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REVIEW

SEX STEROIDS AND BRAIN STRUCTURE IN PUBERTAL BOYS AND GIRLS: A MINI-REVIEW OF NEUROIMAGING STUDIES

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Abstract—Puberty is an important period during development hallmarked by increases in sex steroid levels. Human neuroimaging studies have consistently reported that in typically developing pubertal children, cortical and subcortical gray matter is decreasing, whereas white matter increases well into adulthood. From animal studies it has become clear that sex steroids are capable of influencing brain organization, both during the prenatal period as well as during other periods characterized by massive sex steroid changes such as puberty. Here we review structural neuroimaging studies and show that the changes in sex steroids availability during puberty and adolescence might trigger a period of structural reorganization of grey and white matter in the developing human brain.

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Key words: gray matter, MRI, oestradiol, puberty, testosterone, white matter.

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Abbreviations: AR, androgen receptor; CAG, cytosine adenine guanine; CNS, central nervous system; FSH, follicle stimulating hormone; HPG-axis, hypothalamus-pituitary-gonadal axis; LH, luteinizing hormone; MRI, magnetic resonance imaging; SSC, secondary sexual characteristic.

Puberty represents an important period during development, forming the basis of the biological transition from a non-reproductive state into a reproductive state (Nussey et al., 2001). Puberty is associated with major endocrinological changes, such as a vast increase in the sex steroids testosterone and estradiol released from the gonads. Sex steroids are in turn responsible for the typical development of secondary sexual characteristics, such as breast development, pubic hair, and testicle growth (Marshall and Tanner, 1969, 1970). At the behavioral level, pubertal maturation is associated with increased sensation seeking and impulsivity (Forbes and Dahl, 2010), even after controlling for general effects of age (Steinberg et al., 2008). Children entering puberty also rapidly advance in abstract reasoning, cognitive control, and goal-directed behavior (for reviews see Casey et al., 2005; Yurgelun-Todd, 2007; Spear, 2010). Furthermore, they show development of risk evaluation (Crone and van der Molen, 2007) and develop complex social skills like understanding others' emotions and mental states (Blakemore, 2008; Dahl and Gunnar, 2009). Despite the advances in many cognitive functions, adolescence is also a time of rapidly shifting risks for psychopathology, which emerge differently in males and females (Paus et al., 2008) and have in some cases been linked to pubertal stage rather than age (Angold et al., 1998).

In the last two decades, an increasing number of studies have examined the neural changes occurring during development, as well as the neural correlates which are associated with the behavioral changes during puberty and adolescence (reviewed by Paus, 2005; Durston and Casey, 2006; Blakemore et al., 2010). Pioneering studies reported an initial wave of synaptic overproduction that takes place in childhood, which is followed by selective synaptic elimination during puberty and adolescence (Huttenlocher et al., 1994). This process most likely reflects the elimination of neuronal connections, rather than programmed cell death (Huttenlocher, 1990). In contrast, myelination of axons continues during this period (Yakovlev et al., 1967). These findings from early postmortem work are supported by magnetic resonance imaging (MRI) studies investigating gray and white matter volumes and white matter microstructure (Giedd et al., 1999; Gogtay et al., 2004; Giedd and Rapoport, 2010; Giorgio et al., 2010; Tamnes et al., 2010); for recent reviews see (Giedd and Rapoport, 2010; Schmithorst and Yuan, 2010). Using functional neuroimaging, prior studies

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have suggested that puberty is characterized by immature prefrontal activity (involved in cognitive control and goal-directed behavior) in combination with enhanced activation in subcortical areas such as the striatum and amygdala (among others implicated in encoding the affective valence of stimuli (Somerville et al., 2010)), in comparison to adults (Ernst et al., 2005; Galvan et al., 2007; Luna et al., 2010; Van Leijenhorst et al., 2010a,b). These studies demonstrate that brains of children in puberty (and adolescence) are subjected to intricate and widespread anatomical and functional changes. An important question that comes to mind is to what extent pubertal hormones play a role in affecting brain structure in this critical developmental period.

