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Puberty and the human brain: insights into adolescent development

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Highlights

1. Pubertal associations with subcortical and frontal brain regions.
2. Distinct role of pubertal stage and timing on brain development.
3. Longitudinal studies highlight importance of examining non-linear associations.

4. Discuss potential sources of inconsistencies and recommend future directions.

Abstract

Alongside the exponential flourish of research on age-related trajectories of human brain development during childhood and adolescence in the past two decades, there has been an increase in the body of work examining the association between pubertal development and brain maturation. This review systematically examines empirical research on puberty-related structural and functional brain development in humans, with the aim of identifying convergent patterns of associations. We emphasize longitudinal studies, and discuss pervasive but oft-overlooked methodological issues that may be contributing to inconsistent findings and hindering progress (e.g., conflating distinct pubertal indices and different measurement instruments). We also briefly evaluate support for prominent models of adolescent neurodevelopment that hypothesize puberty-related changes in brain regions involved in affective and motivational processes. For the field to progress, replication studies are needed to help resolve current inconsistencies and gain a clearer understanding of pubertal associations with brain development in humans, knowledge that is crucial to make sense of the changes in psychosocial functioning, risk behavior, and mental health during adolescence.

Keywords: puberty; adolescence; hormones; brain development; structural MRI; functional MRI

Adolescence is a time of risk and resilience, when both positive and negative lifetime trajectories unfold (Dahl, 2004). This developmental period is also shaped by the release of pubertal hormones that trigger the process of sexual maturation, resulting in a myriad of physical and biological changes encompassing increased

growth and metabolic rate, alterations in fat and muscle, breast and genital development and the appearance of secondary sex characteristics. At the same time, adolescents experience marked changes in social, emotional, and cognitive processes that ultimately enable them to attain adult roles and responsibilities (Choudhury, 2010). Along with educational and vocational achievement, this period sees a child dependent on their parents progress to a relatively independent young adult who is more responsible for their own behaviour and actions (Davey et al., 2008). In addition, significant changes in brain structure and function have been identified during this period (Crone and Dahl, 2012; Mills and Tamnes, 2014). One way to integrate across these multilevel changes is to conceptualize puberty as referring to the biological changes and adolescence as referring to the social changes (Sisk and Foster, 2004), with neurodevelopment as a potential mediator of the association between biochemical and psychosocial changes, and thus between puberty and adolescence (Blakemore et al., 2010).

Over the last two decades, there has been much research using MRI to investigate anatomical and functional changes in the brain during adolescence. While most of these studies have focused on the effect of age, there has been a more recent rise in the number of articles examining the effect of pubertal development on the brain. Greater understanding of these associations is crucial to make sense of the psychosocial changes occurring during adolescence, such as heightened social sensitivity and self-awareness (Blakemore and Mills, 2014; Pfeifer and Peake, 2012; Weil et al., 2013), increased parental conflict (Marceau et al., 2012), and social influences on decision-making (Chein et al., 2011; Weigard et al., 2014). Therefore, we aim to systematically review research examining puberty-related brain development, with specific emphasis on studies using longitudinal designs.

1. Puberty

Pubertal development occurs in two phases, adrenarche and gonadarche, which are triggered by activation of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes, respectively. Adrenarche is the earliest sign of puberty, typically occurring between the ages of 6 and 9 years, and earlier in girls than boys (Biro et al., 2014; Patton and Viner, 2007; Tung et al., 2004). It begins when the

adrenal glands release androgens, such as dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S; Palmert et al., 2001). These hormones continue to increase until the early 20s and are responsible for the development of some secondary sex characteristics, including pubic hair growth, body odor and acne (Havelock et al., 2004). Gonadarche is triggered by the hypothalamus releasing substantial amounts of gonadotropin-releasing hormone (GnRH) in a pulsatile manner during sleep (Plant and Barker-Gibb, 2004; Veldhuis, 1996). This reactivates the "dormant" hypothalamic-pituitary-gonadal axis, which was first active during prenatal and early postnatal life, and subsequently shut down by inhibitory gamma-aminobutyric acid inputs to the hypothalamus (Ojeda et al., 2006; Schulz et al., 2009; Sisk and Foster, 2004). The pulsatile release of GnRH triggers the pituitary to produce follicle stimulating and luteinizing hormones (FSH and LH), which in turn stimulate the ovaries and testes to produce sex steroid hormones, such as estrogen and testosterone. These hormones are ultimately responsible for reproductive maturity and other secondary sex characteristics, with estrogen stimulating breast growth, menstruation, and ovulation in females, and testosterone stimulating testicular development and voice changes in males. While it remains uncertain what process triggers the initial increase in GnRH release, it is hypothesised that a combination of metabolic regulation, energy storage and sleep regulation are responsible (Sisk and Foster, 2004). Gonadarche occurs earlier in females, between 9 and 14 years of age, compared to onset in males between 10 and 15 years of age (Dorn et al., 2006).

1.2 Measurement of puberty

1.2.1 Physical changes

The measurement of pubertal development is complicated by the multitude of biological and physical changes, as it remains uncertain which of these features is the best representation of maturation. The most prominent system for measuring pubertal development was proposed by Tanner (1962) who conceptualized pubertal maturation as the progression through five stages of physical development based on changes in the breast (for females), genitalia, and pubic hair. Tanner Stage (TS) 1 is considered to be pre-pubescent, TS 2-4 reflect intermediate stages and TS 5 signifies reproductive maturity. This characterization of pubertal stage is ideally measured using physical

examination by health professionals, but is also commonly assessed using picture based self-report (Dorn and Susman, 2002). Perhaps an even more frequently used measurement of pubertal stage is the self- (or parent-) reported Pubertal Development Scale (PDS), which assesses height growth, body hair and skin changes, as well as breast development and menstruation in females and facial hair and voice changes in males (Petersen et al., 1988). This measure, however, does not directly map onto Tanner staging as it struggles to capture adrenarche and early gonadal development (see section 4.1.1 for further discussion; Dorn et al., 2006). Furthermore, given that self-report scales often suffer from inaccuracies associated with age, relative pubertal stage, and ethnicity (Shirtcliff et al., 2009), physical examination is often considered to be the gold standard (Dorn et al., 2006), but is also subject to its own limitations (e.g., arguably the most expensive and intrusive method).

Aside from pubertal stage, inter-individual differences in pubertal maturation can also be described using the concepts of timing and tempo. Timing describes the pubertal status of a child relative to their same-sex and -age peers, commonly examined by measuring pubertal maturation in a sample of similarly aged individuals or statistically regressing age from puberty (Dorn and Biro, 2011; Ellis and Essex, 2007). In contrast, pubertal tempo refers to the rate of progression through the pubertal stages, and thus requires ideally (a minimum of) three repeated measurements to permit calculation (Marceau et al., 2011). Although research has identified associations between tempo and timing, the direction of association remains inconsistent with some finding faster tempo in earlier maturers (Apter and Vihko, 1985; Marceau et al., 2011), but others finding the inverse association (Pantsiotou et al., 2008).

1.2.2 Hormones

Hormones are one of the most direct indices of biological changes occurring during this developmental period. However, there is skepticism for using hormones as the sole marker of pubertal maturation, as there is wide individual variability in hormone levels both within and across pubertal stages (Dorn et al., 2006). There are also multiple issues associated with their measurement that need to be considered. For example, estradiol levels can vary across the day and menstrual cycle in females

(Buvat and Buvat-Herbaut, 1981), and although testosterone is relatively stable across the cycle, researchers still have to contend with a circadian rhythm (Liening et al., 2010). Studies attempt to overcome some of these issues by collecting more than one sample, usually immediately following awakening when hormones are at their highest concentrations (Matchock et al., 2007), and frequently within the early follicular phase in menstruating females when stage of the cycle is known for certain.

Aside from pubertal maturation, hormone levels also reflect genes, environmental factors, such as diet (Soliman et al., 2014) and being in an MRI scanner (Eatough et al., 2009), behaviors (e.g., exercise; Di Luigi et al., 2006) and other hormone levels (e.g., DHEA/S conversion to testosterone and aromatization to estrogen; Ubuka and Tsutsui, 2014). Differing results have also been identified with various methods of collecting and assaying samples (Handelsman and Wartofsky, 2013; Vesper et al., 2014, 2008; Vesper and Botelho, 2010). Of particular importance, saliva and blood samples index different aspects of hormone levels. Sex steroid hormones are bound to proteins during transportation, such as the sex hormone–binding globulin (SHBG) protein, and only a small percentage are unbound and free to act on receptors, including those within the brain. While saliva samples measure these unbound or "active" hormone levels, serum indexes total levels encompassing both bound and unbound hormones (Hofman, 2001), although measurement of SHBG allows the estimation of active hormone levels (Södergård et al., 1982). Urine samples also measure unbound hormone levels, but they reflect cumulative levels and are affected by urinary density or creatine concentration (Demir et al., 1994). Finally, collection can be intrusive (e.g., blood samples) and/or time consuming (e.g., repeated urine or saliva samples) with certain methodologies.

1.2 Neurobiological changes during puberty

Along with the physical changes occurring during puberty, there are a number of concurrent neural changes during this developmental period. Indeed, it has long been hypothesized that the hormonal shifts driving physical development may also be influencing brain maturation. Phoenix et al. (1959) proposed that hormone-related behavior changes during adolescence were instantiated within the brain; exposure to sex steroid hormones early in life masculinized and defeminized neural circuits, and

subsequent release of these sex hormones during gonadarche gave rise to sex-typical behaviors through their actions on sexually differentiated circuits (Schulz et al., 2009). These processes can be differentiated into 'organizational effects' that refer to permanent changes in neural structure, and 'activational effects' that refer to temporary changes in the activity of neural systems (Sisk and Foster, 2004). Organizational actions of steroid hormones are limited to sensitive periods – prior to or after these windows of time, hormones have limited effects on the brain's structure.

The organization-activation hypothesis has continued to evolve since its introduction. It has long been known that hormones have organizational effects during early neural development, with research in the 1960s and 70s identifying maximally sensitive periods during pre- and peri-natal life when increases in testosterone resulted in masculinization of the male neural circuitry and comparative absence resulted in feminization of the female neural system (Wallen and Baum, 2002). Thus it was initially hypothesized that only activational effects were present during puberty, with gonadal steroid hormones re-activating dormant neural circuits that facilitate reproductive and non-reproductive behaviors (e.g., changes in stress responsivity). However, more recent animal evidence suggests that puberty is a second period when hormones exert organizational effects on the structure of neural circuits (e.g., reviewed in Schulz et al., 2009), including those directly related to the facilitation of reproductive behaviors (i.e., hypothalamus), as well as indirectly via influences on attentional and motivational tendencies (Hebbard et al., 2003; Romeo and Sisk, 2001; Sato et al., 2008).

Conceptualization of this model remains largely driven by animal research (see reviews: Juraska and Willing, 2017; Schulz et al., 2009; Sisk and Foster, 2004). Only recently, with the comparatively new flourish of neuroimaging techniques, have researchers been able to examine data in support of this model in humans. This is increasingly recognized as a crucial area of research that is necessary to gain a better understanding of the complex socio-emotional changes experienced by human adolescents, including trajectories towards adaptive and maladaptive outcomes. Initial investigations into the role of puberty arose from structural MRI studies on grey matter that identified earlier age-related peaks in cortical development in females compared to males (Gogtay et al., 2004; Lenroot et al., 2007), which seemed to correspond with the time of pubertal onset in each sex. Although this finding has not

been consistently replicated (Ducharme et al., 2016; Pfefferbaum et al., 2015; Vijayakumar et al., 2016; Wierenga et al., 2014), it did result in a number of structural and functional MRI studies investigating the role of puberty in neurobiological development. These studies have employed various methods of assessing puberty, as well as different ways of controlling for, or testing interactions with, age. Furthermore, fMRI studies have utilized different tasks to examine various aspects of social, emotional, and cognitive function. We aim to systematically review the structural and functional MRI research in order to identify the pattern of findings emerging from the literature to date, extending a prior review that specifically focused on brain structure (Herting and Sowell, 2017).

The inclusionary criteria comprised the use of pubertal measures (either physical and/or hormonal indices) and neuroimaging methodologies in a sample of children and/or adolescents (see Figure S1). We specifically focus on typical development, and direct interested readers to a recent review that has addressed atypical populations (i.e., disorders of sex development; Bramble et al., 2017). The literature will be broadly grouped into two main categories: brain structure (grey and white matter) and function, and specific emphasis will be placed on longitudinal studies. We highlight when studies have chosen to control for age in pubertal analyses, thus indexing pubertal timing as opposed to stage. We also note when studies have employed pubertal stage assessments other than the gold standard of physical examination, particularly when inconsistent findings are present. We summarize findings at the end of each section, attempting to identify consistent effects in relation to *i)* brain regions, *ii)* the index of pubertal maturation, and *iii)* potential sex differences. Finally, we apply the findings to dominant models of adolescent neurodevelopment that have historically posited pubertal effects on certain aspects of brain maturation.

2. Structural MRI studies

Studies examining the relationship between puberty and structural brain development fall into two major categories: *i)* investigations into changes in grey matter that contains neuron bodies and supporting glial cells, and *ii)* investigations into changes in white matter that contains the myelinated axon fibers of neurons.

