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Review

The amygdala: An agent of change in adolescent neural networks

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ABSTRACT

This article is part of a Special Issue "Puberty and Adolescence".

A unique component of adolescent development is the need to master new developmental tasks in which peer interactions become primary (for the purposes of becoming autonomous from parents, forming intimate friendships, and romantic/sexual partnerships). Previously, it has been suggested that the ability to master these tasks requires an important re-organization in the relation between perceptual, motivational, affective, and cognitive systems in a very general and broad way that is fundamentally influenced by the infusion of sex hormones during pubertal development (Scherf et al., 2012). Herein, we extend this argument to suggest that the amygdala, which is vastly connected with cortical and subcortical regions and contains sex hormone receptors, may lie at the heart of this re-organization. We propose that during adolescent development there is a shift in the attribution of relevance to existing stimuli and contexts that is mediated by the amygdala (e.g., heightened relevance of peer faces, reduced relevance of physical distance from parents). As a result, amygdala inputs to existing stable neural networks are re-weighted (increased or decreased), which destabilizes the functional interactions among regions within these networks and allows for a critical restructuring of the network functional organization. This process of network re-organization enables processing of qualitatively new kinds of social information and the emergence of novel behaviors that support mastery of adolescent-specific developmental tasks.

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Contents

Introduction

Adolescence is rapidly becoming known as a unique developmental period that has implications for important changes in cognitive, affective, and emotional behaviors as well as underlying neural circuitry

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(see Scherf et al., 2012). A central feature of adolescent development is the need to master developmental tasks that are specific to this period of development and that require the emergence of completely novel behaviors. For example, individuals transitioning through adolescence have a new interest in developing romantic and sexual partnerships with peers, in large part because of pubertal development. They also have increasing needs to form loyal friendships with peers and to become autonomous and independent from parents (Eccles et al., 1993; Steinberg and Morris, 2001). These tasks lead adolescents to enhance the primacy of peer interactions and evince a social *reorientation* toward peers (Brown, 2004; Nelson et al., 2005). This reorientation supports the emergence of social competence and high-quality friendships with peers, two developmental tasks that foreshadow the quality of adult relationships and social functioning more generally (Capaldi et al., 2001).

These aspects of adolescent development raise difficult questions about how *new behaviors emerge* from behavioral and neural systems that are becoming increasingly stable across many domains at this very same time (e.g., reasoning abilities, reaction time, immune function; see Dahl, 2004). Previously, it has been argued that the emergence of new behaviors relevant to the developmental tasks of adolescence is likely to 1) require a fundamental re-organization in the way perceptual, cognitive, affective, and motivational systems work together, 2) be reflected in changes in the functional interactions (i.e., functional connectivity) between the neural regions that support these component systems, and 3) be influenced by pubertal hormones (Scherf et al., 2012). For example, in the domain of face processing, specific developmental tasks of adolescence may induce the need to extract qualitatively new kinds of information from faces, such as the attractiveness, trustworthiness, competence, and social status of a face, particularly for peer-aged faces (see Fig. 1). This need may be instantiated neurally in the form of a concomitant functional *re-organization* (i.e., new patterns of functional interactions) among neural circuits that support and integrate perceptual, affective, and cognitive aspects of face processing. Scherf and colleagues also argued that gonadal hormones will likely increase motivational and affective inputs that modulate functional connectivity among existing visuoperceptual, cognitive, social and affective neural regions supporting face processing (see Fig. 1). In other words, they expect that the dynamical interactions (e.g., functional connections) between face processing regions are fundamentally altered as a result of the surge of gonadal hormones and the resulting new task demands for face processing in adolescence. This process fundamentally enables the

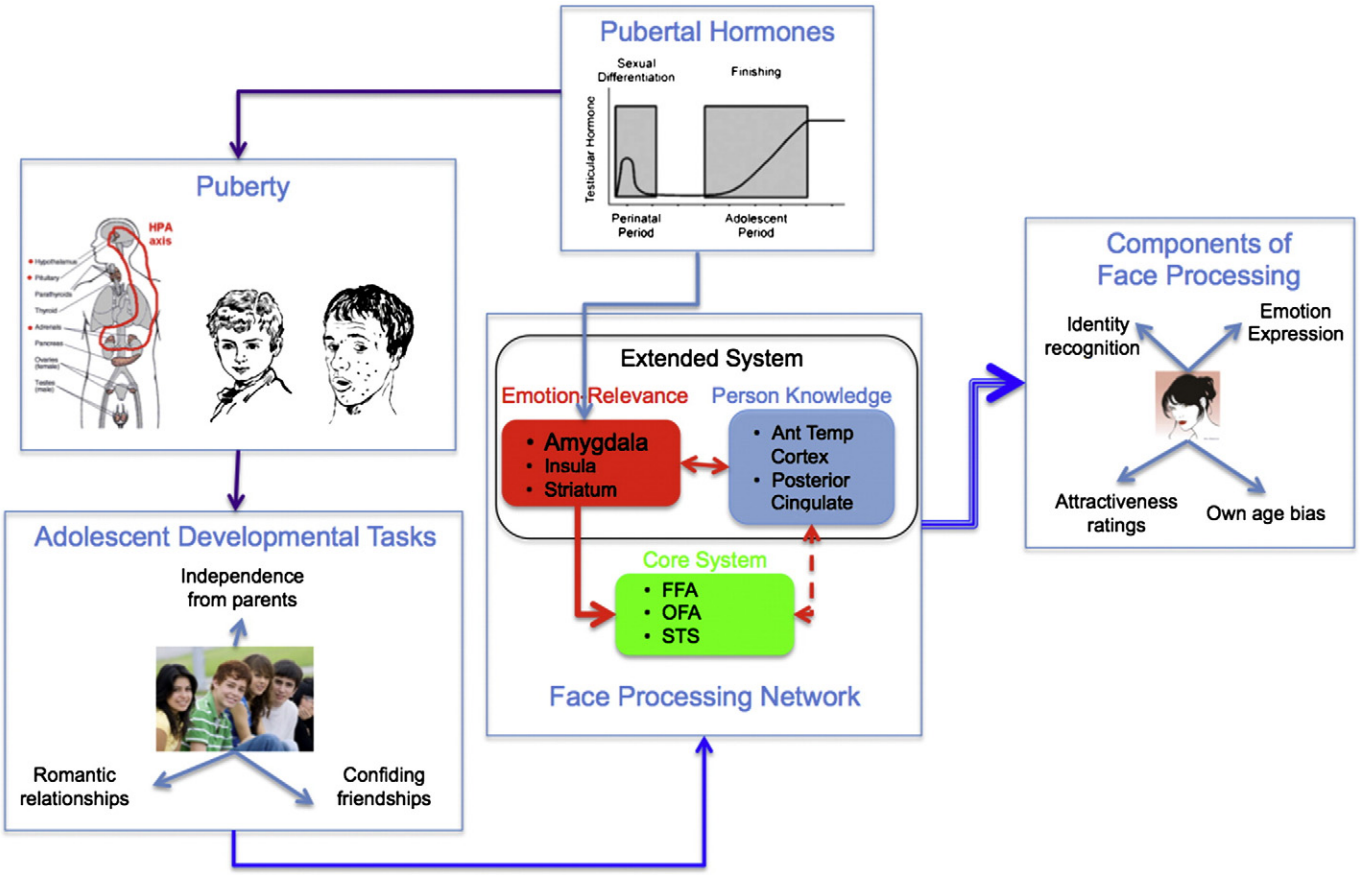

Fig. 1. A schematic representation of the Scherf et al. (2012) network-based model that emphasizes a restructuring of the dynamical interactions between existing neural regions to enable the emergence of new behaviors and particularly those relevant to the specific developmental tasks of adolescence. The model includes three hypotheses about the dynamic changes that are predicted to initiate the emergence of new social and affective components of face processing in adolescence (i.e., fine-tuned attractiveness ratings and an own-age bias in identity recognition). In Hypothesis 1 (dark purple lines), Scherf and colleagues predicted that the pubertal hormones that initiate the development of secondary sex characteristics and sexual dimorphisms in the structure of the face and brain are also likely to influence motivation to master new developmental tasks, such as developing confiding friendships and romantic relationships with peers. This is manifest in the brain as a modulation in the functioning of limbic circuitry (particularly the amygdala), which induces dynamic changes in the functional organization of many neural circuits that interact with the amygdala, including the face processing system. These developmental tasks will in turn, drive the *emergence of new social/affective components of face processing* (Hypothesis 2—blue lines). In other words, puberty induces adolescents to be socially and affectively motivated to encode new social information from faces that is related to these developmental tasks, such as the attractiveness, trustworthiness, competence, and social status of a face, particularly for peer-aged faces. Finally, in Hypothesis 3 (red lines), Scherf and colleagues argued that the dynamical interactions between neural face processing regions are fundamentally altered as a result of the surge of gonadal hormones and the resulting new task demands for face processing. Specifically, the *functional/effective connectivity*, or temporal synchrony, between regions of the face-processing network will change with the emergence of these new components of face processing in adolescence. This reorganization allows for new socially relevant information to be encoded from faces, leading to new components of face processing behavior. Reprinted with permission from Developmental Cognitive Neuroscience.

emergence of new components of face processing that are specifically relevant to accomplishing the developmental tasks of adolescence.

