Structural development of frontal regions in late childhood and adolescence:

a longitudinal MRI study

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Abstract

Adolescence is an important developmental period between childhood and adulthood. During adolescence, significant structural changes take place in the brain and in particularly in the frontal cortex. The frontal cortex plays a crucial role in higher brain functions such as working memory, inhibition and selective attention. Therefore, accurate information about development of the frontal cortex helps to better understanding these functions. In this study, magnetic resonance imaging (MRI) was used to study structural changes in frontal gray and white matter volume during the transition from late childhood to adolescence (age 9 to 17), while taking sex differences and pubertal timing in account. Participants were 76 healthy twin pairs (46 % females). The results showed significant increases in frontal white matter volume and a volume reduction of frontal gray matter throughout late childhood and adolescence. Development of frontal regions appears to occur more rapidly from early adolescence to middle adolescence (ages 12 to 17) than from childhood to early adolescence (ages 9 to 12). Sex differences were found for structural development of frontal gray and white matter. Boys showed more increase of white matter volume throughout late childhood and adolescence, while girls showed more reduction of gray matter volume during this time. There was limited evidence that stage of puberty predicts brain maturation better than age. The study is unique in comparing volumetric changes of the frontal regions between twee periods and future studies need to replicate these findings.

Keywords: adolescence, brain development, frontal lobe, puberty, sex difference

Introduction

Adolescence is the transition period from childhood to adulthood, characterized by significant behavioral, cognitive, and emotional changes (Blakemore& Choudhury, 2006; Crone, 2009; Scherf, Behrmann & Dahl, 2012). During adolescence, considerable structural changes occur in the human brain, which are linked to this cognitive and behavioral development (Crone, 2009; Lebel & Beaulieu, 2011; Sturman & Moghaddam, 2011). There is a steady increase in overall volume of white matter with age, which is counterweighted with non-linear reduction of gray matter volume. Therefore, total cerebral volume shows a subtle increase during this time (Blakemore& Choudhury, 2006; Giedd et. al, 1999; Paus, 2005)

The increase of white matter during late childhood and adolescence suggests an age-related increase in axonal myelination (van Soelen et al., 2012), which is vital for improved communication between the different brain areas (Barnea-Goraly et al., 2005; Paus, 2005; Sowell, Traunner, Gamst, & Jernigan, 2002; Tamnes et al., 2009). Gray matter reduction is possibly related to a massive pruning of synapses (Sowell et al., 2002; Tamnes et al., 2009) or caused by myelination of non-myelinated axons around the cortical layers (Blakemore& Choudhury, 2006; Sowell, Thompson, & Toga, 2004), and is regional and temporal specific (Sowell et al., 1999; Sowell, et al., 2002). These processes are crucial in shaping neural circuits and could be the biological basis for the development of cognitive abilities and behavior (Tamnes et al., 2009). Therefore, studying age-related changes of white matter and gray matter provides more detailed information about neurocognitive development during adolescence.

The frontal lobe plays a crucial role in higher brain functions, i.e., executive functions, which include abilities such as inhibition and switching, working memory, and sustained and selective attention (Alvarez & Emory, 2006; Hughes, 2011; Tamnes et al., 2010). During adolescence, significant structural changes in the frontal cortex take place, which are

associated with age-related improvements of these higher brain functions (Hughes, 2011). Deficits in frontal lobe volume are related to several psychiatric conditions. For example, a volume reduction of the left prefrontal cortex is found in boys with Attention Deficit Hyperactivity Disorder (ADHD) and Tourette syndrome (Kates et al., 2002). Volume reduction of frontal lobe is also investigated in mood disorders (Beyer & Krishnan, 2002; Strakowski, Adler, & DelBello, 2002). The negative symptoms of schizophrenia, such as emotional dullness, impaired judgment, poor initiative, decreased concern for personal hygiene, and social withdrawal, are thought to be a manifestation of impaired frontal lobe function (Ziauddeen, Dibben, Kipps, Hodges, & McKenna, 2011).

