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Cerebral white matter in early puberty is associated with luteinizing hormone concentrations

Jiska S. Peper [a,*], Rachel M. Brouwer [a], Hugo G. Schnack [a], G. Caroline M. van Baal [a], Marieke van Leeuwen [b], Stéphanie M. van den Berg [b,1], Henriëtte A. Delemarre-Van de Waal [c], Andrew L. Janke [d], D. Louis Collins [d], Alan C. Evans [d], Dorret I. Boomsma [b], René S. Kahn [a], Hilleke E. Hulshoff Pol [a]

[a] *Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands*
[b] *Biological Psychology, VU University, Van der Boechorststraat 1, 1081 BT, Amsterdam, The Netherlands*
[c] *Pediatric Endocrinology, VU University Medical Center, De Boelelaan 1117, 1007 MB, Amsterdam, The Netherlands*
[d] *Montreal Neurological Institute, McGill University, 3801 University Street, Montreal, Quebec, Canada*

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Summary Puberty is a period in which cerebral white matter grows considerably, whereas gray matter decreases. The first endocrinological marker of puberty in both boys and girls is an increased secretion of luteinizing hormone (LH). Here we investigated the phenotypic association between LH, global and focal gray and white matter in 104 healthy nine-year-old monozygotic and dizygotic twins. Volumetric MRI and voxel-based morphometry were applied to measure global gray and white matter and to estimate relative concentrations of regional cerebral gray and white matter, respectively. A possible common genetic origin of this association (genetic correlation) was examined. Results showed that higher LH levels are associated with a larger global white matter proportion and with higher regional white matter density. Areas of increased white matter density included the cingulum, middle temporal gyrus and splenium of the corpus callosum. No association between LH and global gray matter proportion or regional gray matter density was found. Our data indicate that a common genetic factor underlies the association between LH level and regional white matter density. We suggest that the increase of white matter growth during puberty reported earlier might be directly or indirectly mediated by LH production. In addition, genes involved in LH production may be promising candidate genes in neuropsychiatric illnesses with an onset in early adolescence.
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* Corresponding author at: University Medical Center Utrecht, Heidelberglaan 100, A01.126, 3584 CX, Utrecht, The Netherlands. Tel.: +31 88 75 53379; fax: +31 88 75 55443.
E-mail address: j.s.peper@umcutrecht.nl (J.S. Peper).
[1] Current address: Veterinary Sciences, Utrecht University, Yalelaan 104, 3584 CM, Utrecht, The Netherlands.

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1. Introduction

Puberty represents the process of physical change towards adulthood leading to the capacity to reproduce. During puberty, global and regional gray matter volumes in the brain decrease (Giedd et al., 1999) and white matter volume increases (Giedd et al., 1999; Paus et al., 1999). Regional white matter increases have been found in the splenium of the corpus callosum and the temporal and parietal lobe (Thompson et al., 2000). Currently, the mechanisms underlying these brain changes during puberty are unclear, although genes are likely to play an important role (Peper et al., 2007). Endocrinologically, puberty is characterized by the activation of the hypothalamic-pituitary-gonadal (HPG) axis. The first measurable endocrinological marker of puberty is a nocturnal rise in luteinizing hormone (LH) from the pituitary gland (Delemarre-van de Waal et al., 1991). In both boys and girls this is reflected in a nightly increase in LH-pulse frequency and amplitude detectable in first morning urine samples (Demir et al., 1996). The nightly LH-pulses are detectable several years before secondary sexual characteristics become apparent (Boyar et al., 1972; Demir et al., 1996) and are an augmentation of the existing prepubertal circadian LH-secretion (Apter et al., 1989). LH, together with the gonadotropin follicle stimulating hormone (FSH), stimulates the production of sex steroids which leads to the production of testosterone in boys and estrogens in girls. From animal studies, it has been established that sex steroids have organizational properties onto the brain that include neurogenesis and neurite outgrowth (McEwen and Alves, 1999), myelination of axons (Yates and Juraska, 2008) and growth of astrocytic processes in white matter (Chowen et al., 2000). In adult humans, pharmacologically induced changes in the levels of testosterone and estrogens have been shown to alter total brain and hypothalamus volumes (Hulshoff Pol et al., 2006a). Although it has been shown that LH can cross the blood–brain barrier (Lukacs et al., 1995) and LH receptors have been found in various brain areas (Lei et al., 1993), the relation between LH and brain morphology remains unclear. In the current study, we explored the association between LH and gray and white matter structure in a cohort of nine-year-old twin pairs, using both volumetric MRI and a voxel-based morphometry approach. In addition, the extent to which a possible association between LH and gray or white matter structure is determined by genetic or environmental factors was explored. This can be accomplished by comparing cross-trait/cross-twin correlations of monozygotic (MZ) twins, who share 100% of their DNA, with dizygotic (DZ) twin pairs, who share on average 50% of their segregating genes. If cross-trait/cross-twin correlations between LH level and white matter, i.e., the LH level in one twin predicts white matter volume in the co-twin, are larger in MZ twins than in DZ twins, this suggests genetic mediation of the association.

