JOURNAL OF
Research on Adolescence

Society for Research on Adolescence
www.s-r-a.org

JOURNAL OF RESEARCH ON ADOLESCENCE, 29(1), 32–53

Understanding the Role of Puberty in Structural and Functional Development of the Adolescent Brain

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Over the past two decades, there has been a tremendous increase in our understanding of structural and functional brain development in adolescence. However, understanding the role of puberty in this process has received much less attention. This review examines this relationship by summarizing recent research studies where the role of puberty was investigated in relation to brain structure, connectivity, and task-related functional magnetic resonance imaging (fMRI). The studies together suggest that puberty may contribute to adolescent neural reorganization and maturational advancement, and sex differences also emerge in puberty. The current body of work shows some mixed results regarding impact and exact direction of pubertal influence. We discuss several limitations of current studies and propose future directions on how to move the field forward.

Adolescence is an important time of change occurring between childhood and adulthood. With the relatively recent discovery that changes in brain structure and function stretch into adulthood (Gogtay et al., 2004), growing interest in adolescent brain development has been mirrored by a dramatic increase in published studies on the topic. For instance, the number of studies in Medline for the search term *adolescent brain* increased from 2,500 in 2000 to over 8,000 in 2015. Some early structural and functional imaging studies hypothesized that many of the age-related brain changes seen during adolescence may be associated with the contemporaneous developmental process of puberty (e.g., Giedd et al., 1999; Lenroot et al., 2007). Puberty refers to the neuroendocrinological development of the adrenal glands, gonads, and growth velocity that leads to reproductive competence and is associated with numerous physical, psychological, and social changes. The hypothesis that pubertal development was the driving force for the structural and functional brain changes seen during adolescence was initially based on apparent differences in maturational timing between males and females for both pubertal and neural changes (Giedd et al., 1999), the emergence of sex-specific differences in mental health pathologies during adolescence (Dahl, 2008; Paus, Keshavan, & Giedd, 2008), and evidence from the animal literature for pubertal hormonal effects on brain structure and behavior (Sisk & Zehr, 2005). An early review (Blakemore, Burnett, & Dahl, 2010) highlighted a lack of empirical data testing this hypothesis and called for studies specifically designed to tackle this key research area. In the years since that overview, a number of empirical studies have been published that incorporate pubertal measures in their study design as well as measures of brain development, alongside a growing animal literature and studies examining sex differences in brain measures.

The aim of this review is to evaluate the evidence for changes in brain structure, function, and connectivity that coincide with pubertal development, drawing on key empirical studies including examples of both animal and human research. It is not intended to be a systematic review of all the available literature, but rather an overview of the current state of the field. We will focus on emerging themes supported by the available research and discuss some of the potential reasons for inconsistencies in the literature and challenges associated with studying puberty-related change. A short overview of methods available to assess pub-

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DOI: 10.1111/jora.12408

erty is incorporated since challenges surrounding acquisition of accurate, standardized pubertal measures remain significant for the field and have an impact on the inferences that can be made from the available literature. In addition to studies specifically reporting pubertal measures, studies investigating sex differences in neural development during adolescence will also be discussed throughout the review. While both the structure and the function of the brain have been shown to be remarkably similar in females and males (Beltz, Blakemore, & Berenbaum, 2013; Cosgrove, Mazure, & Staley, 2007; Giedd & Denker, 2015; Paus, Wong, Syme, & Pausova, 2017), there is nonetheless converging evidence for region-specific structural and functional sex differences which are hypothesized to be associated with changes in sex steroid hormone exposures during pubertal development. Although these data can only provide indirect evidence for a pubertal relationship, they remain an important evidence base. Finally, this review will consider potential future directions for the field to continue to expand our understanding of puberty-related brain development research.

MEASURING PUBERTAL DEVELOPMENT

Puberty encompasses a combination of two distinct physiological processes, adrenarche (the activation of the hypothalamic-pituitary-adrenal axis) and gonadarche (the reactivation of the hypothalamic-pituitary-gonadal axis causing gonadal activation), which together lead to a dramatic rise in the circulating levels of sex steroid hormones including androgens, for example, testosterone, and dehydroepiandrosterone (DHEA), oestrogens (particularly estradiol), and progestagens. Both females and males achieve reproductive competence through puberty, but they differ in the nature and timing of puberty's component processes (for reviews, see Berenbaum, Beltz, & Corley, 2015; Dorn & Biro, 2011). In addition to sexual maturation, puberty results in physical changes such as linear growth, maturation of body organ systems including the hepatic, renal and cardiovascular systems, and changes in body proportion and facial bone structure (Lee & Houk, 2006; Meindl, Windhager, Wallner, & Schaefer, 2012; Verdonck, Gaethofs, Carels, & de Zegher, 1999).

While age is often used as a proxy for pubertal development in animal studies, humans exhibit substantial variability in timing and tempo of puberty, with a 5-year age range in pubertal onset between individuals. Thus, specific measures that capture pubertal development are necessary. In human studies, puberty is broadly measured in two ways, either by assessing levels of sex steroid hormones associated with pubertal development or by assessing objective physical development of characteristics known to be associated with these hormones, for example, body hair development, gonadal development, breast development and menarche (females), and growth velocity (see also Mendle et al., 2019, in this issue). These methods capture different aspects of pubertal development, and it is, therefore, important to consider the aspects of pubertal development that can be inferred from the assessment tool used (see Dorn, Dahl, Woodward, & Biro, 2006).

Phenotypic pubertal assessments, that is, objective or subjective assessment of physical development, provide an integrative measure of the body's exposure to pubertal hormones, reflecting the length of exposure to hormones, the levels of exposure, and the sensitivity to hormones. Examples of phenotypic pubertal assessments are the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988) and the Tanner scale (Marshall & Tanner, 1969, 1970). For both of these scales, participants (or clinicians/parents/teachers) identify their pubertal development by selecting the most appropriate answers to several questions, for example, regarding breast growth and body hair. By assessing an individual's perception of their physical appearance, these phenotypic measures also have the potential to capture the influence of these physical changes on how adolescents perceive themselves and how they are perceived by others, including peers, parents, and wider society (Paikoff & Brooks-Gunn, 1991). There are, however, limitations to phenotypic assessments, as they are susceptible to significant variation between assessors, and are influenced by inter-individual variation, body habitus, and social acceptability. Thus, knowing the measurement method in studies is critical for determining the strength and limitations of the measures and their impact on the aspect of the brain understudy.

In contrast, hormonal measures are assessed using serum, saliva, or urine. Hormonal concentrations can be very informative as these assessments provide nonsubjective measures that can be compared between individuals and within individuals over time, but their use also has limitations and analyses frequently rely on a number of assumptions. Hormonal concentrations exhibit diurnal variation and cyclical patterns (particularly estrogens), and are influenced by environmental and

internal stressors. A detailed understanding of normal variation in hormone concentrations, as well as receptor density and sensitivity, is lacking, as is the concordance between peripheral hormone measurements and concentrations of hormones in the local milieu of targeted brain regions. While there is broad concordance between physical and hormonal measures of pubertal development (Shirtcliff, Dahl, & Pollak, 2009), correlations in different study populations vary widely, emphasizing that the different types of measures are reflecting different aspects of the multifaceted construct of puberty. The absence of a single indicator that accurately encompasses the differing aspects of pubertal development continues to be a major challenge for the field, but despite this there is a growing body of literature on the effects of pubertal development on neural changes.