Increased knowledge about the development of the healthy brain aids understanding of the cognitive and behavioral functions that occur during normal development (Lebel & Beaulieu, 2011; Lenroot & Giedd, 2006; Sowell et al., 2002; Sturman & Moghaddam, 2011; van Soelen et al, 2012), and for understanding when brain development is deviant (Sowell et al., 2002; van Soelen et al., 2012). However, despite this fact studies of normal brain development throughout late childhood and adolescence are relatively few in number in comparison to the large number of brain studies of disease (Sowell et al., 2002). Also, there is considerable individual variation in the maturational process of brain. Therefore, for better understanding of the development of frontal regions, longitudinal studies on the developing adolescent brain are essential. Such a longitudinal study helps in providing more accurate information about structural changes in the brain (Barnea-Goraly et al., 2005; van Soelen et al., 2012) and related individual differences (Lenroot & Giedd, 2006). Two considerations of such a study are sex and pubertal timing.

While sex differences are well known in cognitive and emotional development, differences between girls and boys in brain development are poorly understood (De Bellis et al., 2001; Tamnes et al., 2009). Sex differences in total brain size are the most robust finding

of differential development in the human brain, which is reported to be about 10 % larger in males compared to females (Lenroot & Giedd, 2006; Goldstein et al., 2001). Studies of subcomponents of the brain revealed ambivalent findings with regard to sex differences, after accounting for the total brain size difference (Lenroot et al., 2007). In the literature, temporal differences between girls and boys in the brain volumetric maturational process are also reported. Total cerebral volume peaks at age 10.5-11.5 years in females and 14.5 years in males (Lenroot & Giedd, 2006; Lenroot et al., 2007). Both cortical and subcortical gray matter volume peaks one to two years earlier in girls than boys (Geidd et al., 1999; Lenroot et al., 2007). White matter volume increases linearly with age with a steeper rate in boys (Geidd et al., 1999; Lenroot et al., 2007). In some studies, assessment of sex differences is hampered by small sample sizes (De Bellis et al., 2001; Sowell et al., 1999). Therefore, a longitudinal study in a large sample will enhance our knowledge about sex differences in brain development (Blakemore& Choudhury, 2006; De Bellis et al., 2001; Sowell et al., 1999).

Pubertal is an important factor period during adolescence and involves increased growth, changes in body composition, the development of gonads and secondary sexual organs and characteristics, and cardiovascular and respiratory changes (Falkner &Tanner, 1986). The pubertal period partly overlaps with adolescence, but adolescence refers to behavioral, cognitive, and emotional changes (Sisk & Zehr, 2005). There is considerable individual variation in chronological age regarding the onset, transition, and completion of puberty. This variation is again related to sex differences; puberty ranges from age 10-17 in girls and 12-18 in boys (Falkner &Tanner, 1986). Puberty may be a stronger predictor of structural changes in the brain than the chronological age (Blanton et al., 2012). For example, some studies indicated that maturation of the hippocampus, amygdala (Blanton et al., 2012; Bramen et al., 2011), and cortical gray matter (Bramen et al., 2011) during adolescence is more driven by pubertal stage rather than chronological age. The frontal and parietal gray

matter peaks approximately one year earlier in girls, corresponding with the earlier age of the onset of puberty (Giedd et al., 1999). Therefore, it is crucial to take pubertal stage into account when studying structural development of brain. The effect of pubertal stage can be studied by assessing participants who all have the same chronological age.

The aim of the present longitudinal study is to gain more detailed insight in the structural development of frontal regions during the transition from childhood to adolescence, by looking at gray and white matter volume, while taking sex differences and pubertal timing in account. We compare the change rates of white matter volume and gray matter volume between two periods, from late childhood to early adolescence (ages 9 to12) and from early adolescence to late adolescence (ages 12 to 17). It is expected that there is no difference in the change rate of white matter volume between these two periods, because white matter increases in a linear fashion. It is also expected that gray matter volume shows a smaller decrease from childhood to early adolescence (ages 9 to 12) than from early adolescence to middle adolescence (ages 12 to 17), because gray matter reaches its peaks around the onset of puberty, and then starts to decrease in size. Additionally, it is expected that there are sex differences in the structural changes in the frontal lobe. Due to an earlier onset of puberty, girls are likely to display an earlier advanced maturation. Therefore, it is expected that girls show more decrease in frontal gray matter volume than boys from late childhood to early adolescence, and boys show more decrease in frontal gray matter volume than girls from early adolescence to late adolescence. It is also expected that boys show greater increases in white matter volume than girls in both periods, because white matter has been shown to increase with a steeper rate in boys during adolescence. Furthermore, the relationship between the pubertal stage and structural changes in the frontal cortex will be investigated. It is hypothesized that the stages of puberty are associated with structural changes in the frontal regions, when participants all have the same chronological age.