2. Method

2.1. Participants

Participants were 104 healthy Dutch twins, recruited from the Netherlands Twin Registry (Boomsma et al., 2006; Van Leeuwen et al., 2008) including 24 monozygotic (MZ) pairs (11 female and 13 male, 1 male pair incomplete) and 29 dizygotic (DZ) pairs (9 female, 12 male and 8 opposite sex, 1 female pair incomplete) between 9 years, 0 months and 9 years, 8 months old (Table 1). Physical and mental health was assessed with a medical history inventory. Children with any mental or physical (endocrinological) illness were excluded from the study. Zygosity of the twins was determined based on DNA polymorphisms, using 8–11 highly polymorphic di-, tri- and tetra-nucleotide genetic markers. Parents of subjects gave written informed consent to participate in the study. The study was approved by the Central Committee on Research involving Human Subjects (CCMO) of the Netherlands and experiments were in accordance with the declaration of Helsinki.

Table 1 Demographics of the twin-sample

	Monozygotic	Dizygotic
N (Individuals)	47	57
Age (S.D.)	9.20 (0.10)	9.21 (0.12)
Sex (F/M)	22/25	25/32
Handedness (R/NR)	40/7	47/10
Tanner 0/1 (%)	39/8 (83/17)	44/13 (77/23)
Birth weight (S.D.)	2476.0 (461)	2699.8 (530)
Gestational age (S.D.)	36.7 (1.8)	36.8 (1.8)
LH (U/l) (S.D.)	.22 (.18)	.22 (.19)
Prop. Gray (S.D.)	.51 (.02)	.51 (.02)
Prop. White (S.D.)	.31 (.01)	.31 (.02)

Age in mean (S.D.) years, F, female; M, male; R, right-handed; NR, non-right handed; Tanner 0/1, number with no development/with development (%); LH, Luteinizing hormone in mean Units per Litre (U/l) (S.D.); Prop. Gray, mean proportion gray matter of intracranial volume (S.D.); Prop. White, mean proportion white matter of intracranial volume (S.D.).

2.2. MRI acquisition and processing

MRI scans were acquired from a 1.5 Tesla scanner (Philips, The Netherlands). A three-dimensional T1-weighted coronal spoiled-gradient echo scan of the whole head (256 × 256 matrix, TE = 4.6 ms, TR = 30 ms, flip angle = 30°, 160–180 contiguous slices; 1 mm × 1 mm × 1.2 mm voxels, Field-of-View = 256 mm/70%) was acquired. Furthermore, a single-shot EPI (Echo Planar Imaging) scan was made as part of a diffusion tensor imaging (DTI)-series (SENSE factor 2.5; flip angle 90°; 60 transverse slices of 2.5 mm; no gap; 128 × 96 acquisition matrix; FOV 240 mm; TE = 78 ms) together with a magnetization transfer imaging (MTI) scan (60 transverse slices of 2.5 mm; no gap; 128 × 96 acquisition matrix; FOV 240 mm; flip angle 8°; TE = 4.5 ms; TR = 37.5 ms). Our automatic image-processing pipeline was used for segmentation of intracranial volume and global gray (GM) and white matter (WM) of the cerebrum. The T1-weighted images were automatically put into Talairach orientation (Talairach and Tournoux, 1988) without scaling, by registering them to a model brain in Talairach orientation. The two other scans were registered to the T1-weighted image by minimizing a mutual information joint entropy function (Maes et al., 1997). The co-registered scans were used for automatic segmentation of the intracranial volume, based on histogram analysis and