Traditionally, two types of hormonal action on the brain have been distinguished (Phoenix et al., 1959): (i) organizational effects; that is, steroids act on the CNS to organize neural pathways, which are irreversible and (ii) Activational effects: that is, hormonal stimulation act on neural pathways to activate certain behaviors (for critical reviews see e.g. Arnold and Breedlove, 1985; Arnold, 2009a; McCarthy, 2010). In humans, a critical period for organizational effects of testosterone on brain structure is thought to be between week 8 and 24 of gestation (Collaer and Hines, 1995). Besides the prenatal period, fluctuations in hormonal levels at later stages of life might affect brain tissue as well (Pilgrim and Hutchison, 1994), blurring the distinction between perinatal and pubertal sex steroid effects. Indeed, it has been put forward that puberty, a period characterized by neural development, is a sensitive period for gonadal steroids to organize the brain (Romeo, 2003; Sisk and Zehr, 2005; Ahmed et al., 2008; Schulz et al., 2009). Animal studies have, for instance, shown that rats castrated before puberty have a greater number of androgen receptor cells in the amygdala than rats that have been castrated after puberty (Romeo et al., 2000). Furthermore, prepubertal gonadectomy resulted in a reduction of cells within sexually dimorphic areas of the hypothalamus and amygdala (Ahmed et al., 2008). Also, during puberty pruning of dendrites and spines, in combination with axonal changes have been observed within the medial amygdala (Zehr et al., 2006; Cooke et al., 2007). In addition, androgen administration to pubertal rats induced an increase in neuronal spine density within the amygdala and hippocampus (Cunningham et al., 2007). It is important to also consider differences between the sexes, as boys and girls do not only differ dramatically in pubertal timing and sex-steroid profile (Grumbach et al., 2003), but also show distinct responses to changing levels of sex steroids. For example, work on rodents pointed out that neurogenesis within the male hippocampus was affected by endogenous testosterone fluctuations, whereas only female brains were responsive to oestradiol changes (Galea, 2008). This indicates that there is a complex interaction between sex and sex steroid hormones with respect to brain organizational processes: male and female brains seem to respond differentially to the impact of rising pubertal hormones.

In humans, to what extent brain structure is organized by sex steroids remains largely unknown. Here, we review neuroimaging studies to examine the association between brain structure and sex steroid production of pubertal and adolescent boys and girls.

EXPERIMENTAL PROCEDURES

A PubMed indexed search was carried out with a limitation of human studies using the following keywords: (sex steroids) OR (gonadal hormones) OR (testosterone) OR (estradiol) OR (progesterone) AND (white matter) OR (gray matter) OR (brain development) OR (myelin). Only papers written in English were included, as well as studies using direct measures of sex hormonal levels (e.g. no sex differences). Case studies or qualitative studies were excluded, as well as studies on sex chromosomal or hormonal abnormalities.

RESULTS

Gray matter

MRI-based gray matter is assumed to be comprised of neuronal cell bodies, dendrites, non-myelinated axons, and glial cells. Although the trajectory of change varies across brain regions, 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 and subcortical gray matter volume takes place, peaking around the onset of puberty, which is then followed by a gradual decrease in adolescence and early adulthood (for recent reviews see Giedd and Rapoport, 2010; Gogtay and Thompson, 2010). Interestingly, maximal gray matter volume in frontal and parietal brain areas in girls is reached 1–2 years before boys (Lenroot et al., 2007), paralleling the sex difference in puberty-onset (girls enter puberty on average 1–2 years before boys (Delemarre-van de Waal, 2002)). These findings provide indirect evidence that pubertal hormones influence brain structure in a sex-specific way.

A new area of research attempts to directly relate pubertal measures, including sex steroid hormones, to typical brain development during this phase of life. With respect to gray matter, studies show different associations between sex hormones and cortical areas than between sex hormones and subcortical areas. Moreover, the pattern of associations between sex hormones and brain structure is different for boys and girls.