Methods

Participants

Participants were 112 healthy twin pairs recruited from the Netherlands Twin Register. Data were collected at three time points. At baseline, the sample consisted of 214 children (50.5 % female, mean age = 9.25 years). At the second date wave, 140 children completed the data-collection procedure (47% female, mean age = 12.18). At the third data wave, the sample consisted of 169 children (53% female, mean age = 17.23) at the moment these analyses were done. In total, 76 children (46 % females) participated at all three measurement times. At the baseline, mean age of those participants was 9.22 years (range: 9.05 to 9.65). At the second date wave, mean age of the participants completing three waves was 12.12 (range: 11.71 to 13.11). At the third data wave, mean age of twins that participated three times was 17.22 (range: 16.89 to 17.86).

Pubertal assessment

Pubertal stage was determined by Tanner stage of puberty (Tanner & Whitehouse, 1976). This scale involves characterization of the pubertal changes in breast development in girls, genital development in boys, and pubic hair growth in both. Tanner stages are classified on a 5-item scale (stage 1 represents no pubertal development and stage 5 represents full maturation), with exception Tanner stage of pubic hair growth in boys and girls, and Tanner stages of testes growth in boys. Tanner stage of pubic hair growth in boys and girls are classified on a 6-item scale (stage 1 represents no pubertal development and stage 6 represents full maturation). Tanner stages of testes growth in boys are classified on a 4-item scale (stage 1 represents no pubertal development and stage 4 represents full maturation) (Tanner, 1962). At baseline and second data wave, a researcher supervisor assessed pubertal development. If children did not feel comfortable with this assessment, they were asked to point out their status based on black and white photographs of the different puberty stages, which were

accompanied by oral explanation of the researcher. At third data wave, participants were asked to complete the scale themselves.

Image acquisition

Structural MRI of the whole brain was performed on a 1.5-T Achieva scanner (Phillips, Eindhoven, Netherlands) at the University Medical Center Utrecht for each participant. For the baseline and two follow-up measurements, the same scanner parameters as well as image processing procedures were applied to limit possible differences in scan acquisition. A three-dimensional T1-weighted coronal spoiled-gradient echo scan of the whole head (256 -256 matrix, Echo Time (TE) ¼ 4.6 ms, Repetition Time (TR) ¼ 30 ms, flip angle ¼ 30-, 160-180 contiguous slices; 1 -1 -1.2 mm 3 voxels, field-of-view (FOV) ¼ 256 mm/70%) was acquired for volumetric analysis.

Image processing

Scans were put into a Talairach frame (no scaling) and corrected for in homogeneities in the magnetic field (Sled, Zijdenbos, & Evans, 1998). Quantitative assessment of intracranial volume (IC) of the first measurement was based on the DTI-BT0 and MTI images as described earlier (Peper et al., 2008). The IC segments for the first follow-up were created from the baseline IC segments, using nonlinearly transformations. The IC segments for the second follow-up were created from the IC segments of the first follow up, using nonlinearly transformations. The T1-weighted images of the baseline measurements were nonlinearly warped onto the follow-up measurement up to a scale of 1.2-mm full-width-at-halfmaximum by a combination of nonlinear warpings with increasing precision (Collins, Holmes, Peters, & Evans, 1995). Total brain, and gray and white matter were segmented using a partial volume segmentation method incorporating a nonuniform partial volume distribution (Brouwer, Hulshoff Pol & Schnack, 2010). The frontal lobe was segmented based on transformations to a model brain (Peper et al., 2008) onto which the lobes had been manually demarcated (as

was done in Hulshoff Pol et al., 2002). Brain images were registered to the model brain through the Automatic Nonlinear Image Matching and Anatomical Labeling (ANIMAL) algorithm (Collins et al., 1995) to remove global differences in size and shape of individual brains. The inverse of the transformation process registered the manual segmentations of the model brain to all participants' brain images.