morphology operations. The intracranial volume was subsequently checked visually and edited where necessary. The intracranial segment served as a mask for global gray and white matter segmentation. The software included histogram analysis, mathematical morphology operations, and anatomical knowledge-based rules to connect all voxels of interest, as was validated before (Schnack et al., 2001).

Regional measures of GM and WM concentration (''density'') were generated using voxel-based morphometry (VBM) in a similar manner as was done previously (Hulshoff Pol et al., 2006b). VBM included the following steps. First, a model brain was created on a sample of 298 children aged 9 to 14 (including the 104 children discussed in this report), similar to the method used in Grabner et al. (2006). The use of a model brain specifically created from children's brains ensures an optimal warping from the individual brains to the model. For a detailed description of the creation of this model brain, see supplementary material. Second, the binary gray matter (GM) and white matter (WM) masks with voxels of 1 mm × 1 mm × 1.2 mm were blurred by a 3D Gaussian kernel (FWHM = 8 mm), in order to gain statistical power. The voxel values of these blurred GM and WM segments (between 0 and 1) reflect the local presence, or concentration, of GM or WM, respectively, and these images are referred to as 'density maps'. Third, in order to compare brain tissue at the same anatomical location in all subjects, the GM and WM segments were transformed into a standardized coordinate system (i.e., the model brain). These transformations were calculated in two steps. (A) The T1-weighted images were linearly transformed to the model brain. In this linear step a joint entropy mutual information metric was optimized (Maes et al., 1997). (B) Nonlinear (elastic) transformations were calculated to register the linearly transformed images to the model brain up to a scale of 4 mm (FWHM), thus removing global shape differences between the brains, but retaining local differences. For this step the program ANIMAL (Collins et al., 1995) was used. Fourth, the GM and WM density maps were transformed to the model space by applying the concatenated linear and nonlinear transformations. Finally, the maps were resampled to voxels of size 2 mm × 2 mm × 2.4 mm.

Voxels with an average GM density below 0.1 were excluded from the GM density voxel-based analysis. Similarly, voxels with an average WM density below 0.1 were excluded from the WM density voxel-based analysis.

2.3. LH measurements

LH was determined in morning urine using highly sensitive immunometric assays (Luminiscention), carried out by the endocrinological laboratory of clinical chemistry of the VU Medical Center in Amsterdam (Architect, Abbott Laboratories, Abbott Park, Illinois, USA). Samples were collected on two consecutive mornings directly after waking up. It has been demonstrated that first morning urine samples, using highly sensitive immunometric assays, are able to detect nocturnal rises in LH level at the beginning of puberty, even 1–2 years before serum levels of LH increase or secondary sexual signs of puberty are visible (Demir et al., 1996). The detection limit was 0.1 U/l. Urinary LH levels were divided by creatinine level to correct for variations in urine excretion rate. A creatinine correction has been demonstrated to enhance the detection of LH-surges (Kesner et al., 1998).

Secondary sexual characteristics of puberty were measured by a trained researcher (no self-report) using the Tanner-staging questionnaire (Marshall and Tanner, 1969, 1970).

2.4. Statistical analysis

The two urinary LH measurements were significantly correlated (r = .52, $p < .0001$). In the analyses, the average of the two LH measures was used. The LH means were not normally distributed (Kolmogorov–Smirnov (K–S) test (Chakravarti et al., 1967): D = .24, $p < .05$); therefore, a log-transformation was applied leading to a normal distribution of LH (D = .06, $p > .20$). Brain volumetric data were normally distributed ($ps > 0.2$). In the volumetric analysis of global gray and white matter, a correction for intracranial volume within each person was carried out, by calculating GM and WM proportions of intracranial volume.