ANIMAL EVIDENCE FOR ROLE OF PUBERTY AND PUBERTAL HORMONES IN THE DEVELOPMENT OF THE BRAIN

The role of perinatal sex steroid hormones in organizing neural circuitry in the brain has been well documented (Sisk & Zehr, 2005). Hormonal effects on the brain after the perinatal period had previously been assumed to signal activation of transient changes building on earlier organizational processes. More recently, evidence has emerged supporting a role for gonadal hormones in organizational processes refining the developing adolescent brain, suggesting that adolescence may represent either a second sensitive period for sex steroid hormone effects on the brain, or that the sensitive period beginning in perinatal life may extend to the end of puberty (Schulz & Sisk, 2016).

Animal models have demonstrated that a number of social behaviors including sexual behaviors, aggression, and flank-marking in males fail to develop fully if the animal is deprived of testosterone during puberty (for a review, see Schulz, Molenda-Figueira, & Sisk, 2009; Schulz & Sisk, 2016), and these behaviors do not normalize if the testosterone is replaced in adulthood. The impact of female ovarian hormones during adolescence has been less well studied than that of testosterone in males, but has been associated with feminizing, masculinizing, or defeminizing adult behaviors, depending on the specific behavior studied (Schulz & Sisk, 2016). Thus, estradiol during adolescence has been shown to induce female reproductive behavior in mice (Brock, Baum, & Bakker, 2011) and to be necessary for female play behavior in adulthood (Pellis, 2002). Replacement of ovarian hormones during adolescence in Syrian hamsters ovariectomized neonatally has also been shown to defeminize some adult mating behaviors, for example, lordosis (Schulz & Sisk, 2006; see Schulz & Sisk, 2016 for review).

The influence of pubertal hormones on behavior across animal models provides evidence for sex steroid-dependent organizational development and suggests a role for puberty and pubertal hormones in influencing the brain's structural and functional organization. A building body of research substantiates this hypothesis, providing evidence for multiple mechanisms through which pubertal hormones impact on brain structure including neurogenesis (Ahmed et al., 2008), programmed cell death (Nunez, Sodhi, & Juraska, 2002), and synaptic arborization and pruning (Huttenlocher, 1979). In rats, particular structures of the brain are sexually dimorphic in adulthood, namely the anteroventral periventricular nucleus of the hypothalamus (AVPV), which is larger in female rats than male rats, and the sexually dimorphic nucleus of the preoptic area (SDN) and medial amygdala, which are larger in male rats than female rats (Ahmed et al., 2008). This structural dimorphism has been shown to develop during puberty as a result of neurogenesis and cellular proliferation following exposure to sex steroid hormones. Prepubertal gonadectomy affects this process in a sex-specific manner. In female rats, no pubertally born cells are seen in the AVPV of the adult following prepubertal ovariectomy, and there is no sexual dimorphism between male and female adults, but neurogenesis and sexual dimorphism are seen in the SDN and medial amygdala (Ahmed et al., 2008). Contrastingly, male rats who have been castrated before puberty have no detectable pubertally driven neurogenesis in the SDN or medial amygdala, and no sexual dimorphism is seen in adults, but normal AVPV development is seen, complete with adult dimorphism (Ahmed et al., 2008). Similar effects in the medial amygdala have subsequently also been shown in the Syrian hamster (De Lorme, Schulz, Salas-Ramirez, & Sisk, 2012). This demonstrates the clear effect that sex steroid hormone exposure can have on the structural organization of the brain by inducing new cell formation and proliferation and highlights that the effects may be region-specific and differentially related to different hormones.

In addition to the production and proliferation of new cells, there is some evidence for pubertal influence on controlled cell death. In adult rats, there are sex differences in the volume of the

medial prefrontal cortex (mPFC), where there are larger numbers of cells in males compared with females. This difference appears to be driven by greater cell death of female rats during early puberty, which can be abolished by prepubertal ovariectomy, suggesting that ovarian hormones may promote cell death in the mPFC during puberty (Koss, Lloyd, Sadowski, Wise, & Juraska, 2015; Markham, Morris, & Juraska, 2007).

A third way in which pubertal hormones have been shown to affect brain structure and organization is by influencing the complexity and organization of neural dendrites in the brain (Murphy & Segal, 1996; Zehr, Nichols, Schulz, & Sisk, 2008). Dendrites in the dentate gyrus in the hippocampus of Syrian hamsters have been shown to reduce in both length and the number of intersections during puberty (Zehr et al., 2008). However, this effect was only seen in selected areas and not throughout the dentate gyrus, highlighting the specificity of pubertal effects on the brain. In vivo and in vitro animal studies have directly related the presence of gonadal hormones, both testosterone and estradiol, to region-specific changes in dendritic spine density (Meyer, Ferres-Torres, & Mas, 1978; Murphy & Segal, 1996).

Sex steroid hormones likely influence not only structural brain development but also functional brain development, as evidenced by animal model studies. Functional brain development is influenced through hormonal binding to specific receptors. Both androgen receptors (AR) and estrogen receptors (ER) have been identified in the brain. There are different types of ER including classic nuclear receptors (a and b) and membrane receptors (e.g., GPR30 and ER-X) and each are thought to have differing effects on the functioning of the brain (Cui, Shen, & Li, 2013). While estrogens are thought to predominantly bind to ERs, androgens (including testosterone and DHEA) work both directly on ARs but also on ERs, after being converted into estrogens locally via the enzyme aromatase (Kawata, 1995). Both ARs and ERs are found in multiple regions of the brain in varying concentrations, with high levels in subcortical regions, particularly the hippocampus and amygdala, both in animal species and in humans (Abdelgadir, Roselli, Choate, & Resko, 1999; Clark, MacLusky, & Goldman-Rakic, 1988; Sholl & Kim, 1989; Shughrue, Lane, & Merchenthaler, 1997). While a small number of studies have demonstrated links between specific receptor expression and behavior, for example, social decision making in naked mole-rats (Holmes, Goldman, & Forger, 2008), object recognition, and placement tasks in mice (Walf, Koonce, & Frye, 2008), overall our understanding of the actions of hormones via these receptors is still limited.

Despite a growing animal literature linking sex steroid hormones during puberty with structural brain changes, it is important to recognize that not all changes seen during puberty show this pattern, and some brain changes appear to occur independently of hormonal changes at this time. For example, Ho, Villacis, Svirsky, Foilb, and Romeo (2012) found that the puberty-related decline in cellular proliferation and neurogenesis in the dentate gyrus of the hippocampus of male rats occurs independently of the measured rise in pubertal hormones. It is, therefore, important to consider the potential alternative mechanisms linking pubertal development with brain development in both animal and human models. Teasing apart the role of pubertal hormones from other aspects of pubertal development in humans is particularly challenging.

While animal models allow the manipulation of sex steroid hormones and use of cellular labeling techniques, and the use of killing the animal, there are limitations to the knowledge that can be gained for human research from studying animal models. Across mammalian species, there are extensive differences both in brain structure and in functional networks, and in some species androgens undergo different processes of aromatization than they do in human beings. Thus, many of the sexual dimorphisms seen in rodent species do not translate directly to human patterns, but instead show the potential impact of sex steroid hormones on regionally selective populations of neurons. This is a particular limitation for studies of adolescent behavior and cognition, where the focus of developmental change lies in brain regions responsible for complex social behaviors and decision making, which do not have direct equivalents in other species. Animal models of puberty are furthermore limited to assessing the role of changes in sex steroid hormone concentration and are unable to incorporate the scope of pubertal maturation experienced by humans, where hormonal changes are accompanied by psychosocial and cultural changes.

The advent of magnetic resonance imaging technology has resulted in a major expansion of research into human adolescent structural and functional brain development as it provides a safe, noninvasive assessment method, enabling the study of large numbers of participants, and the potential for repeated measures of both structure and function.