In this paper, we focus on the role of the *amygdala* in this process and suggest that it may lie at the heart of this functional reorganization within many of the broadly distributed neural circuits that support emerging and changing behaviors in adolescence. Our emphasis on the amygdala is motivated by several recent findings about its unique structural and functional properties. First, the amygdala is extensively interconnected with the vast majority of both cortical and subcortical regions, indicating that it participates in many distributed neural circuits (Pessoa, 2008). As a result, small changes in amygdala activation are likely to have pervasive effects on the many functional networks in which it participates. Second, recent models of amygdala function suggest that it critically modulates the determination of *subjective salience* (e.g., impact) and *relevance* of stimuli (relevance reflects the *contextual and goal-dependent value of a stimulus within a personal situation*) (e.g., Adolphs, 2010). Given that social signals take on new relevance and salience in the *behavior* of adolescents (e.g., peers), we suggest that this process is largely supported by changes in amygdala functioning and its interactions with many other neural regions (e.g., fusiform gyrus, orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex, thalamus, striatum, hypothalamus). Finally, the amygdala is one of the only neural regions in which both animal and human studies have validated the presence of estrogen and androgen receptors (e.g., Perlman et al., 2004; Roselli et al., 2001).[1] As a result, amygdala activation and functional connectivity patterns may be *directly altered* by sex hormones, which may influence the way in which the amygdala gages the salience and relevance of stimuli. *The core hypothesis of this paper is that this combination of characteristics uniquely positions the amygdala to function as an agent of change in the functional organization of neural networks, particularly during adolescence when there is a surge in sex hormones concomitant with pubertal development and there are increasing demands to process social information and behave in social contexts in novel ways.*

Importantly, although we focus on the role of the amygdala in functionally re-organizing neural networks that support behaviors relevant to the developmental tasks of adolescence, we are not suggesting that it is *solely* responsible for alterations in neural circuitry during adolescence. In fact, it is because of the vast connectivity that the amygdala exhibits with the majority of the brain that we focus on its potential contribution to these processes and acknowledge the essential nature of the functional interactions between the amygdala and many other regions to support these processes. Unfortunately, it is beyond the scope of this paper to review the functional properties and contributions of these other regions at length.[2]

To build this argument about the role of the amygdala in helping to reorganize neural networks in adolescence, we begin by describing the structural organization and hub-like architecture of the amygdala and review current models of amygdala functioning that emphasize its role in determining the relevance and significance of sensory inputs to the goals of the individual (Adolphs, 2010; Pessoa and Adolphs, 2010). Next, we review the evidence for structural and functional changes in the amygdala in human adolescents. We highlight findings that have linked pubertal maturation as a contributing factor to these changes. Finally, we emphasize how the amygdala is centrally involved in supporting several important behaviors (face processing, fear learning, stress responsivity) that change in human adolescence and that may be critical to accomplishing core developmental tasks of adolescence. These findings lay a foundation from which we can argue our central point, namely that the amygdala registers new relevance for existing stimuli, particularly social stimuli, and thereby re-weights inputs to existing neural networks. In so doing, this induces a destabilization in these networks, which allows for a critical re-organization in the functional interactions among regions within these networks. This process of network re-organization enables processing of qualitatively new kinds of social information and the emergence of novel behaviors that support mastery of adolescent-specific developmental tasks. In conclusion, we suggest additional work that will help evaluate the hypothesis that the amygdala may be an important agent of change in the organizational properties of neural networks and structure–function–behavior correspondences that specifically enable adolescents to master their unique challenges and developmental tasks.

Amygdala: structural organization and hub-like architecture

The amygdala is an almond-shaped structure in the medial temporal lobe. It is a complex of nuclei, the largest of which include the lateral, basal, accessory basal, and central nuclei (Schumann and Amaral, 2005). The amygdala is one of the most highly connected regions of the brain (Swanson, 2006; Young et al., 1994). In one analysis of structural brain connectivity, Young et al. (1994) concluded that the amygdala "occupies a position at the very geometric center of the topological map". Specifically, it exhibits a hub-like architecture in that it has extensive reciprocal structural connections with cortex and subcortical regions (Young et al., 1994). It receives inputs from visual, gustatory and visceral, auditory, olfactory, and somatosensory modalities (see Fig. 2). It also receives extensive inputs from the inferotemporal and prefrontal cortices, and has strong reciprocal connections with the regions in the medial temporal memory systems, including the hippocampus, perirhinal cortex, and entorhinal cortex.

There are also widespread reciprocal projections from the amygdala to subcortical regions including striatal, hypothalamic and brain stem regions. fMRI studies have also provided evidence of functional connections (i.e., temporal synchrony in activation patterns) between the amygdala and many of these regions to which it is structurally connected (Bickart et al., 2012; Mishra et al., 2013). This pattern of widespread structural and functional connectivity in and out of the amygdala highlights its unique position to integrate information, and particularly sensory, cognitive, and affective information (Pessoa, 2008). As mentioned previously, it also suggests that functional changes in the amygdala are likely to have widespread consequences on the network dynamics within the extensive circuitry that connects in and out of the amygdala.

In addition to functioning as a structural (and functional) hub of neural circuits in the brain, the amygdala is unique in that it is one of only a small number of regions that has receptors for sex hormones (e.g., Clark et al., 1988; Österlund et al., 1999; Perlman et al., 2004; Roselli et al., 2001; Rubinow and Schmidt, 1996). Functional neuroimaging studies have shown that sex hormones modulate amygdala activation (Bos et al., 2012; van Wingen et al., 2009) and functional connectivity between the amygdala and other regions (e.g., ventrolateral prefrontal cortex) in response to social stimuli (Volman et al., 2011). This provides support for our notion that pubertal hormones may directly influence changes in amygdala function, particularly during pubertal development, which could, in turn, impact the functional organization of the many neural networks in which the amygdala participates.

Determining relevance and significance of stimuli

Early lesion studies in monkeys and humans implicated the amygdala in processing threat- and fear-related information (Kluver and

[1] The hypothalamus and hippocampus are other such regions (see McEwen et al., 2012 for review).

[2] Many of these other important regions have been discussed in existing reviews of adolescent brain development. For example, we refer the reader to the following articles on the neural basis of changes in adolescent reward processing (Fareri et al., 2008; Galvan, 2010), face processing (Scherf et al., 2012), motivated behavior (Ernst and Fudge, 2009), cognitive control (Luna, 2009; Somerville and Casey, 2010), and risk-taking (Steinberg, 2008).

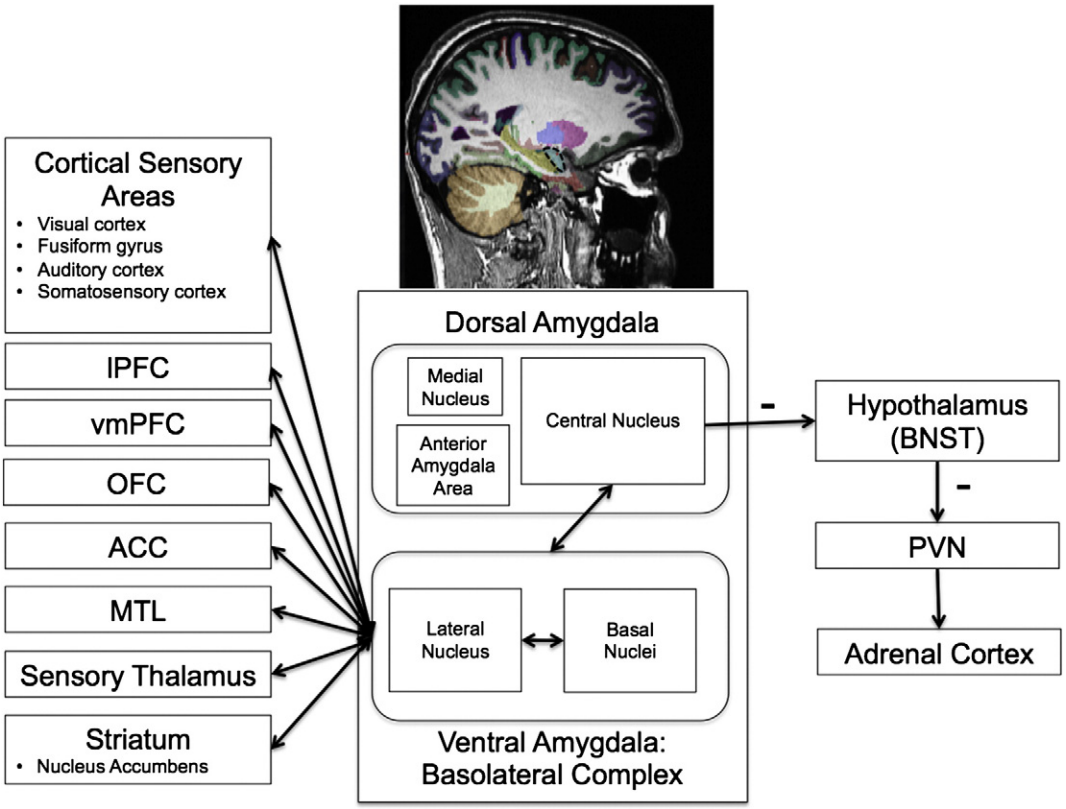

Fig. 2. Schematic diagram of the structural organization of the nuclei within the amygdaloid complex and the major structural connections in and out of the amygdala. The set of connections is not comprehensive, but does highlight the connections with other regions that are strongly implicated in supporting behaviors that change in adolescence and are related to the hypotheses in this manuscript. Abbreviations: ACC (anterior cingulate cortex), BNST (bed nucleus of stria terminalis), lPFC (lateral prefrontal cortex), MTL (medial temporal lobe), PVN (paraventricular nucleus of the hypothalamus), OFC (orbitofrontal cortex).