In a sample of 10-to-15-year old boys and girls (Table 1), associations between gray matter density of the whole brain and testosterone and estradiol levels were examined (Peper et al., 2009a). In both sexes, estradiol levels were determined in first morning urine and testosterone levels were established in saliva on two consecutive days at the same time directly after waking up. It was found that higher levels of estradiol in girls were associated with decreased gray matter densities in the orbitofrontal cortex, supramarginal, and angular gyri of the parietal lobe and middle temporal gyrus (Fig. 1). Estradiol-related gray matter increases were also found, albeit less pronounced than estradiol-related decreases,

Table 1. Main findings of studies discussed in the paper

Authors	Sex	Age	*n*	TS	Main findings
Perrin et al. (2008)	M	15.1 (1.9)	204	3.5 (0.9)	M: +T→ +WM whole brain (mainly in HF *AR*-gene)
	F	15.3 (2.0)	204	4.2 (0.7)	F: T not associated with WM
Peper et al. (2008)	M	9.2 (0.1)	57	1.1 (0.3)	M+F: +LH→ +WM whole brain
	F	9.2 (0.1)	47	1.2 (0.5)	M+F: +LH→ +WM density in cingulum, MTG and splenium
Neufang et al. (2009)	M	11.7 (2.3)	15	2.6 (1.3)	M+F: +T→ +GM amygdala and hippocampus
	F	10.9 (2.1)	15	2.1 (1.5)	M: +T→ +GM hypothalamus and mam. bodies
					F: +E→ +GM parahippocampus and uncus
Peper et al. (2009a)	M	11.7 (1.0)	37	1.6 (0.7)	F: +E → −GM OFC, SupM, AG, MTG
	F	12.1 (1.2)	41	2.9 (1.1)	F: +E → +GM MFG, ITG, OCC
					M+F: T not associated with GM or WM
Peper et al. (2009b)	M	9.2 (0.1)	96	1.1 (0.3)	F: TS-yes versus TS-no: GM decrease in frontal and parietal areas
	F	9.2 (0.1)	99	1.2 (0.5)	
Bramen et al. (2011)	M	12.9 (0.7)	32	2.9 (0.9)	F: +TS→ −GM whole cortex
	F	12.0 (0.7)	48	3.2 (1.2)	F: +T→ −GM whole cortex and amygdala
Paus et al. (2010)	M	See Perrin et al. (2008)			HF *AR*-gene better predicts age-related WM increase than LF *AR*-gene.
	F				
Raznahan et al. (2010)	M	14.6 (3.5)[a]	153	NA	M: HF *AR*-gene→ attenuation of cortical thickness in IPG
	F	14.3 (3.5)[a]	131	NA	F: HF *AR*-gene→ increased loss of cortical thickness in IFG
Peper et al. (2010)	M	See Peper et al. (2009a)			F: +FSH→ +pituitary volume
	F				
Asato et al. (2010)	M+F[b]	15.5 (4.5)	112	1–2: 28 (13 F)[b]	M+F: +TS→ +Integrity of WM within fronto-temporal and cortico-subcortical connections
				3–4: 49 (28 F)	
				(5) 35 (22 F)	

AG, angular gyrus; AR, androgen receptor; E, estradiol; F, females; FSH, follicle stimulating hormone; GM, gray matter; HF, high functioning; IFG, inferior frontal gyrus; IPG, inferior parietal gyrus; ITG, interior temporal gyrus; LF, low functioning; LH, luteinizing hormone; M, males; mam. bodies, mammilary bodies; MFG, middle frontal gyrus; MTG, middle temporal gyrus; NA, not available; OCC, occipital lobe; OFC, orbitofrontal cortex; SupM, supramarginal gyrus; T, testosterone; TS, Tanner stage (NB. This is an average measure of genital and pubic hair development (ranging from 1, pre-puberty, to 5, fully mature) (Marshall and Tanner, 1969, 1970); WM, white matter.

[a] Mean age at 1, 2, 3 or 4 scans (age distribution between all scans: 8–22.8 years), [b] Asato et al. (2010) do not report mean ages and puberty stages for males and females separately, and mean pubertal stage is not provided for groups (the number of participants is given in three different pubertal phases).

in the middle frontal gyrus, the inferior temporal gyrus and the middle occipital gyrus (Peper et al., 2009a). These estradiol-related gray matter changes were found on top of overall age-related gray matter decreases. In boys, estradiol and testosterone levels were not related to changes in brain structures, nor were testosterone levels in girls.