HUMAN STUDIES ON THE ROLE OF PUBERTY AND PUBERTAL HORMONES IN THE DEVELOPMENT OF THE BRAIN

Puberty and Structural Brain Changes in Humans

Data from an early National Institutes of Health (NIH) study of structural brain development (Giedd et al., 1999; Lenroot et al., 2007) described an inverted-U shaped maturational trajectory for cortical gray matter during childhood and adolescence, with girls achieving average peak volume (i.e., the inflection point between neuronal proliferation and pruning) about 2 years before boys (Lenroot et al., 2007), coinciding with the established sex differences in pubertal timing (although puberty was not measured in this study). These data, together with animal-based studies of hormonal effects and behavioral data, were tentatively used to hypothesize a possible causal link between puberty and gray matter maturation. However, subsequent longitudinal studies of cortical development do not replicate the sex differences in timing of gray matter developmental trajectory found in this early study, and instead indicate that gray matter volume declines linearly from late childhood through early adulthood, and that sex differences depend on methods used to correct for overall brain volume (Mills et al., 2016). Given this lack of replication across cohorts of a clear age-related pattern correlating with pubertal timing, it is important to evaluate the evidence supporting the hypothesis linking puberty and structural brain development.

A number of studies of structural development are now available that have incorporated specific measures of puberty (see Herting & Sowell, 2017 for a review), and in particular, longitudinal data sets have been analyzed from different cohorts (Brouwer et al., 2015; Goddings et al., 2014; Herting, Gautam, Spielberg, Dahl, & Sowell, 2015; Herting et al., 2014; Nguyen, Gower et al., 2016; Nguyen, McCracken, et al., 2016; Nguyen, McCracken, Ducharme, Botteron et al., 2013; Nguyen, McCracken, Ducharme, Cropp et al., 2013; Wierenga et al., 2018). Longitudinal analyses have a number of advantages over cross-sectional studies, providing greater statistical power (Steen, Hamer, & Lieberman, 2007) and more reliable results (Kraemer, Yesavage, Taylor, & Kupfer, 2000) with greater potential to disentangle pubertal and age effects (Crone & Elzinga, 2015), and we, therefore, focus our summary of the literature on these studies. Each cohort has used different measures of assessing physical and hormonal pubertal development and has focused on different outcome measures.

Cortical development. Of these longitudinal studies, only analyses using the Pittsburgh cohort included volume indices for total cortical gray matter and reported that indices of more advanced pubertal development were related to decreases in gray matter volume (increasing physician-assessed Tanner stage scores in both sexes, higher estradiol concentrations in females), and increases in white matter volume in both males and females (Herting et al., 2014). To our knowledge, this is the only published longitudinal study to date to report white matter structural indices in relation to pubertal development.

Cortical gray matter structure can be subdivided into cortical thickness and surface area, and studies reporting these indices have shown correlations with pubertal development, although the exact relationships are specific to each study and analysis technique. For example, cortical thinning was reported with advancing puberty (as measured by testosterone concentration) in the posterior cingulate and dorsolateral prefrontal cortex for pubertal males in one sample (Nguyen, McCracken, Ducharme, Botteron et al., 2013), as well as testosterone effects in females on the somatosensory cortex that varied with pubertal stage (as measured by PDS). A second article from the same research group reported a positive correlation between cortical thickness and DHEA concentrations in the dorsolateral prefrontal, temporoparietal, premotor, and entorhinal cortices of both males and females aged 4–13 years (Nguyen, McCracken, Ducharme, Cropp et al., 2013). Meanwhile, in a second sample, increasing physician-assessed Tanner stage and higher estradiol levels predicted cortical thinning in the temporal lobe of females (Herting et al., 2015). An alternative method to quantify gray matter structural development uses voxel-based morphometry to provide a measure of gray matter density. A group from The Netherlands using this technique found a negative correlation between estradiol and gray matter density in left frontal and parietal regions in girls aged 12 years, but no longitudinal associations with sex steroid hormones were seen (Brouwer et al., 2015). While the findings reported across these studies are not mutually exclusive, our ability to interpret them or evaluate whether the findings are consistent between studies and cohorts is limited by the lack of replication between studies of both structural brain indices and pubertal measures.

Subcortical development. Some of the above longitudinal studies have assessed the association between subcortical development and puberty. Goddings et al. (2014) report increases in amygdala and hippocampal volumes and decreasing volumes of globus pallidus, caudate, putamen, and nucleus accumbens with increasing self-assessed Tanner stage in males and females aged 7–20 years, with differing developmental trajectories seen between the two sexes (Goddings et al., 2014). This study highlighted nonlinear developmental trajectories for many of these structures, and distinct but overlapping associations with age and pubertal variables. A second study has again recently shown interactive effects of puberty (using a self-report measure and testosterone levels) and age on subcortical brain development (Wierenga et al., 2018). While these two articles both suggest pubertal influences on structural brain development, the developmental patterns described by the two studies show some discrepancies with the later study showing, for example, decreasing volumes in the globus pallidus and putamen during adolescence (Wierenga et al., 2018).

In a different cohort, decreasing caudate volumes were again reported with advancing puberty, measured by physician-assessed Tanner stage, and testosterone concentration (Herting et al., 2014), although changes were not seen in the hippocampus or the thalamus. For the amygdala, a sex-specific and hemisphere-specific pattern was seen, with increasing Tanner stage correlating with decreases in right amygdala volume in males, but increases in females, while a more complex relationship was described between amygdala development and testosterone concentrations in males, with males with low testosterone concentrations for their age showing increasing volumes, and those with high concentrations showing decreasing volumes (Herting et al., 2014). A different approach was taken by Nguyen and colleagues, who showed a correlation between testosterone levels and the structural covariance between left amygdala volume and cortical thickness in the right rostral anterior cingulate cortex and orbitofrontal cortex in both sexes. Lower testosterone levels were associated with a positive correlation between these two regional metrics, while higher levels were associated with a negative correlation (Nguyen, McCracken et al., 2016). In a separate analysis using the same technique, DHEA was associated with the structural covariance of the amygdala and cortical thickness in the left occipital pole, the right somatosensory cortex, and the right subgenual anterior cingulate cortex, with lower DHEA levels being associated with positive correlations and higher levels associated with negative correlations in both males and females (Nguyen, Gower et al., 2016).

As with the cortical literature, the variation in measurements used and analysis methods between published studies make drawing clear conclusions on the role of puberty in subcortical brain development challenging. However, the available longitudinal data illustrate that the relationship between puberty and structural brain development is likely to be complex and nonlinear, and interacting with the distinct but contemporaneous effects of age. These data highlight that differing measures of puberty, for example, hormones versus physical scales, may relate differently to structural brain development, likely reflecting the different underlying physiological processes they represent, and suggest an ongoing need for further studies to replicate and add to the current available literature.

Sex differences in brain structure. The most well-known and well-replicated sex difference in the brain is in overall volume (cerebral and intracranial), with boys and men having larger average brains than girls and women across development; this difference is partially, but not fully, explained by the sex difference in body size (reviewed in Beltz et al., 2013; Cosgrove et al., 2007; Giedd & Denker, 2015). This has important implications for neuroscience research on sex-related characteristics, such as puberty. Researchers must carefully consider whether and how to correct for the sex difference in brain volume when examining regional brain volumes or extracting volumetric regions of interest (ROIs), and they must interpret their findings accordingly. Corrections can be challenging because most are linear, but the relation between overall brain volume and regional brain volume may not be. Moreover, the sex difference in brain volume both helps and hinders interpretation of other neural sex differences, or the lack thereof (see Mills et al., 2016). On one hand, it—along with differential rates of development across the brain—confounds research on sex differences in gray matter, white matter, and regional volume. For example, women are generally shown to have greater gray matter volume than men, and men to have greater white matter volume than women (reviewed in Beltz et al., 2013; Cosgrove et al., 2007; Giedd & Denker, 2015), but some evidence indicates that this may be a function of linear corrections for brain volume (e.g., Leonard et al., 2008). On the other hand, it contextualizes sex differences

in brain structure. For example, some studies have found greater cortical complexity and regional corpus callosum thickness for women than for men, and results have been interpreted in terms of offsetting women's smaller brain volume (Dubb, Gur, Avants, & Gee, 2003; Luders et al., 2004).

