Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24

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A B S T R A C T

Developmental imaging studies show that cortical grey matter decreases in volume during childhood and adolescence. However, considerably less research has addressed the development of subcortical regions (caudate, putamen, pallidum, accumbens, thalamus, amygdala, hippocampus and the cerebellar cortex), in particular not in longitudinal designs. We used the automatic labeling procedure in FreeSurfer to estimate the developmental trajectories of the volume of these subcortical structures in 147 participants (age 7.0–24.3 years old. 94 males; 53 females) of whom 53 participants were scanned twice or more. A total of 223 magnetic resonance imaging (MRI) scans (acquired at 1.5-T) were analyzed. Substantial diversity in the developmental trajectories was observed between the different subcortical gray matter structures: the volume of caudate, putamen and nucleus accumbens decreased with age, whereas the volume of hippocampus, amygdala, pallidum and cerebellum showed an inverted U-shaped developmental trajectory. The thalamus showed an initial small increase in volume followed by a slight decrease. All structures had a larger volume in males than females over the whole age range, except for the cerebellum that had a sexually dimorphic developmental trajectory. Thus, subcortical structures appear to not yet be fully developed in childhood, similar to the cerebral cortex, and continue to show maturational changes into adolescence. In addition, there is substantial heterogeneity between the developmental trajectories of these structures.

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Introduction

Brain development is an extremely complex process that is guided by genetic programs, environmental exposure and experiences (Tau and Peterson, 2009). Its course is protracted, continuing into adolescence and adulthood: for example, overall gray matter volume shows an inverted U-shaped trajectory, peaking in early adolescence (Dennison et al., 2013; Giedd and Rapoport, 2010; Goddings et al., 2014; Koolschijn and Crone, 2013; Lenroot et al., 2007; Ostby et al., 2009; Reiss et al., 1996; Sowell et al., 1999, 2002; Tau and Peterson, 2009; Wilke et al., 2007). White matter, in contrast, continues to increase in volume into adulthood (Paus et al., 2008; Walhovd et al., 2011). However, the developmental patterns of other structures, such as the striatum, limbic structures and the cerebellum, have been studied less frequently and findings have often been inconsistent: for example, both increases and decreases in caudate volume have been reported in children and adolescents (Giedd and Rapoport, 2010; Giedd et al., 1996a, 1996b; Goddings et al., 2014; Koolschijn and Crone, 2013; Lenroot et al., 2007; Ostby et al., 2009; Reiss et al., 1996; Sowell et al., 1999, 2002; Tau and Peterson, 2009; Wilke et al., 2007). In addition, most studies of such structures have investigated only one single structure, or a few, making it difficult to address the dynamic interplay between subcortical structures as they develop. Furthermore, differences in methodology or sample characteristics between studies complicate direct comparisons between reported findings. It is therefore pivotal to investigate multiple structures in the same sample (as in Dennison et al., 2013; Goddings et al., 2014; Koolschijn and Crone, 2013; Ostby et al., 2009). Furthermore, most studies to date have used cross-sectional designs, thus limiting their ability to draw inferences about development. Particularly given the large inter-individual variation, it is important to use longitudinal designs to investigate brain development. Therefore, we set out to investigate the dynamic changes in subcortical structures with development, as well as the relationship between them in the present longitudinal study. We investigated changes in the volume of caudate nucleus, putamen, pallidum, accumbens, thalamus, amygdala, hippocampus and cerebellum. We were particularly interested in these structures, as they play an important role in cognitive development (Bunge, 2009; Diamond, 2000; Ito, 2008; Lavenex and Banta Lavenex, 2013; Scherf et al., 2013) and because they have been implicated in various developmental disorders, such as autism (Langen et al., 2013; Philip et al., 2012), attention deficit/hyperactivity disorder (Carmona et al., 2009; Krain and Castellanos, 2006), schizophrenia (Ballmaier et al., 2008; Mamah et al., 2008), and substance use disorders (Berman et al., 2008; Koob, 2006; Volkow et al., 2007). Interestingly, many of these disorders first manifest themselves during childhood or adolescence (Durston et al., 2001; Paus

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et al., 2008), underlining that brain development in this period is pivotal in healthy development.

Recently, we reported on the development of cortical volume, thickness and surface area in a large cohort of typically developing children, using a combined cross-sectional and longitudinal study design (Wierenga et al., 2014). Here, we report on the development of eight subcortical structures in a larger cohort. We focused on those subcortical structures that have been implicated most frequently in developmental disorders (caudate nucleus, putamen, pallidum, accumbens, thalamus, amygdala, hippocampus and the cerebellum). A total of 223 MRI scans from 147 typical developing children and adolescents (64% males) were included, where more than one third of the participants was scanned twice or more. On average, the time interval between two successive scans was two years (ranging from 1.5 to 5.6 years). We aimed to describe the developmental trajectories of these subcortical structures. In addition, we investigated gender differences, as some studies have reported sexually dimorphic developmental trajectories (e.g. Dennison et al., 2013). We explored developmental change in the volume of amygdala and hippocampus, striatum and cerebellum.