The interrelations between sex steroid hormones (in serum) and gray matter areas have also been investigated in an, on average, slightly younger sample of 8–15 year old boys and girls (Neufang et al., 2009). A larger amygdala and hippocampus volume were related to increased levels of testosterone in both sexes. In girls only, increased levels of estrogen were associated with increased parahippocampal and uncal gray matter. In boys, higher levels of testosterone were related to larger diencephalic brain structures, such as the hypothalamus and mammilary bodies (Fig. 2) (Neufang et al., 2009). These authors speculated that the increase in circulating levels of hormones might parallel a volume increase within the involved structures like the hypothalamus and the pituitary gland suggesting a bidirectional relationship between cir-

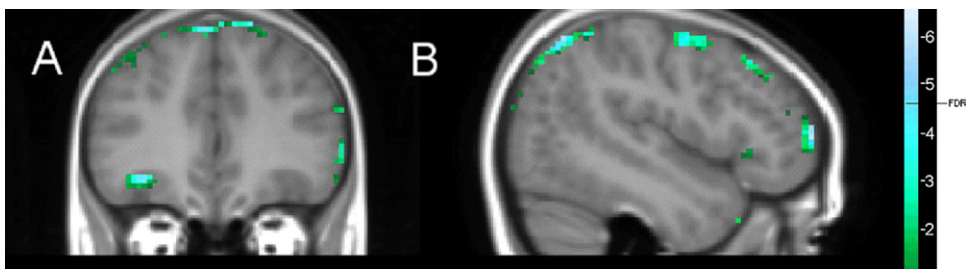

Fig. 1. Estradiol and gray matter decrease in pubertal girls. The figure depicts estradiol-related gray matter density decrease (measured with voxel-based morphometry) in girls ($n=35$) between 10 and 15 years, corrected for age. (A) Bilateral superior- and left orbitofrontal gyri, (B) right inferior frontal and angular gyri. Critical level of significance is $t=-4.6$ ($\alpha=0.05$, corrected for multiple comparisons according to the False Discovery Rate (FDR)). Adapted from Peper et al. (2009a), reprinted with permission).

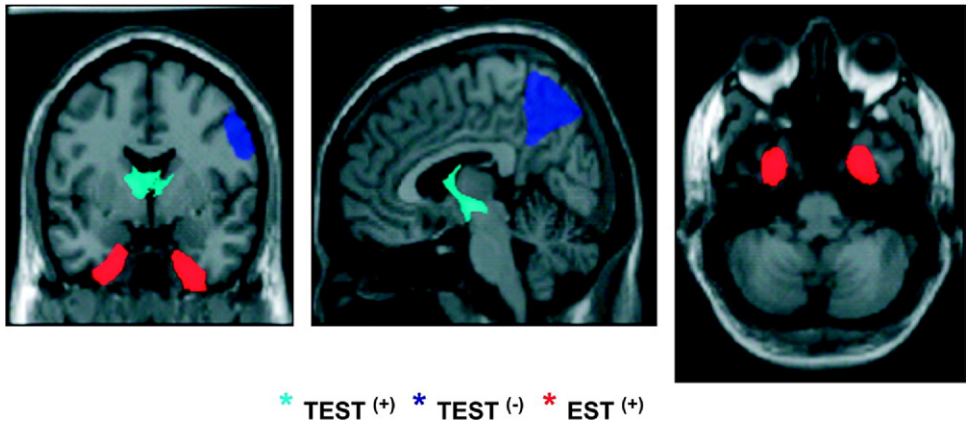

Fig. 2. Testosterone and estradiol and gray matter volume in boys and girls. Impact of circulating steroid levels on gray matter volumes across 8–15 year old boys ($n=15$) and girls ($n=15$) resulting from whole-brain regression analyses, thresholded at $P<0.001$ on voxel level, corrected for multiple comparisons at $P<0.05$ on cluster level, and overlaid on a mean structural image of the sex-specific group. Turquoise color represents positive testosterone (TEST) effects, blue color negative TEST effects, and red color positive estradiol (EST) effects on GM volumes. (Neufang et al., 2009, reprinted with permission).

culating hormonal levels and brain structure/function in these particular brain regions.