Bucy, 1937, 1939), but also in supporting social behavior and affiliation (Emery et al., 2001). Since those early studies, an immense literature has implicated the amygdala in a myriad of psychological processes across mammals. For example, in addition to processing negatively valenced stimuli (i.e., threat or fear related), the amygdala responds to positively valenced stimuli as well (for review see Ball et al., 2009). The amygdala also engages in responses to unpredictable and/or ambiguous stimuli (Whalen et al., 1998). For example, in both mice and humans, the amygdala is more responsive when listening to unpredictable compared to predictable streams of tones (Herry et al., 2007). These results lead researchers to emphasize the role of the amygdala in allocating processing resources toward stimuli that have more than one possible interpretation, and thus more than one prediction about subsequent events (Whalen, 2007; Whalen et al., 1998).

Recently, Adolphs (2010) and Pessoa and Adolphs (2010) have argued that these seemingly incompatible components of amygdala functioning are actually consistent with the idea that it processes the *subjective salience* (e.g., impact) and *relevance* of stimuli (relevance reflects the *contextual and goal-dependent value of a stimulus within a personal situation*). Importantly, Adolphs emphasizes a highly dynamic and context-sensitive role for the amygdala in evaluating the value of stimuli. In support of this view, he suggests that lesion and electrophysiological results in animal studies are largely consistent with the argument that the amygdala codes a continuously updated and flexibly deployed representation of stimulus value, regardless of valence. For example, selective lesions of the amygdala in non-human primates impair learning in tasks where information about stimulus value must be flexibly updated (Murray, 2007).

Using this model, we argue that the amygdala mediates a central feature of adolescent development involving a qualitative shift in the attribution of relevance and salience to existing stimuli (social stimuli in particular). For example, peer relations take on new salience as adolescents evaluate and test loyalty and develop a new interest in romantic and sexual relationships (Brown, 2004). In support of this process, we predict that the amygdala plays a central role in the process of re-evaluating and increasingly weighting the salience of peer faces and social contexts involving peers. Specifically, with the influx of pubertal hormones, the amygdala may begin to respond more strongly to peer faces, which could have downstream consequences for the functional organization of neural networks supporting motivated behavior (i.e., toward peers). Similarly, during pubertal development, the amygdala may exhibit reduced activation to social contexts that typically elicit fear in young children (e.g., physical separation from a parent), but that are no longer threatening to adolescents because of their need to become increasingly autonomous from parents. In sum, the relevance and salience of many social stimuli and contexts are changing in adolescence, which we argue, are likely to be reflected in modulations (increases and decreases) in amygdala activation. Furthermore, these modulations in activation will have pervasive downstream consequences on the functional networks in which the amygdala participates, which may have profound effects on the behaviors that these networks support.

Adolescence: structural changes in the amygdala

Structurally, the human amygdala undergoes rapid development early in life (Tottenham et al., 2009). Although the basic neuroanatomical architecture of the amygdala is present at birth in humans (Humphrey, 1968; Ulfig et al., 2003), there is continued growth of the amygdala volume through childhood and adolescence (Uematsu et al., 2012). Several recent cross-sectional studies tracked age-related changes in amygdala volume from infancy through early adulthood (Uematsu et al., 2012), childhood through adolescence (Giedd et al.,

1996; Merke et al., 2003) and childhood through adulthood (Greimel et al., 2012; Guo et al., 2007; Ostby et al., 2009). These studies consistently report that raw amygdala volumes increase into early adulthood (Greimel et al., 2012; Ostby et al., 2009) and the age-related increases are even more apparent when the raw volumes are normalized for differences in total brain volume (Blanton et al., 2012; Ostby et al., 2009). Very recently, volumetric analyses of the amygdala in 4–18 year-old healthy participants from the NIH Pediatric Database revealed a quadratic pattern of change in the raw volume of the right amygdala in both boys and girls (and in girls in the left amygdala as well), indicating peak volumes during adolescence (approximately age 14 for girls) and smaller volumes in the youngest and oldest participants (Hu et al., 2013). Importantly, the rate of growth of the amygdala volume was related to pubertal development in both boys and girls, such that after the onset of puberty, the amygdala stopped growing (i.e., increasing in volume).

This finding is consistent with earlier reports that growth in amygdala volume is specifically related to pubertal development in both boys and girls (Blanton et al., 2012; Bramen et al., 2011; Neufang et al., 2009). For example, adolescent boys in later stages of pubertal development (i.e., Tanners stages 4–5) exhibit larger amygdala volume compared to age-matched adolescents in earlier stages of pubertal development (Tanner stages 1–3) (Bramen et al., 2011; Neufang et al., 2009). Neufang et al. (2009) also found a significant relation between testosterone levels and amygdala volume in both boys and girls and concluded that it accounts for 13–15% of the variance in amygdala volume among adolescents. There is some evidence that the trajectories of increasing amygdala volume in adolescence may be sexually dimorphic, with girls beginning to show a plateau or reduction in volume sooner than boys (Bramen et al., 2011; Hu et al., 2013; Merke et al., 2003). Together, these findings indicate that the amygdala, one of the most interconnected regions of the brain, is undergoing a developmental increase in volume during the adolescent period that is importantly tied to pubertal development and gonadal hormones. Note that this pattern of changing grey matter (GM) volume in the amygdala during adolescence is fairly unique in that the vast majority of other cortical and subcortical regions are exhibiting reductions in GM volume in adolescence (see Gogtay et al., 2004). Together, these findings support our notion that the amygdala is an important region to focus investigations of adolescent brain development as well as potentially unique changes in brain–behavior correspondences that are influenced by pubertal development and that are likely to be relevant to mastering the developmental tasks of adolescence.

Adolescence: functional changes in the amygdala

In addition to structural changes, the amygdala also undergoes functional changes in adolescence. In comparison to the structural studies, there are fewer large-scale cross-sectional (or longitudinal) studies investigating changes in amygdala function from childhood through adulthood. Most of the existing studies have utilized affective faces as stimuli in functional neuroimaging (fMRI) paradigms since they are effective at activating the amygdala in adults (Morris et al., 1998; Whalen et al., 1998) and adolescents (Baird et al., 1999). As reviewed in Malter Cohen et al. (2013), there are some reports of hyperactivation in the amygdala in adolescence compared to both children and adults. For example, Hare et al. (2008) used fMRI to scan 60 participants between the ages of 7 and 32 years in an emotional expression task. Adolescents exhibited more activation in the amygdala bilaterally in response to all emotional expressions (i.e., happy, fearful, calm) than either the children or the adults. This pattern of functional changes in the amygdala mirrors reports of nonlinear changes in amygdala volume that peak in adolescence (Hu et al., 2013). Other cross-sectional studies using a similar age range of participants (e.g., 9–40 years) have also reported hyperactivation in the amygdala in older children and adolescents in response to affective faces compared to adults (Guyer et al., 2008).

Recent longitudinal fMRI studies have reported increasing amygdala activation specifically during the transition from late childhood to early adolescence and as a function of pubertal development. Pfeifer and colleagues scanned children (10 years old) transitioning into early adolescence (13 years old) as they observed affective faces (Pfeifer et al., 2011). Activation in both the right and left amygdala tended to increase across all emotional expressions during this developmental transition into adolescence. Importantly, activation in both the ventral striatum and the ventromedial prefrontal cortex significantly increased in response to the affective faces as children transitioned into adolescence as well. Recall that these regions are highly interconnected with the amygdala (see Fig. 2). The authors suggested that these changing cortical and subcortical responses to facial expressions in the transition to adolescence may reflect changing abilities to regulate affective responses to the environment.

Using this same sample, Moore et al. (2012) reported that even at age 10 when most participants were in the earliest stages of pubertal development, there was a positive correlation between stage of pubertal development and the magnitude of activation within the amygdala. The authors also reported similar relations between pubertal development and activation in the thalamus and extrastriate cortex, regions that work with the amygdala to process the salience and relevance of social signals (Adolphs, 2008). These relations between pubertal development and activation in the amygdala, thalamus, and extrastriate cortex *increased through age 13*, as participants began to enter later stages of pubertal development. The authors interpreted these findings to reflect the neural foundations of how puberty may 'reorient' adolescents toward social stimuli, such that complex emotional expressions begin to take on increased relevance in the transition to adolescence.

There are also a small number of studies that have failed to report hyperactivation in the amygdala in children and/or adolescents compared to adults during face processing tasks. However, some of these same studies failed to elicit activation in the amygdala in both the developmental and the adult groups (Nelson et al., 2003) or did not have imaging protocols that were specifically optimized to measure amygdala activation (Deeley et al., 2008; Pine et al., 2001). One study reported a decrease in activation in response to neutral faces in 11–13 year olds in later stages of pubertal development compared to age-match individuals in earlier stages of pubertal development (Forbes et al., 2011). Interestingly, the two groups produced similar amygdala activation to fearful faces. One interpretation of these data that is consistent with the core hypothesis in this paper is that faces with neutral expressions are becoming less relevant to adolescents as a function of pubertal development. In other words, as adolescents become increasingly better at discriminating and interpreting facial expressions, the neutral face may become less and less relevant and/or confusable compared to other expressions.