Statistical analyses

For each subject, frontal white matter and gray matter volume were calculated in millilitre (ml) at each time point. Then, paired-samples t-tests were conducted to examine any significant differences of white and/or gray matter volume between first measurement point (at the age of 9) and second measurement point (at the age of 12) and between second measurement point (at the age of 12) and third measurement point (at the age of 17). The change rates between measurement points were computed per year to compare development of the brain between two periods, from late childhood to early adolescence (ages 9 to12) and from early adolescence to middle adolescence (ages12 to17).

The first research question concerned whether maturation per year in the first period (ages 9 to 12) differed from the second period (ages 12 to 17). This was done using a Repeated Measure Analyses of Variance (rANOVA) for volumetric change rates per year of frontal white matter and gray matter volume. The next research question concerned sex differences in the development patterns of the frontal lobe. This was examined using a rANOVA with sex as between-subject factors. The last research question concerned the influence of pubertal development on brain maturation. Because of the fact that age and pubertal stage are intertwined, we used the set-up of the sample to disentangle the two: at each measurement all subjects have the same age, which means that variation in volume maturation cannot be explained by age. We performed a univariate ANOVA with frontal volume as

dependent variable and Tanner stage as a random factor on the data of each wave, to determine whether Tanner stage accounts for spread in white matter and gray matter volume.

Results

Frontal white matter

Frontal white matter volume showed a significant increase throughout childhood and adolescence. Results from paired-samples t-tests indicated a significant difference in average frontal white matter volume in late childhood (M =163.64 ml, SD = 19.61) and early adolescence (M = 171.02 ml, SD = 20.36), $t(76)$= 6.60, p-value < .001, and also between early adolescence (M = 171.02 ml, SD = 20.36) and middle adolescence (M = 185.84 ml, SD = 27.11), $t(76)$= 10.60, p-value < .001 (see Table 1 for the volumes for the sexes separately). Frontal white matter volume increased in average 2.66 ml per year from childhood to early adolescence (ages 9 to 12), and 2.93 ml per year from early adolescence to middle adolescence (ages 12 to17). Results from one-way analysis of variance (ANOVA) revealed no significant difference in average change rate per year, ($F(1, 75) = 0.26$, $p = .61$, $\eta^2 = 0.00$) between two periods (from childhood to early adolescence and from early adolescence to middle adolescence), suggesting an increase of white matter volume in a linear fashion (see Table 2 for change rates per year for frontal white and gray matter, for the sexes separately).

Frontal gray matter

Frontal gray matter volume showed a significant decrease throughout childhood and adolescence. Results from paired-samples t-tests indicated a significant difference in average frontal gray matter volume in late childhood (M = 235.42 ml, SD = 18.37) and early adolescence (M = 230.94 ml, SD = 19.67), $t(76)$ = - 4.07, p-value < .001, and also in early adolescence (M = 230.94 ml, SD = 19.67) and middle adolescence (M = 208.78 ml, SD = 21.07), $t(76)$ = - 20.22, p-value < .001 (see Table 3 for the volumes for the sexes separately).

Frontal gray matter volume decreased in average -1.64 ml per year from childhood to early adolescence (ages 9 to 12), and -4.35 ml per year from early adolescence to middle adolescence (ages 12 to 17). Results from one-way analysis of variance (ANOVA) indicated that frontal gray matter volume showed smaller decreases per year from childhood to early adolescence ($F(1, 75) = 37.91$, $p < .001$, $\eta^2 = 0.34$) rather than from early adolescence to middle adolescence, suggesting the faster decrease of gray matter volume during early to middle adolescence (see Table 2 for change rates per year for frontal white and gray matter, for the sexes separately). The effect size for this effect was medium.