A recent large multisample study of longitudinal changes assessed sex differences in subcortical regions across the three samples included in the analysis (Herting et al., 2018). Taking the samples together, females showed smaller volumes than males in all the subcortical regions assessed (thalamus, pallidum, caudate, putamen, nucleus accumbens, hippocampus, amygdala), with diverging trajectories seen through adolescence increasing this volumetric difference. When analyzed separately using general additive mixed models (GAMM), however, there were significant differences in the developmental trajectories for the thalamus, pallidum, caudate, and hippocampus across the three samples (Herting et al., 2018) despite identical methods of analysis. The authors suggested that this may reflect factors including population differences, sampling strategy, scanning protocols, sample age ranges, and statistical power (Herting et al., 2018). All of these factors continue to be relevant when assessing the puberty-focused literature and are likely to account for some of the variation in findings between studies. This article adds to the preexisting literature looking at sex differences in subcortical structural development and may help to explain much of the inconsistency in the literature, with some studies finding evidence for sex differences in developmental trajectories (e.g., Dennison et al., 2013; Raznahan et al., 2014), while others report no differences (e.g., Narvacan, Treit, Camicioli, Martin, & Beaulieu, 2017; Wierenga et al., 2014). Aside from sex differences in the means of brain volumes, it has recently been demonstrated that the variability in brain volumes is larger in boys than it is in girls (Wierenga, Sexton, Laake, Giedd, & Tamnes, 2017), which may further impact on the importance of sample size and the age ranges used in studies assessing sex and puberty differences.

Puberty and Functional Change in Humans

A growing line of research examines how pubertal development is associated with neurodevelopmental changes in brain activity, that is, neural responses in the brain while participants perform a cognitive or social-affective task. Two research lines inspire the questions that are addressed in these studies. First, there is consistent evidence that in mid-adolescence there is heightened neural activity in subcortical brain regions (ventral striatum and amygdala) that are associated with processing basic emotions, such as reward, happiness, and fear (Casey, 2015; Crone & Dahl, 2012). Several researchers have suggested that this increase in neural activity is driven by the onset of puberty, based on the assumption that pubertal hormones may increase sensitivity in these brain regions (Blakemore et al., 2010). Second, researchers have suggested that pubertal development may advance social-cognitive processes, which rely on social brain network areas such as the dorsomedial prefrontal cortex, anterior temporal lobe, temporal parietal junction, and superior temporal sulcus. It is well documented that these regions gradually become more involved in processing social emotions over the course of adolescent development (Blakemore & Mills, 2014), and puberty is thought to possibly advance or accelerate this development. The studies summarized below tested these questions by correlating brain activity while participants performed affective and social-cognitive tasks to individual differences in self-report puberty (PDS, Tanner staging) and hormones measured from saliva, specifically testosterone and estradiol (Table 1). Even though some initial evidence is present for these two hypotheses, the results remain mixed and the findings remain inconclusive. Nonetheless, several interesting findings have been reported that pose interesting questions for future research.

Reward processing. One of the first studies that tested the relation between puberty and reward sensitivity included boys and girls at different stages of pubertal development in a cross-sectional design (Op de Macks et al., 2011). In the magnetic resonance imaging (MRI) scanner, participants played a Jackpot gambling task where they could pass or play. The pass option was safe; participants would not gain or lose anything. The play option was the risky choice, with high and low probabilities of winning and losing. When participants played and won, relative to played and lost, this resulted in heightened activity in the bilateral ventral striatum and ventral medial prefrontal cortex (VMPFC). The ventral striatum and VMPFC are often implicated as the core reward network in the brain (Haber & Knutson, 2010). Next, the authors correlated neural activity with levels of testosterone and estradiol, as an index of pubertal maturation. In both boys and girls, higher levels of testosterone were correlated with stronger activity in the ventral

TABLE 1
Detailed Information of Domains, Experimental Paradigms, Age Selection, and Pubertal Assessment of Studies That Related Puberty to fMRI

First author	*Year*	*Paradigm*	*Ages and sample sizes*	*Puberty assessments*
Monetary rewards				
Op de Macks	2011	Reward processing	10–16, $n = 50$	PDS and testosterone
Van Duijvenvoorde	2014	Reward processing	10–22 $n = 75$; longitudinal $n = 33$	PDS
Braams	2015	Reward processing	8–27, longitudinal, $n = 299$ (t1); $n = 254$ (t2)	PDS and testosterone
Forbes	2010	Reward anticipation	11–13, $n = 77$	PDS and testosterone
Op de Macks	2016	Reward processing	11–13 girls, $n = 58$	PDS, testosterone, and estradiol
Emotional faces				
Ferri	2014	Emotional faces	8–15 years; $n = 60$	PDS
Spielberg	2015	Emotional faces	11–14 years, longitudinal, $n = 38$	PDS and testosterone
Forbes	2011	Emotional faces	11–13 years, $n = 76$	Tanner stage
Moore	2012	Emotional faces	10–13, longitudinal, $n = 45$	PDS
Silk	2014	Social rejection	11–17 years, $n = 48$	PDS
Control of incongruent emotions				
Tyborowska	2016	Approach avoidance	14 years, $n = 47$	PDS and testosterone
Cservenka	2015	Emotional incongruence	10–15 years, $n = 44$	PDS, testosterone, and estradiol
Social-cognitive emotions				
Goddings	2012	Mentalizing	11–13 girls, $n = 42$	PDS, testosterone, and estradiol
Op de Macks	2016	Social rank sensitivity	11–13 girls, $n = 58$	PDS, testosterone, and estradiol
Self-related processes				
Pfeifer	2013	Self processing	10–13 years, longitudinal, $n = 27$	PDS
Masten	2013	Witnessing peer rejection	10–13 longitudinal, $n = 16$	PDS

Note. PDS = Puberty Development Scale (Petersen et al., 1988).

striatum when winning. Furthermore, in girls, higher levels of estradiol were correlated with stronger activity in the VMPFC. A follow-up study, however, that made use of self-report puberty measures (PDS) could not replicate this effect (but see van Duijvenvoorde et al., 2014), suggesting that these effects are either restricted to hormone relations or are less robust. A study that included participants in a more narrow age range (11–13 years) observed that boys with more testosterone showed more activity in the ventral striatum when anticipating rewards (Forbes et al., 2010), consistent with sex differences favoring men in reward processing. The advantage of this narrow age range is that the analyses could be specifically targeted at variations in pubertal development, without the confounding influence of age or experience-related changes.

In a longitudinal fMRI study with a larger sample size and spanning a large age range, it was again found that reward processing after gambling was significantly associated with testosterone levels in both boys and girls (Braams, van Duijvenvoorde, Peper, & Crone, 2015). In this study, participants played a simple gambling task, in which they guessed if the computer would pick heads or tails. In cases where their choice matched the computer choice (50% of the time), participants won money. This task was comparable to the Jackpot gambling task with the exception that it was not possible to pass. The authors measured PDS and testosterone as indices of pubertal maturation. Interestingly, stronger increases in testosterone over a time period of 2 years were correlated with higher activity in the ventral striatum over time. Together, these findings suggest that higher concentrations of circulating testosterone during adolescence, an indicator of relatively more advanced puberty, is associated with stronger reward reactivity in the ventral striatum, although this is not found in all studies.