There is only one study, to our knowledge, that used non-face images to investigate developmental changes in amygdala functioning during adolescence. Vasa et al. (2011) tested adolescents (ages 12–17 years) and adults in a subsequent-memory paradigm. Stimuli included positively, negatively, and neutrally valenced non-face images. Participants were scanned while they rated the images along several different dimensions and the data were then sorted according to which images were subsequently remembered in the surprise memory test following the scan. Interestingly, adolescents and adults exhibited similar magnitudes of activation in the amygdala in response to the remembered negative images. In contrast, adolescents exhibited higher magnitude responses in the right amygdala than did adults in response to the remembered *positive* images. The authors suggested that this positive encoding bias in the adolescents might be related to the increased reward and novelty seeking behavior exhibited in adolescence, which in turn supports the need for

increasing autonomy and individuation. This idea is consistent with the core hypothesis of this paper regarding the role of the amygdala in re-evaluating the relevance of stimuli that are central to accomplishing the developmental tasks of adolescence.

Finally, there are a very small number of studies investigating age-related changes in the profile of amygdala functional connectivity. One study used resting-state functional magnetic resonance imaging to examine age-related variations in the intrinsic connectivity of the amygdala in children (ages 7–9 years) and young adults (Qin et al., 2012). Compared with adults, children exhibited weaker intrinsic functional connectivity between the amygdala and ventromedial prefrontal cortex (PFC), cingulate gyrus, anterior temporal pole, and subcortical structures including the caudate, putamen, midbrain and cerebellum. Furthermore, when they examined differences in the connectivity networks of amygdala subregions (basolateral amygdala versus centromedial amygdala—see Fig. 2), they found that children exhibited less differentiation and more overlap in these subregion networks than did adults. In other words, the intrinsic connectivity patterns of the amygdala become stronger and more differentiated across subregions of the amygdala in the transition from late childhood to early adulthood. The authors described these changes as "development-related reconfiguration of intrinsic functional networks" that likely "underlies the maturation of increasingly complex affective functions that typically occur during adolescence." Although the authors did not include adolescents in this analysis, the notion that there is a massive transition in the organization of the resting state amygdala functional connectivity between late childhood and early adulthood suggests that the connectivity networks of the amygdala may not be adult-like even in adolescence. Again, this notion is consistent with the core hypothesis of the current paper. However, it will be imperative to evaluate the resting state functional connectivity patterns of early and later adolescents to evaluate this claim.

Other studies have investigated developmental task-related modulations in amygdala functional connectivity, and report that 1) connectivity between the amygdala and the anterior cingulate gyrus during fearful face processing increases with age across middle childhood (5–11 years of age) but is weaker overall than in adults (Perlman and Pelphrey, 2011), and 2) amygdala–medial prefrontal connectivity actually *reverses valence* from positive to negative around age 10 (Gee et al., 2013), when adrenal androgens are reaching adult levels. This negative connectivity between the amygdala and the medial PFC remains through early adulthood, suggesting the emergence of a regulatory role of medial PFC on the amygdala. Together, these studies suggest that in addition to changes in the functional profile of activation in the amygdala, the interactions between the amygdala and many other regions are changing, in potentially qualitative ways, over the course of late childhood.

This series of studies demonstrates that there are measurable changes in the functional response of the amygdala and its functional connections from childhood to adolescence and adulthood, particularly in response to facial expressions but also to positively valenced non-face images. Generally, this includes stronger magnitude responses in adolescents than either children or adults and strengthening and differentiating of functional networks involving the amygdala. Importantly, these conclusions are largely based on findings from cross-sectional studies. Additional longitudinal work is needed to understand the full developmental trajectory of amygdala functional activation from childhood through early adulthood and to further evaluate the notion that there are *adolescent-specific* changes in such activation. For example, as we will discuss later (fear learning in adolescence), there are very few studies that specifically investigate potential *reductions* in amygdala responses as a function of adolescent development. We argue that both increases and reductions in amygdala activation can lead to wide-spread changes in the functional profile of the neural networks in which the amygdala participates. Additionally, it is critical that future studies investigate changes in the functional connectivity of the amygdala during rest and/or under task conditions in the transition from late childhood to early and later adolescence in typically developing individuals.

In the next sections of the paper, we garner support for our core hypothesis regarding the role of the amygdala in altering neural network organization during adolescence. We review evidence that several behaviors particularly relevant to the developmental tasks of adolescence are largely dependent on neural networks revolving around the amygdala, and also exhibit impressive changes over the course of adolescence. These include adolescent-specific changes in behavior and neural circuitry supporting face processing, fear learning, and physiological and psychological responses to stressors.

Adolescent changes in face processing

Faces are the pre-eminent social signal and, as adults, we seamlessly extract multiple kinds of information from face structure, such as identity, gender, age, and emotional state, even as faces change dynamically as a function of expression and speech production and vary across many transformations (i.e., changes in lighting, viewpoint, context). Additionally, people use the structure of the face to form impressions about mate potential, social status, intentions, and personality traits, like trustworthiness, approachability, warmth, power, extraversion, aggressiveness, and competence (for review, see Todorov et al., 2007). As a result, processing of faces is highly relevant to many of the developmental tasks of adolescence, and particularly those that have to do with forming more adult-like relationships with peers and beginning to form age-appropriate romantic relationships.

There is a wealth of data suggesting that face-processing abilities develop through and beyond adolescence. Although infants have early proclivities for face processing (e.g., Farroni et al., 2005) and even very young children exhibit some of the behavioral markers of adult-like face processing (e.g., Crookes and McKone, 2009), studies investigating face processing abilities of older children and adolescents suggest that both *emotional expression* recognition and *identity* recognition abilities develop long into adolescence and even early adulthood.

Explicit memory for emotional expressions improves from late childhood through adolescence (Herba and Phillips, 2004; Herba et al., 2006; Pine et al., 2004; Thomas et al., 2007). Recognition of emotional expressions also emerges slowly during childhood and may even be delayed compared to recognition of the verbal labels for the expressions (Camaras and Allison, 1985; Durand et al., 2007). Furthermore, it is not until middle childhood that individuals become fairly accurate at identifying conflicting or mixed emotional expressions and understanding display rules (Brown and Dunn, 1996).

Similarly, the ability to recognize *face identity* follows a delayed developmental trajectory beyond adolescence (e.g., Carey and Diamond, 1977; Carey et al., 1980; Diamond et al., 1983; Mondloch et al., 2004; O'Hearn et al., 2010). These results have been reported across a wide range of recognition tasks and age range from childhood through early and later adulthood. For example, O'Hearn et al. (2010) studied face recognition abilities in both typically developing children (ages 9–12 years), adolescents (ages 13–17), and young adults (ages 18–29 years) as well as in those with autism using the Cambridge Face Memory Task (CFMT). They reported large improvements in face recognition performance across the entire age range in the typically developing individuals. Similarly, Germine et al. (2011) tested identity recognition abilities using the same CFMT in more than 60,000 participants ranging in age from 10 to 70 years. Across a series of three experiments, they consistently found that the peak age of performance for face recognition was approximately 30 years of age, which was contrasted with a peak age of recognition for inverted faces and words at 23 years of age. In sum, there are a large number of cross-sectional behavioral studies that converge on the conclusion

that face-processing abilities improve through (and even beyond) adolescence.

Interestingly, there is also evidence that the developmental trajectory of face expression and identity recognition abilities is actually *temporarily disrupted* during adolescence, especially during puberty (Carey et al., 1980; Diamond and Carey, 1977; Diamond et al., 1983; Flin, 1980; Lawrence et al., 2008; McGivern et al., 2002). The initial study to report this temporary disruption in face-processing skills during pubertal development tested children and adolescents (8–16 years) in a face identity recognition task (Diamond et al., 1983). Diamond and colleagues identified a stasis in face identity recognition, with an actual decline in performance at age 12. In two follow-up studies, they evaluated the contribution of pubertal status to performance differences on the same face identity task in more than 200 girls ages 10–14 years. Across both studies, the authors found that girls in the midst of pubertal change make more errors in the face identity task than do pre- or post-pubescent girls (Diamond et al., 1983). The researchers suggested that this adolescent-specific disruption in face processing skills may be directly tied to gonadal hormonal changes that influence the neural substrate for face processing.

The neural substrate of face processing in adults is widely distributed and includes a set of "core" visuoperceptual regions (i.e., fusiform face area [FFA], occipital face area, posterior superior temporal sulcus) as well as a set of "extended" regions that include the amygdala, posterior cingulate cortex, anterior temporal lobe, striatum, insula, and ventromedial prefrontal cortex (see Fig. 3a) (Gobbini and Haxby, 2007). The overwhelming majority of studies investigating developmental changes in the neural basis of face processing have focused on the amygdala in expression tasks or the posterior "core" regions during recognition tasks. As reviewed above, many studies have reported that amygdala activation increases from childhood to adolescence during emotion expression tasks (e.g., Guyer et al., 2008; Hare et al., 2008; Moore et al., 2012; Pfeifer et al., 2011). Similarly, the neuroimaging studies measuring age-related changes in the "core" face processing regions converge on the finding that children younger than 8 years of age, as a group, do not consistently activate the FFA. Furthermore, they consistently report that the transition between childhood and early adolescence is important for the emergence of adult-like face-related activation in core face-processing regions (Aylward et al., 2005; Gathers et al., 2004; Golarai et al., 2007, 2010; Joseph et al., 2011; Passarotti et al., 2003, 2007; Peelen et al., 2009; Scherf et al., 2007, 2012). One study also reported a correlation between face recognition behavior and activation patterns in these core regions in adolescents (Golarai et al., 2010). Importantly, none of these studies has explained the neural basis of the reported temporary disruption in face recognition skills during pubertal development.