2.1 Grey matter changes

Investigations into grey matter primarily employ two main analytic methods: *i)* voxel-based morphometry (VBM) that tests for differences in grey matter density, and *ii)* surface-based morphometry (SBM) that provides estimates of cortical thickness, surface area and volume. Research on normative developmental patterns of grey matter during adolescence has identified increases in surface area, along with reductions in thickness and volume with age (Ducharme et al., 2016, 2015; Mills et al., 2016; Vijayakumar et al., 2016; Wierenga et al., 2014). Similarly, research on puberty has identified negative associations between global grey matter volume and pubertal stage and gonadal hormone levels, although more inconsistencies are evident when controlling for age (see Table 1; Bramen et al., 2011; Paus et al., 2010; Peper et al., 2009a; Pfefferbaum et al., 2015). Of more interest, though, is research that examines regional differences in these associations given *i)* variation in the density of hormone receptors (see Holder and Blaustein, 2014) and *ii)* different rates of maturation across the brain (Tamnes et al., 2010; Vijayakumar et al., 2016; Wierenga et al., 2014).

2.1.1 Cortical development

2.1.1.1 Cross-sectional research

Similar to studies on age-related grey matter changes, studies examining associations between pubertal stage and cortical grey matter have predominantly identified negative associations across adolescence (refer to Table 2 for an overview of all structural studies that were reviewed). This includes extensive and widespread negative associations between PDS scores and regional density/thickness and volume (Hu et al., 2013; Koolschijn et al., 2014; Peper et al., 2009b; Pfefferbaum et al., 2015). Findings from studies that accounted for age are depicted in Figure 1.

Similar negative associations have been identified in relation to testosterone levels. Almost all of these studies controlled for age and much of the results converge in the frontal lobe, particularly in the orbitofrontal cortex (OFC) and anterior cingulate

cortex (ACC) (see Figure 1; Bramen et al., 2012; Koolschijn et al., 2014). Some sex differences have been noted, with one study finding stronger negative associations in males within the left parietal lobe in 8-15 year olds (Neufang et al., 2009), and another finding stronger negative associations in females of a similar age in the frontal, inferior parietal and middle temporal gyri (Bramen et al., 2012). Sex differences in the occipital lobe have also been characterized by negative associations with testosterone levels in females and positive associations in males (Bramen et al., 2012). Nevertheless, thus far, it is difficult to confirm any strong sex differences for specific brain regions.

Negative associations between estradiol levels and brain structure also predominate, with all studies controlling for age (see Figure 1; Brouwer et al., 2015; Koolschijn et al., 2014). Two of these studies found sex differences characterized by negative relationships between estradiol levels and prefrontal (PFC) and parietal cortices in females alone (Brouwer et al., 2015; Peper et al., 2009a), although some positive associations in females have been identified in the inferior temporal, middle occipital and middle frontal regions (Peper et al., 2009a).

Table 2. *Overview of studies on pubertal associations with grey and white matter research in humans.*

Authors	N (F)	Age	Puberty	Study design	Imaging modality	Image processing	Outcome of interest
Asato et al., 2010	112 (63)	8-28	TS (pic)	Cross-sectional	DTI	voxelwise TBSS	RD
	87 (47)	9-10	DHEA, TEST (saliva)	Cross-sectional	DTI	voxelwise TBSS	FA, MD, RA, AD
Barendse et al., 2018							
Bava et al., 2011	58 (29)	12-14	PDS	Cross-sectional	DTI	voxelwise TBSS	FA, MD, RD, AD
Blanton et al., 2012	54 (54)	9-16	TS, menarcheal status	Cross-sectional	sMRI	VBM	Amygdala & hippocampus volumes
Bramen et al., 2011	80, 48	10-14	TS, TEST (blood)	Cross-sectional	sMRI	SBM	Subcortical & global GM volume
Bramen et al., 2012	85 (49)	10-14	TEST (blood)	Cross-sectional	sMRI	SBM	Vertex-level CT
Brouwer et al., 2015	113 (53)	9-12	LH (urine), FSH (urine), EST (urine), TEST (saliva)	Single cohort longitudinal	sMRI	VBM	Voxel-level GM
Chavarria et al., 2014	124 (62)	5-18	PDS	Cross-sectional	sMRI	VBM	Corpus callosum volume
Genc et al., 2017	74 (31)	9-12	PDS	Cross-sectional	DTI	Fixel-based analysis	Fibre density, fibre crosssection
Goddings et al., 2014	275 (117); 711 scans	7-20	TS (pic)	Accelerated longitudinal	sMRI	SBM	Subcortical volumes
Herting et al., 2012	77 (39)	10-16	PDS, TEST, EST (blood)	Cross-sectional	DTI	voxelwise TBSS	FA, MD, RD, AD
Herting et al., 2014	116 (59); 189 scans	10-14	TS, TEST, EST (blood)	Single cohort longitudinal	sMRI	SBM	Global & subcortical volumes
Herting et al., 2015	81 (48)	10-14	TS, TEST, EST (blood)	Single cohort longitudinal	sMRI	SBM	Vertex-level CT & SA
Herting et al., 2017	33 (15); 66 scans	10-20	PDS	Accelerated longitudinal	DTI	voxelwise TBSS	FA, MD, RD, AD
Herve et al., 2009	404 (200)	12-18	TEST (blood, active levels estimated)	Cross-sectional	sMRI	VBM	Corticospinal tract volume
Hu et al., 2013	306 (167)	4-18	PDS	Cross-sectional	sMRI	VBM	Mesial temporal lobe volume
Klauser et al., 2015	85 (48)	9	DHEA (saliva)	Cross-sectional	sMRI	VBM	Voxel-level WM
Koolschijn et al., 2014	215 (113)	8-25	PDS, TEST (saliva), EST (saliva), LH (urine)	Cross-sectional	sMRI	SBM	Global GM & subcortical volume, vertex-level CT

Menzies et al., 2015	61 (0)	13-16	TS (pic), TEST, EST, DHEA (saliva)	Cross-sectional	DTI	voxelwise TBSS	FA, MD, RD, AD
Murray et al., 2016	95 (50)	9	DHEA, TEST (saliva)	Cross-sectional	sMRI	SBM	Pituitary volume
Neufang et al., 2009	46 (23)	8-15	TEST, EST (blood)	Cross-sectional	sMRI	VBM	Voxel-level GM
Nguyen et al., 2013a	255 (143); 407 scans	4-22	DHEA, TEST (saliva)	Accelerated longitudinal	sMRI	SBM	Vertex-level CT
Nguyen et al., 2013b	281 (154); 469 scans	4-22	PDS, TEST (saliva)	Accelerated longitudinal	sMRI	SBM	Vertex-level CT
Paus et al., 2010	204 (0)	12-18	TEST (blood, active levels estimated), AR gene	Cross-sectional	sMRI	VBM	Global GM & WM volume, voxel-level WM
Peper et al., 2008	104 (47)	9	LH (urine)	Cross-sectional	sMRI	VBM	Voxel-level WM
Peper et al., 2009	78 (41)	10-15	TEST (saliva), EST (urine)	Cross-sectional	sMRI	VBM	Global & voxel-level GM, WM
Peper et al., 2009	214 (107)	9	TS	Cross-sectional	sMRI	VBM	Global & voxel-level GM, WM
Peper et al., 2009	214 (107)	9	TS	Cross-sectional	sMRI	VBM	Global & voxel-level GM, WM
Peper et al., 2010	85 (46)	10-15	LH (urine), FSH (urine), EST (urine), TEST (saliva)	Cross-sectional	sMRI	VBM	Pituitary & hypothalamus volumes
Peper et al., 2015	258 (132)	8-25	TEST, EST (saliva)	Cross-sectional	DTI	deterministic tractography	FA, MD, RD, LD
Perrin et al., 2008	204 (0)	12-18	TEST (blood, active levels estimated)	Cross-sectional	sMRI	VBM	Global WM volume
Perrin et al., 2009	408 (204)	12-18	PDS	Cross-sectional	sMRI	VBM	Voxel-level WM
Pfefferbaum et al., 2015	674, (340)	12-22	PDS	Cross-sectional	sMRI	SBM	Global WM volume
Pangelinan et al., 2016	941 (480)	12-19	PDS, TEST (blood, active levels estimated)	Cross-sectional	sMRI	VBM	Corticospinal tract volume
Satterthwaite et al., 2014	524 (335)	10-22	TS (pic)	Cross-sectional	sMRI	VBM	Amygdala & hippocampus volumes
Schutter et al., 2017	149 (76)	12-27	TEST (saliva)	Cross-sectional	sMRI	SBM	Cerebellar volume

Urosevic et al., 2014	126 (63)	9-18	PDS, TS (pic)	Cross-sectional	sMRI	SBM	Subcortical volumes
Whittle et al., 2012	154 (72)	11-16	PDS	Cross-sectional	sMRI	SBM	Pituitary volume
Wong et al., 2014	962 (495)	11-19	PDS, TEST, EST (blood)	Cross-sectional	sMRI	VBM	Pituitary volume

NB: The "Puberty" column only notes a single method of collection when it was utilized for all hormones. AD = axial diffusivity, AR = angroden receptor, CT = cortical thickness, DHEA = dehydroepiandrosterone, DTI = diffusion tensor imaging, EST = Estradiol, FA = fractional anisoptropy, FSH = follicle-stimulating hormone, GM = grey matter, LD = longitudinal diffusivity, LH = lutenizing hormone, MD = mean diffusivity, PDS = Pubertal Development Scale, RA = radial diffusivity, SA = surface area, SBM = surface-based morphometry, sMRI = structural MRI, TBSS = tract-based spatial statistics, TEST = testosterone TS = Tanner stage, VBM = voxel-based morphometry, WM = white matter

2.1.1.2 Longitudinal research

Longitudinal studies are especially helpful for research on puberty as they allow for age and pubertal stage to be more easily differentiated than cross-sectional research. Unfortunately, only four longitudinal studies were identified that examined pubertal associations with cortical development. Using an accelerated longitudinal sample of 4 to 22 year olds, Nguyen and colleagues (2012) found significant negative associations between testosterone and thickness in more developed adolescents (PDS "stages" 3-5, following conversion from raw scores). This included the left posterior cingulate, precuneus, dorsolateral (dl)PFC and ACC in males, and right somatosensory cortex in females. These effects accounted for age and remained significant when controlling for PDS. While similar effects were present when examining PDS alone, they did not survive correction for testosterone levels. These results are largely consistent with cross-sectional findings, but also suggest that cortical thinning may be driven by testosterone and emerges over the course of pubertal development with normative increases in testosterone.

Subsequent analyses of this sample identified significant positive associations between DHEA and the left dlPFC, right entorhinal and perirhinal cortices, as well as the temporoparietal junction (TPJ), in the pre-pubertal group (PDS stages 1-2; Nguyen et al., 2013). DHEA levels also moderated the association between testosterone and regional thickness, such that it was stronger in those with lower DHEA levels relative to those with higher DHEA levels. The authors speculate that different competing time-dependent processes may mediate these interactive effects, and emphasize the importance of examining hormone levels together rather than in isolation, along with the importance of adrenarche as a critical period for brain development.

While accelerated longitudinal designs permit the examination of a large age range within a shorter time frame, non-accelerated designs have increased power to examine intraindividual change. Employing such a design, Herting and colleagues (2015) constrained

the age span of participants at each wave given their primary interest in pubertal processes, recruiting 10-12 year old females and 12-14 year old males. Over a two-year follow-up (and after controlling for age and pubertal stage at baseline) greater increases in estradiol were related to greater thinning in the left middle temporal cortex in females, while greater TS change was related to less thinning of the superior frontal and right superior temporal cortices (the latter finding being stronger in females). The opposing findings of pubertal stage and estradiol are hypothesized to arise from TS capturing a broader range of the various hormonal processes occurring during puberty. They also identified sex-specific associations between pubertal changes and maturation of cortical surface area, suggesting that puberty may have unique effects on differing properties of the cortical mantle. This is not surprising given that thickness and surface area capture distinct cellular processes (Chenn and Walsh, 2002). Further research on surface area may thus provide novel insight into pubertal effects that are neglected when focusing on thickness, or potentially obscured when investigating volumetric estimates that are the product of surface area and thickness.

Interestingly, another non-accelerated study of 9 year old twins failed to identify any associations between grey matter development and changes in testosterone, estradiol or LH levels over 3 years (Brouwer et al., 2015). Aside from the age range of the sample, another potentially important difference from Herting and colleagues' (2015) study is the use of VBM methodology, which suggests that analytic technique may be a source of noise in the literature (see section 4.1.2 for further discussion). They did find that changes in FSH levels were positively associated with changes in the left PFC, left hippocampus, and right cerebellar density in females. More than half of significant voxels were explained by environmental factors unique to the individual, as opposed to common environment or shared genetic factors, indicating an important role of environmental factors in adolescent brain development.

2.1.2 Subcortical development

2.1.2.1 Cross-sectional research

There has been particular interest in the effect of puberty on the hippocampus and amygdala given the prevalence of sex steroid hormone receptors in these regions (Abdelgadir et al., 1999).