A question that was not yet addressed in these studies was whether the neural activity in ventral striatum and VMPFC also mediated possible relations between pubertal hormones (testosterone or estradiol) and risk taking. It is often assumed that neural activity in the striatum is implicated in stronger risk taking tendencies (van Duijvenvoorde et al., 2014), but the exact association with puberty is not yet well understood. This question was addressed in a study including girls between ages 11–13 years for whom testosterone and estradiol were measured as indices of pubertal maturation (Op de Macks et al., 2016). In this study, participants played the Jackpot gambling task but with more variation in risk levels. This allowed the

authors to test more precisely how pubertal hormones and brain activity were associated with changes in risk taking. Consistent with prior studies (Braams et al., 2015; Op de Macks et al., 2011), the fMRI results showed that playing versus passing was associated with increased activity in the ventral striatum and VMPFC, and this was even stronger when the playing choice was followed by reward relative to loss. The subsequent mediation analyses showed intriguing results pointing toward differential contributions of testosterone and estradiol on risk taking. That is to say, more testosterone was related to more risk taking, and this was mediated by more activity in the VMPFC when taking risks. These findings fit well with earlier studies showing that more testosterone may increase reward values. Estradiol, on the other hand, was not significantly related to risk taking. However, more estradiol was associated with more activity in the ventral striatum, and this was associated with decreased risk taking. This study only included girls, so it remains to be determined if similar effects are found in boys and if the detection of effects depends on range restriction (with girls showing less variation in testosterone and boys in estradiol). Nonetheless, the results show that possibly in girls, estradiol has dampening effects on risk taking, whereas testosterone has amplifying effects on risk taking (see also Peper, Koolschijn, & Crone, 2013).

Emotional faces. Whereas ventral striatum activity is often implicated in processing rewards, the amygdala is more active when participants process emotions on faces. Specifically, viewing fearful faces is associated with more activity in the amygdala, and the neural response in the amygdala when viewing fearful faces peaks in mid-adolescence (Guyer et al., 2008), although more amygdala activity is sometimes found for happy faces as well (van den Bulk et al., 2013), and results depend on sex. A longitudinal study including girls and boys in a narrow age range carefully tested for pubertal-specific changes over a period of 2 years (girls were 11–12 years to 13–14 years, and boys were 12–13 years to 14–15 years) by measuring pubertal hormones testosterone from saliva (Spielberg et al., 2015). Participants performed a standard face-matching task where faces could be fearful or neutral. Longitudinal comparisons showed that larger increases in testosterone levels were associated with larger increases in activity in both the amygdala and the ventral striatum when observing fearful faces in boys and girls. Those adolescents who showed stronger increases in ventral striatum activity also showed stronger activity increases in the amygdala, suggesting that both fear and reward feelings may be involved at the same time when processing facial expressions. In another longitudinal study, it was found that the correlation between puberty, as assessed with PDS self-report, and amygdala activity when viewing fearful faces is stronger in emerging puberty (10-year-olds) than in later puberty (13-year-olds) (Moore et al., 2012), which could suggest that puberty has the largest effects at the early phases. Two other studies showed that activity in the amygdala decreases with more advanced puberty, as assessed with PDS or Tanner report, when processing neutral faces compared with a control condition (Ferri, Bress, Eaton, & Proudfit, 2014; Forbes, Phillips, Silk, Ryan, & Dahl, 2011). One interpretation of these findings is that with more advanced pubertal development adolescents show more neural dissociation in the amygdala for emotional and neutral faces. It is not yet understood why effects are in some studies observed for fearful faces and in other studies for neutral faces. This question should be addressed in more detail in future studies. Interestingly, the positive correlation between puberty, as measured with the PDS self-report measure, and amygdala activation was also observed for neutral faces signaling social rejection (relative to neutral faces signaling acceptance) (Silk et al., 2014), suggesting that amplified effects of facial cues are not only observed for direct emotions but also for signals of rejection.

Emotional faces can also have an impact on how individuals control thoughts and actions. Two studies have examined how adolescents control these emotions, and how this is associated with pubertal development. In the first study, the researchers examined how male and female participants resolved incongruent information by showing incongruent or congruent emotional labels on happy and fearful faces (Cservenka, Stroup, Etkin, & Nagel, 2015). Puberty was measured using PDS self-report and testosterone levels from saliva. Higher levels of testosterone were associated with reduced activity in several cortical and subcortical regions. Given that these changes were found in both cortical and subcortical regions, it was not yet clear whether more advanced puberty was associated with either a delayed or advanced ability to control emotions. More directional evidence for an effect of testosterone on control was obtained in a second study (Tyborowska, Volman, Smeekens, Toni, & Roelofs, 2016). This study included 14-

year-old male and female participants with varying levels of pubertal development, as assessed with PDS self-report and testosterone levels from saliva, who performed an approach/avoidance task where they were instructed to approach happy and avoid angry faces (congruent condition) or avoid happy faces and approach angry faces (incongruent condition). Adolescents of both sexes who had higher testosterone levels showed more activity in the anterior prefrontal cortex for the incongruent condition. In contrast, adolescents who had less testosterone showed stronger activity in the amygdala for incongruent trials. These findings were interpreted to suggest that pubertal maturation shifted activity from limbic affective activity (amygdala) to more prefrontal control activity (anterior prefrontal cortex).

Social-cognitive emotions. The prior studies focused on the processing and control of basic emotions, but an important change in adolescence is also the development of processing social-cognitive emotions. Two prior studies examined the role of pubertal development on social-cognitive emotions. In the first study, participants performed a social-cognitive emotions task where they read sentences about social or neutral events (Goddings, Heyes, Bird, Viner, & Blakemore, 2012). Prior research already demonstrated that reading social sentences results in robust activity in the social brain network, including the dorsal medial prefrontal cortex (DMPFC), anterior temporal lobe (ATL), precuneus and superior temporal sulcus (Blakemore & Mills, 2014). To test if pubertal development is related to advanced activity in these areas when reading social sentences, girls between ages 11–13 years performed the task while in the MRI scanner, and puberty was assessed using PDS self-report, and testosterone and estradiol from saliva. Interestingly, some brain regions were more sensitive to age-related differences, such as activity in DMPFC, but not to puberty differences. Only activity in the ATL was correlated with hormones, such that higher levels of testosterone and estradiol were associated with more activity in the ATL. These findings suggest that pubertal development may advance neural-cognitive development in important social brain regions.

A second social processing study combined the Jackpot gambling task with giving feedback about social ranking relative to other players (Op de Macks et al., 2017). This study included the same 11- to 13-year-old female participants (n = 58) as in the study without social rank (Op de Macks et al., 2016), and puberty was assessed using PDS self-report, and the hormones testosterone and estradiol measured from saliva. The social rank feedback was found to result in activity in the insula, and this was more pronounced for girls with higher estradiol levels. Insula activity is also often implicated in social and affective processing, and puberty may drive these changes as well (Dalgleish et al., 2017; van Leijenhorst et al., 2010). Future studies are necessary to test these hypotheses longitudinally.

Two final studies examined the role of puberty in processing self-relevant emotions. Processing information about self is also a highly important task in adolescence that has only been examined in a few studies. In the first longitudinal study, male and female participants read sentences with positive and negative self-descriptions (Pfeifer et al., 2013), and puberty was measured using PDS self-report. Participants of both sexes who advanced more in pubertal status over time also showed stronger increases in VMPFC activity over time. A similar effect was found in a second longitudinal study in which male and female participants were included at age 10 and 13 years (Masten, Eisenberger, Pfeifer, Colich, & Dapretto, 2013), and again puberty was measured using PDS self-report. In this study, participants witnessed exclusion of another peer, which is often associated with increased activity in DMPFC. Participants who were more advanced in puberty showed stronger recruitment of the DMPFC, although the sample size of this study was small, so the results need to be replicated in future studies. These findings may suggest that participants who are more advanced in puberty may be more mature relative to their age-matched peers, but the exact role of DMPFC activity in terms of development is not yet well understood.