There are two recent studies that evaluate developmental changes in the functional connectivity within the broader face processing system (Cohen Kadosh et al., 2011; Joseph et al., 2012). Each of these studies uses different analytic approaches (dynamic causal modeling and graph-theory approach respectively) for evaluating age-related changes in functional connectivity in children and adults. In addition, Joseph et al. (2012) also included young adolescents. Both studies reported age-related changes in the global patterns of functional connectivity within the core (Cohen Kadosh et al., 2011; Joseph et al., 2012) and extended (Joseph et al., 2012) face processing regions. For example, Joseph et al. (2012) reported that during face viewing, the connectivity patterns among the face-processing network exhibited a significant "reorganization" across age that involved both integration and segregation of nodes within and across sub-modules within the larger face-processing network. In other words, the nodes of the face-processing network were grouped into different sub-networks at different ages, with adults exhibiting fewer, more integrated sub-networks. Unfortunately, neither of these connectivity studies included the amygdala as a node in their network analyses. However, the results are consistent with the idea that there are large-scale age-related re-configurations in the functional organization of the nodes within the broader face-processing network.

Previously, it has been argued that more social aspects of face processing, like the ability to evaluate attractiveness, trustworthiness, social status, and dominance are likely to emerge in adolescence (Scherf et al., 2012). The amygdala is largely implicated in many of these social components of face processing (Todorov et al., 2013). Importantly, there are no behavioral or neuroimaging studies (to our knowledge) that evaluate developmental changes in the amygdala-mediated social components of face processing, which may be central to the developmental tasks of adolescence. Furthermore, Scherf and colleagues predicted that, with increasing pubertal development, stronger inputs from the amygdala will ultimately support these new social components of face processing, which may in turn disrupt the existing coordination among regions that compute visuoperceptual and cognitive components of face processing like identity recognition (Scherf et al., 2012). Herein, we extend this argument to suggest that pubertal hormones might directly alter amygdala functioning, enabling the emergence of these more social components of face processing, which would lead to stronger connectivity from the amygdala to the FFA during socially oriented face processing tasks (e.g., judging attractiveness of a face), and potentially weaker functional connectivity among the core face processing regions during recognition tasks, particularly when the recognition tasks are executed in the context of affective or highly socially relevant (e.g., very attractive peer) faces. This pattern of results would help explain the previous findings of a behavioral disruption in face recognition abilities with pubertal development. An evaluation of this hypothesis will require future studies investigating developmental changes in 1) the nature of the face-related computations that are mediated by the amygdala and FFA (using fMRI-adaptation paradigms—see Scherf et al., 2012) and 2) modulations in the functional and effective connectivity between the amygdala and fusiform gyrus and other face processing regions as children, adolescents at varying stages of pubertal development, and adults view faces in a variety of tasks that modulate the relative social demands of face processing. This kind of approach may provide a unique opportunity to evaluate the potentially critical role of the amygdala in affecting whether and how functional reorganization occurs among broadly distributed neural networks in adolescence.

Changes in adolescent fear learning

There is a drastic increase in risk-taking behaviors in adolescence (see Dahl, 2004), suggesting that the processing of potentially fearful stimuli and contexts may be altered in at this time developmentally. Importantly, changes in fear learning may be central to the developmental tasks of adolescence. Consistent with this notion, adolescents do exhibit an increase in novelty- and sensation-seeking behaviors, which might reflect weaker aversive conditioning (i.e., imbuing neutral stimuli with negative value; Ernst et al., 2011), that arguably facilitates the learning of new skills for initiating new kinds of romantic and sexual relationships (Crone and Dahl, 2012). We evaluate the evidence in support of the notion that fear learning and extinction, which are largely mediated by a distributed neural circuit that centers around the amygdala and its connections (LeDoux, 2007) (see Fig. 3b), are altered during adolescence.

From an evolutionary perspective, fear has an important and adaptive function: to get an organism to predict potentially negative outcomes and prepare itself for escape. Fear learning is usually studied in the laboratory using Pavlovian classical conditioning paradigms (Pavlov and Anrep, 1927) in which a neutral event, such as a tone (the CS), is paired with an aversive event, such as a shock (the US). Over repeated CS–US pairings, the presentation of the tone alone will come to elicit a conditioned fear response (CR). Across species, the amygdala has emerged as a critical structure involved in the acquisition and expression of fear conditioning (LeDoux, 2000; Maren,

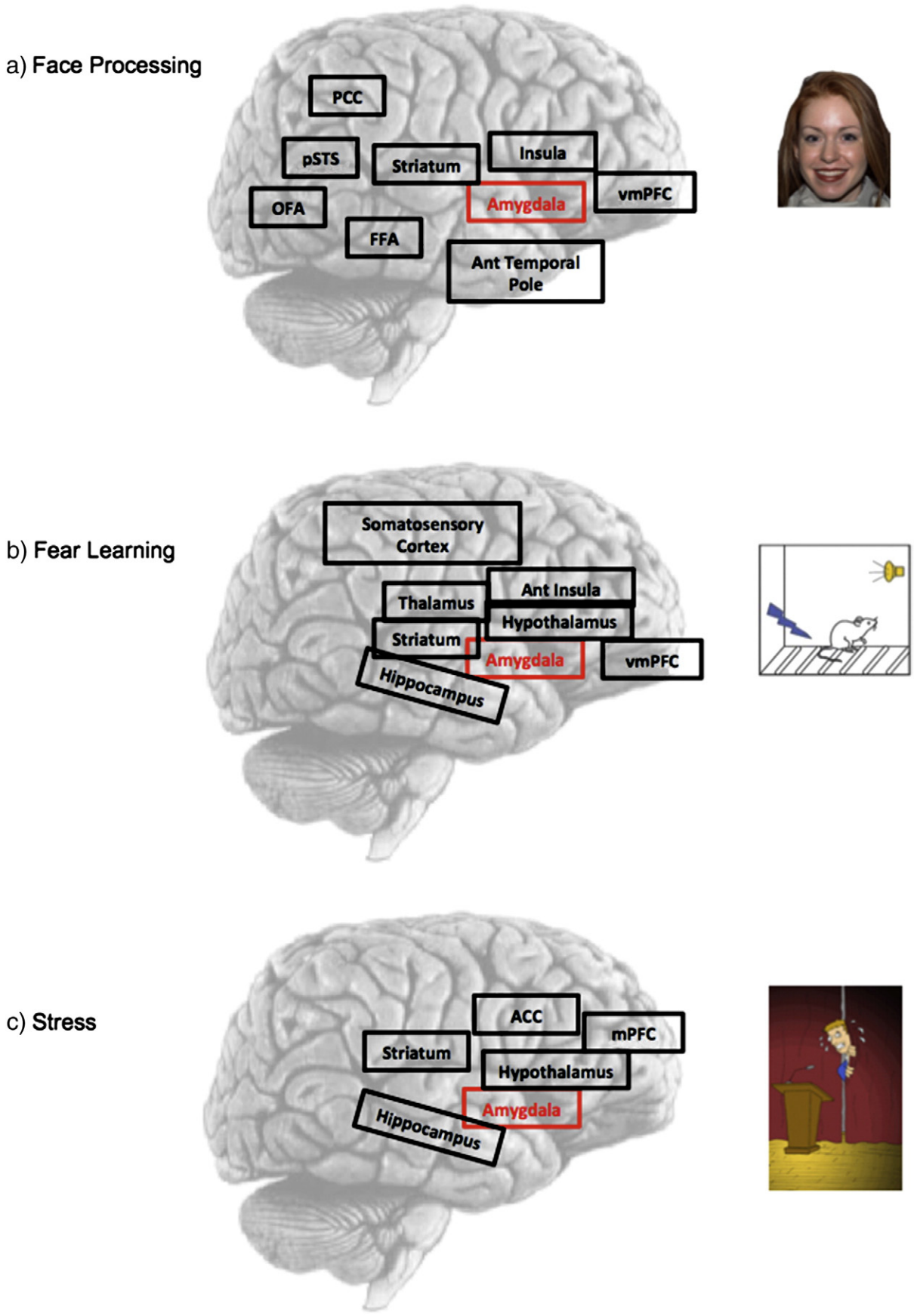

Fig. 3. Distributed neural circuits mediating a) face processing, b) fear learning and extinction, and c) stress responsivity. Abbreviations: ACC (anterior cingulate cortex), Ant (anterior), FFA (fusiform face area), OFA (occipital face area), pSTS (posterior superior temporal sulcus), vmPFC (ventromedial prefrontal cortex).

2001; Phelps and LeDoux, 2005). For instance, in human adults, neuroimaging studies report increasing amygdala activation in response to CSs that predict shock (LaBar et al., 1998; Morris et al., 1998). Also, amygdala-lesioned patients demonstrate a lack of conditioned fear response even though they exhibit explicit knowledge of contingencies between the CS and US (Bechara et al., 1995; LaBar et al., 1995).