Phenotypic correlations (r_p) with 95% confidence intervals (CI) between global GM and WM proportion and LH level were estimated with maximum likelihood using the structural equation modeling software package Mx (Neale et al., 2003). The within-person correlation between LH level and brain structure (r_p), which is independent of zygosity, was estimated while taking into account the dependency of the twin data. Within the applied genetic twin model, phenotypic correlations of MZ and DZ pairs are by definition constrained to be equal. Analyses were done in the entire sample correcting for sex effects on mean gray and white matter or mean LH-level. Furthermore, r_p was estimated for boys and girls separately. To test whether LH level and GM and WM proportion share a common origin, r_p was decomposed into a genetic and environmental part using a standard bivariate twin-model (Neale and Cardon, 1992, or see http://www.psy.vu.nl/mxbib/). This decomposition was based on cross-trait/cross-twin correlations in MZ and DZ twins: for example, when the correlation between WM proportion in twin 1 and LH level in twin 2 is higher in MZ twins than in DZ twins, this indicates that a common genetic factor influences LH level and WM proportion. The amount of overlap is reflected by the genetic correlation (r_g). r_g gives the correlation between genetic factors influencing both phenotypes.

The same statistical analyses as applied on global GM and WM proportions, were carried out on regional GM and WM densities throughout the brain, but with a covariate for handedness (right vs. non-right), as handedness has been associated with subtle changes in brain structure (Amunts et al., 2000). In addition, given the number of voxels in the brain, a correction for multiple comparisons was carried out according to the false discovery rate ($\alpha < 0.05$, two-tailed), allowing for an overall 5% chance of false positives (Genovese et al., 2002). To that end, r_p-maps needed transformation into Z-values via a Fisher-transformation. The critical z-value was 3.39 and the corresponding uncorrected p-value was 0.0007.

3. Results

A larger proportion of overall white matter volume was associated with a higher level of LH (r_p = .31 (CI = .11–.47))

Table 2 Phenotypic (r_p) and genetic (r_g) correlations between LH level and white matter

Area	Talairach coordinates			r_p	z-value	r_g	Heritability
	X	*Y*	*Z*				
Total white matter proportion*	–	–	–	.31 (.11–.47)	–	.36 (–.02–.74) NS	82%
Cingulum (L anterior)	–13	23	36	.44 (.26–.58)	4.49	.95 (.20–1.00)	18%
Cingulum (L medial)	–18	44	8	.46 (.28–.60)	4.79	.52 (.12–.83)	43%
Cingulum (L posterior)	–22	–21	41	.35 (.15–.51)	3.40	.61 (.25–1.00)	65%
Splenium	–6	–38	17	.32 (.13–.48)	3.44	.76 (.27–1.00)	39%
Mid Temporal Gyrus (R posterior)	55	–31	–8	.38 (.19–.54)	3.77	.37 (–.12–.73) NS	46%
Mid Temporal Gyrus (R medial)	54	–59	11	.44 (.27–.57)	4.69	.67 (.26–1.00)	34%
Mid Temporal Gyrus (L posterior)	–47	–73	12	.40 (.22–.55)	4.11	.80 (.35–1.00)	37%
Sup Frontal Gyrus (R)	17	–31	51	.38 (.18–.55)	3.51	.90 (.40–1.00)	36%

R, right hemisphere; L, left hemisphere; Mid, middle; Sup, superior; r_p, observed phenotypic correlation (95% confidence interval (CI)); r_g, genetic correlation (95% CI); NS, not significant. Correlations were transformed to z-values (Fisher transformation). The critical z-value was 3.39 (corrected for multiple comparisons). Heritability is the proportion genetic variance over the total variance. The heritability of LH was estimated at 76% (28–97%).

* White matter volume was calculated as a proportion of intracranial volume.