Sex differences

Results from analysis of variance (ANOVA) with sex as between-subject factors for the change rates of white matter volumes revealed no significant main effect for time ($F(1, 74) = 0.20$, $p = .66$, $\eta^2 = 0.00$) throughout late childhood and adolescence, as was found in the analysis above. There was a main effect of sex for volumetric changes of frontal white matter through childhood and adolescence ($F(1, 74) = 6.15$, $p = .02$, $\eta^2 = 0.07$). The effect size for this effect was small. In both periods (from childhood to early adolescence and from early adolescence to middle adolescence), boys showed a greater increase in white matter volume than girls (see Table 2 for change rates per year for frontal white and gray matter, for the sexes separately). There was no significant interaction between sex and time ($F(1, 74) = 0.62$, $p = .43$, $\eta^2 = 0.00$), indicating that the effect of time did not depend on sex.

Results from analysis of variance (ANOVA) with sex as between-subject factors for the change rates of gray matter volumes revealed a significant main effect for time ($F(1, 74) = 36.84$, $p < .001$, $\eta^2 = 0.33$) throughout late childhood and adolescence, as it was previously mentioned. The effect size for this effect was medium. There was a significant main effect of sex ($F(1, 75) = 9.43$, $p = .003$, $\eta^2 = 0.11$). The effect size for this effect was small. In both periods (from childhood to early adolescence and from early adolescence to middle

adolescence), girls showed a greater decrease of gray matter volume than boys (see Table 2 for change rates per year for frontal white and gray matter, for the sexes separately). The impact of time did not depend on sex, since the interaction between sex and time was not significant ($F(1, 74) = 0.21$, $p = .64$, $\eta^2 = 0.00$).

Pubertal stages

To explore the relation between pubertal Tanner stages and changes of frontal volumes (gray and white matter) throughout childhood and adolescence, thirty one-way between-groups analysis of variance (ANOVA) were conducted. Only three analyses showed statistically significant differences in the mean scores on frontal volumes across pubertal stages (at $p < .05$); at the age of 9, there were statistically significant differences for frontal white matter volume across Tanner stage breast development in girls ($F(1, 102) = 4.00$, $p = .05$, $\eta^2 = 0.04$), indicating that more breast development is associated with more white matter volume in girls (see Table 4 for frontal white matter volume across Tanner stages of breast development in girls at the age of 9). The effect size for this effect was small. At the age of 12, there was statistically significant differences for frontal white matter volume across Tanner stage breast development in girls ($F(4, 54)$, $p = .02$, $\eta^2 = 0.08$), indicating that more breast development is associated with more white matter volume in girls (see Table 4 for frontal white matter volume across Tanner stages of breast development in girls at the age of 12). The effect size for this effect was small. At the age of 17, there were statistically significant differences for frontal white matter volume across Tanner stage pubic hair growth in boys ($F(4, 48) = 2.90$, $p = .03$, $\eta^2 = 0.19$). The effect size for this effect was small and when this analysis was repeated removing two outliers, this finding was not significant.

Discussion

The aim of this present study was to gain more insight in the structural development of frontal brain regions during the transition from late childhood to adolescence (ages 9 to 17) in

a longitudinal design. We looked at gray and white matter volume, while taking sex differences and pubertal timing in account. As expected, we found significant volume increases in frontal white matter and a volume reduction in frontal gray matter throughout late childhood and adolescence. We compared the rates of frontal volumetric changes per year between two periods, from childhood to early adolescence (ages 9 to 12) and from early adolescence to middle adolescence (ages 12 to 17). There was no difference in the change rate of white matter volume between these two periods. Frontal gray matter volume showed a larger decrease from early adolescence to middle adolescence (ages 12 to 17) than from childhood to early adolescence (ages 9 to 12). Sex differences were found for structural development of frontal gray and white matter. Boys showed more increase in white matter volume throughout late childhood and adolescence, while girls showed more reduction of gray matter volume during this time. Pubertal status had some influence on brain maturation, but since significant differences were only found for two of thirty analyses (Tanner stages of breast development in girls at age 9 and 12 years), we should be careful while interpreting these finding.