In an attempt to investigate whether a larger volume of the hypothalamus and/or pituitary gland (i.e. the two brain areas in the HPG-axis) is indeed implicated in increased pubertal hormone production, these volumes were manually segmented on MRI scans and correlated with LH, FSH, estradiol, and testosterone levels (Peper et al., 2010). It was found that only pituitary gland volume (not hypothalamic volumes) was significantly associated with hormonal levels. After correcting for age, a larger pituitary gland was associated with higher FSH levels in girls only (Peper et al., 2010). Thus, the direct relationship between increased pubertal hormone production and structures within the HPG-axis could not readily be established (using MRI). Other hormones produced from the pituitary gland, and increasing with pubertal maturation, such as corticotropin (ACTH) (Netherton et al., 2004), thyroid stimulating hormone (TSH), growth hormone (GH), and oxytocin (Tran et al., 2004), might play an important role in this process.

Although no hormone levels were measured directly, the influence of pubertal stage was investigated in gray matter density in a 9-year-old sample (Peper et al., 2009b). Girls with the first external signs of puberty were compared to girls without any signs of secondary sexual characteristics (SSCs). SSCs captured both gonadal as well as adrenal maturation, since a combined variable was created based on breast development (ovarian hormones) and pubic hair development (adrenal hormones). It was found that early pubertal girls had less gray matter density in prefrontal and parietal brain areas compared to non-pubertal girls (Peper et al., 2009b). These data provide a lead that the possible process of pruning in frontal and parietal regions (Giedd et al., 1999; Sowell et al., 2001; Paus, 2005) might be initiated by the onset of puberty.

Recent evidence from (Bramen et al., 2011) supports this hypothesis in a sample where, next to a physical examination of SSCs, plasma testosterone levels were determined. In their study, boys and girls were matched on pubertal stage rather than age, in order to better interpret sex differences in brain maturation. It is well known that girls advance into puberty earlier than boys, thus, when boys and girls are age-matched, the sample will contain an overrepresentation of pubertal stage more advanced in girls compared to boys. After correcting for age, they found that more advanced pubertal stage predicted gray matter decreases. Moreover, adolescent girls with higher levels of testosterone had smaller right amygdala volumes and smaller bilateral cortical gray matter than adolescents girls of the same age with lower levels of testosterone (Bramen et al., 2011), although these correlations were partly dependent on age. The associations between gray matter volumes and testosterone level were not present in boys.

The question then arises what causes gray matter changes at puberty-onset, given that there is so much individual variability. Several lines of research argue that the functioning of (variants of) the androgen receptor (AR) gene is important for the neurobehavioral manifestation of androgen effects in primates (for review see: Wallen, 2005). Genetic variants of the *AR*-gene were found to play a role in adolescent gray matter development, as was recently reported by (Raznahan et al., 2010). The AR contains a polymorphic trinucleotide (CAG)-repeat in exon 1, whose length modulates AR action: a smaller number of CAG repeats within the *AR*-gene was associated with higher basal levels of testosterone (Brum et al., 2005). In a longitudinal study on pubertal and adolescent subjects, Raznahan et al., 2010 reported that a greater *AR*-efficiency (i.e. a smaller number of CAG-repeats) in males was specifically associated with a more “masculine” pattern of cortical maturation (i.e. attenuation of loss) in the inferior parietal cortex (involved in visuospatial skills Poldrack, 2002). Greater androgen receptor efficiency in females was associated with a more masculine pattern of cortical maturation (i.e. increase of loss) in the left inferior frontal gyrus (involved in response inhibition; Aron et al., 2004).

To summarize, both circulating sex steroid levels as well as the androgen receptor gene seem to play a role in regulating gray matter development during puberty and adolescence. Overall, decreased cortical gray matter seems to be related to increased levels of estradiol in girls and to increased levels of testosterone in boys.

It is well known that changes in gray matter do not occur independently of their connecting white matter bundles. Therefore, the association between sex steroids and white matter will now be considered.

White matter

MRI-based white matter is thought to consist of myelinated axons. Myelin is an insulating substance created by glial cells that is responsible for the tissue's white appearance. The presence of a myelin membrane around the axon improves signal transduction (Sherman and Brophy, 2005). Histological studies pointed out that myelination of axons persists well into early adulthood (Yakovlev et al., 1967; Huttenlocher, 1990). These post-mortem studies have been replicated by structural neuroimaging work, showing an increase of white matter volume (Paus et al., 2001) and white matter integrity (Asato et al., 2010) with development (for recent reviews see Paus, 2010; Schmithorst and Yuan, 2010). During adolescence, white matter growth follows a remarkably different trajectory in girls and boys; it increases with age slightly in girls and steeply in boys (De Bellis et al., 2001; Lenroot et al., 2007; Perrin et al., 2009). These studies again provide indirect evidence that pubertal hormones influence brain structure in a sex-specific way.

