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Review

Neurobiology of the development of motivated behaviors in adolescence: A window into a neural systems model

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ABSTRACT

Adaptive motivated behaviors are at the core of a successful life. Conversely, perturbed motivated behaviors are the hallmark of psychiatric disorders. Based on the notion that most psychopathology is developmental in nature, understanding the neural mechanisms that control motivated behavior across development and in psychopathology is a critical step for preventing and treating psychiatric diseases. This review focuses on adolescence, which is the critical developmental period that determines the successful passage into adulthood. We first present a heuristic neural systems model of motivated behavior (triadic model) that integrates neuroscience theories and the emerging body of functional neuroimaging work on the neurodevelopment of motivated behavior. As a key feature of adolescence, social reorientation is particularly emphasized through the presentation of a parallel model of social integration processing network. Although not yet integrated in the triadic model, pubertal changes and their possible contribution to adolescent motivated behavior are reviewed. Similarly, given its central role in motivated actions, the dopamine system is discussed from the perspective of animal studies dedicated to changes of this system across adolescence. This review reveals vast gaps in knowledge about the neurobiology of motivated behavior in normally developing individuals, which makes the translation to psychopathology only tentative. However, it provides clear directions for future research.

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1. Introduction

One of the most fundamental paradigm shifts that has recently taken place in psychiatry is the recognition of the neurodevelopmental nature of virtually all psychiatric disorders. This reframing of psychopathology is now guiding a huge body of neuroscience and clinical research. This research is adopting a new vista by integrating, and at times even prioritizing, the developmental aspects of cognitive/affective processes and their neural correlates. In this effort, there is a dire need for heuristic models to guide such research. This is one of the goals of this review.

Here, we propose and describe a neural systems model of adolescent motivated behavior, the triadic model. This model is broad, by virtue of the early stage of this line of work, and leaves room to integrate other aspects of developmental neurobiological research, including hormonal and neurotransmitter functional changes. The triadic model is focused on the neurodevelopmental changes that affect specifically motivated behaviors from the perspective of risk-taking. However, other facets of behavior, such as responses to threat, or social information processing, could be examined using this model.

The present work is focused on the transition period of adolescence, and addresses three cardinal aspects of this period: neurodevelopment, hormonal changes, and ontogeny of the dopamine system. In the future, the emergence of new studies providing information on the reciprocal interactions of these factors will permit to update the triadic neural systems model described below by integrating neurochemical and molecular influences. A particularly promising area of research is the development of neurocomputational models (e.g., Frank et al., 2007). The hope is that the present work, together with the emergence of new data, can foster the formulation of such models dedicated to neurodevelopment and prediction of behavior in adolescents.

The first part of this review will focus on the maturation of neural systems that underlie the coding of motivated behaviors, central to the clinical manifestations of any psychiatric pathology. The second part will qualify these changes by reviewing the potential contribution of the pubertal activation of the hypothalamo-pituitary-adrenal axis to these neural refinements. The third part will address the ontogenic changes throughout adolescence of the dopamine system, which plays a critical role in behavioral expressions.

Although we do not explicitly address psychopathology, and particularly addiction, this review strongly supports the thesis that the neurobiological changes that occur during adolescence confer significant risk for the development of substance use problems. The decision to initiate and continue to take drugs of abuse belongs to the realm of motivated behaviors. The adolescent pattern of motivated behaviors as described below, and the neural underpinnings of this pattern are consistent with what epidemiological studies tell us about the sharp increase of drug use in this age range (Angold et al., 1998; Wagner and Anthony, 2007; Robins and Przybeck, 1985; Anthony and Petronis, 1995; O'Malley et al., 1998). The contribution of hormonal changes and of maturation of the dopamine systems to enhance vulnerability to substance use in adolescence has also been substantially acknowledged in the literature (Chambers and Potenza, 2003; Spear, 2000; McCormick et al., 2005; Windle et al., 2008; Adriani et al., 2003). The goal of this review is to put together these lines of research, which support the notion that preventive intervention should be, by nature, comprehensive and multi-targeted.

2. Neural systems in adolescence

2.1. Motivated behaviors during adolescence

Motivated behaviors is a term that encompasses a wide range of behaviors. All motivated behaviors are goal-directed. However, goals can be schematically divided into two types, goals that are explicit and goals that are biologically driven to provide the organisms with optimal and most adaptive responses to the environment. Here, we restrict this review to motivated behaviors oriented towards an explicit goal.