Focusing on the amygdala, there is support for sex differences in the effect of pubertal stage (see Figure 2), with one study identifying a negative association with TS in females and a positive association in males (Bramen et al., 2011). Others have found converging evidence when considering specific aspects of pubertal development, including negative associations between amygdala volume and breast development in females (Blanton et al., 2012; Hu et al., 2013), and positive associations with hair and skin changes in males (Hu et al., 2013). In relation to the hippocampus, there is some support for reductions in volume with increasing pubertal stage (Blanton et al., 2012; Neufang et al., 2009), although two studies have noted differing patterns of association in males and females (see Figure 2; Bramen et al., 2011; Hu et al., 2013). Across both the amygdala and hippocampus, much more inconsistencies exist when considering pubertal timing, across different measurement indices (TS: Blanton et al., 2012; Bramen et al., 2011; Peper et al., 2009b; PDS: Koolschijn et al., 2014; factor score of PDS and pictorial ratings: Urosevic et al., 2014) and also when using large age-spans (Koolschijn et al., 2014; Satterthwaite et al., 2014; Urosevic et al., 2014).

Results are predominantly non-significant when considering the relationship between gonadal hormones and either amygdala or hippocampus volume. Most studies controlled for age, and only one out of these five identified significant associations between testosterone levels and volume (positive with amygdala and negative with hippocampus; Neufang et al., 2009). None of the four studies on estradiol levels identified significant relationships with either structure. The only study that did not control for age found a significant negative association between testosterone levels and amygdala volume in females alone, but no such association with the hippocampus (Bramen et al., 2011).

The nucleus accumbens (NAcc) is of particular interest in this literature given behavioral changes in reward processing during adolescence (Silverman et al., 2015), but there is minimal support for the morphological properties of this region being associated with puberty (see Figure 2; Brouwer et al., 2015; Koolschijn et al., 2014; Neufang et al., 2009; Peper et al., 2009a; Peper et al., 2009b). The only study to find effects noted significantly smaller volumes in more mature females and a trend towards larger volumes in more mature males, after accounting for age in a sample of 9-18 year olds (based on a factor score of PDS and pictorial ratings; Urosevic et al., 2014).

Another subcortical region that has received some interest given its role in the secretion of FSH and LH is the pituitary gland. Two out of four studies identified positive

associations with PDS score, both with (Whittle et al., 2012; Wong et al., 2014) and without (Wong et al., 2014) controlling for age. Others have noted positive associations with estradiol, testosterone, FSH and DHEA levels, most of which remains when accounting for age (Murray et al., 2016; Peper et al., 2010; Wong et al., 2014). There is also some support for pubertal effects in the diencephalon (i.e., hypothalamus, mammillary bodies and thalamus; Bramen et al., 2011; Neufang et al., 2009; Urosevic et al., 2014), although others have failed to replicate these results (Koolschijn et al., 2014; Peper et al., 2010, 2009a).

2.1.2.2 Longitudinal research

Comparatively fewer longitudinal studies have examined associations between puberty and subcortical development. An accelerated longitudinal study of 7-20 year olds identified positive associations between TS (based on pictorial ratings) and amygdala and hippocampus volume, but negative associations with striatal structures (i.e., NAcc, caudate, pallidum and putamen; Goddings et al., 2014). Significant interactions between age and puberty, as well as qualitative sex differences in development trajectories, were identified. Quantitative sex differences in the relationship between TS and subcortical volume were also reported in a non-accelerated longitudinal study (described in section 2.1.1.2), along with significant interactions between age, testosterone levels and sex (Herting et al., 2014). As illustrated in Figure 3, amygdala findings from both studies are broadly consistent with sex differences in cross-sectional research. However, they do suggest nonlinear changes in subcortical volume as a function of pubertal development, and emphasize the need for further longitudinal research to explore such trajectories.

Moving beyond traditional investigations of structural brain development, a series of studies by Nguyen and colleagues (2017, 2016a, 2016b) examined the relationship between puberty and structural covariance (i.e., how structural properties, such as volume or thickness, of different regions correlate with each other Alexander-Bloch et al., 2013; Zielinski et al., 2010). In an accelerated-longitudinal sample of 6-22 year olds, testosterone levels moderated covariance between the amygdala and right OFC, such that individuals with lower testosterone levels exhibited positive covariance (i.e., larger amygdala and greater cortical thickness), whereas those with higher levels exhibited negative covariance (Nguyen et al., 2016b). Results remained significant when controlling for pubertal (PDS) stage and estradiol.

Similar associations were identified between DHEA levels and cortico-amygdala covariance (Nguyen et al., 2016a). Testosterone levels also moderated coritco-hippocampus covariance in males, although in the opposite direction to the amygdala (Nguyen et al., 2017). Analyses across all studies accounted for age-related maturation. These studies extend the structural neuroimaging literature by using a network-based approach to examine the relationship between hormones and coordinated development of brain regions. Such an approach is valuable given that animal literature predominantly supports direct mechanisms within the hypothalamus, amygdala, hippocampus, medial PFC and visual cortex (Juraska and Willing, 2017), but pubertal associations with grey matter structure are pervasive across the cortex.

2.1.3 Summary of grey matter research

There appears to be a general pattern of reductions in cortical grey matter associated with greater pubertal (stage) development and testosterone levels, and predominantly similar associations when accounting for age (i.e., pubertal timing). Less consistency in these patterns exists for estradiol levels, although negative associations dominate in females. There is also some preliminary evidence that different hormones may play a role in different periods of development, with DHEA and testosterone being implicated in early and late pubertal stages, respectively, and exhibiting different patterns of association with cortical structure. Although not specifically tested, DHEA results are consistent with adrenarche-related brain changes occurring earlier in development. Across the different pubertal indices, the most consistent effects appear to be present in the frontal lobe, although the temporal lobes have also been identified to a lesser extent. Finally, it is thus far difficult to identify clear sex differences in the associations between pubertal developmental and cortical grey matter structures.

However, there is converging evidence that puberty may contribute to sexually dimorphic changes seen in the amygdala. Multiple studies found that females exhibited negative associations with pubertal stage, while males exhibited positive associations. Moreover, longitudinal research suggests complex nonlinear interactions between puberty, age and sex. While both sexes show predominantly negative associations between pubertal stage and hippocampus volume, some studies did identify sex differences. While animal research indicates that such sex differences are related to the effects of sex steroids on receptors, support for hormonal associations with subcortical structure is limited in crosssectional studies on humans. However, the only longitudinal study does suggest that

subcortical maturation is related to hormone levels, highlighting the need for further targeted longitudinal research to fully understand these relationships.

2.2 White matter changes

Initial research on white matter development was conducted using VBM analyses, but more recent work has employed Diffusion Tensor Imaging (DTI) to measure the diffusion of water molecules through tissues, providing a measure of net directionality and magnitude (diffusivity). The net directionality of diffusion is indexed by fractional anisotropy (FA), which is often assumed to reflect myelination, but has also been associated with axonal loss (Barkovich, 2000), changes in cell packing density (Beaulieu, 2002) , myelin pathology (Shimony et al., 1999), as well as less coherent or crossing fibers within a voxel (Mädler et al., 2008; Virta et al., 1999). Mean diffusivity (MD) is another frequently used index that quantifies overall diffusion within a particular voxel in any direction, with higher values suggestive of disrupted axonal integrity. While other diffusivity indices exist (i.e., axial and radial diffusivity), we focus on MD as it is the most commonly studied metric thus far, but list studies using other indices in Table 2. Research on normative developmental patterns of white matter integrity has identified significant increases in FA and decreases in MD during childhood and adolescence across all the major fiber tracts (Asato et al., 2010; Pfefferbaum et al., 2015). Next, we review the relationship between puberty and white matter development, with an overview of the findings presented in Table 3.

2.2.1 Cross-sectional research

2.2.1.1 VBM studies

As highlighted in Table 3a, a number of studies have identified positive associations between global/regional white matter volume and pubertal (PDS) stage (Chavarria et al., 2014; Perrin et al., 2009; Pfefferbaum et al., 2015) as well as testosterone levels (Hervé et al., 2009; Paus et al., 2010; Perrin et al., 2008). However, when accounting for age, inconsistent effects are present for both pubertal stage (Pangelinan et al., 2016; Peper et al., 2009b) and testosterone (Hervé et al., 2009; Pangelinan et al., 2016; Peper et al., 2009a). The only study focusing on estradiol also failed to identify any associations with global or regional white matter when controlling for age (Peper et al., 2009a). Studies on separate 9 year old samples

have found negative associations between DHEA levels and white matter density around the left anterior corona radiata (Klauser et al., 2015), and positive associations between LH levels and white matter density in the right splenium of the corpus callosum and superior frontal gyrus, bilateral middle temporal cortex and left cingulum (Peper et al., 2008).

2.2.1.2 DTI studies

Findings from DTI studies are summarized in Table 3b. There appears to be a trend for increased FA at higher pubertal stages. Such positive associations with PDS score have been identified in the internal capsule, superior temporal, superior and inferior frontal, and angular gyri, after controlling for age in a sample of 10-16 years (Herting et al., 2012). A similar trending positive association was identified in a study of 13-16 year old boys using TS (based on pictorial ratings; Menzies et al., 2015). However, negative PDS associations with FA have also been noted in the superior frontal and precentral gyri in females (Herting et al., 2012), and others have failed to identify any significant associations (Bava et al., 2011). Only one out of three studies identified significant associations between pubertal stage and MD. Specifically, reduced MD was found at later pubertal stages in the superior and inferior longitudinal fasciculus, cortico-subcortical and projection tracts (Menzies et al., 2015).

Four studies have examined associations of gonadal hormonal levels with white matter development using DTI. One of the three studies to examine FA found positive associations with testosterone levels in the internal capsule, corpus callosum, and superior temporal, frontal, and angular gyri in males, and precentral gyrus in females, in a sample of 10-16 year olds after controlling for age (Herting et al., 2012). Interestingly, two out of four studies identified positive associations between testosterone levels and MD after controlling for age - within the superior frontal gyrus in 10-16 year old males (Herting et al., 2012), and subcortico-temporal tract in 8-25 year old females (Peper et al., 2015). This pattern of findings contradicts expected negative associations based on age- and pubertal stage-related changes in MD. However, the only study that did not control for age did find such negative associations between testosterone levels and MD in a cluster comprising the superior and inferior longitudinal fasciculi, as well as cortico-limbic and -spinal tracts, in 13-16 year old males (Menzies et al., 2015).

When considering estradiol, one of the two studies examining FA identified positive associations in the bilateral inferior cingulum and precuneus in males, and negative

associations in the right angular gyrus and superior longitudinal fasciculus in females when controlling for age (Herting et al., 2012). None of the three studies examining MD found significant associations when either controlling (Herting et al., 2012; Peper et al., 2015) or not controlling for age (Menzies et al., 2015).

Two studies have examined the role of DHEA in white matter development; one study of 13-16 year old boys failed to identify significant associations with MD (Menzies et al., 2015), but another study of 9 year olds found widespread positive associations with MD (strongest peaks were in the splenium, superior and posterior corona radiata and superior longitudinal fasiculus; Barendse et al., 2018). We hypothesize that inconsistencies likely relate to age differences between the samples, and may reflect the role of DHEA in white matter development during adrenarche. Barendse and colleagues (2018) also found that DHEA and testosterone levels interacted, such that children with lower DHEA levels had negative associations between testosterone and FA, and positive associations with MD, relative to children with higher DHEA levels. These findings echo the interactive effects of testosterone and DHEA on grey matter development (Nguyen et al., 2013), further highlighting the value of exploring the interplay between different hormones in predicting brain development.

2.2.2 Longitudinal research

One longitudinal study of white matter development using SBM estimates found greater increases in global white matter volume at earlier TS in a sample of 10-16 year olds, and similar associations with testosterone (trend-level) and estradiol (examined in females alone; Herting et al., 2014). A subsequent DTI study of 10-18 year olds followed up after a 2year interval identified unique effects of adrenal and gonadal changes on FA (Herting et al., 2017). Specifically, adrenal changes were related to increased FA in the thalamus and precentral gyrus, while gonadal changes were related to reductions in FA in the corpus callosum (genu), superior and anterior corona radiata, and superior frontal gyrus. In addition, sex differences were characterized by gonadal changes being related to increased FA in males, but decreased FA in females, in the superior frontal and precentral gyrus.

2.2.3 Summary of white matter research

A somewhat consistent picture appears when examining the relationship between pubertal maturation and changes in white matter volume or density, with a general trend of increased white matter density/volume over time. Similar effects are present for testosterone levels, as well as estradiol levels in females. Findings are mixed when considering associations with DTI indices; while there is some support for positive associations between pubertal stage and FA, findings are inconsistent when considering the relationship between gonadal hormones and FA, and between any pubertal index and MD, with overall minimal research to date. Of the significant findings that were identified, as with the grey matter literature, many of these effects (across both pubertal stage and testosterone) lay within the frontal and temporal lobes, as well as cortico-cortical and cortico-subcortical association tracts that connect these regions. Thus far, no consistent sex differences have been identified in the literature. Finally, there is preliminary evidence from cross-sectional and longitudinal studies that adrenal changes also play an important role in white matter development.