Only a limited number of human studies address the association between pubertal hormones and white matter development. Among the first studies is work from Perrin et al., 2008. In a large sample of adolescents between 12 and 18 years, they found that increased levels of testosterone predicted whole brain white matter volume increase in boys, but not in girls. The strength of the association between white matter volume and testosterone depended on the type of AR polymorphism: boys with relatively short variants exhibited a stronger association between testosterone level and white matter volume (Perrin et al., 2008). Moreover, the functional polymorphism in *AR* modulated age-related increase in relative white matter volume in boys (Paus et al., 2010). This finding is comparable to Raznahan et al., 2010, who reported that the *AR* gene modulates gray matter decreases in male adolescents.

Before sex steroids are produced from the gonads, in the earliest stage of puberty the pituitary gland produces gonadotropins FSH and LH. Especially nocturnal peaks of LH—being released in a pulsatile manner—can be used as early endocrinological markers of puberty in both boys and girls (Delemarre-van de Waal et al., 1991). Importantly, 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). In a sample of 9-year old twins we examined LH levels in relation to white matter (Peper et al., 2008). LH was measured in first morning urine samples using highly sensitive immunometric assays. This method allows researchers to detect nocturnal rises in LH level that mark the beginning of puberty, even 1–2 years before serum levels of sex steroids increase or secondary sexual characteristics of puberty are present (Demir et al., 1996). It was found that an increased production of LH in both sexes was associated with larger global white matter, corrected for intracranial volume. This association could not be due to general age-related effects, since all participants were 9 years of age during MRI and hormonal measurements. Regionally, increased LH-levels were associated with larger white matter density within the splenium of the corpus callosum, middle temporal gyri, and the cingulum (Peper et al., 2008). Strikingly, these areas in white matter were previously found to develop fastest in children between 9 and 13 years, compared to younger and older children (Thompson et al., 2000). Indeed, in a recent study using Diffusion Tensor Imaging (DTI; assumed to measure white matter microstructure), higher integrity of white matter connections between frontal and temporal regions and between frontal and subcortical regions was related to more advanced pubertal stage (based on secondary sexual characteristics) (Asato et al., 2010). These findings are consistent with the idea that pubertal hormones may influence organization of white matter pathways between (or within) the frontal and temporal cortices.

We can only speculate whether LH directly affects white matter, or via another related mechanism such as the production of sex steroids. It has, for instance, been found that astrocyte plasticity in the hypothalamus affects LH-surges in rats (Cashion et al., 2003), suggesting that LH-production is directly related to morphological processes in the brain. Alternatively, the observed effect of LH might be an indirect result of sex steroids, being 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).

In summary, the association between white matter and pubertal hormones has only been examined in a relatively small number of studies. These findings are consistent with the idea that testosterone (in boys) and its precursor LH (in both sexes) may influence puberty-related increases in global white matter and regional white matter growth in areas connecting the frontal and temporal lobes. These findings may also support the notion that connections between brain regions involved in cognitive control, executive functioning, and socio-emotional processing continue to develop along with pubertal maturation.

DISCUSSION

We reviewed associations between sex steroids and brain structure in pubertal boys and girls, measured with neuroimaging. Overall, testosterone, estradiol as well as their precursor LH were associated with dynamic brain changes in this period. In particular, typical gray matter decreases in prefrontal, parietal, and temporal cortices taking place during puberty and adolescence (Giedd et al., 1999; Sowell et

al., 2002; Gogtay et al., 2004; Bramen et al., 2011; Ziermans et al., in press), were found to be related to increased levels of estradiol in girls and to increased levels of testosterone in boys. Subcortical gray matter areas showing a significant relationship with increasing sex steroid hormones during pubertal development included the hypothalamus, thalamus, amygdale, and (para)hippocampus, areas known for their high density of sex steroid receptors (Simerly et al., 1990) and for their implication in social cognition and emotional processing (LeDoux, 1993; Fuster, 2008; Hermans et al., 2008). The association between pubertal development (as a proxy for sex hormonal production) and medial temporal structures such as the hippocampus and amygdala depended on sex as well: a positive association was found with the amygdala in boys and a negative association with the hippocampus in girls.

