of childhood and adolescence: in childhood a global increase of cortical gray matter volume takes place, peaking around the onset of puberty, which is then followed by a gradual decrease in adolescence and early adulthood (Giedd and Rapoport, 2010; Gogtay and Thompson, 2010; Raznahan et al., 2011; Shaw et al., 2008; Taki et al., 2012). Cortical thinning occurs throughout adolescence and extends well into adulthood,

* Corresponding author at: Institute of Psychology, Brain and Development Lab, Leiden University, 3B33.A, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands. Tel.: +31 71 527 79 59.
E-mail addresses: koolschijnpcmp@gmail.com (P.C.M.P. Koolschijn), ecrone@fsw.leidenuniv.nl (E.A. Crone).

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http://dx.doi.org/10.1016/j.dcn.2013.02.003

but patterns (e.g. linear, quadratic, cubic) differ across brain regions and are also dependent on the studied age range (Østby et al., 2009; Raznahan et al., 2011; Shaw et al., 2008; Sowell et al., 2004, 2007; Tamnes et al., 2009). In contrast, total white matter volume increases even until approximately the fifth decade of life and declines thereafter (Paus, 2010a; Paus et al., 2001; Walhovd et al., 2005). For subcortical regions, developmental patterns are less clear. For example, age-related volume increases for the hippocampus and amygdala (Østby et al., 2009; Taki et al., 2012), but see (Gogtay et al., 2004), and age-related volume decreases in the caudate, putamen, pallidum and accumbens have been reported (Østby et al., 2009; Sowell et al., 2002, 2004).

1.2. Sex differences in brain structures

Sex differences account in part for the aforementioned different developmental growth trajectories. Cerebral and gray matter volume in the frontal and parietal lobes peak earlier in girls than in boys (though the exact ages vary depending on the subregion), a pattern which may relate to sex differences in timing of puberty (Lenroot et al., 2007). Moreover, sex differences have been demonstrated in the hippocampus (larger in females; but see (Bramen et al., 2011)), amygdala (larger in males) (Neufang et al., 2009) and thalamus (larger in males) (Bramen et al., 2011), but see (Sowell et al., 2002). Some of these findings have also been replicated in a VBM (voxel-based morphometry) study, showing pronounced sexual dimorphism (males larger than females) in amygdala, thalamus, putamen and insula (Peper et al., 2009).

Sex differences have also been reported in cortical thickness, indicating thicker cortices in parietal and temporal regions in females compared to males (age-range 8–87) (Sowell et al., 2007), but the opposite has also been reported (Raznahan et al., 2011). In a sample with a narrow age range (10–14 years), no sex differences were present in cortical thickness (Bramen et al., 2012). However, significant sex differences were present when gonadal hormones, in this case testosterone, were used as a predictor of cortical thickness (Bramen et al., 2012; Nguyen et al., 2012). Furthermore, maturational patterns for whole brain thickness show different trajectories between sexes (Raznahan et al., 2011).

These studies have provided important insights in the complex changes in brain development in late childhood and adolescence. However, there is still no general consensus on the developmental trajectories of all (sub)cortical brain structures in early and mid adolescence.

The aim of the current study was to perform a replication study focusing on cross-sectional age- and sex-related structural brain differences in a European sample ($n = 442$; 223 females, 219 males) in the age range of 8–30 years. Specifically, we used structural magnetic resonance imaging (MRI) to gain information on brain volumes, cortical thickness and surface area measurements. We had the following objectives: (1) examine age-related differences in (sub)cortical brain volumes, cortical thickness and surface area with possible sex-related differences. (2) The second goal was to examine the relationship between gray matter volume, cortical thickness and surface area with age and between sexes.

Table 1
Age and sex distribution of the sample.

Age groups	Sex		Total
	Females (*N*)	Males (*N*)	
8–9	16	20	36
10–11	23	31	54
12–13	30	31	61
14–15	31	28	59
16–17	27	31	58
18–20	46	33	79
21–23	34	31	65
24–29	16	14	30
Total	223	219	442

2. Materials and methods

2.1. Participants

We combined data sets from several different imaging 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 healthy participants. Four hundred forty-two (219 males; 223 females) unrelated typically developing children and young adults were included. The age range was between 8 and 30 with an about equal distribution across age cohorts (see Table 1 for subgroups).

There were no differences in mean age between males (mean: 16.3 (SD = 4.74)) and females (mean: 17.0 (SD = 4.77; $p = 0.08$), and no differences in sex or age distribution and time of scan (all p's > 0.8). 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 primary caregivers (for minors) 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°, 140 slices, 0.875 mm × 0.875 mm × 1.2 mm, FOV = 224.000 × 168.000 × 177.333. All anatomical scans were reviewed and cleared by a radiologist.

2.3. (Sub)cortical volumes, thickness and area

Cortical reconstruction and volumetric segmentation was measured automatically using the software FreeSurfer version 5.0 (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999a).