Decision-making is the archetype of such motivated behaviors and implies the selection of an option among other alternatives. The entire process of decision-making encompasses a series of more elemental operations: (1) assessment and discriminative/comparative evaluation of options, (2) formation of a preference, (3) execution of the preference, (4) anticipation of the outcome of the action, (5) response to outcome and update of the value of options (Ernst and Paulus, 2005). These operations rely on distinct, although overlapping, neural circuits. Perturbations at any level of this sequence of operations can impair the quality of decision-making.

Generally, adolescent decision-making shows a propensity towards risk-taking, novelty-seeking, a relative disregard for negative consequences in favor of the greater lure of positive consequences, and a considerable modulation by social context (Steinberg, 1987; Dahl, 2004; Ernst and Spear, in press; Crews et al., 2007). Such generic description captures the within-subjects trend of behavioral changes with age. However, adolescent behavior is also characterized by considerable inter-individual variability that is crystallized in the temperament literature (e.g., Kagan and Snidman, 2004).

The relatively stereotypical nature of these behavioral changes points to a biologically determined remodeling of brain systems that mediate motivated behaviors. This idea is further supported by the recognition of similar behavioral changes across most mammalian species, which further argues for a role of evolutionary fitness (Steinberg, 1989; Steinberg and Belsky, 1996). These changes would contribute to the ultimate goal of species reproduction, while avoiding genetic inbreeding. During adolescence, individuals become attracted by novelty and manifest a desire to move away from the safe familial nest, whereas, at the same time, acceptance by social peers becomes an unprecedented determinant of behavior.

From a neurocognitive perspective, these behavioral changes are expected to be reflected at the individual level of each of the subprocesses that together embody decision-making, as described above (Ernst and Paulus, 2005). This framework suggests a research approach for the study of the neural correlates of changes in motivated behavior during adolescence. This approach is based on the decomposition of complex processes into elemental units or subprocesses, which map onto distinct neural systems. Thus, a neural systems model of motivated behavior can provide a backdrop against which to predict alterations at the subprocess level.

Two such models have recently been proposed, one that focuses on motivated behavior at large, *the triadic model* (Ernst et al., 2006), and another that considers social information processing, the Social Information Processing Network (SIPN) (Nelson et al., 2005). These models were put forward within a developmental framework, addressing particularly the mechanisms underlying the adolescent behavioral changes of enhanced risk-taking and social re-orientation. The novelty of these models comes from the integration of the latest functional neuroimaging findings with earlier theories.

2.2. Neural systems models of motivated behavior (triadic model) and of social reorientation (SIPN)

2.2.1. The triadic model

2.2.1.1. Description. The triadic model was inspired by three lines of research. First, temperament research has recognized that motivated behavior can be characterized along a dimensional continuum extending between two poles, i.e., one extreme dominated by approach behavior vs. the other extreme dominated by avoidance behavior (Kagan and Snidman, 2004). Second, neuroscience research has identified key brain structures involved in the coding of these