3. Functional MRI studies

Studies examining the relationship between puberty and functional brain development have largely focused on two different aspects of psychosocial functioning: *i)* affective processes underlying motivational and emotional tendencies, and *ii)* cognitive processes that enable individuals to understand and interpret social situations. However, it should be noted that affective and cognitive processes work in conjunction with each other to support social functioning. In addition, we discuss a few preliminary studies that have examined non-social cognitive processes that are also known to develop during adolescence, as well as resting-state functional connectivity. Refer to Table 4 for an overview of all functional studies that were reviewed.

Table 4. *Overview of studies on pubertal associations with brain function in humans.*

Authors	N (F)	Age	Puberty	Study design	Imaging modality	Imaging details
Alarcon et al., 2014	49 (23)	10-16	TEST (blood)	Cross-sectional	fMRI	spatial working memory
Braams et al., 2015	249 (147)	8-27	PDS, TEST (saliva)	Accelerated longitudinal	fMRI	reward sensitivity – outcome
Cservenka et al., 2015	44 (22)	10-15	PDS, TEST, EST (blood)	Cross-sectional	fMRI	affective faces – emotional incongruence
Fareri et al., 2015	50 (23)	4-23	TEST (saliva)	Cross-sectional	rs-fc MRI	VS seed
Ferri et al., 2014	60 (60)	8-15	TS (pic), PDS	Cross-sectional	fMRI	affective faces – emotional reactivity
Forbes et al., 2010	77 (40)	11-13	TEST (blood)	Cross-sectional	fMRI	reward sensitivity – anticipation & outcome
Forbes et al., 2011	76 (40)	11-13	TS	Cross-sectional	fMRI	affective faces – emotional reactivity
Goddings et al., 2012	42 (42)	11-13.7	TS, menarcheal status, TEST, EST, DHEA (saliva)	Cross-sectional	fMRI	social cognition – mentalising
Jankowski et al., 2014	18 (9)	11-14	PDS	Cross-sectional	fMRI	social cognition – self vs other evaluations
Klapwijk et al., 2013	35 (35) 36 (36)	11-13.7 9-14	TS, menarcheal status, menarcheal status	Cross-sectional Cross-sectional	fMRI (PPI) fMRI	social cognition – mentalising reward sensitivity – anticipation	TEST, EST, DHEA (saliva)
Le Moult et al., 2015	45 (26)	10-13	PDS	Single cohort longitudinal	fMRI	affective faces – emotional reactivity
Moore et al., 2012	72 (40)	11-13	TS	Cross-sectional	fMRI	reward sensitivity – anticipation & outcome
Morgan et al., 2013	50 (33)	10-16	TEST, EST, DHEA (saliva)	Cross-sectional	fMRI	reward sensitivity – outcome
Op de Macks et al., 2011	58 (58)	11-13	PDS, TEST, EST (saliva)	Cross-sectional	fMRI	risk taking
Op de Macks et al., 2016a	58 (58)	11-13	PDS, TEST, EST (saliva)	Cross-sectional	fMRI	risk taking – social vs monetary feedback
Op de Macks et al., 2016b	Peters et al., 2014					
	Peters et al., 2015					

Pfeifer et al., 2013	learning with performance feedback					
Schweinsburg et al., 2005	173 (86)	12-25	TEST (saliva)	Cross-sectional	rs-fc MRI	amygdala seed
Spielberg et al., 2014	27 (18)	10-13	PDS	Single cohort longitudinal	fMRI	social cognition – self vs other evaluations
Spielberg et al., 2015	49 (25)	12-17	PDS	Cross-sectional	fMRI	spatial working memory
Telzer et al., 2015	38 (21)	11-15	TEST (blood)	Single cohort longitudinal	fMRI	affective faces – emotional reactivity
Tyborowska et al., 2016	41 (21)	11-15	TEST (blood)	Single cohort longitudinal	fMRI (PPI)	affective faces – emotional reactivity
van Duijvenvoorde et al., 2014	30	9-16	PDS – parent	Cross-sectional	fMRI	affective faces – opposite sex
Whittle et a., 2015	47 (26)	14	TEST (saliva)	Cross-sectional	fMRI	affective faces – emotional incongruence
	268 (138) 8-25	PDS, TEST, EST (saliva)		Cross-sectional and accelerated longitudinal	fMRI	reward sensitivity – outcome
	47 (32); 31 (18)	10–16; 2-year follow-up	PDS			
	83 (43)	9	DHEA (saliva)	Cross-sectional	fMRI	affective faces – emotional reactivity
	Cross-sectional fMRI rule-					

NB: The "Puberty" column only notes a single method of collection when it was utilized for all hormones.

DHEA = dehydroepiandrosterone; EST = Estradiol, fMRI = functional MRI; PDS = Pubertal Development Scale; PPI = Psychophysiological interactions; rs-fc MRI = resting-state functional connectivity MRI; TEST = testosterone; TS = Tanner stage; VBM = voxel-based morphometry; VS = ventral striatum

3.1 Reward processes

Reward-related processing has largely been investigated as neural responses to monetary gains in gambling and card-guessing paradigms. A recent quantitative metaanalysis showed that although adolescents and adults activate similar regions during reward processing – including the ventral and dorsal striatum, insula, and posterior cingulate cortex – reward-related neural activation tends to be greater in adolescents compared to adults (Silverman et al., 2015). Furthermore, despite conflicting findings from cross-sectional studies (reviewed in Galvan, 2010), a longitudinal study provides evidence for a mid-adolescent peak in reward-related activation in the ventral striatum (VS; Braams et al., 2015).

3.1.1 Cross-sectional studies

Studies focusing on the effect of pubertal development on reward-related neural processing are highlighted in Figure 4. Reward-related processing is often separated into the anticipation and receipt of reward. When considering the anticipation phase, a study of 9-14 year old females found that menarcheal status and TS (based on pictorial ratings) were related to greater VS activation during anticipation of both gain (trending) and loss in a monetary incentive delay task (LeMoult et al., 2015). Another study of 11-13 year olds found that more pubertally advanced adolescents ("mid/late: TS 3-5" compared to "pre/early: TS 1-2" groups) exhibited less BA10 activation during reward anticipation (Morgan et al., 2013), although prior analyses of the same data failed to identify any effects of pubertal *timing* (i.e., controlling for age) within the VS or medial PFC (Forbes et al., 2010).

Conflicting results have also been observed when considering the effect of puberty on neural activation to reward outcomes. One study found that adolescents at later TS exhibited less caudate and more medial PFC (extending into the dorsal ACC) activation in 11-13 year olds, after controlling for age (Forbes et al., 2010), but separate analyses of the same sample found less rostral ACC activation without

controlling for age (Morgan et al., 2013). Others have failed to identify significant effects when using self-report measures of pubertal stage in both early adolescent and extended age ranges, with and without controlling for age (Op de Macks et al., 2016b; van Duijvenvoorde et al., 2014).

Focusing on testosterone, the only study investigating reward anticipation identified positive associations with caudate activity in males, but not females, when controlling for age (Forbes et al., 2010). Positive associations with medial OFC activity have also been found in 11-13 year old females when choosing to play on risky trials, after controlling for age (Op de Macks et al., 2016b). Of the three studies that examined reward outcomes, two identified positive associations between testosterone levels and VS activity during early to mid-adolescence, with (Alarcón et al., 2017) and without controlling for age (Op de Macks et al., 2011). The third study, however, found negative associations with caudate activity in 11-13 year olds, after controlling for age (Forbes et al., 2010).

Finally, estradiol levels have been found to positively correlate with activation to monetary reward outcomes in a sample of 10-16 year olds, within the dorsal striatum, dlPFC, and medial PFC (using an uncorrected threshold; Op de Macks et al., 2011). Positive associations have also been identified with NAcc activation during decision making (choosing to play vs. pass) in 11-13 year old females after accounting for age (Op de Macks et al., 2016b), and similar associations with anterior insula activity were present when choosing to play in social, but not monetary, feedback conditions (Op de Macks et al., 2016a). However, null effects have also been noted for reward outcomes in a sample of 12-17 years, after accounting for age (Alarcón et al., 2017).

3.1.2 Longitudinal studies

Only one study was identified in the fMRI literature that employed multilevel modelling to analyze accelerated longitudinal data. Braams and colleagues (2015) identified a quadratic effect of age on NAcc response to wins over losses in a gambling task, characterized by

a mid-adolescent peak in activation, in a sample of 827 year olds. In comparison, NAcc response increased linearly with PDS score. Similar linear associations were found in relation to testosterone levels, and moreover, testosterone effects were close to three times larger than the PDS.

3.2 Social-affective processes

Research on social-affective processing has commonly examined neural responses to emotionally-laden faces. Many of these studies have revealed greater subcortical activation during adolescence, including some evidence for an adolescent peak in amygdala activation in response to fearful faces (Guyer et al., 2008; Hare et al., 2008; Monk et al., 2003). Others have identified greater VS activation in response to happy faces relative to rest (i.e., null) events (Pfeifer et al., 2011; Somerville et al., 2011), suggesting there might be enhanced processing of both negatively- and positively-valenced social stimuli during adolescence.

3.2.1 Cross-sectional studies

An overview of studies examining social-affective processes is presented in Figure 5. Only two cross-sectional studies were identified that investigated pubertal associations with neural processing of emotionally-laden facial stimuli. Both studies found reductions in amygdala activation to emotionally neutral faces with pubertal development, with (Forbes et al., 2011) and without controlling (Ferri et al., 2014) for age. The former study additionally found that mid/late-pubertal adolescents (TS 34), compared to those at earlier stages, exhibited less ventrolateral (vl)PFC reactivity to fearful faces, but more reactivity to angry faces (Forbes et al., 2011). These findings were interpreted as a reduction in threat-related brain function for ambiguous stimuli (i.e., fear and neutral faces), paired with an increase for unambiguous stimuli (i.e., angry faces), with pubertal maturation.

No cross-sectional studies were identified that examined the effect of gonadal hormones on reactivity to emotionally-laden facial stimuli. However, DHEA levels have been shown to be (predominantly) negatively associated with functional activation in 9 year olds, including cingulate activity while viewing positively- and negatively-valenced emotional faces, as well as caudate and dlPFC activity to negatively-valenced faces (Whittle et al., 2015).

Aside from the aforementioned investigations of emotions, studies have also used facial stimuli to examine other factors that may influence social-affective processing. For example, amygdala and VS activation has been found to increase with pubertal stage (PDS) when viewing opposite-sex relative to same-sex affective faces in a sample of 9-16 year olds, after accounting for age (Telzer et al., 2015). Interestingly, increasing age was related to *lower* amygdala activation with and without controlling for PDS, suggesting that pubertal maturation relative to sameaged peers has a unique effect of making opposite sex faces more salient.

Finally, there is some evidence that neural activation during emotional conflict is association with gonadal hormones. Neural responses to emotional conflict, defined as emotion-incongruent vs. -congruent face-word stimuli, were positively related to estradiol levels in the right dorsal ACC and left cerebellum, but negatively associated with testosterone levels in the left putamen and middle frontal gyrus, in a sample of 10-15 year old males (Cservenka et al., 2015). Similar direction of associations with each hormone was present in females, although regions of significance differed (e.g., testosterone effects were in the precuneus). Another study defining emotional conflict as engaging in an approach response to angry faces and avoidance response to happy faces also found negative associations between testosterone levels and amygdala and thalamus activity in 14 year olds (Tyborowska et al., 2016). However, positive associations were also identified in the anterior PFC.

3.2.2 Longitudinal studies

A longitudinal study of early to mid-adolescents (i.e., 11 – 15 years) identified increased amygdala and NAcc activity (Spielberg et al., 2014), as well as reduced amygdala-OFC functional coupling (Spielberg et al., 2015), to threat-related stimuli (i.e., angry/fearful faces compared to neutral faces/shapes) with increases in testosterone. Others have noted a generalized increase in reactivity to positively- and negatively-valenced emotions with pubertal development. Specifically, Moore and colleagues (2012) found that earlier pubertal timing (PDS regressed for age) was positively related to activity in the amygdala, thalamus and visual cortical areas at age 10, and this increased in magnitude and extent at age 13. At 13 years of age, pubertal timing was also related to greater reactivity in the temporal pole, vlPFC and dorsomedial (dm)PFC.

3.3 Social-cognitive processes

Among the most crucial cognitive abilities to support adolescents' engagement in social behaviors is mentalizing, the ability to recognize and interpret other people's feelings, intentions, and desires (Frith and Frith, 2003). Advanced perspective-taking continues to be refined throughout adolescence (Dumontheil et al., 2010; Sodian, 2011), and is supported by the development of the medial PFC, precuneus, anterior temporal and temporo-parietal cortices. Adolescence is also characterized by the emergence of a differentiated sense of self and intensification of self-evaluative processes, especially in the social domain. Neural activation, particularly in the vmPFC and VS, increases over adolescence when engaging in self-evaluative processes (Jankowski et al., 2014; Pfeifer et al., 2013).

3.3.1 Cross-sectional studies

Testosterone levels have been found to positively correlate with activity in social brain regions during mentalizing, specifically within the anterior temporal cortex (ATC) in 11-14 year old girls, with and without controlling for age (Goddings et al., 2012). Similar trend-level associations were present for other hormones (estradiol and DHEA), but not for pubertal stage. Meanwhile, dmPFC activation was negatively correlated with age even after controlling for hormones, suggesting potentially independent effects of puberty and age on different brain regions. Followup analyses of the same sample identified puberty-related changes in functional connectivity of the social brain network; dmPFC-ATC coupling was stronger in later TS stages, and dmPFC-TPJ connectivity was stronger at higher estradiol levels, after accounting for age (Klapwijk et al., 2013).