Methods and materials

The Institutional Review Board of the University Medical Center Utrecht, The Netherlands approved this study and its procedures. Subjects aged 18 years and older signed for their own consent. For children under 18 years of age, a parent signed for consent.

Participants

The present study included a total of 223 MRI-scans from 147 typically developing individuals (94 males; 53 females); 53 participants were scanned twice or more (41 males; 12 females). Scans were acquired with an average interval of two years (ranging from 1.5 to 5.6 years). Participants were aged between 7.0 and 23.3 years old, with above average intellectual levels (see Table 1 for participant characteristics).

Participants were recruited through schools and other educational centers in the area. For all participants under 18 years of age, a parent participated in a semi-structured interview session with a trained rater to confirm absence of any psychiatric diagnosis (Diagnostic Interview Schedule for Children; DISC-P). Older subjects participated in the Mini-International Neuropsychiatric Interview (MINI) to confirm absence of psychopathological symptoms (Sheehan et al., 1998). Individuals with a psychiatric diagnosis (current or prior), major physical illness of the cardiovascular, the endocrine, the pulmonary or the gastrointestinal system, neurological illness, a history of unconsciousness, organ dysfunction, alcohol or other drug dependence, or full IQ below 75 were excluded from participation. In addition, individuals with a first-degree relative suffering from a psychiatric illness were excluded.

Written informed consent was obtained for all participants. All individuals participated in at least one or more MRI scanning sessions and intelligence testing (children older than 16 years of age: Wechsler Adult Intelligence Scale/Wechsler Adult Intelligence Scale-Third Edition [WAIS/WAIS-III] (Stinissen et al., 1970; Wechsler, 2000); children of 16 years or younger: Wechsler Intelligence Scale for Children-Revised/Wechsler Intelligence Scale for Children-Third Edition [WISC-R/WISC-III] (Kort et al., 2005; Van Haasen et al., 1986). Furthermore, participants and their parents filled out a short questionnaire on hand preference and a questionnaire related to major physical or neurological illness. Children under 13 years of age were acclimated to the scanning procedure in a dummy-scan session prior to the actual MRI session (Durston et al., 2009; Mega and Cummings, 1994). An independent clinical neuroradiologist evaluated all MRI-scans. No gross abnormalities were reported for any of the participants.

Image acquisition

Magnetic resonance imaging (MRI) scans were acquired on a 1.5-T scanner (Philips, Best, The Netherlands). For definition of all brain measures, a whole brain T1-weighted three-dimensional fast field echo scan with 160–180; 1 mm × 1 mm × 1.2 mm contiguous coronal slices was acquired (256 × 256 matrix, FoV = 256 mm, echo time (TE) = 4.6 ms, repetition time (TR) = 30 ms, flip angle = 30°).

Image processing

Cortical reconstruction and volumetric segmentation

All MRI scans were coded to ensure rater blindness to subject identity. Scans were processed and analyzed using the neuroimaging computer network of the Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht. FreeSurfer v 5.1.0 software was used to estimate the volume of our regions of interest (ROIs): caudate nucleus, putamen, pallidum, accumbens, thalamus, amygdala, hippocampus and the cerebellar cortex. This is a well-validated and well-documented software program that is freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Technical details of the automated reconstruction scheme are described elsewhere (Carmona et al., 2009; Dale et al., 1999; Fischl et al., 1999).

In short, neuroanatomical labels are automatically assigned to each voxel based on probabilistic information from a manually labeled set. This automatic labeling method shows similar results to manual labeling, and low reproducibility errors (Fischl et al., 2002; Jovicich et al., 2006; Tae et al., 2008). Before quantitative analyses can be performed, output requires qualitative inspection (Dewey et al., 2010). Manual edits were performed where needed by three experienced raters (LW, SA, SvD). Edits included the removal of non-brain tissue and perfecting the white matter mask. The standardized procedures, documented on the FreeSurfer website, were used for these manual edits.

Total CSF volume was calculated as the sum of all ventricles. Total cerebral subcortical gray volume was calculated as the sum of all subcortical ROIs, excluding the cerebellum (caudate nucleus, putamen, pallidum, accumbens, thalamus, amygdala, and hippocampus). The brain stem was not included as its volume depends on the field of view at acquisition.