Despite the abundance of findings implicating the amygdala in fear learning across species and within human adults, much less is known about changes in the behavioral foundation and neural mechanisms supporting fear learning across development, particularly during adolescence. This is unfortunate given that adolescence is a time of heightened sensitivity to salient stimuli, such as fearful stimuli, that can influence exploratory behavior (see Dahl, 2004). One of the reasons for this parity of research in fear learning across development is that it is difficult to employ the same paradigms in young children and adolescents that are used to study fear learning in adults because there are ethical limitations in the ability to use particular USs (like mild shock). While less noxious stimuli are somewhat effective in eliciting a CR in adults (e.g., losing money, Delgado et al., 2011) and adolescents (e.g., fearful expressions, Monk et al., 2003, accompanied by screams, Lau et al., 2008), these responses do not necessarily rely on amygdala mechanisms (Delgado et al., 2011) or involve fear per se.

Thus far, only one human developmental neuroimaging study has evaluated potential age-related differences in fear learning. Lau et al. (2011) designed a novel fear-conditioning task in which they paired a neutral face with a fearful face and a scream. Fear learning was associated with disproportionately higher activation in adolescents compared to adults in the right amygdala in response to the fear-reinforced neutral face (compared to the non-reinforced face). In addition, the adolescents were less able than adults to discriminate threatening from safe stimuli, which may reflect an amplified state of vigilance promoted by the heightened amygdala activation. Despite the interesting finding, there is a clear need for additional studies in order to understand potential differences in the behavioral and neural mechanisms of fear learning in human adolescents.

The need for future studies investigating the developmental trajectory of fear learning across childhood and adolescence is underscored by results from rodent studies. These studies report that there are age-related differences in amygdala functioning that vary with type of conditioning (which may involve amygdala interactions with different regions) and period of adolescence. For instance, Pattwell et al. (2011) evaluated the acquisition, retrieval, and expression of fear memories in four separate cohorts of mice whose age corresponded to early, middle, and late adolescence, and mature adulthood. The mice were conditioned with tone–foot shock pairings and tested for behavioral evidence of subsequent contextual fear learning (e.g., freezing behavior when put back in the conditioning chamber). The early adolescent mice exhibited significantly less freezing behavior at test, indicating weaker contextual fear learning, than did the older adolescent and adult mice. In a follow-up study, the researchers demonstrated that these weaker responses were specific to the adolescent developmental period, in that younger, pre-pubescent mice showed the same magnitude contextual fear response as adult mice. In other words, the magnitude of the contextual fear response exhibited an inverted U-shaped pattern of development, such that prepubescent and sexually mature animals exhibited the same magnitude response, while early adolescent mice showed a relatively blunted response (i.e., weaker and less contextualized fear learning). Furthermore, the suppression of contextual fear learning was associated with blunting of amygdala synaptic activity and altered protein kinase functioning in the hippocampus in the adolescent mice. The authors interpreted these data to indicate that the weaker contextual fear learning reflects an adaptive function to blunt amygdala responses as mice transition to more explorative approach behaviors and leave the nest (as proposed by Pattwell et al., 2011 and based on Spear and Brake, 1983), which is consistent with the hypotheses proposed in the current paper. However, it is also important to note that these alterations in contextual fear learning could also be related to decreased learning given changes in hippocampal function in early puberty (Shen et al., 2010) and/or to changing interactions between the amygdala and hippocampus during contextual fear conditioning (e.g., Guyer et al., 2008). In sum, these results indicate that there may be alterations in contextual fear learning, specifically during adolescence. However, more research is needed to fully understand the factors that influence the amygdala's involvement in fear acquisition and expression during adolescence.

An important next step in this area of research will be to investigate how interactions between the amygdala and other regions promote developmental changes in fear learning. In adults, active coping in response to fear reactions depends on amygdala–striatal connections (Killcross et al., 1997; LeDoux and Gorman, 2001). In fact, activation in these two regions is positively correlated during adult avoidance learning (Delgado et al., 2009). A potentially innovative strategy to investigate changing dynamics between striatal and amygdala activation during adolescence would be to employ dynamic paradigms of avoidance learning that use developmentally appropriate reinforcers for juvenile participants, including faces (Hare et al., 2005), money (Niznikiewicz and Delgado, 2011), and video game characters (Nadler et al., 2011). Indeed, this approach has been used to show that threatening cues (e.g., snake) elicit activation in both the striatum and amygdala during an avoidance paradigm in young adolescents and that amygdala responses correlate with avoidance response rates (Schlund and Cataldo, 2010). Also, behaviorally inhibited adolescents (i.e., extremely shy) exhibit increased striatal activity in anticipation of potential monetary losses in a similar avoidance paradigm (Guyer et al., 2006).

Another region that is highly interconnected with the amygdala is the ventromedial prefrontal cortex (vmPFC; see Fig. 2), and in adults the two regions are often inversely correlated during tasks requiring emotion regulation (e.g., cognitive reappraisal to attenuate negative affect elicited by unpleasant photographs, Urry et al., 2006). Importantly, functional connectivity between these regions appears to be immature in adolescents performing similar emotion regulation tasks (Hare et al., 2008). The human vmPFC has been linked to various processes ranging from valuation and decision-making (see Rangel et al., 2008 for review) to extinction (Milad et al., 2007; Phelps et al., 2004) and emotion regulation (Delgado et al., 2008) of conditioned fear. Pattwell et al. (2012) recently provided an elegant example of work highlighting developmental changes in prefrontal cortical function and the potential downstream influence on fear-related amygdala activity during adolescence. They showed that extinction learning (the process in which a CS is presented without a reinforcer, which leads to new learning; Davis, 1992) is attenuated in both mice and human adolescents (Pattwell et al., 2012), which has been recently observed in adolescent rats as well (Zang and Rosenkranz, 2013). In other words, it takes many more presentations of the CS in the absence of the reinforcer to extinguish the conditioned fear response in both adolescent mice and humans compared to younger and adult aged participants. The authors further demonstrated that a lack of synaptic plasticity specifically with the vmPFC was associated with the blunted extinction learning in mice, highlighting the potential neural mechanism through which the attenuation of extinction may be occurring. Pattwell et al. (2012) argued that these data support the notion that top–down prefrontal regulation of subcortical structures, and the amygdala in particular, is diminished in adolescence, which results from compromised amygdala–vmPFC interactions. This interpretation is consistent with reports that the intrinsic (i.e., resting state) functional connectivity between the amygdala and vmPFC is inversely correlated with concurrent anxiety symptoms in adolescent girls (Burghy et al., 2012).

Together, the scant evidence suggests that fear learning and extinction exhibit alterations in rodent and human adolescents compared to

either pre-pubescent individuals or sexually mature adults, which may be tied to intrinsic changes in amygdala activation, but also to alterations in amygdala–striatal, amygdala–hippocampal, as well as amygdala–prefrontal interactions. Interestingly, some of the findings from these studies are consistent with our assertion that the amygdala is implicated in mediating changes in important behaviors, like processing of potentially fearful stimuli and situations, that change in human adolescence and that are critical to accomplishing core developmental tasks of adolescence. However, it is important to recognize that understanding the developmental trajectory of changes in fear acquisition and extinction is complex and that much work needs to be done to evaluate this hypothesis. Understanding the processes associated with fear learning, like avoidance behaviors and emotion regulation abilities, may be particularly helpful for sorting out whether and how responses to fearful stimuli and their resultant consequences for behavior are fundamentally altered in adolescence.

Adolescent changes in stress responses

Recently, Spear (2009) proposed that an increase in stress reactivity in adolescence could provide greater physiological support for competent functioning in the face of significant cognitive and emotional stressors, and particularly social-evaluative stressors. Given that the amygdala is centrally involved in regulating stress reactivity, this proposal is consistent with the central notion of this paper. As a result, we review the evidence that an increase in stress reactivity occurs in early adolescence. Further, we evaluate the claim that such changes might support the acquisition of competencies to respond to the social, affective, and cognitive challenges imposed by the new developmental tasks of adolescence (Spear, 2009).

Together with the hippocampus and prefrontal cortex, the amygdala modulates the hypothalamic–pituitary–adrenal (HPA) axis (Herman et al., 2003), which secretes stress hormones to mobilize an organism to respond to both internal and external demands imposed by stressful stimuli (for review see Romeo, 2010b). There is an emerging body of evidence from both human (Gunnar et al., 2009a; Stroud et al., 2009; Sumter et al., 2010) and animal (Romeo et al., 2006) studies suggesting that there is an increase in HPA activity in the transition from late childhood to early adolescence. Furthermore, animal studies have also shown that pubertal animals exhibit higher sensitivity to stress-induced alterations in brain and behavior than do adult animals. There are several outstanding reviews of the evidence indicating that stress responses increase in human (e.g., Spear, 2000, 2009) and rodent (Romeo, 2010a, 2010b) adolescents. It is beyond the scope of this paper to provide a comprehensive review of this evidence. Instead, we highlight findings from the animal and human studies that specifically reflect on our hypothesis about the role of the amygdala in modulating neural circuitry that supports the perceptual, cognitive, social, and affective behaviors that are essential for navigating the developmental tasks of adolescence.

Activation of the HPA axis is initiated in the paraventricular nucleus (PVN) of the hypothalamus (for review see Romeo, 2010b). The PVN secretes corticotrophin-releasing hormone, the downstream consequences of which include subsequent increases in cortisol released from the adrenal cortex. Cortisol is a primary stress hormone that, among other functions, helps mobilize an organism to respond to the internal and external demands imposed by stressors. Importantly, the amygdala can modulate HPA activity. The central nucleus of the amygdala projects to and inhibits the bed nucleus of stria terminalis (BNST) in the hypothalamus, which itself provides inhibitory inputs to the PVN (see Fig. 2). As a result, the amygdala can inhibit inhibitory inputs to the PVN. The net result is an increase in PVN activation and the subsequent increase in the release of adrenocorticotropin and corticosterone secretion (Prewitt and Herman, 1997). In other words, increased activation in the amygdala can increase stress responses.