As expected, there was a significant increase in the volume of frontal white matter throughout late childhood and adolescence (ages 9 to 17). These findings are consistent with previous studies (De Bellis et al., 2001; Giedd et. al, 1999; Sowell et al., 2002; Tamnes et al., 2009; Tamnes et al., 2010). We found no difference in the change rate of white matter volume between two periods (from childhood to early adolescence and from early adolescence to middle adolescence) consistent with earlier findings that white matter increases linearly with age (De Bellis et al., 2001; Giedd et. al, 1999; Sowell et al., 2002; Tamnes et al., 2009; Tamnes et al., 2010).

In agreement with the previous studies, we found a significant volume reduction in frontal gray matter throughout late childhood and adolescence (De Bellis et al., 2001; Giedd

et. al, 1999; Sowell et al., 2002; Tamnes et al., 2009; Tamnes et al., 2010). We also observed that frontal gray matter volume showed greater a decrease from early adolescence to middle adolescence (age 12 to age 17) than from childhood to early adolescence (age 9 to age 12). This reduction of gray matter in a different tempo across the different periods could be representation of this fact that gray matter volume decreases in a non-linear developmental course (Giedd et. al, 1999; Sowell et al., 2002; Tamnes et al., 2009). The reduction of gray matter might reflect pruning of synapses (Sowell et al., 2002; Tamnes et al., 2009) or caused by myelination of non-myelinated axons around the cortical layers (Blakemore& Choudhury, 2006; Sowell et al., 2004). The reduction of gray matter volume in combination with increases in white matter volume may reflect increases of myelinated axons during adolescence, which leads to more efficient communication between the different brain areas (Barnea-Goraly et al., 2005; Paus, 2005; Sowell et al., 2002; Tamnes et al., 2009). Therefore, greater decrease of gray matter from early adolescence to middle adolescence than from childhood to early adolescence, suggest more rapid developmental process in the frontal regions during adolescence (ages 12 to 17), which may represent more efficient brain function.

We also investigated sex differences in volumetric changes of frontal regions. Boys showed a larger increase in white matter volume than girls in both periods, consistent with previous studies (De Bellis et al., 2001; Giedd et al., 1999; Lenroot et al., 2007). This greater increase of frontal white matter in boys could be related to the fact that boys have a greater white matter volume in comparison with girls throughout late childhood and adolescence. (Giedd et al., 1999). However, other study indicated that girls have greater neuronal processes in white matter structure despite of smaller white matter volume in compared with males (Schmithorst, Holland, & Dardzinski, 2008). Using neuroimaging techniques that assess the microstructual organization of white matter could help us to explain these sex differences in white matter structure (Ladouceura, Peper, Crone, & Dahl, 2012).

Due to an earlier onset of puberty in girls, it was expected that girls showed more decrease in frontal gray matter volume than boys during first period, while boys showed more decrease in frontal gray matter volume than girls during second period. In contrast to what we expected, we found girls had a greater loss of frontal gray matter volume than boys in both periods. This finding is similar to one previous study (Giedd et al., 1999). But one other study reported that total gray matter volume showed significantly greater decrease in boys than girls (De Bellis et al., 2001). These differences in findings could be related to design of studies; longitudinal versus cross-sectional design.

It is hypothesized that the stages of puberty are associated with structural changes of the frontal regions, when participants all have the same chronological age. But only two of thirty analyses showed statistically significant differences in the mean scores of frontal volumes across pubertal stages. In girls, there were statistically significant differences for frontal white matter volumes across Tanner stages of breast development at the age of 9 and 12 years. To our knowledge, there is a little known about relation between Tanner stage and volumetric changes of the brain. Some previous studies revealed similar findings. They reported a relation between Tanner stage of breast development and total volume of the amygdala (Blanton et al., 2012) and gray matter volume of amygdala in girls (Bramen et al., 2010). Therefore, stages of breast development may be a predicator for brain development.

This study is subject to several strengths and limitations. The first strength of our study is the longitudinal design whereby we controlled inter-individual differences. The study is unique in comparing volumetric changes of the frontal regions between twee periods, from late childhood to early adolescence and from early adolescence to middle adolescence. We studied the relation between pubertal stage and the volumetric changes of frontal lobe. There are few studies that investigated this relation. Fourth, our participants all have the same age at

each measurement point. Therefore, the variation in volume maturation did not explain by age when studying the effect of pubertal stage on the volumetric changes of the brain.