The relationship between white matter and sex steroids during puberty and adolescence has only been investigated in a limited number of studies. Overall, testosterone (boys) as well as its precursor LH (both sexes) could predict white matter increases in the whole brain and in areas connecting the (pre) frontal and temporal cortices. Interestingly, maturation of the prefrontal cortex and (medial) temporal lobes, as well as their connecting fibers have been implicated in typical adolescent behaviors including development of social skills, enhanced reward sensitivity and reduced cognitive control (Blakemore, 2008; Berns et al., 2009; Olson et al., 2009; Van Leijenhorst et al., 2010a,b).

Pubertal and adolescent restructuring of the brain is thought to reflect adaptational processes to adulthood. Based on the highly dynamic neuronal processes during puberty and adolescence it can be proposed that brain development in this phase of life is of critical importance to how the adult brain will ultimately function. A widely adopted view is that perhaps the 'blueprint' of synapses and neuronal connections created during pre/neonatal life is being fine-tuned in this period. In other words, connections that are not used will be eliminated (Zehr et al., 2006). Identifying brain areas and their interconnected white matter pathways which show a particular association with sex steroids during human puberty and adolescence, provides important insights into neurobiological underpinnings of normal and abnormal adolescent brain development. For example, it might help to explain why several neuropsychiatric disorders such as (but not limited to) depression, anxiety disorders, schizophrenia, and eating disorders have their onset during this period (Kessler et al., 2005; Paus et al., 2008; Kuhn et al., 2010) and why these disorders often display a sex-specific prevalence or course of the illness (Westberg and Eriksson, 2008; Martel et al., 2009). Recently, the role of pubertal maturation in adolescent (social) behavior has been extensively reviewed (Forbes and Dahl, 2010). From their review it becomes clear that sexual maturation plays a role in social and affective processing, however, studies directly relating sex steroid levels to typical adolescent behavior and brain functioning are still limited. For instance, enhanced pubertal maturation and testosterone levels have been associated with less activation in the striatum and more activation of the medial PFC in response to winning a monetary reward (Forbes et al., 2010).

Limitations and future challenges

Not all studies were able to reveal a relationship between testosterone and focal gray matter structure in girls (Peper et al., 2009a) or boys (Peper et al., 2009a; Bramen et al., 2011). This could be due to a number of factors. For example, structural MRI with its current resolution may not yet be able to properly capture sex-steroid effects on brain structure. Furthermore, relatively young subjects might have had rather low levels of circulating testosterone, which were possibly insufficient to induce an effect on regional gray or white matter. Or, conversely, the 'condition' of the brain at a certain time-point during development could have determined the impact that sex steroids have on neuronal parameters: possibly, that 'critical' time-point had not been reached yet. Another explanation for null findings with respect to testosterone levels and brain structure might be related to genetic make-up. Recent studies indicate that testosterone-related effects on gray and white matter are affected by the genetic variant of the androgen receptor gene, with the most effective polymorphism explaining a stronger relationship between hormone levels and brain changes (Perrin et al., 2008; Paus et al., 2010; Raznahan et al., 2010). Possibly, an (unintentional) selection bias in genetic make-up could have masked some of the results. With respect to genetic effects, it should furthermore be mentioned that sex chromosomes exert important effects on brain organizational processes (even before the gonadal organs are active) (Arnold, 2009b) and different dosages of sex chromosome genes affect brain development also (for review see: Lenroot et al., 2009). Furthermore, brain structure and brain structural changes (Peper et al., 2007, 2009b; Brans et al., 2010) as well as sex hormone levels (Hoekstra et al., 2006; Kuijper et al., 2007) have been found to be (highly) heritable based on studies in twins. Although studies are ongoing to disentangle to which extent the genetic contribution to brain structure and sex steroid hormone production may overlap, non-hormone related genetic influences and environmental factors evidently exert their effects on brain structure throughout life.

In both sexes testosterone is (partly) metabolized into estradiol (Collaer and Hines, 1995). So even in boys, levels of estradiol might actually explain a substantial part of the variance in gray and white matter (although Peper et al., 2009a did not find evidence for this). Moreover, androgens produced from the adrenal gland such as dehydroepiandrosterone (DHEA) or DHEA-sulfate (Garcia-Segura, 2009; Yadid et al., 2010), might contribute to brain organizational processes.