When considering self-evaluative processes, bilateral VS activation increased with pubertal stage (PDS) during social, but not academic, evaluations in a sample of 11-14 year olds (Jankowski et al., 2014). These findings remained when controlling for age.

3.3.2 Longitudinal studies

Only one longitudinal study has related neural activity elicited by socialcognitive processes and pubertal development. Change in pubertal stage (PDS) in 1013 year olds was related to greater increases in vmPFC activation when evaluating the self, relative to another target in the social, but not academic domain. While age (operationalized by study wave) also produced increases in vmPFC activity during self-evaluation in both domains, the effect of pubertal stage on social self-evaluation remained even after controlling for age (Pfeifer et al., 2013).

3.4 Cognitive control processes

To date, comparatively less research has examined pubertal influences on cognitive control processes (e.g., working memory, inhibitory control, cognitive flexibility, performance monitoring). While these abilities are present early in development, higher-order executive processes continue to be refined throughout adolescence, along with continued maturation of implicated neural substrates, including the dlPFC, ACC and parietal cortices (Asato et al., 2006; Huizinga et al., 2006; Luna, 2009).

An early study investigating pubertal effects on brain function found that pubertal stage was negatively associated with activation in the right superior parietal cortex, after controlling for age, in a sample of 12-17 year olds performing a spatial working memory task (Schweinsburg et al., 2005). However, it was not associated with activation in numerous other frontal and parietal clusters that were related to age. Similarly, more recent imaging studies have failed to identify a role of puberty in cognitive function. For example, sex differences in neural activation related to spatial working memory, after accounting for age effects, were not mediated by testosterone levels in 10-16 year olds (Alarcon et al., 2014). Furthermore, neither testosterone, estradiol, or pubertal stage were associated with neural activation during feedback learning in a sorting task after accounting for age, which itself was significantly associated with neural response in a sample of 8-25 year olds (Peters et al., 2014).

3.5 Resting-state functional connectivity

The examination of intrinsic or resting-state functional connectivity in the brain can be approached using either seed-based analyses or topological properties of brain networks using graph theory. Only two studies were identified that examined pubertal associations with resting-state functional connectivity, which used seedbased approaches focusing on the amygdala and VS.

There has been particular interest in examining developmental changes in resting-state functional connectivity between the amygdala and medial PFC, with preliminary data suggesting age-related increases in connectivity with the vmPFC (Gabard-Durnam et al., 2014). In comparison, a similar cluster within the vmPFC was found to exhibit decreased connectivity with the amygdala at higher testosterone levels in a sample of 12-25 year olds, after controlling for age (Peters et al., 2015), consistent with findings of reduced amygdala-OFC task-based connectivity with increasing testosterone levels (Spielberg et al., 2015; discussed in section 3.2.2). While age-related findings have been interpreted as reflecting greater integration of the fronto-limbic network with development (Alarcon et al., 2015; Gabard-Durnam et al., 2014), the hormonal findings suggest potentially unique developmental processes being captured by puberty and age.

In comparison to the amygdala, resting-state functional connectivity of the VS broadly decreases with age across a number of regions, including the temporal lobe, precuneus, amygdala, medial PFC and ACC (Fareri et al., 2015; Padmanabhan et al., 2013). Similar reductions in VS-subgenual ACC connectivity were identified with increasing testosterone levels in a sample of 4-23 year olds, and moreover, testosterone mediated the negative association between age and connectivity (Fareri et al., 2015). In comparison to the integration hypothesis discussed above, the authors suggest these changes may reflect functional specialization of the VS and subgenual ACC to support differential processes over time.

3.6 Summary of functional research

Overall, certain aspects of brain function seem to be more closely related to pubertal maturation than others. Gonadal hormone levels seem largely associated with increases in functional activation elicited by various aspects of reward-related processing within the VS and medial PFC, while more inconsistencies exist in relation to pubertal stage. In comparison, both pubertal stage and testosterone levels appear to be associated with decreases in amygdala activation elicited by neutral faces, and decreases in lateral PFC responses to fearful faces.

There is also some indication that functional connectivity of regions may decrease in relation to specific emotions (i.e., fear) with pubertal maturation. Findings also indicate a general pattern of increased activation of social brain regions when engaging in social-cognitive processes such as mentalizing and self-evaluation, as well as potentially increased connectivity among these regions, with pubertal maturation. In comparison, the limited studies focusing on cognitive control suggest that pubertal maturation may not be related to associated neural responses. Finally, there is preliminary evidence that DHEA relates to socioemotional processing during adrenarche and that increases in testosterone reduces resting-state functional connectivity between limbic and medial prefrontal regions. However, it is important to note inconsistencies in the literature that hinder strong conclusions, and to draw attention to methodological considerations discussed in section 4.1 that limit the replication of findings.

4. Overview

It is evident from this systematic review of structural and functional neuroimaging research that certain aspects of brain development are more strongly related to pubertal maturation than others. Structural development of subcortical regions is the most extensively investigated area thus far, with findings highlighting sex differences in the relationship between pubertal stage and amygdala volume, and to a lesser extent, hippocampal volume. The limited longitudinal research suggests that gonadal hormones may be responsible, despite inconsistent support from crosssectional studies. In the cortex, reductions in grey matter are evident with increasing pubertal stage, earlier pubertal timing, and rising testosterone levels. These effects are most pronounced in the frontal lobe, followed by the temporal lobe. Consistent with these cortical findings, but still preliminary in nature, are associations between pubertal development and white matter in similar regions, as well as cortico-cortical and cortico-subcortical association tracts that connect these regions. Importantly, longitudinal studies implicate the role of pubertal tempo and intra-individual changes in hormone levels on cortical and subcortical development during

adolescence; specifically that nonlinear trajectories may best describe certain associations between pubertal maturation and brain development. Taken together, findings suggest that longitudinal pubertal and hormonal processes, rather than absolute stages or levels, are more likely to shed valuable insight on brain development.

Drawing conclusions from the functional neuroimaging literature is more difficult given variations in task design, but there appears to be an overall trend of increased activity associated with motivational processing in the VS and medial PFC with rising gonadal hormone levels. Similar puberty-related increases in the processing of emotionally-laden faces have been identified within the amygdala and prefrontal cortices, although functional connectivity of these regions may decrease with maturation. There is also a general pattern of increased activity associated with social-cognitive processes in the social brain network with pubertal maturation. However, it is important to reiterate acknowledgment of inconsistencies in the literature, particularly when comparing different pubertal and hormonal indices, that hinder strong conclusions.

Conflicting findings in the literature likely arise, at least partly, from vast variations in study design, such as the age range of participants, pubertal measurements, neuroimaging processing techniques, and sampling and analytic strategies. This has resulted in very few empirical investigations of overlapping aspects of pubertal and brain development. Consequently, it is difficult to draw robust conclusions regarding the consistency and replicability of findings. In order to aide progression of the field and evolution of our theories, we discuss methodological considerations when interpreting current findings, as well as planning future studies.

Box 1. Models of adolescent neurodevelopment

The interest in examining pubertal associations with brain development in humans largely originated from prominent models of adolescent neurodevelopment, which historically postulated a mismatch between the development of subcortical regions implicated in

affective reactivity and cortical regions implicated in cognitive control (Casey et al., 2008; Nelson et al., 2005; Spielberg et al., 2015). In particular, the dual-systems (Steinberg, 2008) and social information processing network (SIPN; Nelson et al., 2005) models, and to a lesser degree the imbalance model (Somerville and Casey, 2010), proposed that pubertal maturation was driving alterations in neural processing of affective stimuli around early adolescence, while age- or experiencerelated maturation was responsible for more protracted changes in the cognitive regulatory system. Although these models differ in a number of ways, this mismatch was broadly held responsible for numerous adverse outcomes during adolescence (e.g., health-risking behaviors, substance abuse, depression). As such, the examination of pubertal associations with brain development represent crucial empirical assessments of the prevailing heuristic models of adolescent neurodevelopment. However, we do note that all models have evolved significantly since their introductions, and while puberty remains a core component of the dualsystems model (Shulman et al., 2016; Smith et al., 2013), emphasis on puberty within the SIPN and imbalance models appears to have decreased (Casey et al., 2016; Nelson et al., 2016).

Our review of the functional neuroimaging literature suggests that certain indices of pubertal maturation do influence motivational and affective processing. However, the very limited studies examining cognitive control have thus far failed to identify any effects of puberty. While these findings may be considered to provide preliminary support for aforementioned models, it should be noted that there are a number of null findings for motivational and social-affective processes. It is also possible that current models have deterred more extensive research on cognitive control. When considering specific models in more detail, further inconsistencies arise. For example, the dual-systems model hypothesizes an inverted-U shaped trajectory of striatal activation to reward processing (Shulman et al., 2016), but the only study to examine such nonlinear associations between puberty (both stage and testosterone levels) and reward-related activation identified solely linear effects across adolescence and young adulthood (Braams et al., 2015). Such conflicting findings, in combination with certain aspects of brain development being more extensively investigated than others, hinders strong conclusions from being drawn regarding support for “mismatch” models of adolescent neurodevelopment. Findings of pubertal associations with social-cognitive processes also highlight the

need for our theories to account for social factors that play a prominent role in influencing adolescent behavior, as proposed by a number of research groups (Crone and Dahl, 2012; Kilford et al., 2016; Nelson et al., 2016; Pfeifer and Allen, 2016; van den Bos and Eppinger, 2016). Overlooking these changes may result in an inaccurate assumption that behavioral changes related to pubertal maturation are solely driven by brain regions subserving reward and other affective processes.

"Mismatch" models are also rooted in early structural neuroimaging findings that showed protracted age-related maturation of prefrontal regions implicated in cognitive control and emotion regulation (Gogtay et al., 2004; Shaw et al., 2008), relative to hypothesized earlier maturation of subcortical regions that were presumed to be related to puberty. In support of prevalent theories, development of the amygdala and hippocampus does appear to be linked to puberty. However, less attention has been directed to the structure of the VS, with primarily null findings, despite the importance of this region to models of adolescent neurodevelopment. Moreover, our review indicates that frontal regions are among the most consistently correlated cortical structures with pubertal maturation, including the superior and inferior frontal, and anterior cingulate, cortices, that are thought to play a role in emotional, attentional and cognitive control. These cortical regions also appear to exhibit more consistent associations with gonadal hormones in comparison to subcortical structures. Such findings contradict theories of solely age- or experiencedriven cortical maturation of regions subserving emotional and cognitive control, thus challenging the premise of "mismatch" models. Cortical associations with pubertal maturation may also be driven by neural interactions with subcortical systems, either via structural or functional connectivity, and there is increasing acknowledgement of this network perspective in more recent adaptations of these models (e.g., Casey et al., 2016). Further empirical studies using such network analytic approaches are now required to advance this line of research.

Box 2. Pubertal mechanisms

Significant findings beg the question of what underlying mechanisms might be mediating the relationship between puberty and brain development. Much of our knowledge comes from animal research, where there is evidence for changes in neurons and supporting processes during puberty, such as pruning of dendrites and synapses in the amygdala, hippocampus and medial PFC (Cooke and Woolley, 2005; Drzewiecki et al., 2015; Zehr et al., 2008, 2006), and increased myelination in the corpus callosum (Kim and Juraska, 1997). Rising testosterone levels increased the number of neurons in the amygdala in male Syrian hamsters (De Lorme et al., 2012), and androgen administration during puberty increased spine density in the amygdala and hippocampus (Cunningham et al., 2007). Comparatively, ovariectomy in female rats resulted in greater neurons and glia, as well as dendritic spines, in the medial PFC and visual cortex (Antonio Mun˜oz-Cueto et al., 1990; Koss et al., 2015). These findings are suggestive of sex differences in the role of gonadal hormones in neural organization; consistently, the removal of gonads prior to puberty resulted in less sex differences within the hypothalamus and amygdala (Ahmed et al., 2008). A number of studies have also noted changes in receptor density during puberty, including increased androgen receptors in the hypothalamus and amygdala following the onset of puberty (Kashon and Sisk, 1994) and more specifically with rising testosterone levels (Meek et al., 1997). Estrogen receptor (ER) α has been found to decrease prior to pubertal onset within the medial PFC, while ER β comparatively increased, in mice
(Westberry and Wilson, 2012). For a recent review of the animal literature, refer to Juraska & Willing (2017).

Interpretation of findings also needs to consider indirect mechanisms that may be partly responsible for the relationship between puberty and brain development. Alternate hypotheses largely focus on socio-environmental influences associated with the myriad of physical and behavioral changes. Specifically, adolescents may be treated differently by others in their environment (e.g., peers, parents, teachers) as a result of their physical changes, or alterations in their own behaviors could trigger different socio-environmental influences (Blakemore, 2008; Mendle et al., 2012). Based on a growing literature implicating a role of the environment in structural and function brain development

(Richmond et al., 2016; Schriber and Guyer, 2016), this represents an important area for future research to more thoroughly investigate and incorporate environmental influences into our theoretical and analytic models.