(Table 2), in the total sample and in boys and girls separately. No significant correlation was found between LH and gray matter proportion. The genetic correlation between LH-level and overall white matter proportion did not reach statistical significance (r_g = .36 (CI = –.02–.74)). With respect to the voxel-wise analysis, a higher level of LH was significantly correlated with higher white matter density in parts of the left cingulum (Table 2, Figs. 1 and 2) (r_p from .35 (posterior) to .46 (medial)), in the middle temporal gyrus bilaterally (.40 (left) to .44 (right)), right superior frontal gyrus (.38) and splenium of the corpus callosum (.32). These positive associations between LH and white matter density were shown in the total sample. However, r_p estimates in boys and girls separately failed to reach significance due to smaller sample

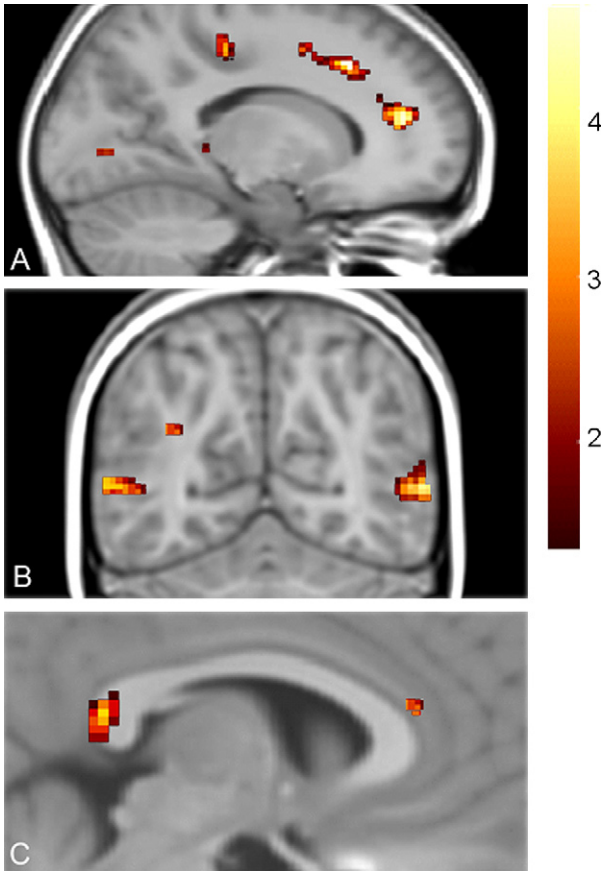

Figure 1 Positive phenotypic associations between LH level and regional white matter density in 104 9-year-old twins. (A) Left cingulum, (B) bilateral middle temporal gyrus, (C) splenium of the corpus callosum. Displayed are z-values. The critical z-value was 3.39 (corrected for multiple comparisons according to the false discovery rate, α = .05.