In addition, given the presence of estrogen and androgen receptors in the amygdala, it may also be a central structure for mediating interactions between HPA axis activity and the hypothalamic–pituitary–gonadal (HPG) axis activity (Romeo, 2010b), the system responsible for the release of gonadal hormones during pubertal maturation. For example, in adult male rats testosterone reduces stress reactivity (e.g., peak and recovery time of the hormonal stress response) but estradiol and progesterone tend to heighten stress responses in adult female rats (reviewed in Romeo, 2010a). Given this sensitivity to gonadal hormone modulation of stress reactivity in adult animals, it is plausible that the infusion of gonadal hormones during pubertal development has a measurable influence on stress reactivity in adolescence. An interesting question is whether this influence functionally contributes to the mastery of developmental tasks in adolescence.

Much of the animal work investigating adolescent-related changes in stress responsivity suggests that there are increases in stress responsivity in the transition to adolescence, but that it then *declines* as animals progress through pubertal development (i.e., and inverted U-shaped function of stress responsivity). Two of the most consistent findings from the animal literature are that basal levels of stress hormones do *not* differ between pre-pubertal and sexually mature adult animals, but that responses to acute stressors do differ. For example, following 30 min of restraint, pre-pubertal animals exhibit a higher peak in the stress hormone response as well as a longer time for the stress hormone response to recover to basal levels compared to sexually mature adult animals (Romeo, 2005). These findings suggest that HPA axis reactivity is higher prior to pubertal development than in sexually mature adults and that it decreases in reactivity following pubertal maturation. An important caveat about this work, however, is that the vast majority of it compares pre-pubertal and sexually mature animals. Much less of it tracks changes in stress responsivity specifically as a function of pubertal development. Importantly, there is an emerging body of work in human adolescents evaluating changes in stress responsivity specifically as a function of adolescence and pubertal development.

The pattern of results emerging from the developing literature on pubertal development and stress reactivity in human adolescences converges on, but is also a bit different from, the findings in the animal literature. Importantly, and particularly relevant for the current paper, the human literature has largely focused on adolescent-specific responses to ecologically valid *social-evaluative stressors*, like being evaluated by peers during an episode of public speaking or experiencing peer rejection (e.g., Dickerson, 2008). Many of the human adolescent stress studies have incorporated measures of pubertal development that allow for the evaluation of changes in stress responses as a function of pubertal development. Unlike in the animal work, very little of the human work investigates developmental transitions in stress responsivity in the transition from adolescence to early adulthood, which may limit our understanding of how changes in stress responsivity change throughout the course of adolescence.

Although the animal literature suggests that basal levels of stress hormones do not change as a function of adolescent development, the human literature suggests otherwise (e.g., Adam, 2006; Elmlinger et al., 2002; Netherton et al., 2004). For example, Adam (2006) evaluated the relation between stages of pubertal development and basal cortisol levels by collecting multiple samples from adolescents in naturalistic settings over the course of a two-day period. She found that later stages of pubertal development were associated with higher daytime basal cortisol levels. More recent studies have also provided converging evidence that basal cortisol levels increase with age and pubertal development in adolescents (Gunnar et al., 2009a). The interpretation of these findings is that they reflect an increase in the tonic level of HPA axis activity in adolescents. Importantly, it is not clear why such an increase should necessarily occur in adolescence. One possibility is that this reflects the emergence of HPA axis modulation by the HPG system, as a result of the influx of pubertal hormones at this time in development.

Alternatively (or in addition), an increase in the tonic level of HPA axis activity during adolescence could also reflect age-related differences in the frequency and/or intensity of exposure to daily stressors in adolescence. In other words, as adolescents become increasingly autonomous from parents and begin to take on adult social roles and responsibilities, they may be encountering more frequent and more intense daily stressors, which are reflected in higher cortisol levels. Another potential explanation for the increase in basal cortisol levels is that it reflects the more risky environments that adolescents seek out as a result of their increasing motivation to engage in novelty- and sensation-seeking behaviors. In other words, HPA axis activity may be registering (and providing feedback about) the level of risk in their changing environments. This would lead to the prediction that adolescents who exhibit the highest levels of novelty- and sensation-seeking as well as risk-taking behaviors may also have the highest HPA axis reactivity in age-appropriate stressor paradigms.

There is also evidence for heightened *stress reactivity* in human adolescents. Importantly, existing studies have employed public speaking tasks in which the stressor is the social evaluative threat of negative judgment by others. These public speaking tasks include the three elements of psychological stress or paradigms that are critical to provoking cortisol levels in adults, including unpredictability, uncontrollability, and social-evaluative threat (Dickerson and Kemeny, 2004). In one of the first studies of its kind, Gunnar et al. (2009a) measured pubertal development and salivary cortisol during 1) a baseline adaptation period prior to the task, 2) while participants were preparing their speech, and 3) following the delivery of a public speech in 9 to 15 year-old individuals. Basal cortisol levels in the baseline period were significantly and positively associated with age, particularly in the transition between 13 and 15 years of age. Older adolescents (13 and 15 year-olds) also exhibited higher peak cortisol levels following the delivery of the speech than younger adolescents and children, as well as longer recovery times (approximately 50 min to return to baseline levels in the 15-yr-olds versus 40 min for the younger groups). Correlational analyses suggested that pubertal development was moderately associated with cortisol levels both at baseline and following the stressor task.

Similarly, Stroud et al. (2009) compared stress responses of children and young adolescents (ages 7–12 years) to those of older adolescents (ages 13–17 years) elicited by both peer rejection and performance-oriented tasks (e.g., public speaking). In response to both types of stressors, the older adolescents exhibited higher cortisol levels and longer recovery periods than did the children and younger adolescents; however, the group differences were only statistically significant in response to the performance-related stressors. The peer rejection stressor elicited more sympathetic nervous system activation (i.e., saliva alpha amylase levels) and stronger cardiovascular stress responses in the older (relative to younger) adolescents.

Finally, in an attempt to disentangle effects of age and pubertal status on stress responsivity, Sumter et al. (2010) employed a modified version of a public speaking task in which they included a substantial period (one week) of anticipation for the participants (ages 9 to 17 years) prior to giving a speech. Age and pubertal status both contributed to increases in cortisol levels from baseline in response to the task, particularly during the anticipation period. These results suggest that biological stress reactivity does appear to increase in adolescence in humans, particularly during later stages of pubertal development.

Together, these studies provide preliminary but converging evidence for the notion that stress responses to *social-evaluative stressors* increase in the transition from late childhood to early and later adolescence and that pubertal hormones may modulate this increased sensitivity. However, it is important to note that many studies using public speaking tasks (including Gunnar et al., 2009a) with children and adolescents report that children under the age of 13 do not exhibit a consistent increase in cortisol in response to this task (for review see Dickerson and Kemeny, 2004). This finding evokes questions about what "counts" as a psychological stressor and whether/how that determination changes with age and pubertal development. One interpretation of the difficulty finding consistent cortisol increases in these public speaking tasks in young adolescents is that social-evaluation only becomes a strong psychological stressor with age and/or pubertal development. This interpretation would be consistent with the notion that adolescents are becoming increasingly aware of social cues about their social value (or status) across varying social contexts. In other words, the extant findings of age- and pubertal-related increases in *cortisol reactivity to social-evaluative stressors* might specifically reflect important changes in adolescent social information processing that are related to the developmental tasks of beginning to evaluate peers (and one's self) for potential romantic and sexual partnerships.

An interesting test of this hypothesis would involve evaluating age- and puberty-related changes in cortisol responses by testing the same individuals across a variety of stressor paradigms. For example, comparing age- and puberty-related changes in cortisol responses to non-social, noxious stressors (i.e., mild pain from venipuncture), to stressors that may be more relevant to children than to adolescents and adults (e.g., maternal separation), as well as to those observed in response to a social evaluative stressor would be particularly useful in evaluating this hypothesis. To our knowledge, there are no studies that utilize within-person designs (across multiple stressor paradigms) to evaluate developmental changes in stress responsivity. However, there are some findings in the literature that suggest that stressor paradigms are most effective in eliciting cortisol increases when they reflect the developmental tasks of a particular age group. For example, although maternal separation elicits cortisol increases in 9- and 12-month infants, it is associated with a decrease in cortisol in young children (ages 3–5 years; see full review of studies in Gunnar et al., 2009b). Based on these findings, we would expect to see little to no HPA reactivity in older children and young adolescents in response to maternal separation, which would suggest that adolescents do not exhibit a general increase in HPA axis reactivity to all stressors. In adults, physical stressors, like immersing one's hand in ice water, often do not elicit strong cortisol elevations (although they do drive strong sympathetic nervous system activation) unless a social-evaluative component is incorporated into the task (e.g., men being watched by women during the task; Schwabe et al., 2008). This finding suggests that HPA axis reactivity in adults may be particularly sensitive to processing ambiguous social information (e.g., "does she think I am a weak guy?"), particularly as it is related to one's own social standing. Using a social and non-social cold pressor task as has been used with adults would be particularly helpful for sorting out whether adolescents have increased HPA axis activity to all stressor types, or whether there are selective age-related and/or puberty-related increases in sensitivity of the HPA axis unique to social evaluation.