There are also some limitations to this study. First, there were three years between first and second measurement points, but five years between second and third measurement points. However we computed change rates between measurement points per year to compare development of the brain between two periods, we lost maybe some information. Second, we studied only volumetric changes of frontal regions and not the whole brain. Future studies need to study the volumetric changes of other lobes of the brain to compare the brain development of different regions. Third, we used Tanner stages of puberty as assessment of pubertal stage to study relation between puberty and volumetric changes of the brain. Level of sex steroid hormones such as estrogen, progesterone, and testosterone may be a better predicator for the volumetric changes of the brain than Tanner stages (Blanton et al., 2012). Future researches needs to study the relation between sex steroid hormones and frontal volumetric changes. Fourth, in our statistical methods, we did not take this fact into account that our subjects were twins.

In conclusion, our findings suggest that significant volumetric changes occur in the frontal gray and white matter throughout late childhood and adolescence. There are different patterns of development for each type of brain tissues (gray and white matter). While white matter increases linearly with age, gray matter shows a non-linear reduction throughout late childhood and adolescence. In addition, tempo of brain development differs between different age ranges: brain development of frontal regions appears to be more rapid during adolescence than late childhood. Sex effects volumetric changes of frontal regions; boys showed a greater increase in white matter volume than girls throughout late childhood and adolescence and girls showed a greater decrease of gray matter volume than boys. There was limited evidence that stage of puberty predicts brain maturation better than age.

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Table 1: Absolute age-related white matter volume per measurement wave for boys and girls

		White matter volume		
Age		9	12	17
	N	M (SD)	M (SD)	M (SD)
Female	36	150.27 (15.84)	156.75 (17.54)	167.60 (24.20)
Male	41	175.04 (14.74)	183.56 (13.20)	201.85 (17.93)
Total	77	163.46 (19.61)	171.02 (20.36)	185.84 (27.10)

Note. White matter volume reported in millilitre, M = mean, SD = standard deviation.

Table 2: Change rates per year of frontal white and gray matter volumes per sex

		White matter change rate per year		Gray matter change rate per year	
		Ages 9 to 12	Ages 12 to 17	Ages 9 to12	Ages 12 to 17
	N	M (SD)	M (SD)	M (SD)	M (SD)
Female	35	2.30 (3.24)	2.11 (2.50)	- 2.43(2.92)	- 4.97 (1.43)
Male	41	2.95 (3.87)	3.61 (2.07)	- 0.89 (3.73)	- 3.85 (2.12)
Total	76	2.65 (3.59)	2.92 (2.38)	- 1.60 (3.45)	- 4.36 (1.90)

Note. Change rate of white matter volume reported per year and in millilitre, M= mean, SD = standard deviation.

Table 3: Absolute age-related gray matter volume per measurement wave for boys and girls

	Gray matter volume			
	Age	9	12	17
	N	M (SD)	M (SD)	M (SD)
Female	36	225.70 (15.06)	219.23 (16.58)	194.06 (14.80)
Male	41	243.96 (16.82)	241.22 (16.22)	221.34 (16.86)
Total	77	235.42 (18.37)	230.94 (19.67)	208.77 (21.07)

Note. Gray matter volume reported in millilitre, M = mean, SD = standard deviation.

Table 4: Frontal white matter volume across Tanner stages of breast development in girls at the age of 9 and 12

	At the age of 9		At the age of 12	
Tanner stages	M (SD)	N	M (SD)	N
1	150.30 (14.64)	84	145.00 (12.51)	6
2	157.27 (17.94)	20	157.63 (13.35)	12
3	-	-	159.18 (15.96)	25
4	-	-	155.84 (16.88)	11
5	-	-	178.13 (20.92)	5
Total	151.78 (15.53)	104	158.41 (16.91)	59

Note. Tanner stages are classified on a 5-item scale, stage 1 represents no pubertal development and stage 5 represents full maturation, M = mean, SD= standard deviation.