4.1 Methodological considerations

4.1.1 Pubertal assessments

One of the largest sources of noise within this literature likely relates to the conflation of pubertal stage and timing. When puberty is examined alone, higher scores indicate greater pubertal maturation. When age is incorporated via study design or statistical modelling, the resultant pubertal metric is more akin to "stage-for-age" (i.e., timing), with higher scores indicating greater maturation than same-aged peers. While both pubertal stage and timing are important, they are fundamentally different constructs that the current neuroimaging literature has largely failed to differentiate. Many studies that account for age do not specifically interpret findings as reflecting pubertal timing. However, our review suggests that normative transition through pubertal stages influences brain development differently than earlier or later maturation relative to same-aged peers. Greater awareness of the distinction between these constructs will eliminate some of the inconsistencies in the literature. It may also allow us to develop a clearer understanding of what is more important for normative versus aberrant trajectories of brain development, as well as potential underlying mechanisms.

Inconsistencies in findings are also likely to be impacted by variations in the measurement of pubertal stage. As discussed in the introduction (section 1.2.1) PDS and TS tap into different aspects of pubertal maturation, with PDS under-representing gonadal development. As such, individuals with low PDS scores can actually be quite physically developed according to TS, particularly in males as the PDS does not track genital development (i.e., penile and testicular changes) despite it primarily defining the first 3 Tanner stages (Deardorff et al., in press). Given these differences, certain inconsistencies in the literature between TS and PDS may, to some extent, reflect

nonlinear relationships between puberty and brain development. For example, some studies identified amygdala volume increases with TS in males (Bramen et al., 2011; Neufang et al., 2009), but other studies that might be capturing later pubertal development with the PDS have failed to replicate these effects (Koolschijn et al., 2014). One way to minimize this issue is to use scoring methods that try to transform the PDS into TS, such as that proposed by Shirtcliff et al. (2009) that differentially codes gonadal and adrenal hormonal signals of physical development. Studies using self-report measures may also benefit from using both the PDS and pictorial ratings of TS to ensure all phases of development are better captured.

More refined coding schemes of puberty will also help us overcome the use of global operationalizations that integrate a number of physical changes, each developing at differing rates, including those driven by adrenal vs. gonadal hormones. This seems particularly important given a growing literature on brain development related to adrenarche during late childhood (see Byrne et al., 2017), with potentially differential patterns of brain development to gonadarche (i.e., Herting et al., 2017; Nguyen et al., 2013, vs 2012). Others have shown that different aspects of physical development (i.e., hair, breast, voice) exhibit varied associations with subcortical structure (Blanton et al., 2012; Hu et al., 2013). As such, we speculate that reliance on global metrics may be obscuring important information.

Another important methodological consideration is the analytic strategy employed by studies to account for the correlated nature of certain hormones with each other and/or pubertal stage (Shirtcliff et al., 2009). Many studies examine each hormonal/pubertal index separately, thus limiting the specificity of their findings (as results may be driven by shared variance among different pubertal indices). On the other hand, modelling multiple indices within a given analysis is likely to significantly change the interpretation of findings, particularly when the same approach is employed across sex. For example, controlling for testosterone in pubertal stage analyses would account for different variance in males and females. It is not possible to suggest a single strategy to deal with this issue; rather, analysis should be determined based on the research question of interest and findings need to be carefully interpreted given the analytic strategy.

As described in section 1.2.2, it is also widely known that extraneous factors such as the circadian rhythm and menstruation, as well as anovulation in early female adolescents, are additional sources of variance for basal hormone levels (Berenbaum et al., 2015). This may account for the oftentimes inconsistent or null findings in relation to estradiol. More frequent and systematic measurements of hormones, particularly of estradiol across the menstrual cycle, may help us better capture pubertal processes and identify potential neurodevelopmental effects (Shirtcliff et al., 2009). Finally, inconsistent findings may also be attributable to the use of saliva vs. blood samples that measure free and total hormone levels, respectively (see Herting et al., 2017 for further discussion).

4.1.2 Neuroimaging assessments

Inconsistencies in the current literature may be, at least partly, also attributable to differences in neuroimaging methodologies across studies. This can be difficult to overcome as studies frequently employ newer and more advanced techniques than prior literature. This is particularly evident in structural neuroimaging, with a shift from VBM to SBM and DTI for grey and white matter properties, respectively. In the functional neuroimaging literature, studies frequently employ different experimental paradigms to examine the same topic of interest. For example, some studies on reward-related processing model the choice to engage in reward-related behaviors, others focus on the subsequent anticipatory processes, and some examine neural response to reward outcomes. These design variations, in combination with differences in pubertal indices and methods of controlling for age, result in only one or two studies investigating a particular topic of interest and using comparable measures and analysis techniques (as highlighted in Figures 4 and 5). While it remains essential that we continue to advance our methods, it is equally important to replicate studies where possible to consolidate prior findings, particularly when it is feasible to achieve both goals. For example, studies using an affective faces task could report pubertal associations with reactivity to different emotionally-laden stimuli in addition to other experimental manipulations, such as the gender of facial stimuli.

Another important consideration in neuroimaging analyses is the choice between whole-brain and region-of-interest (ROI) analyses. While some studies have employed the latter approach with specific hypotheses regarding the location of effects, this can hinder conclusions about the specificity of pubertal relationships to particular brain regions. The inclusion of whole brain (i.e., vertex/voxel-wise or parcellation-based) analyses in NeuroVault (or as supplementary material) can help overcome this issue, and also facilitates comparison across studies with differing ROIs. NeuroVault can also help overcome the issue of differing methods of correction for multiple comparisons across studies, which can potentially bias findings when lower thresholds are employed with ROI analyses. In addition, whole brain analyses can highlight potentially unexpected areas of significance that converge across different studies. This combination of hypothesis-driven and exploratory approaches is most likely to help us build on current findings as well as identify promising paths for future research.

4.1.3 Study design and analysis

While the literature is dominated by cross-sectional studies, inferences about developmental processes from these studies can be misleading (Kraemer et al., 2000), given individual differences in puberty and brain structure/function. Some crosssectional studies attempt to maximize variance in pubertal maturation while minimizing potential age-effects by sampling participants within a narrow age-band around the onset of puberty, although these designs often under-represent the upper range of pubertal development. Alternatively, studies with broader age ranges have to deal with high correlations between puberty and age, along with issues related to controlling for age when specifically interested in pubertal stage (see section 4.1.1). Only longitudinal designs with repeated within-subjects measurements are able to distinguish differences between age- and puberty-related maturation.

While there is an increasing number of longitudinal studies, those examining pubertal tempo (i.e., intra-individual change) have predominantly modelled linear trajectories given limitations with the number of time points available. However, a child transitioning from

TS 1 to 2 is likely to be experiencing very different brain changes from an adolescent going from TS 4 to 5. An analytic model that imposes a linear effect of pubertal tempo assumes similarity across both these transitions. This speaks to the importance of examining nonlinear trajectories that account for potentially differential effects of puberty at different stages of development. Ideally, studies would have a minimum of four time points to study nonlinear trajectories at the *individual* level (i.e., without over-fitting models or relying on group-level changes).

Another important consideration for longitudinal studies is the overall duration, as researchers need to sample over a decade to capture the entire age span during which puberty may impact brain development. Moreover, hormone levels continue to change following TS 5 (Braams et al., 2015), highlighting potentially longer periods of interest. Accelerated longitudinal designs can cover greater age spans with a shorter study duration, but are less powered to capture intra-individual processes during any given time frame. This issue is exemplified when studies are not specifically designed to study pubertal processes, and thus recruit cohorts based on age. Future studies using this design may benefit from selecting cohorts based on pubertal stage to increase their power to examine pubertal questions. As discussed by Herting et al. (2017), time interval between assessments is another important consideration, with participant burden also playing a role.

Finally, we note that most studies in the literature undertake multiple sets of analyses, whether this relates to the examination of numerous ROIs and/or comparison across different measures of pubertal maturation. Oftentimes, statistical thresholds do not account for these multiple comparisons, especially if examination in a given region is strongly hypothesis-driven. While lowered statistical thresholds can be beneficial in early exploratory research where it is important to minimize false negatives, moving forward, we need to ensure that appropriate multiple comparison procedures are undertaken to account for the plurality of analyses in future hypothesis-driven studies that build on current findings.

4.2 Functional relevance

Aside from the biological changes occurring during adolescence, this period is also characterized by significant affective, behavioral and social changes, as well as a sharp increase in the prevalence of psychopathology (World Health Organization, 2014). It is often postulated that puberty-related brain development may be partly responsible for these functional outcomes. However, very few studies have examined associations between puberty, brain development and health behaviors or mental health outcomes. Most of these studies focused on pubertal timing, as earlier maturation relative to same-age peers has consistently been implicated in mental health problems during adolescence (Harden et al., 2012; Harden and Mendle, 2012). Findings highlight a potential role of pituitary structure, with larger volumes mediating the relationship between earlier pubertal timing and increases in depressive symptomatology (Whittle et al., 2012), as well as the relationship between greater DHEA levels and social anxiety symptoms (Murray et al., 2016). When considering brain function, blunted activation of the posterior insula to happy faces mediated the relationship between DHEA levels and externalizing symptoms (Whittle et al., 2015). Even fewer studies have examined the role of puberty and brain development in adolescent health risking behaviors. Pubertal stage has been found to moderate the association between limbic brain structure and risky sexual behaviors (Feldstein Ewing et al., 2018), and greater testosterone levels has been associated with increased alcohol use in males via amygdala-OFC resting state connectivity (Peters et al., 2015). Interestingly, there has been no research to date on how puberty and brain development may *together* predict positive outcomes such as prosociality, normative sexual development and health promoting behaviors (see Suleiman et al., 2017). Such a shift away from the "risk framework" will help us identify how biological processes ultimately promote the goals of adolescence, such as attaining adult social roles, responsibilities and status.

4.3 Conclusions

The extant literature highlights that pubertal development is associated with concurrent neurobiological maturation during adolescence. Regional variation exists, with both structure and function of subcortical and frontal regions being the most consistently implicated. However, results may be biased from neuroimaging practices that focus on these regions. Many inconsistent findings were also identified, and we presume that variations in study design, including measurement of pubertal maturation and consideration of age effects (i.e., timing vs. stage), are important contributing factors. In addition, potential nonlinear effects of puberty might be obscuring important findings. Moving forward, replication studies are needed to help us resolve inconsistencies and gain a clearer understanding of pubertal associations with brain development. Longitudinal investigations that are better able to distinguish pubertal and age-related processes are critical. Finally, integration of different neuroimaging modalities, and the assessment of multiple hormones in addition to physical changes, may help us develop a broader understanding of pubertal influences on brain development and associated functioning.

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Figure Captions

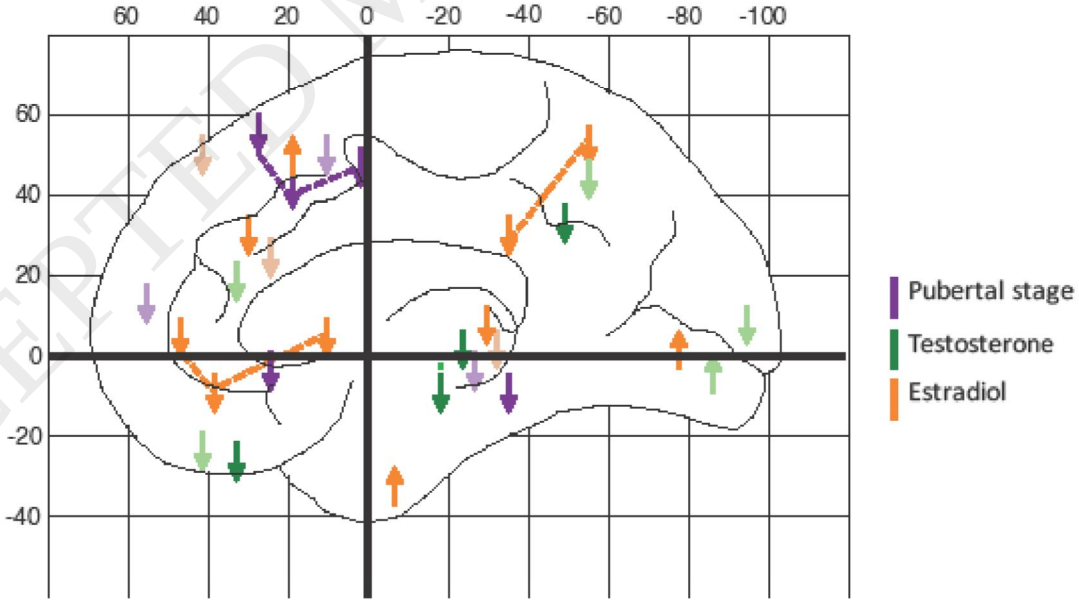


Figure 1. Pubertal associations with regional cortical grey matter (from crosssectional studies), after accounting for age. Darker arrows represent lateral findings, while lighter arrows represent medial findings. Dashed lines connect findings from same study that fall within same anatomical subdivisions. Upward and downward arrows represent positive and negative correlations, respectively. Readers who would like further orientation to brain structure may consider exploring the interactive viewer available at http://www.brainfacts.org/3D-Brain. Pubertal stage: Hu et al., 2013; Koolschijn et al., 2014; Peper et al., 2009b; Pfefferbaum et al., 2015. Testosterone: Bramen et al., 2012; Koolschijn et al., 2014; Neufang et al., 2009 (null effects: Peper et al., 2009a). Estradiol: Brouwer et al., 2015; Koolschijn et al., 2014; Neufang et al., 2009; Peper et al., 2009a.