To return to our central hypothesis, we suggest that although these data about increasing stress sensitivity in adolescence do not explicitly implicate the amygdala, it is a central component of the neural systems that regulate stress responses. Therefore, the existing findings are consistent with the hypothesis we are presenting in this paper. Recall that increased amygdala activation can increase stress responsivity (by inhibiting inhibitory inputs to the PVN). Considering the reports of a developmental increase in amygdala activation in adolescence, another potential explanation for the observed increase in basal cortisol levels, particularly in later stages of pubertal development, may be that it reflects a downstream consequence of increased amygdala activation that is elicited by new demands on social information processing. In other words, the change in the set point of the HPA axis in adolescence may be a result of dramatic changes in the profile of functioning within the amygdala, which may also help shape the sensitivity of HPA axis reactivity to social evaluation that is consistently observed in adults. This explanation would lead to the prediction that increases in basal levels of cortisol should be positively correlated with increasing amygdala activation across age and

pubertal development, particularly in the context of tasks that require processing of social information in ways that are likely to be qualitatively new to adolescents, like evaluating faces for mate potential.

Amygdala as an agent of change in adolescent neural networks

Thus far, we have reviewed evidence suggesting that distributed neural networks that are largely organized around the amygdala subserve behaviors that are emerging and are changing qualitatively in adolescence. We also presented evidence that the structural and functional properties of the amygdala and its patterns of functional connectivity are changing in adolescence. Together, this evidence is consistent with our hypothesis that the amygdala may be a central agent of change in the functional organization of neural networks that are becoming re-configured in adolescence in response to pubertal hormones and new adolescent-specific developmental tasks. Here, we provide a more specific model of this hypothesis.

First, we argue that pubertal hormones initiate the cascade of effects that ultimately enables the emergence of new behaviors and the functional reorganization of neural networks in the adolescent brain. The hormones alter amygdala function, particularly with respect to evaluating the salience and relevance of social stimuli that are relevant for the developmental task of forming romantic and sexual relationships with peers. As a result, the salience of some stimuli/social contexts is enhanced (e.g., peer faces), whereas the salience of other stimuli/social contexts is reduced (e.g., parental separation). In turn, these alterations in amygdala activation have widespread consequences for the functional organization of the many networks in which the amygdala participates. These effects would likely be reflected in modulations to the strength and/or directionality of the functional connections between the amygdala and other regions (dependent on the specific network of interest). Effectively, these changes in the patterns of functional connectivity essentially disrupt the existing functional relationships between regions that were established during the first 10 years of life, allowing for a re-organization (new patterns of connectivity) within these networks and, ultimately, the emergence of novel behaviors (e.g., evaluating peers for mate potential) that are rapidly developing during puberty.

Consistent with our previous work, this model is based on Dynamic Systems (DS) theories of developmental change (e.g., Smith, 2005; Smith and Thelen, 2003; Thelen and Smith, 1994; van Geert, 1994), which are particularly useful for explaining how novel outcomes emerge from a stable system. DS theories predict that new higher-order components of development (i.e., novel behaviors or qualitative changes in behavior) emerge through a process of *self-organization* in which recursive interactions (i.e., functional connections in our model) from simpler component systems (i.e., neural regions) spontaneously induce new developmental outcomes (i.e., network re-organization), particularly during periods of instability in the system when old patterns break down and new ones appear (Lewis, 2000) (e.g., as when individuals confront new developmental tasks).

This kind of self-organized learning has been modeled extensively with connectionist neural networks with the goal of learning about some of the mechanisms supporting these changes in self-organized learning. Connectionist models learn a set of weights on connections among neuron-like processing units. Overtime, learning and development occur through small, non-linear adjustments in the connection weights that support the generation of appropriate, context-sensitive, conditional expectations (see McClelland et al., 2010; Munakata and McClelland, 2003). Information processing in connectionist models is highly interactive, which, under many conditions, leads them to settle to *attractor states*, or low energy states in which the connection weights are very stable and resistant to change. These attractor states provide for fast, efficient, and accurate performance as long as the inputs/environmental structure stay the same.

However, when the environmental structure changes (e.g., when presented with new task demands or new environmental structure), learning can only proceed once the attractor state is *disrupted*. This leads to a period of network instability until the connection weights are re-adjusted to accommodate the new inputs, which can lead to novel network outputs in response to the changing input structure. Herein, we propose that pubertal hormones modulate amygdala activation, which destabilizes the existing organization within neural networks in which the amygdala participates, particularly among networks that support behaviors relevant to the developmental tasks of adolescence (e.g., face processing, novelty-seeking, fear processing). This state of destabilization provides an opportunity for the relevant neural networks to be shaped by new environments and experiences and ultimately for the emergence of novel behaviors, like sensitivity to dominance in faces (as proposed by Scherf et al., 2012). Therefore, target networks that exhibit stable patterns of functional connections in childhood are likely to be characterized by increasingly inconsistent and highly variable functional connections as pubertal development progresses. The degree of network disruption across individuals might be related to temporary decrements in behavioral performance (as in the dip in face recognition performance during pubertal development). In contrast, the transition from late adolescence to early adulthood is likely to be characterized by increasing stability (i.e., reduced variability) and strengthening of the functional connections within target neural networks that may ultimately be organized (in terms of number, strength, consistency, directionality of connections within the network) quite differently from the corresponding networks in childhood.

Alternative models of adolescent brain development

Over the last 10 years, neuroimaging studies of normative adolescent brain development have largely converged on the notion that there is temporal asynchrony in the structural and functional development of two primary systems, the motivational limbic systems (especially the amygdala and the striatum) and prefrontal control regions (e.g., Casey et al., 2010; Steinberg, 2010). The central argument is that earlier structural and functional development of the ventral affective (limbic) systems in combination with a relative delay in the development of the prefrontal control systems leads to an imbalance between heightened reward seeking behaviors and underdeveloped cognitive control abilities (for review see Casey et al., 2011). In other words, the underlying assumption is that greater activation in the limbic motivational systems (particularly the ventral striatum) is detrimental to adaptive outcomes, particularly in adolescence (Pfeifer and Allen, 2012). At first glance, this notion could appear to be at odds with the hypothesized adaptive influence of the amygdala in restructuring adolescent neural networks being proposed in this paper. However, it is important to remember that there are extensive connections between the amygdala and ventral striatum and the amygdala and medial PFC that could provide a means by which changes in amygdala activation could modify both striatal and medial PFC responses. For example, increased activation in the amygdala in response to highly relevant/salient stimuli (e.g., peers for adolescents) might invoke strong ventral striatal responses to these same stimuli, which could enhance the reward value and motivate approach-related behavior toward the stimuli. This positive association between amygdala and striatal responses to highly relevant stimuli might help explain why the mere presence of peers increases activation in the ventral striatum during reward processing (Fareri et al., 2012) and in particular in adolescents performing a decision-making task (Chein et al., 2011). In fact, these hypotheses are consistent with the Triadic Model of adolescent brain development (Ernst and Fudge, 2009), which proposes that goal-directed behavior is governed by a careful integration and balance among approach (striatum) and avoidance

(amygdala) systems that is executed by regulatory (medial prefrontal cortex) neural systems.

Conclusions: amygdala as the agent of change in cortical reorganization

To summarize our argument, we suggest that a central feature of adolescence involves a fundamental re-evaluation of the relevance and salience of existing stimuli, and particularly social stimuli, which is largely computed by the amygdala. We have reviewed evidence to suggest that the amygdala grows in volume and changes in activation to socially relevant stimuli and contexts during adolescence. We suggest that this reflects the role of the amygdala in re-evaluating the relevance of social stimuli, particular for the context of the social developmental tasks during adolescence. Given its broad connectivity with the cortex and other subcortical structures, we argue that these changes in the functional profile of the amygdala likely induce an extensive functional re-organization (e.g., change in functional connectivity) among existing neural circuits, which ultimately influences the ability to master adolescent-specific developmental tasks. Additionally, we argue that pubertal hormones are likely to be influential in initiating the motivation to re-evaluate these stimuli, given the presence of androgen and estrogen receptors in the amygdala. As a result, we suggest that the amygdala may be an important agent of change in the functional organization of neural networks, particularly those that process social information, and structure–function–behavior correspondences that specifically enable adolescents to master their unique challenges and developmental tasks.

A strong empirical evaluation of our hypotheses will require large-scale cross-sectional and longitudinal studies of multiple aspects of behavior that is mediated by the amygdala from childhood through early adulthood. Much of the evidence we have presented is not specifically designed to address the core hypotheses that we propose here. As a result, we encourage future work on adolescent brain development that specifically focuses on evaluating particular task constraints under which amygdala activation changes (increases or decreases) disproportionately in adolescents compared to both children and adults. For example, we suggest that it will be critical to compare potential differences in amygdala activation in the context of experimental tasks that are highly relevant to the developmental tasks of adolescents (e.g., tasks involving social evaluation of/from peers) versus those that are not (e.g., tasks involving social evaluation of/from pre-pubescent children). Future studies investigating amygdala-mediated behaviors that change in adolescence should also include measures of pubertal status via Tanner staging and/or hormonal assay to evaluate whether and how the onset of gonadal hormones fundamentally influences reorganization in the dynamics of widely-distributed cortical networks and brain–behavior relations that are specific to adolescence.

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