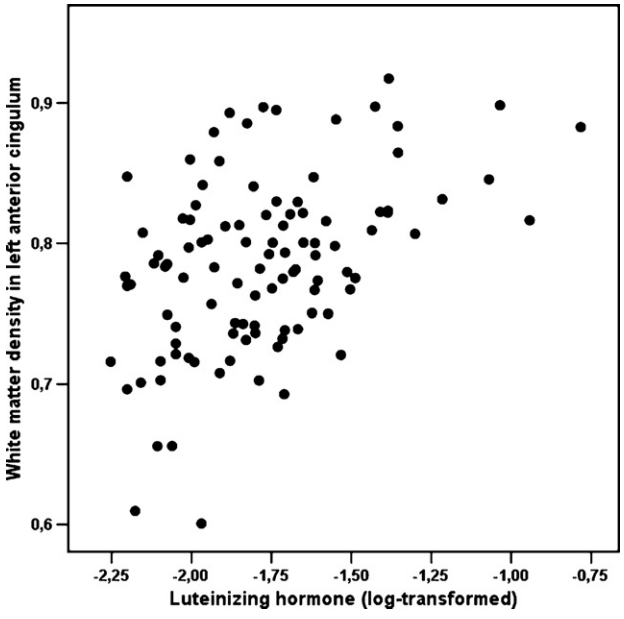

Figure 2 Scatterplot of phenotypic association between LH level and white matter density in the left anterior cingulum Depicted are LH levels versus white matter densities in the left anterior cingulum (Talairach *x*, *y* and *z* coordinates –13, 23 and 36). The phenotypic correlation coefficient is 0.44 (95% CI = 0.26–0.58). The LH-values are log-transformed and ranged between –2.25 and –.78, corresponding to LH values ranging between 0.056 and 0.167 U/l (divided by creatinine-level). The actual raw uncorrected LH values range between 0.1 and 1.1 U/l.

sizes. Genetic correlations (r_g) were significant and ranged from .52 in the posterior cingulum, to .67 in the middle temporal gyrus and .76 in the splenium (Table 2). LH level and gray matter density were not significantly correlated, although some prefrontal and temporal areas suggested a trend for a negative association. Twenty percent of the current sample ($N = 21$) was already showing the first signs of secondary sexual development (8 boys, 13 girls), indicating that our measurements were carried out at the onset of puberty. LH levels of children showing secondary sexual development were equal to LH levels of children without secondary sexual characteristics. In addition, both groups consisted of an equal number of MZ and DZ twin pairs. Leaving the children with secondary sexual development out of the analyses did not change the results.

4. Discussion

In a sample of nine-year-old twins, we demonstrated that an elevation of the first endocrinological marker of puberty, LH production, is associated with an overall larger cerebral white matter proportion of intracranial volume. In addition, we found that a higher LH level was correlated with higher regional white matter density in the left cingulum, the middle temporal gyrus bilaterally, superior frontal gyrus and the splenium of the corpus callosum. A common genetic factor underlies the association between LH level and regional white matter density. The current findings could not be explained by age variation (i.e., all children were 9 years of age) and largely preceded the development of secondary sexual characteristics.

The splenium of the corpus callosum as well as the temporal areas were found to develop most rapidly between 9 and 13 years of age as compared to younger and older children (Thompson et al., 2000). Strikingly, the areas that we found to be positively associated with LH level at 9 years are in fact those that develop fastest in children between 9 and 13 years (Thompson et al., 2000). Since parts of the cingulum bundle and splenium both project to the temporal lobes (Wakana et al., 2004), these areas might present a neural network susceptible to the influence of increased LH production in early puberty. Evidently, from our data a causal relation between LH-level and white matter cannot be inferred and studies into LH and its effects on brain morphology have been limited. Therefore, we can merely speculate on the underlying mechanism(s) of the associations we report here. Possibly, LH-production is directly associated with morphological processes in the brain. For example, it has been found that astrocyte plasticity in the hypothalamus affects LH-surges in rats (Cashion et al., 2003). Alternatively, the observed effect of LH might be an indirect result of sex steroids, as sex steroids are the end-products of the HPG-axis. Indeed, myelination of axons in the splenium is affected by manipulating levels of estrogen as demonstrated in pubertal rats (Yates and Juraska, 2008). Consequently, we are not able to exclude the contribution of other (sex steroid) hormones to the association between LH and white matter structure. However, in the early stages of puberty it has been found that the pulsatile production of LH during the night precedes the secretion of gonadal steroids by 1–2 years (Demir et al., 1996). It might be argued that at this age there is little gonadal hormone production, indirectly shown by the small number of children demonstrating secondary sexual characteristics of puberty. Furthermore, leaving these children with signs of secondary sexual characteristics out of the analyses did not change the results.