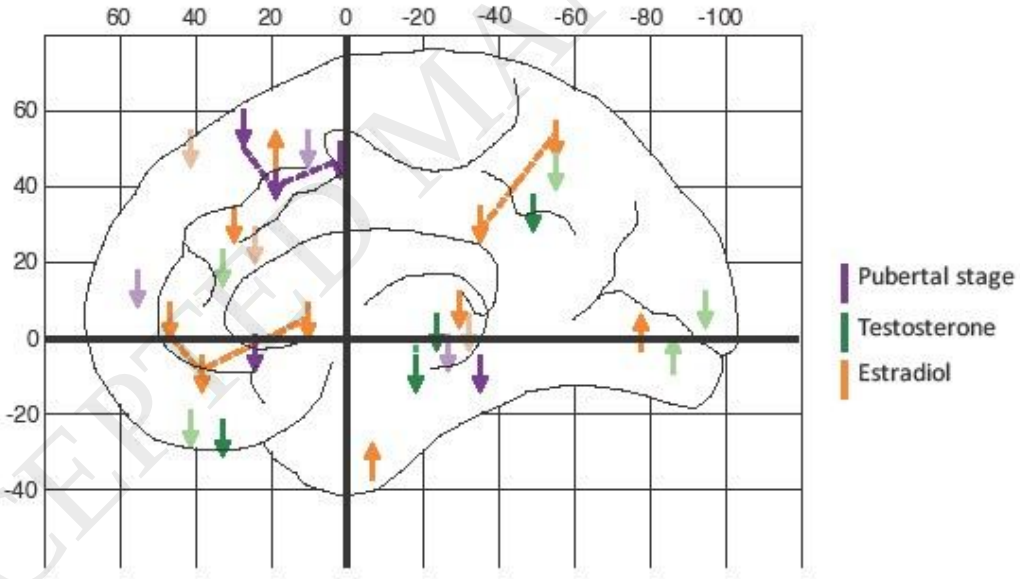


Figure 2. Pubertal associations with subcortical grey matter (from cross-sectional studies) in males (M) and females (F). Circles represent findings from studies that ran analyses both controlling and not controlling for age. Pubertal stage: Blanton et al., 2012*; Bramen et al., 2011*; Hu et al., 2013*; Koolschijn et al., 2014; Neufang et al., 2009; Peper et al., 2009b; Satterthwaite et al., 2014*; Urosevic et al., 2014. Testosterone: Bramen et al., 2011*; Koolschijn et al., 2014; Neufang et al., 2009; Peper et al., 2009a; Brouwer et al., 2015. Estradiol: Koolschijn et al., 2014; Neufang et al., 2009; Peper et al., 2009a; Brouwer et al., 2015. *Studies only examined amygdala and hippocampus.

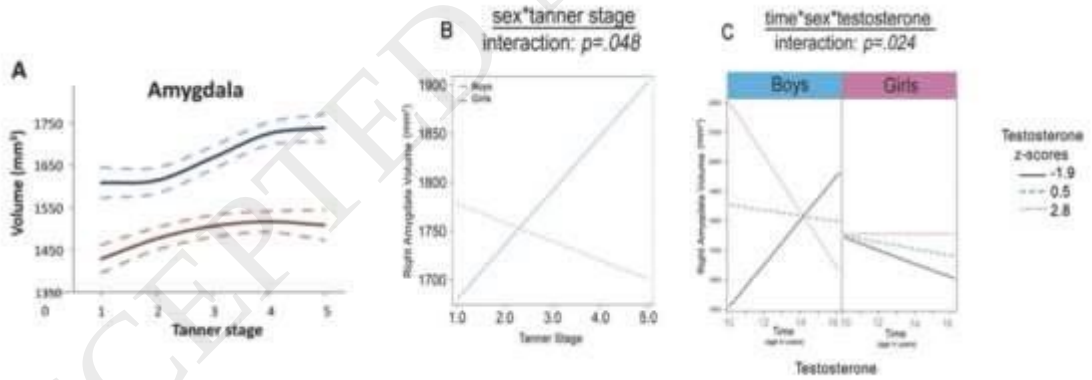


Figure 3. Pubertal associations with amygdala development from longitudinal studies. *a)* Goddings et al., 2014; *b,c)* Herting et al., 2014.

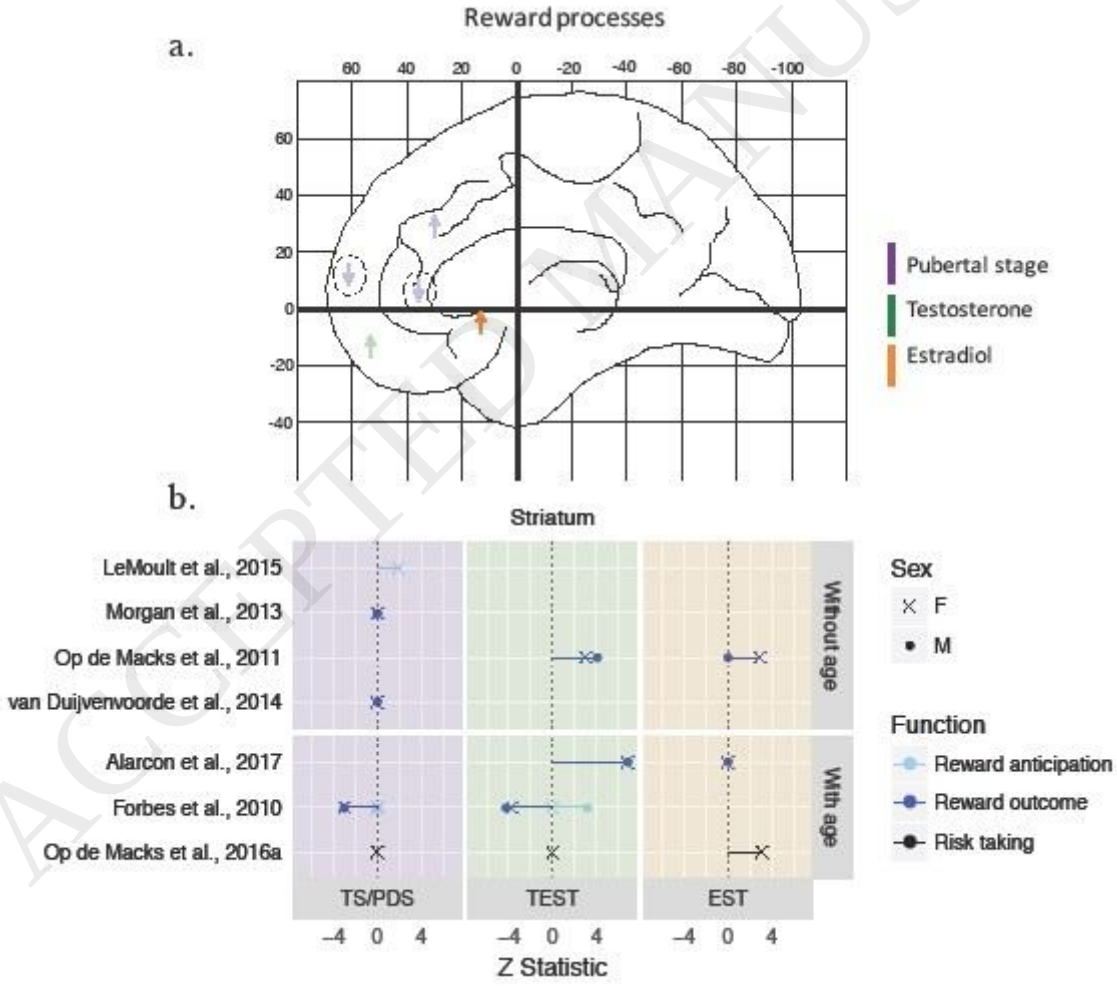


Figure 4. Pubertal associations with reward-related brain function. *a)* Darker arrows represent lateral findings, while lighter arrows represent medial findings. Dashed circles highlight findings that did not control for age. NB: Results using lowered (uncorrected) statistical thresholds from Op de Macks et al. (2011) are not presented.

b) Striatal findings (all studies used ROIs). NB: Longitudinal findings from Braams et al., (2015) are not presented. T statistics and correlation coefficients were converted to Z statistics for consistency across studies.

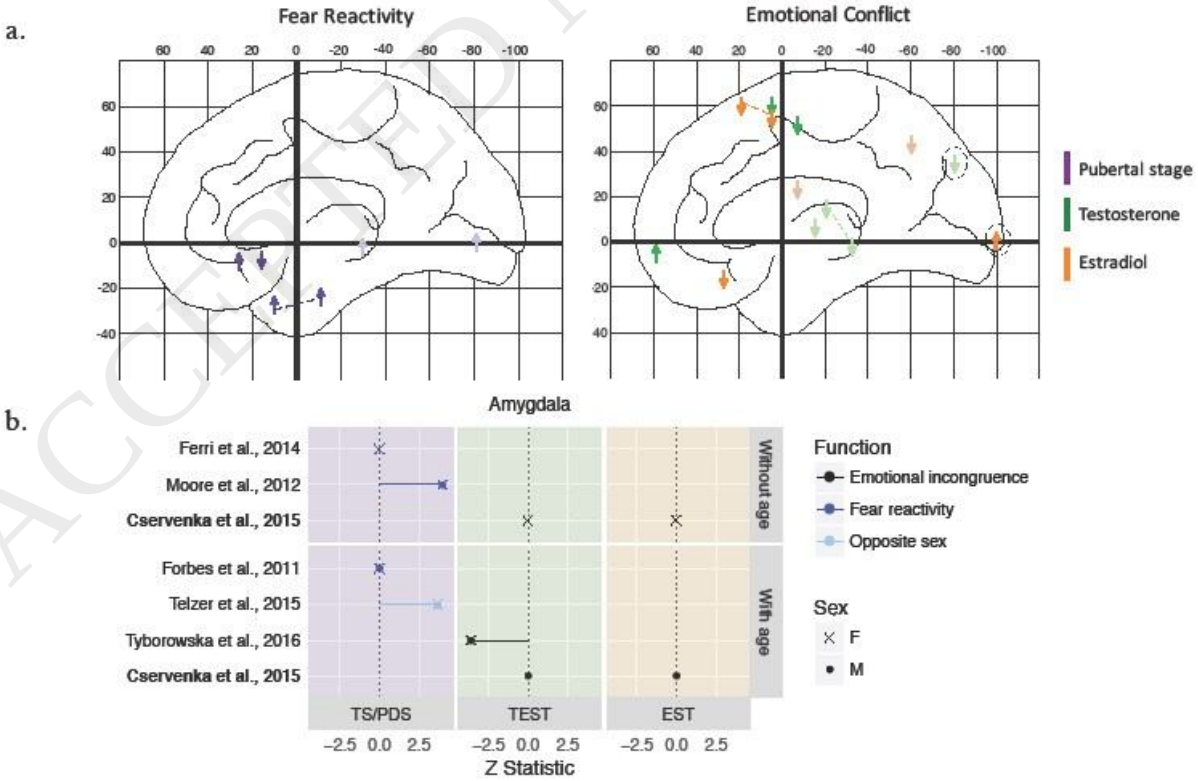
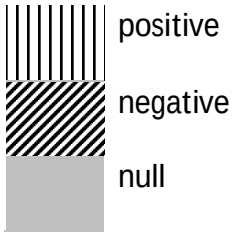


Figure 5. Pubertal associations with affect-related brain function. a) Darker arrows represent lateral findings, while lighter arrows represent medial findings. Dashed circles highlight findings that did not control for age. Dashed lines connect findings from same study that fall within the same anatomical subdivision. b) Amygdala findings (studies using whole brain analyses highlighted in bold). NB: Longitudinal findings from Spielberg et al. (2014; 2015) on task-based connectivity are not presented. T statistics and correlation coefficients were converted to Z statistics for consistency across studies.

Figure S1. PRISMA flowchart of systematic review. An electronic search was conducted in PubMed using the key words *adolescence, brain, MRI OR DTI OR fMRI,* and *puberty OR hormones OR pubertal hormones OR gonadarche OR adrenarche OR gonadal hormones OR adrenarcheal hormones,* to identify studies published in this field to date (February 2018). Inclusion criteria included *i)* the use of pubertal measures (either physical and/or hormonal indices), *ii)* neuroimaging methodologies (sMRI, DTI, fMRI, rs-fcMRI), *iii)* in a sample of typically developing children and/or adolescents (lower limit of age range less than 18 years).

Table 1
Pubertal associations with global cortical grey matter.