In conclusion, current fMRI studies provide evidence for some changes in neural activity that are contemporaneous with pubertal changes and could indicate puberty-related effects on neural activity, but the literature is mixed and, importantly, some published studies show no neural changes despite changes in pubertal status. Some research suggests that pubertal hormones may amplify neural reactivity to emotional stimuli, and other studies suggest that pubertal development accelerates neural development. Very few studies made the direct link with behavior (but see Op de Macks et al., 2016) or statistically compared sexes, which are important directions for future research. Further directions for future research are to carefully

control for menstrual cycle (see Braams et al., 2015), to include both self/other report and hormones levels as pubertal indices, and to include both sexes in all studies. These studies may indicate whether pubertal development has reorganizing or accelerating effects on brain development.

Sex differences in puberty-related neural activity. Across development, brain function is remarkably similar in the sexes, but there is converging evidence for differences in several domains important to adolescent development that may be related to puberty (Beltz et al., 2013; Cosgrove et al., 2007; Giedd & Denker, 2015; Paus et al., 2017). These differences have the potential to elucidate or contextualize puberty effects on brain function reviewed above. For example, sex differences in adulthood can mark equifinal or multifinal endpoints of puberty-related trajectories (Cicchetti & Rogosch, 1996). It would also be reasonable to expect that a behavior or aspect of brain function that shows a female-advantaged sex difference in adolescents or adults would be linked to estrogen increases or low levels of androgens at puberty.

Sex differences are not unilaterally found, complicating the interpretation of studies in which sex differences are detected (reviewed in Beltz et al., 2013; Cosgrove et al., 2007; Giedd & Denker, 2015; Paus et al., 2017). It is important to note, however, that many studies do not explicitly examine sex differences and are not adequately powered to detect them, especially when they interact with other study effects (e.g., puberty), and that gender should only be used as a covariate when it is not related to the independent variable (Miller & Chapman, 2001), which is an oft-violated assumption in the puberty literature.

Reward processing develops in adolescence, and sex differences in it have also been reported in adults. For example, during an fMRI incentive delay task, men showed more extensive monetary reward-related activation in the putamen (part of the striatum) than did women, but women showed greater social reward-related activation in the putamen than did men (Spreckelmeyer et al., 2009). As reviewed above, pubertal testosterone is related to reward processing in this region for both boys and girls, potentially highlighting the importance of adrenarche for girls (as most ovarian androgens are converted to estradiol) and both adrenarche and gonadarche for boys, with this combined influence contributing to sex differences that persist into adulthood. Sex differences are not always found in adolescence or adulthood, though, and this might be due to the nature of the reward (e.g., monetary or social) or size of the sample, as some studies are too small to examine the effects of sex.

Emotional processing (e.g., using a faces paradigm) also develops in adolescence, and there is evidence for sex differences in adulthood. A recent meta-analysis revealed greater activity in the amygdala and periaqueductal gray matter for women than for men, and greater activity in the insula and (medial) prefrontal cortex for men than for women (Filkowski, Olsen, Duda, Wanger, & Sabatinelli, 2017). Results from another meta-analysis, homing in on left amygdala activation and emotional valence, showed a sex difference favoring women during negatively valenced visual cues, but a sex difference favoring men during positively valenced visual cues (Stevens & Hamann, 2012). Converging evidence for puberty-related sex differences has yet to emerge with respect to emotional processing. This may be due to limited work on pubertal estradiol (testosterone has been the focus to date) and amygdala laterality. It is also possible that effects are not mediated by sex during pubertal development and that differences seen in adults emerge after puberty.

Finally, cognition develops in adolescence, and some sex differences have been reported in spatial tasks favoring boys and men, and in verbal tasks favoring girls and women across development (reviewed in Beltz et al., 2013; D. F. Halpern, 2013). In spatial tasks, both men and women show significant parietal activation, but women show frontal lobe activation that men do not, potentially compensating for their average poorer performance (Beltz et al., 2013). In verbal tasks, both sexes strongly recruit left temporal regions, but women additionally show right hemisphere activation, perhaps owing to their bilateral language representation facilitated by a larger corpus callosum (Beltz et al., 2013). Functional neuroimaging work linking pubertal development to adolescent cognition irrespective of social influences is scarce. This is an area ripe for future research, given other puberty-related brain changes and a growing literature on sex hormone influences on cognition throughout the lifespan (Beltz et al., 2013).

The Role of Puberty in Brain Connectivity

In the previous sections, we focused on the role of puberty and/or pubertal hormones in structural and functional development of the brain. Although structural connectivity has long been an area of investigation, human neuroscience over the past

decade has demonstrated that our brain operates via functionally interconnected networks (for review see, e.g., Vértes & Bullmore, 2015) and a growing number of studies have shown that functional connectivity—the temporal relation between distant neurophysiological events—provides important insights into the organization of the human brain: that is, how regions are interconnected together and how efficiently regions communicate with each other (Bullmore & Sporns, 2009; van den Heuvel & Hulshoff Pol, 2010). Deficits in structural and functional connectivity are implicated in neuropsychiatric illnesses with a typical onset during puberty (Ladouceur, Peper, Crone, & Dahl, 2012), such as depression (Zeng et al., 2012) and schizophrenia (Bohlken et al., 2016), such that lower connectivity is found in these illnesses as compared with healthy controls. As sex hormones are able to influence connectivity directly through affecting myelination (Melcangi, Magnaghi, Galbiati, & Martini, 2001), it renders brain connectivity an important biological target to examine in relation to the sex hormonal increases during puberty (Juraska & Willing, 2017; Peper, van den Heuvel, Mandl, Hulshoff Pol, & van Honk, 2011).

Structural connectivity. Communication between brain regions is accomplished by axonal pathways making up the structural white matter of the brain. Histological work has shown that myelination of these axonal pathways increases well into adolescence (Huttenlocher, 1990), findings which have been replicated by neuroimaging studies using diffusion weighted imaging (DWI) (Jones, 2010; Le Bihan & Johansen-Berg, 2012). Two key metrics that can be derived from DWI to study the quality (or integrity) of white matter connections are fractional anisotropy (FA), which measures the directionality of the diffusion profile of water molecules, and mean diffusivity (MD), which reflects the rate of water diffusion independently of the directionality and is thought to represent axonal coherence (Jones & Cercignani, 2010). Longitudinal DWI studies have reported decreases in MD during childhood and adolescence, which might be interpreted as increases in the size/density of axon bundles, myelin, and/or number of cells, as well as increases in FA with age (Bava et al., 2010; Lebel & Beaulieu, 2011; Simmonds, Hallquist, Asato, & Luna, 2014; Wang et al., 2012), suggesting greater myelin and/or fiber organization. Moreover, male adolescents have been reported to exhibit higher MD and FA within white matter tracts than adolescent females (Schmithorst & Yuan, 2010). Other structural connectivity metrics and recent studies on the volume of interhemispheric commissures show enhanced *inter*hemispheric communication for girls and women, but enhanced *intra*hemispheric communication for boys and men (Beltz et al., 2013; Dubb et al., 2003; Ingalhalikar et al., 2014; Luders et al., 2004) (but for an exception, see Bishop & Wahlsten, 1997). These contradictory findings demonstrate the need for multimodal imaging methods, as structural connectivity metrics derived from DWI do not necessarily correspond to functional communication across white matter fiber bundles. Moreover, the effect of sex on the variability of white matter connections remains to be unraveled.