LH is a sensitive index of early pubertal development (Demir et al., 1996). However, it has also been suggested that the LH/FSH-ratio is a sensitive index of early pubertal development (Demir et al., 1995). Therefore, in a posthoc analysis, the ratio between urinary LH and FSH was calculated. FSH was determined in first morning urine samples using immunometric assays (Luminiscention). The ratio between LH and FSH was not significantly correlated with global gray or white matter proportion or with regional gray or white matter densities. We could therefore argue that LH, and not FSH, is underlying the associations with white matter structure. Another pituitary hormone interrelated with LH-release (Dunger et al., 1991; Rosenfield, 1994) is prolactin. Interestingly, in the murine central nervous system, prolactin treatment was capable of increasing myelination of axons, by oligodendrocyte regeneration (Gregg et al., 2007). Around the onset of puberty, there might be involvement of prolactin production in the observed increased white matter density. However, in early puberty it has been demonstrated that there is a substantial sex difference in the production of prolactin (Dunger et al., 1991). In the current study, we found similar associations between LH level and white matter density in both sexes. It therefore seems unlikely that in this early pubertal period, prolactin is involved in the observed associations.

Our results indicate that the association between LH-level and white matter density is driven by a common genetic factor, reflected by a significant genetic correlation between the two traits. It must be noted that the 95% confidence intervals corresponding to these genetic correlations are wide (due to the sample size). Recent studies point to the importance of the KiSS1-gene in the initiation of puberty. More specifically, a peptide-product of the KiSS1-gene, kisspeptine, is expressed throughout the brain (for review see Smith and Clarke, 2007). During puberty, mRNA expression of the KiSS1-gene was reported to be upregulated in the hypothalamus (Navarro et al., 2004). Kisspeptine, together with its G-coupled receptor GPR54, was found to stimulate LH secretion in both mice (Dungan et al., 2007) and humans (Dhillo et al., 2005). The KiSS1 gene might be a member of a network of genes that contributes to integrating glia-to-neuron communication into a functional unit capable of initiating puberty (Ojeda et al., 2006). It may be speculated that integration of glia-to-neuron communication could be reflected in increased white matter density as we found in MRI scans with increasing stage of puberty. However, this requires further investigation.

Human studies that examine the effects of LH on brain structure are currently lacking. However, several neuropsychiatric illnesses such as schizophrenia and Alzheimer disease have been associated with abnormal levels of LH (Ferrier et al., 1983; Bowen et al., 2000) together with white matter abnormalities (Hulshoff Pol et al., 2004; Xie et al., 2006; Sydykova et al., 2007). Interestingly, schizophrenia has a typical onset around puberty (Sham et al., 1994). One may therefore hypothesize that the onset of mental disorders like schizophrenia is related to altered hormonal (LH) influences,

leading to abnormal brain development. Our finding that there is a common genetic factor to LH level and regional white matter densities, suggest that genes involved in LH production may be promising candidate genes in psychiatric illnesses with an onset in early adolescence. Among these potential candidate genes are for example the earlier mentioned KiSS1-gene, the LH-receptor gene (Wu et al., 2000), and the ErbB-1 and ErbB-4 genes (belonging to the family of epidermal growth factors). The ErbB-1 and ErbB-4 receptors are located on astrocytes, and both genes have been implicated in LH secretion and pubertal development (Prevot et al., 2005).

In the current study we were unable to demonstrate an association between global gray matter proportion or regional gray matter density and LH. A possible explanation for this might be that the gray matter decrease around puberty-onset observed in earlier studies (Giedd et al., 1999; Sowell et al., 2002) might not have begun in the main part of our sample at 9 years of age. Also, the possible underlying neural substrates including nuclear size, dendrite length or number of synapses might be less sensitive (if at all) to the first endocrinological marker of puberty. Alternatively, one can argue that endogenous LH levels were currently too low to be able to affect gray matter.

The narrow age range of the subjects can both be considered as an advantage (one can measure associations between LH levels and brain structure without being affected by age-related factors) as well as a limitation. Since all subjects were 9 years of age, we cannot state that the observed association between LH and white matter is specific for this age period.

In conclusion, our results suggest that the earlier reported white matter growth during puberty might be directly or indirectly mediated by LH production. In addition, genes involved in LH production may be promising candidate genes in neuropsychiatric illnesses with an onset in early adolescence. The results of this study provide important new leads into the complex interplay between pubertal hormones and the developing human brain.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.psyneuen.2008.03.017.

Conflict of interest

None declared.

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