	Female	Male	Female	Male		
Pubertal stage						
Peper et al., 2009b			null		9	214
Koolschijn et al., 2014			null		8-25	215
Bramen et al., 2011	negative	null	negative	null	10-14	80
Pfefferbaum et al., 2015	negative				12-22	674
Testosterone						
Peper et al., 2009c			null	positive	10-15	78



Koolschijn et al., 2014		8-25	215
Bramen et al., 2011		10-14	80
Paus et al., 2010		12-18	419
Estradiol			
Peper et al., 2009c		10-15	78
Koolschijn et al., 2014		8-25	215

Note: only cross-sectional studies are presented.

Table 2

Table 2. *Overview of studies on pubertal associations with grey and white matter research in humans.*

Authors	N (F)	Age	Puberty	Study design	Imaging modality	Image processing	Outcome of interest
Asato et al., 2010	112 (63)	8-28	TS (pic)	Cross-sectional	DTI	voxelwise TBSS	RD
Barendse et al., 2018	87 (47)	9-10	DHEA, TEST (saliva)	Cross-sectional	DTI	voxelwise TBSS	FA, MD, RA, AD
Bava et al., 2011	58 (29)	12-14	PDS	Cross-sectional	DTI	voxelwise TBSS	FA, MD, RD, AD
Blanton et al., 2012	54 (54)	9-16	TS, menarcheal status	Cross-sectional	sMRI	VBM	Amygdala & hippocampus volumes
Bramen et al., 2011	80, 48	10-14	TS, TEST (blood)	Cross-sectional	sMRI	SBM	Subcortical & global GM volume
Bramen et al., 2012	85 (49)	10-14	TEST (blood)	Cross-sectional	sMRI	SBM	Vertex-level CT
Brouwer et al., 2015	113 (53)	9-12	LH (urine), FSH (urine), EST (urine), TEST (saliva)	Single cohort longitudinal	sMRI	VBM	Voxel-level GM
Chavarria et al., 2014	124 (62)	5-18	PDS	Cross-sectional	sMRI	VBM	Corpus callosum volume
Genc et al., 2017	74 (31)	9-12	PDS	Cross-sectional	DTI	Fixel-based analysis	Fibre density, fibre cross-section
Goddings et al., 2014	275 (117); 711 scans	7-20	TS (pic)	Accelerated longitudinal	sMRI	SBM	Subcortical volumes

Herting et al., 2012	77 (39)	10-16	PDS, TEST, EST (blood)	Cross-sectional	DTI	voxelwise TBSS	FA, MD, RD, AD
Herting et al., 2014	116 (59); 189 scans	10-14	TS, TEST, EST (blood)	Single cohort longitudinal	sMRI	SBM	Global & subcortical volumes
Herting et al., 2015	81 (48)	10-14	TS, TEST, EST (blood)	Single cohort longitudinal	sMRI	SBM	Vertex-level CT & SA
Herting et al., 2017	33 (15); 66 scans	10-20	PDS	Accelerated longitudinal	DTI	voxelwise TBSS	FA, MD, RD, AD
Herve et al., 2009	404 (200)	12-18	TEST (blood, active levels estimated)	Cross-sectional	sMRI	VBM	Corticospinal tract volume
Hu et al., 2013	306 (167)	4-18	PDS	Cross-sectional	sMRI	VBM	Mesial temporal lobe volume
Klauser et al., 2015	85 (48)	9	DHEA (saliva)	Cross-sectional	sMRI	VBM	Voxel-level WM
Koolschijn et al., 2014	215 (113)	8-25	PDS, TEST (saliva), EST (saliva), LH (urine)	Cross-sectional	sMRI	SBM	Global GM & subcortical volume, vertex-level CT
Menzies et al., 2015	61 (0)	13-16	TS (pic), TEST, EST, DHEA (saliva)	Cross-sectional	DTI	voxelwise TBSS	FA, MD, RD, AD

Murray et al., 2016	95 (50)	9	DHEA, TEST (saliva)	Cross-sectional	sMRI	SBM	Pituitary volume
Neufang et al., 2009	46 (23)	8-15	TEST, EST (blood)	Cross-sectional	sMRI	VBM	Voxel-level GM
Nguyen et al., 2013a	255 (143); 407 scans	4-22	DHEA, TEST (saliva)	Accelerated longitudinal	sMRI	SBM	Vertex-level CT
Nguyen et al., 2013b	281 (154); 469 scans	4-22	PDS, TEST (saliva)	Accelerated longitudinal	sMRI	SBM	Vertex-level CT
Paus et al., 2010	204 (0)	12-18	TEST (blood, active levels estimated), AR gene	Cross-sectional	sMRI	VBM	Global GM & WM volume, voxel-level WM
Peper et al., 2008	104 (47)	9	LH (urine)	Cross-sectional	sMRI	VBM	Voxel-level WM
Peper et al., 2009	78 (41)	10-15	TEST (saliva), EST (urine)	Cross-sectional	sMRI	VBM	Global & voxel-level GM, WM
Peper et al., 2009	214 (107)	9	TS	Cross-sectional	sMRI	VBM	Global & voxel-level GM, WM
Peper et al., 2009	214 (107)	9	TS	Cross-sectional	sMRI	VBM	Global & voxel-level GM, WM

Peper et al., 2010	85 (46)	10-15	LH (urine), FSH (urine), EST (urine), TEST (saliva)	Cross-sectional	sMRI	VBM	Pituitary & hypothalamus volumes
Peper et al., 2015	258 (132)	8-25	TEST, EST (saliva)	Cross-sectional	DTI	deterministic tractography	FA, MD, RD, LD
Perrin et al., 2008	204 (0)	12-18	TEST (blood, active levels estimated)	Cross-sectional	sMRI	VBM	Global WM volume
Perrin et al., 2009	408 (204)	12-18	PDS	Cross-sectional	sMRI	VBM	Voxel-level WM
Pfefferbaum et al., 2015	674, (340)	12-22	PDS	Cross-sectional	sMRI	SBM	Global WM volume
Pangelinan et al., 2016	941 (480)	12-19	PDS, TEST (blood, active levels estimated)	Cross-sectional	sMRI	VBM	Corticospinal tract volume
Satterthwaite et al., 2014	524 (335)	10-22	TS (pic)	Cross-sectional	sMRI	VBM	Amygdala & hippocampus volumes
Schutter et al., 2017	149 (76)	12-27	TEST (saliva)	Cross-sectional	sMRI	SBM	Cerebellar volume

Urosevic et al., 2014	126 (63)	9-18	PDS, TS (pic)	Cross-sectional	sMRI	SBM	Subcortical volumes
Whittle et al., 2012	154 (72)	11-16	PDS	Cross-sectional	sMRI	SBM	Pituitary volume
Wong et al., 2014	962 (495)	11-19	PDS, TEST, EST (blood)	Cross-sectional	sMRI	VBM	Pituitary volume

NB: The "Puberty" column only notes a single method of collection when it was utilized for all hormones. AD = axial diffusivity, AR = angroden receptor, CT = cortical thickness, DHEA = dehydroepiandrosterone, DTI = diffusion tensor imaging, EST = Estradiol, FA = fractional anisoptropy, FSH = follicle-stimulating hormone, GM = grey matter, LD = longitudinal diffusivity, LH = lutenizing hormone, MD = mean diffusivity, PDS = Pubertal Development Scale, RA = radial diffusivity, SA = surface area, SBM = surface-based morphometry, sMRI = structural MRI, TBSS = tract-based spatial statistics, TEST = testosterone TS = Tanner stage, VBM = voxel-based morphometry, WM = white matter

Table 3. *Pubertal associations with (a) white matter volume/density and (b) DTI indices of FA and MD.*

	Without age	With age
Pubertal stage		
Chavarria et al., 2014	CC	
Pfefferbaum et al., 2015	global	
Perrin et al., 2009	all lobes	
Peper et al., 2009b		occipital
Pangelinan et al., 2016		CST
Testosterone		
Paus et al., 2010	global	

	Female	Male	Female	Male
Pubertal stage				
Bava et al., 2012	CST, SCR		ILF, forceps major	
Herting et al., 2012	insula			
		superior front		
Menzies et al., 2015		SLF, ILF, CLT, CST		
Testosterone				
Barendse et al., 2018				
Herting et al., 2012	precentral	superior temp, front, angular		superior front

positive

null

Herve et al., 2009	CST	CST
Perrin et al., 2008	global	
Peper et al., 2009c		global/regional
Pangelinan et al., 2016		
Estradiol		
Paus et al., 2010		global/regional

Peper et al., 2015		gyrus, thalamus, CC, IC		
			subcortico-temp	
Menzies et al., 2015 *				
Estradiol				
Herting et al., 2012		Cingulum, superior front, precuneus, thalamus		
Peper et al., 2015				
Menzies et al., 2015 *				SLF, ILF, CLT, CST

Note: Only findings from cross-sectional studies are presented. Within part b), analyses that did not include age in model are marked with "*". CC = corpus callosum, CLT = cortico-limbic tract, CST = cortico-spinal tract, front = frontal lobe, IC = internal capsule, ILF = inferior longitudinal fasiculus,

SCR = Superior corona radiata, SLF = superior longitudinal fasiculus, temp = temporal lobe

Table 4. *Overview of studies on pubertal associations with brain function in humans.*

Authors	**N (F)**	**Age**	**Puberty**	**Study design**	**Imaging modality**	**Imaging details**
Alarcon et al., 2014	49 (23)	10-16	TEST (blood)	Cross-sectional	fMRI	spatial working memory
Braams et al., 2015	249 (147)	8-27	PDS, TEST (saliva)	Accelerated longitudinal	fMRI	reward sensitivity – outcome
Cservenka et al., 2015	44 (22)	10-15	PDS, TEST, EST (blood)	Cross-sectional	fMRI	affective faces – emotional incongruence
Fareri et al., 2015	50 (23)	4-23	TEST (saliva)	Cross-sectional	rs-fc MRI	VS seed
Ferri et al., 2014	60 (60)	8-15	TS (pic), PDS	Cross-sectional	fMRI	affective faces – emotional reactivity
Forbes et al., 2010	77 (40)	11-13	TEST (blood)	Cross-sectional	fMRI	reward sensitivity – anticipation & outcome
Forbes et al., 2011	76 (40)	11-13	TS	Cross-sectional	fMRI	affective faces – emotional reactivity
Goddings et al., 2012	42 (42)	11-13.7	TS, menarcheal status, TEST, EST, DHEA (saliva)	Cross-sectional	fMRI	social cognition – mentalising

Jankowski et al., 2014	18 (9)	11-14	PDS	Cross-sectional	fMRI	social cognition – self vs other evaluations
Klapwijk et al., 2013	35 (35)	11-13.7	TS, menarcheal status, TEST, EST, DHEA (saliva)	Cross-sectional	fMRI (PPI)	social cognition – mentalising
Le Moult et al., 2015	36 (36)	9-14	menarcheal status	Cross-sectional	fMRI	reward sensitivity – anticipation
Moore et al., 2012	45 (26)	10-13	PDS	Single cohort longitudinal	fMRI	affective faces – emotional reactivity
Morgan et al., 2013	72 (40)	11-13	TS	Cross-sectional	fMRI	reward sensitivity – anticipation & outcome
Op de Macks et al., 2011	50 (33)	10-16	TEST, EST, DHEA (saliva)	Cross-sectional	fMRI	reward sensitivity – outcome
Op de Macks et al., 2016a	58 (58)	11-13	PDS, TEST, EST (saliva)	Cross-sectional	fMRI	risk taking
Op de Macks et al., 2016b	58 (58)	11-13	PDS, TEST, EST (saliva)	Cross-sectional	fMRI	risk taking – social vs monetary feedback
Peters et al., 2014	268 (138)	8-25	PDS, TEST, EST (saliva)	Cross-sectional	fMRI	rule-learning with performance feedback
Peters et al., 2015	173 (86)	12-25	TEST (saliva)	Cross-sectional	rs-fc MRI	amygdala seed

Pfeifer et al., 2013	27 (18)	10-13	PDS	Single cohort longitudinal	fMRI	social cognition – self vs other evaluations
Schweinsburg et al., 2005	49 (25)	12-17	PDS	Cross-sectional	fMRI	spatial working memory
Spielberg et al., 2014	38 (21)	11-15	TEST (blood)	Single cohort longitudinal	fMRI	affective faces – emotional reactivity
Spielberg et al., 2015	41 (21)	11-15	TEST (blood)	Single cohort longitudinal	fMRI (PPI)	affective faces – emotional reactivity
Telzer et al., 2015	30	9-16	PDS – parent	Cross-sectional	fMRI	affective faces – opposite sex
Tyborowska et al., 2016	47 (26)	14	TEST (saliva)	Cross-sectional	fMRI	affective faces – emotional incongruence
van Duijvenvoorde et al., 2014	47 (32); 31 (18)	10–16; 2-year follow-up	PDS	Cross-sectional and accelerated longitudinal	fMRI	reward sensitivity – outcome
Whittle et a., 2015	83 (43)	9	DHEA (saliva)	Cross-sectional	fMRI	affective faces – emotional reactivity

NB: The “Puberty” column only notes a single method of collection when it was utilized for all hormones.

DHEA = dehydroepiandrosterone; EST = Estradiol, fMRI = functional MRI; PDS = Pubertal Development Scale; PPI = Psychophysiological interactions; rs-fc MRI = resting-state functional connectivity MRI; TEST = testosterone; TS = Tanner stage; VBM = voxel-based morphometry; VS = ventral striatum