It remains to be investigated whether hormonal changes during puberty and adolescence are causally involved in these brain maturational processes. Much of what is known about the effects of sex steroids and brain plasticity is derived from animal research (Garcia-Segura, 2009), in which levels of hormones can be experimentally

manipulated. Evidently, such manipulations in (healthy) humans are not possible and studies reviewed here remain of correlational nature. Also, whether pubertal hormones directly affect gray and white matter development, or whether other factors are involved remains unclear. As mentioned earlier, evidence is starting to accumulate that steroid-linked genes play an important role in human pubertal brain development (Perrin et al., 2008; Paus et al., 2010; Raznahan et al., 2010). Moreover, from animal studies it has become clear that glial cells, responsible for myelin production, are also capable of regulating steroid hormone secretion (glial steroidogenesis) (Garcia-Segura and Melcangi, 2006). Speculatively, this might imply that certain brain morphological processes, such as myelination, are required for appropriate pubertal steroid secretion. Evidently, based on these reciprocal functions between endocrinological and brain morphological processes, it is complicated to specify the source of the reported associations between pubertal brain structure and sex steroid levels.

When designing studies around this topic, several other methodological issues should be taken into account. One example is hormonal fluctuations within circadian or monthly cycles, such as the menstrual cycle. A way to possibly overcome this issue could be by investigating (female) subjects at the same time and the same day during their cycle. Neufang et al., 2009 successfully applied this approach, by investigating post-menarchal girls within their follicular phase. On the other hand, especially in early puberty, this can pose a problem since girls do not experience a regular cycle yet. One of the reasons why studying brain structure during the pubertal period is valuable is because of the naturally increasing levels of sex steroids. It is nonetheless difficult to dissociate general age-related effects on the brain from effects purely related to sex steroid hormones. Although in the majority of papers discussed here hormonal levels seemed to explain more variance in brain structure than age alone, the associations between sex steroid levels and brain structure mostly did not survive a stringent age-correction. Most samples, except for (Raznahan et al., 2010), measured hormonal and brain maturation cross-sectionally; longitudinal designs are needed to estimate hormonal and brain changes within individuals over time.

Another methodological issue that needs to be considered when interpreting the current results concerns different types of hormonal measurements, for example, from saliva or from plasma. Testosterone levels derived from saliva are highly correlated with testosterone levels determined in plasma, with correlation coefficients$>$0.83 (Butler et al., 1989; Ohzeki et al., 1991; Rilling et al., 1996). However, the biologically active fraction of testosterone (i.e. unbound by sex hormone binding globulin (SHGB)) is thought to be represented better by saliva than by plasma, whereas plasma testosterone more clearly distinguishes between different stages of genital development in puberty (Rilling et al., 1996). Although steroid levels determined from saliva or from blood plasma are highly correlated, the direct comparison between levels is complicated. At least from a practical point of view, it can be argued that non-invasive measurements of hormonal levels (i.e. saliva) in healthy pubertal children are preferred.

Finally, data described in this mini-review have made use of different ways for quantifying gray matter estimates, that is, gray matter volume (Neufang et al., 2009; Bramen et al., 2011), gray matter density (Peper et al., 2009a) or cortical thickness (Raznahan et al., 2010). Each type of assessment has its advantages (for discussions see Im et al., 2008; Panizzon et al., 2009), but direct comparisons between different kinds of gray matter measurements cannot easily be made.

CONCLUSION

It can be concluded that the changes in sex steroids availability during puberty and adolescence might be involved in triggering a period of structural reorganization of grey and white matter in the developing human brain. Although causal conclusions cannot be drawn from human studies, it can be acknowledged that studying the contribution of sex steroids to the dynamically changing brain during puberty and adolescence is an exciting new field of research. It can provide us with important insights into specific brain structures that are susceptible to changing hormonal milieus. Ultimately, identifying brain areas that are related to sex hormones might also help to better understand the etiology of neuropsychiatric disorders with typical sex differences in prevalence rates, such as depression, anxiety disorders, eating disorders, schizophrenia or attention deficit hyperactivity disorder (Kessler et al., 2005; Cahill, 2006; Paus et al., 2008).

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