Longitudinal processing

In order to reduce within subject variability between scan sessions, a longitudinal analysis method was developed for FreeSurfer (Gogtay et al., 2006; Reuter and Fischl, 2011). This method increases repeatability and statistical power (Gogtay et al., 2006; Lenroot et al., 2007; Reuter et al., 2010; Wilke et al., 2007). All second, third and fourth scans (n = 53) were processed using this procedure. An unbiased within-subject

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals, n</td>
<td>94</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Hand preference, n</td>
<td>74</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Right-handed</td>
<td>20</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Height, mean (SD)</td>
<td>163.2 (20.6)</td>
<td>155.6 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Weight, mean (SD)</td>
<td>52.5 (19.0)</td>
<td>48.7 (15.5)</td>
<td></td>
</tr>
<tr>
<td>IQ, mean (SD)</td>
<td>113.2 (16.1)</td>
<td>122.6 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Total number of scans, n</td>
<td>153</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Scanner</td>
<td>n Mean age (SD)</td>
<td>n Mean age (SD)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>94</td>
<td>12.6 (4.0)</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>15.9 (4.0)</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>16.2 (2.7)</td>
<td>5</td>
</tr>
</tbody>
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SD = standard deviation.
The eijk term represents the normally distributed residual error. Each \( \beta \) represents a parameter estimate; for example the quadratic age effect parameter is represented by \( \beta_3 \). Furthermore, the interaction effects of gender and age are modeled. The full model was tested against models including linear or quadratic age terms only. Intercept, gender and age effects were fixed, while within person dependence, nested within family (dij), was modeled as a random effect. All possible developmental models were run using mean-centered age terms (age 13.5).

The choice of the best model fit was based on three steps: First, cubic, quadratic and linear age effects were fitted on the volumes of each ROI (region of interest). If the cubic age effect was not significant at \( p < 0.05 \), we stepped down to the quadratic developmental model, etc. Second, we investigated whether the developmental trajectories differed between genders. Hence, using the Bayesian Information Criterion (BIC), a full model containing both the main effects of age and gender, as well as interaction effects, was compared to a simpler model including the main effects of age and gender only. We tested whether the full model allowing for differences in growth trajectories between genders explained more variance than the simpler model. Third, if this was not the case the simpler model including the main effects of age and gender was compared to the best-fit developmental model selected in step one including age terms only. Again the best-fit model was selected using BIC values, resulting in the model that explained most variance accounting for the amount of parameters included in the model and herewith minimize the effects of overfitting the data. Confidence intervals for intercepts were estimated using a bootstrap method with 1000 case resamples. Sampling with replacement was used to reestimate the intercept parameter. Furthermore, age at peak volume was calculated from the first-order derivative of non-linear growth curves. Confidence intervals of age at peak volume were calculated using the above-mentioned bootstrap method.

Results

Developmental trajectories

Results of the regression models for each ROI are shown in Fig. 1 and Table 2. Total brain volume decreased in a curvilinear fashion, peaking at age 7.0 for both males and females. There was no interaction between age and gender, but there was a main effect of gender, where total brain volume was larger for males than females over the entire age range. All subcortical structures also showed an association with age, as well as a main effect of gender, with larger gray matter volumes for males than females. There were linear decreases with age in the volume of caudate nucleus, putamen and accumbens, whereas the volume of pallidum showed a quadratic developmental trajectory with a peak at age 17.2 years. The volume of thalamus, hippocampus and amygdala also followed inverted-U shaped developmental trajectories, with peaks at