A study focusing specifically on the relation between pubertal developmental stage (self-reported Tanner stage) and white matter connectivity reported higher white matter integrity in major fiber bundles in postpubertal adolescents compared with mid-pubertal adolescents while correcting for chronological age (Asato, Terwilliger, Woo, & Luna, 2010). More recently, within an age-restricted sample of 12- to 16-year-old males, it was found that both chronological age and pubertal stage explained the maturation of white matter microstructure (Menzies, Goddings, Whitaker, Blakemore, & Viner, 2015).

Studies examining the association between DWI quantification of white matter microstructure and pubertal hormones directly are scarce. The first study—carried out in 10- to 16-year-old boys and girls—found a decrease or increase in FA depending on the hormone and the direction of sexual differences in that particular white matter tract: positive testosterone-FA-related associations were found in tracts where males have higher FA than females, whereas positive estradiol-related FA associations were found in tracts showing higher FA in females (Herting, Maxwell, Irvine, & Nagel, 2012). Moreover, in a cross-sectional study carried out across the full period of adolescence (8 and 25 years), a positive correlation was reported between testosterone and MD in subcortico-subcortical and frontotemporal tracts in males. In females, a similar positive correlation between testosterone and MD in subcortico-temporal white tracts was found, as well as a negative correlation between testosterone and FA in subcortico-frontal tracts (Peper, De Reus, Van Den Heuvel, & Schutter, 2015). However, a negative correlation between testosterone in males and MD across multiple white matter pathways was reported as well (Menzies et al., 2015), but this analysis was uncorrected

for age. The latter study did not observe an association between estradiol or DHEA and white matter microstructure.

Others studied the contribution of pubertal testosterone to axonal properties of the corticospinal tract (CST) (Pangelinan et al., 2016), the thickest fiber bundle of the brain. They found that in males, but not females, testosterone was associated with age-related increases in white matter structure of the CST, such that testosterone increased age-related reductions in white matter intensity within the CST. By combining several imaging modalities, the authors hypothesized that testosterone is not affecting myelination, but rather the axonal diameter and/or axonal coherence (Pesaresi et al., 2015).

Taken together, studies investigating white matter connections and pubertal hormones directly are still limited. However, first evidence provides some support for the hypothesis that estradiol and particularly testosterone are related to the microstructure of white matter and that pubertal development may be associated with the maturation of white matter connectivity on top of just chronological age. To truly address the issue of accelerated (or arrested) development of structural connectivity due to the increased production of pubertal hormones, longitudinal studies are warranted enabling the study of individual change.

Functional connectivity. Recent review articles have addressed the normative development of functional brain connectivity across development (Grayson & Fair, 2017; van Duijvenvoorde, Achterberg, Braams, Peters, & Crone, 2016). In brief, compared with adults, children and adolescents show diffuse patterns of functional connections and mostly short-range connectivity, whereas adults seem to exhibit a more focal pattern of functional connectivity and long-distance connections. In addition, during adolescence fine-tuning of connections between subcortical and cortical prefrontal and limbic circuits takes place (Ernst, Pine, & Hardin, 2006; Somerville, Hare, & Casey, 2011), which is hypothesized to underlie the adolescent increased capacity for behavioral control (Casey, 2015).

Functional brain connections have also been examined in the context of sex hormones. In adults, it has been shown that testosterone administration disrupts subcortico-cortical functional connectivity (Bos et al., 2016; Schutter, Peper, Koppeschaar, Kahn, & van Honk, 2005; van Wingen, Ossewaarde, Backstrom, Hermans, & Fernandez, 2011); therefore, it might be argued that functional connections are affected during the rapidly changing hormonal milieus occurring at puberty. There are consistently reported sex differences in large-scale resting state brain networks, particularly for greater default mode network (DMN) connectivity in women than in men. The DMN involves—but is not limited to—the posterior cingulate cortex, the medial prefrontal cortex, the angular cortex hippocampus, and precuneus, brain areas associated with mentalizing and memory. Also, greater resting state connectivity is reported in visual and dorsal attention networks in men than in women (Biswal et al., 2010; Filippi et al., 2013).

One of the first studies linking puberty to functional brain connectivity carried out in 11- to 13-year-old girls reported that a more advanced pubertal stage, measured using physician-assessed Tanner stage, was associated with heightened functional connectivity between the dorsomedial prefrontal cortex (DMPFC) and the left anterior temporal cortex (ATC) during social relative to basic emotion processing, independent of chronological age (Klapwijk et al., 2013). Moreover, increasing estradiol levels were correlated with increased functional connectivity between the DMPFC and the right temporoparietal junction (TPJ) during social relative to basic emotion processing, corrected for age (Klapwijk et al., 2013). These findings suggest that advanced pubertal development is specifically related to socially relevant information processing.

More recently, amygdala-OFC functional connectivity was investigated in a longitudinal study of puberty-matched girls and boys (on average 11 and 12 years, respectively) (Spielberg et al., 2015). It was found that a larger increase in testosterone over time was related to a larger "decoupled" functional connectivity between the OFC and amygdala, which in turn was associated with increased threat reactivity. In a larger age range (8–25 years), the same functional connection between the OFC and amygdala was targeted (during rest) and related with testosterone levels in boys (Peters, Jolles, Van Duijvenvoorde, Crone, & Peper, 2015). This study also confirmed decreased functional coupling between subcortical (amygdala) and cortical (OFC) brain areas with higher testosterone levels. Furthermore, Peters et al. (2015) reported that reduced amygdala-OFC connectivity was related to increased alcohol intake, but only in boys.

In summary, studies into the association between pubertal hormones and brain connectivity are scarce. The few studies that have been carried

out provide some limited evidence for a potential role for puberty in microstructural development of white matter, although this depends on gender and anatomical tracts, and functional connectivity, with estradiol associated with increased cortico-cortical functional connectivity, and testosterone with decreased subcortico-cortical connections. As functional and structural connectivity are to a substantial extent correlated (van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009), it remains challenging to integrate the puberty-related findings. Normative developmental neuroimaging studies in humans generally report a better integration of structural and functional connectivity across adolescence (Bos et al., 2016; Fair et al., 2009; Sripada, Swain, Evans, Welsh, & Liberzon, 2014). Although these data—in combination with animal work demonstrating the neurotrophic effects of hormones—could reflect that pubertal hormones contribute to these developmental effects in brain connectivity in humans, to date evidence to support or refute this hypothesis remains lacking.

Future research should focus on whole brain approaches such as connectomics (i.e., the study of all connections in the brain and its general topological organization) (Wierenga et al., 2016) to get a better understanding of the global aspects of hormone-related influences on general brain architecture. For example, as all connections in the brain contribute to network topology, even small changes in white matter may have large effects on the characteristics of the network as a whole. Recent advances in network analysis now allow us to examine such aspects of network organization (Wierenga et al., 2016).

DISCUSSION AND FUTURE DIRECTIONS

Overall, this review reveals a mixed literature concerning the role of puberty in the development of the adolescent brain. Evidence from animal studies reveals that puberty has effects, some sex-specific, on development of different brain regions. Furthermore, manipulation of pubertal hormones in animal models has shown that delaying or preventing puberty impacts brain development. Although the number of studies investigating the relationship between puberty and different aspects of human brain development has increased in the past few years, this review demonstrates that there continues to be limited data across neuroimaging domains, and the data available are not always consistent. While a number of studies in this review have reported correlations between pubertal measures and indices of structural and functional brain development, differences in pubertal indicators and measurement methods, together with different MRI analysis strategies and outcomes of interest, limit comparison of the results and replication of findings. Evidence from longitudinal structural brain development studies suggests that the relationship with puberty is likely to be nonlinear and interactive with age and sex. There is evidence for both cortical and subcortical structural development associated with pubertal maturation, but further studies are necessary. Pubertal hormones may amplify neural reactivity to emotional stimuli and accelerate neural development, but the functional imaging literature reports mixed findings that focus on testosterone and evidence for a link with real-life behavior has rarely been included as an outcome in studies. Structural connectivity data suggest a possible role for puberty in microstructural development, and there is some early data linking puberty to functional connectivity but studies on connectivity and puberty are particularly scarce, and it is therefore not possible to draw any strong conclusions on these associations.