![Fig. 1. Developmental trajectories for total gray matter volume: Age 7.0–23.3 years old. Mean volume in cm³ (y-axis) by age in years (x-axis) is shown for males (n = 94, blue) and females (n = 53, red). The shade around the regression lines represents the 95% confidence interval of the intercept.](image-url)
We investigated the development of subcortical brain structures in typically developing children, using a mixed cross-sectional and longitudinal design. Subcortical structures showed developmental patterns that were markedly different from the global decrease in cortical volume that has been described during childhood and adolescence (Dennison et al., 2013; Giedd and Rapoport, 2010; Goddings et al., 2014; Koolschijn and Crone, 2013; Lenroot et al., 2007; Ostby et al., 2009; Reiss et al., 1996; Sowell et al., 1999, 2002; Tamnes et al., 2013; Tau and Peterson, 2009; Wilke et al., 2007). We found inverted U-shaped developmental patterns in gray matter volume across our age range for the hippocampus, amygdala, pallidum, thalamus and cerebellar cortex, while linear decreases were observed in the caudate, putamen and nucleus accumbens. Furthermore, all subcortical structures were larger in males than females over the whole age range. The cerebellum was the only structure to show a sexually dimorphic...
developmental trajectory, with an earlier peak volume in females than males. The developmental patterns observed in the present study are broadly consistent with previous findings for the striatum (Dennison et al., 2013; Giedd et al., 1996a, 1996b; Goddings et al., 2014; Ostby et al., 2009; Tamnes et al., 2013) although most of these studies were cross-sectional. However, one of the few longitudinal studies did not observe a decrease in the striatum (Raznahan et al., 2014). They showed substantial heterogeneity in development of subdivisions of the striatum, which may have been obscured in our data. In addition, differences in developmental trajectories between our study and the one by Raznahan et al. could partly be attributable to differences in the number of subjects. Furthermore, our results are consistent with previous findings on protracted development of hippocampus and amygdala volumes (e.g., Goddings et al., 2014; Mosconi et al., 2009; Ostby et al., 2009). Additionally, not all studies observed a protracted development in hippocampal volume, as decreases in a similar age range have also been reported (Mattai et al., 2011; Tamnes et al., 2013). However, this discrepancy could be related to our use of raw volumes rather than intracranial corrected volume (as in Mattai et al., 2011). Furthermore, our results are in line with findings on thalamus volume (Brown and Jernigan, 2012; Giedd et al., 1996a, 1996b; Ostby et al., 2009; Schumann et al., 2004; Tamnes et al., 2013), and the cerebellum (Ostby et al., 2009; Tiemeier et al., 2010) However, the observed increase in the volume of the pallidum is not in line with previous literature (Giedd et al., 1999; Goddings et al., 2014; Ostby et al., 2009; Raznahan et al., 2014). This discrepancy may be attributable to our choice not to correct for overall brain volume, as two earlier studies did report increases in uncorrected pallidum volume (Dennison et al., 2013; Ostby et al., 2009). Also, our study is one of few to capture developmental changes in thalamus volume (Brown and Jernigan, 2012; Dennison et al., 2013; Giedd et al., 1996a, 1996b; Ostby et al., 2009; Reiss et al., 1996). This may be related to the small magnitude of the change (approximately 2%, see Supplementary Fig. 1), as this might render it particularly difficult to detect in cross-sectional designs (Giedd et al., 1996a, 1996b; Ostby et al., 2009; Reiss et al., 1996). In addition, the thalamus shows protracted development compared to total grey matter, but peak volume occurs before the hippocampus and amygdala. Hence the thalamus may therefore mature earlier than the hippocampus and amygdala. However, whether the age at peak volume reflects homologous biological processes and hence is a meaningful biological marker in terms of developmental timing, remains unclear. Alternatively, rate of change, which is moderate for thalamus development, may also be an important indicator of developmental timing. Finally, we replicated an earlier report of an age × gender effect on cerebellar volume (Brown and Jernigan, 2012). The cerebellum plays an important role in cognitive functioning (Ito, 2008). This finding may therefore reflect the role of cerebellum in the development of cognitive functions during adolescence, and possibly gender differences in the rate of development.

We did not replicate previous reports of sexually dimorphic developmental trajectories for thalamus (Dennison et al., 2013; Lenroot et al., 2007, Raznahan et al., 2014) and caudate nucleus or putamen (Dennison et al., 2013; Goddings et al., 2014, Raznahan et al., 2014). This may be related to differences in methodology as some of these studies allowed for growth trajectories to vary in shape between males and females early in the model selection procedure. While our selection method procedure may have been more strict and herewith perhaps have underestimated the age × gender interaction effects. But also the limited amount of female longitudinal scans in our dataset may have resulted in a lack of a significant gender × age interaction effect. Previous studies have suggested that sexually dimorphic developmental trajectories may relate to differences in pubertal measures, including steroid hormones (Goddings et al., 2014; Peper et al., 2011). Although we did not investigate such measures of puberty, our findings do not support the notion of hormonally driven gender differences in the timing of brain development, with the possible exception of the cerebellum.

The neuroanatomical processes underlying the developmental changes in brain volume remain unclear. The heterogeneity in developmental trajectories between structures suggests that these processes may vary between them and perhaps even over developmental time. They may be related to changes in gray matter, such as changes in the number of oligodendrocytes, that have been associated with developmental changes in amygdala volume (Chareyron et al., 2012). Alternatively, they could also be related to changes in the surrounding white matter, such as increased myelination of axonal projections, that have been related to developmental reductions in striatum (Ostby et al., 2009; Shaw et al., 2008).

Some limitations of the present study should be acknowledged. First, we looked at the whole volume of the subcortical structures, rather than the substructures that form them or at deformations on their surface that may show where in the structure changes are occurring (Raznahan et al., 2014). As such, we may have overlooked any heterogeneity in the development of these substructures (e.g., Gogtay et al., 2006). Second, our dataset included more males than females. As such, we may have been somewhat underpowered to investigate gender differences.

We described the developmental trajectories of a number of subcortical structures using a mixed longitudinal and cross-sectional dataset in a population of typically developing individuals. The observed heterogeneity in the development of subcortical brain structures indicates dynamic developmental changes during development that are likely to be related to changes in behavioral and cognitive development. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.03.072.

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References