Within the structural and functional literature, the mixed results reported are most likely due to limitations of current methodologies to assess pubertal hormones and pubertal status, and inconsistency in study design and methodology used in studies. First, there is a high correlation between age and pubertal development. To accurately assess the unique contribution of pubertal development, studies should have sufficient power to detect the differences between variability attributed to age and puberty. Two main strategies to achieve this are either to recruit participants within a very narrow age range who exhibit a range of pubertal development (e.g., Forbes et al., 2010; Op de Macks et al., 2011) or else to include a sufficiently large sample that age and puberty can be disentangled using statistical methods (e.g., Goddings et al., 2014; Herting et al., 2014). Each of these strategies has been employed in some of the studies discussed in this review, and each has different advantages depending on the research question. For many of the studies included in this review, however, puberty and age are confounded due to relatively small sample sizes with a wide age range, particularly in functional magnetic resonance imaging (fMRI) studies which are costly to perform, limiting numbers of participants, and the power of current samples is often low.

The need for large longitudinal studies is recognized throughout this review, and funding for at

least two large-scale longitudinal studies has recently been awarded to the Human Connectome Project in Development (HCPD) and the Adolescent Brain Cognitive Development (ABCD) projects. HCPD is an extension of the Human Connectome Project, which is a project for which normative data from a large sample of typically developing adults was selected. The HCPD aims to collect data from a large sample of developing youth. This sample is a reflection of the population in the United States and will have similar spread in variables such as socioeconomic status and race. The HCPD aims to investigate structural and functional changes in the developing brain, and as part of this project multiple measures of pubertal development will be collected. ABCD is the largest long-term study of brain development and child health in the United States, aiming to recruit 10,000 children aged 9–10 years from across the United States who will be followed through to young adulthood. Among the multitude of measures to be collected will be both physical and hormonal pubertal indicators as well as both structural and functional MRI imaging. These data sets will provide a wealth of information to answer questions regarding the unique contributions of age and puberty to brain development, as well as to significantly add to the literature investigating sex differences in the brain. Furthermore, the large amount of neuroimaging information being gathered in these studies will hopefully allow different modalities to be included within the same analyses to help elucidate how structural, functional, and connectivity changes during adolescence and puberty may covary, and how these relate to real-life behaviors. In addition to these large-scale projects, it is important to recognize the value in smaller (but adequately powered) studies specifically designed to look at pubertal maturation and more specific, evolving questions of brain development. These two methodologies should be considered complementary and mutually necessary to improve our understanding of adolescent brain development.

Puberty is a complex process, and there is high variation across people in timing, tempo—that is, how long it takes an individual to complete puberty once started—and hormone levels, since exact hormone levels can vary across subjects within the same pubertal stage. To date, the majority of studies investigating puberty and brain development have focused on pubertal timing, that is, comparing brain metrics between individuals at different stages of puberty. This focus may, in part, result from the challenges for study design, particularly cross-sectional study designs that measure hormone levels just once, and which are unable to assess changes in hormone levels or tempo of pubertal development. Large-scale longitudinal studies like those described above can help investigate other potentially important aspects of puberty, including the impact on brain maturation of undergoing pubertal changes over a longer or shorter duration than one's peers or of experiencing puberty out of sync with one's peers. These effects may not be static with age, that is, experiencing relatively early pubertal onset could potentially lead to differential brain maturation in early adolescence, and these may persist over time, or others may "catch up" as they also experience puberty. Variations in pubertal timing and tempo are not seen in commonly used animal models. Understanding these nuances of pubertal variation is crucial for the field to better elucidate relationships between pubertal and neural development.

Measuring pubertal development continues to present a challenge to those researching the phenomenon. Self-report measures of puberty are variable in their accuracy and measure the outcome of long-term systemic hormonal effects, limiting how well results can be interpreted in terms of potential mechanisms causing change. The advent of techniques to accurately measure hormone levels through saliva or urine samples in addition to serum means that these data are being more commonly used in studies of pubertal development. However, the levels of hormones detected in these samples could differ from intracranial hormone levels, and to our knowledge, little work has been undertaken to assess the correlation between circulating and intracranial hormonal concentrations. To complicate matters further, there is no single agreed testing protocol to test hormones, and published studies have followed different guidelines. This is problematic given that it is known that hormones fluctuate during the day and there is variation in hormone levels within participants between days. This is particularly a feature of estrogens and progestagens although there is also diurnal variation in androgen hormones (e.g., Plymate, Tenover, & Bremner, 1989) and may explain why relatively few studies examine estrogen effects on brain maturation, with most favoring analyses using androgens, particularly testosterone. A standardized multisample testing protocol for hormone assessments would facilitate comparison between studies and could provide data to examine the effects of cyclical sex steroid hormones. Longitudinal studies where participant hormonal levels are measured

throughout puberty could again be used to address some of these challenges, giving invaluable information on individual developmental trajectories.

It is important, however, not to focus solely on hormonal measurements as indicators of pubertal development as they fail to capture, even in a longitudinal design, the physical and psychosocial aspects of puberty that make it a defining event in the human life course. While some of the physical aspects are captured in using the self-report measures described above, many of the studies discussed in this review and available in the literature overlook how the psychosocial consequences of puberty may influence the developing brain. Across many societies, physical appearance, body image, gender stereotypes, and prejudices continue to influence how we are perceived by ourselves as well as by our peers, our families, and wider society, and the onset of puberty may limit or expand the opportunities available to us. For example, in females, early pubertal maturation compared with one's peers is associated with an earlier engagement in dating, earlier initiation of sexually intimate behaviors, and greater likelihood to become involved with older boyfriends (see Mendle, Turkheimer, & Emery, 2007 for review). In turn, having an older romantic partner has been associated with participating in risk behaviors (C. T. Halpern, Kaestle, & Hallfors, 2007). Psychosocial mechanisms to explain the relationship between relative pubertal timing and emerging mental health pathologies including depression and eating disorders have also been conjectured (Mendle et al., 2007). Thus, the relationship between puberty and brain maturation may be multidirectional, with environmental exposures resulting from pubertal change leading to structural and functional brain changes. To our knowledge, this avenue has yet to be empirically investigated and would likely require a greater focus on individuals' perceptions of their own pubertal development and their psychological and social experiences in addition to more traditional quantitative and imaging metrics, as well as a comparison of these different methods.

In conclusion, there is some evidence across neuroimaging domains supporting an association between pubertal maturation and adolescent brain development, but the data are inconsistent and variable in quality and the exact role of puberty in the development of adolescent brain remains unclear. While the inclusion of accurate and standardized pubertal measures, for example, physician-assessed pubertal development or appropriately measured hormonal indicators in study design continues to be a challenge for the field, pubertal development is an important factor to take into account when doing studies on brain development as it may explain some of the age-related changes seen. There are a number of areas where more research is needed, and great potential for this research to be undertaken using emerging large longitudinal data sets incorporating reliable and valid pubertal measures (e.g., HCPD, ABCD) as well as smaller, focused studies. Broadening investigative directions to include how pubertal tempo and the psychosocial consequences of puberty may be associated with brain development during adolescence may also improve our understanding of this complex, multifaceted topic.

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