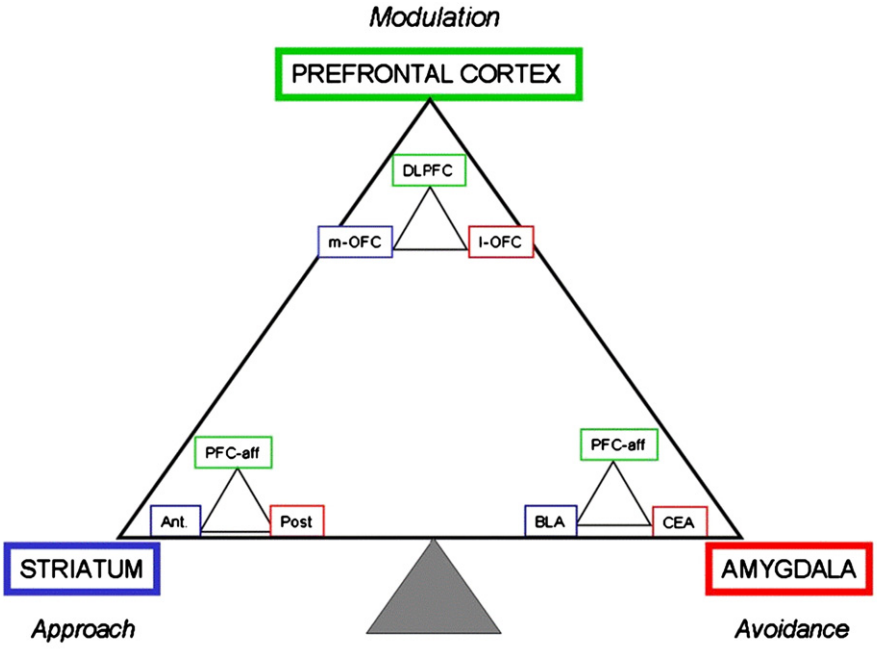

Fig. 1. The fractal triadic model is a neural systems approach developed to provide an understanding of the neural underpinnings of patterns of motivated behavior and of their changes across development or psychopathology. This model comprises three nodes that each presents a functional dominance over approach (striatum), avoidance (amygdala) and behavioral regulation (prefrontal cortex). However, each of these nodes participates in the coding of the behavioral responses to positive and negative stimuli, and their regulation. Previous work has identified specific regions within these nodes, as seen in the figure, that could support these functional specializations (see Ernst and Fudge, 2009). Green represents modulatory processes, blue represents approach and red represents avoidance. DLPFC = dorsolateral prefrontal cortex, m-OFC = medial orbital frontal cortex, l-OFC lateral orbital frontal cortex, PFC-aff, prefrontal cortical afferents, Ant = anterior striatum, Post = posterior striatum, BLA = basolateral amygdala, CEA = central amygdala fractal triadic model (courtesy of Ernst and Fudge, 2009). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

behaviors, i.e., amygdala (Davis, 2006; LeDoux, 2000), nucleus accumbens/ventral striatum (Wise, 2004; Di Chiara and Bassareo, 2007a; Di Chiara, 2002), and prefrontal cortex for navigating the balance between these polarities. Third, experts in clinical research on adolescence have proposed an imbalance between affective maturation and cognitive maturation, leading to a lag in emotional maturity relative to cognitive maturity (Steinberg, 2005; Dahl, 2004). The triadic model integrates these concepts by proposing a three systems equilibrium that modulates motivated behavior.

These systems include the amygdala and related circuits, the ventral striatum and related circuits, and the prefrontal cortex. The *dominant* role of each of these systems is respectively the processing of avoidance, the processing of approach, and the modulation of avoidance vs. approach. Besides their specific dominant role, each of these systems also carries the other two complementary functions. The resulting model mimics a fractal organization, i.e., a fragmented geometric shape that can be subdivided in parts, each of which being a small copy of the whole (see Fig. 1) (Ernst and Fudge, 2009). This model renders the heterogeneous nature of these nodes, both anatomically and functionally (see, Ernst and Fudge, 2009) (See Table 1). The pattern of involvement of these systems will depend on the context in which the motivated behavior occurs.

This last point is critical for the understanding of how different contexts can tone down or tone up the appetitive (positive affect) and/or aversive (negative affect) systems in adolescence. In Figs. 2 and 3, we present two scenarios depicting the simple cases of neural responses to either a positive stimulus or a negative stimulus in both adults and adolescents. The instance of risk is more complex as it entails both positive and negative stimuli.

2.2.1.2. Application to the neural coding of a simple economic decision-making. To clarify the potential dynamics of the model, we present the case of an economic decision-making situation, when individuals have to decide whether to take a bet (approach), consisting of a possible large gain paired with a possible large loss, or to pass (avoidance) on the bet. The decision to take the bet is based on the lure of a gain that prevails over the fear of a loss, or the preference of a risky situation over a safe situation.

The neural coding of the values of presented options have been fairly well characterized, and result from somatosensory (somatosensory cortices) and autonomic (insula) signals that are integrated at the level of the amygdala and striatum, and stored within the orbitofrontal cortex (for review, see Ernst and Paulus, 2005). However, responses to these values engage the amygdala more strongly when the affective value is negative, and the ventral striatum when the affective value is positive (for review, see Ernst and Spear, in press). As depicted in Figs. 1 and 2, brain systems in adolescence, compared to adulthood, seem to be hyper-responsive when selectively challenged, i.e., enhanced striatal responses to positive stimuli (e.g., Ernst et al., 2005; Galvan et al., 2006), and enhanced amygdala response to negative stimuli (e.g., Guyer et al., 2008). However, when appetitive stimuli are pitted against aversive stimuli in a probabilistic way, as in risky situations, regulatory mechanisms will tend to bias behavior

Table 1
Anatomical and functional diversity of the triadic nodes.

Amygdala	Striatum	Medial PFC
Anatomy		
Basolateral nucleus	Caudate nucleus	Frontal pole (area 10)
Central nucleus	Putamen	Medial orbital (areas 13a, b)
Medial nucleus	Nucleus accumbens	Anterior cingulate (areas 25, 24)
Function		
Attention orienting	Motor responses	Self-assessment
Conditioned fear response	Habits	Conflict monitoring
Affective intensity	Motivation	Action planning
Salience detector	Incentive learning	Conditioning
Reward processing	Reward processing	Affective value
Dominant role		
Avoidance	Approach	Modulation

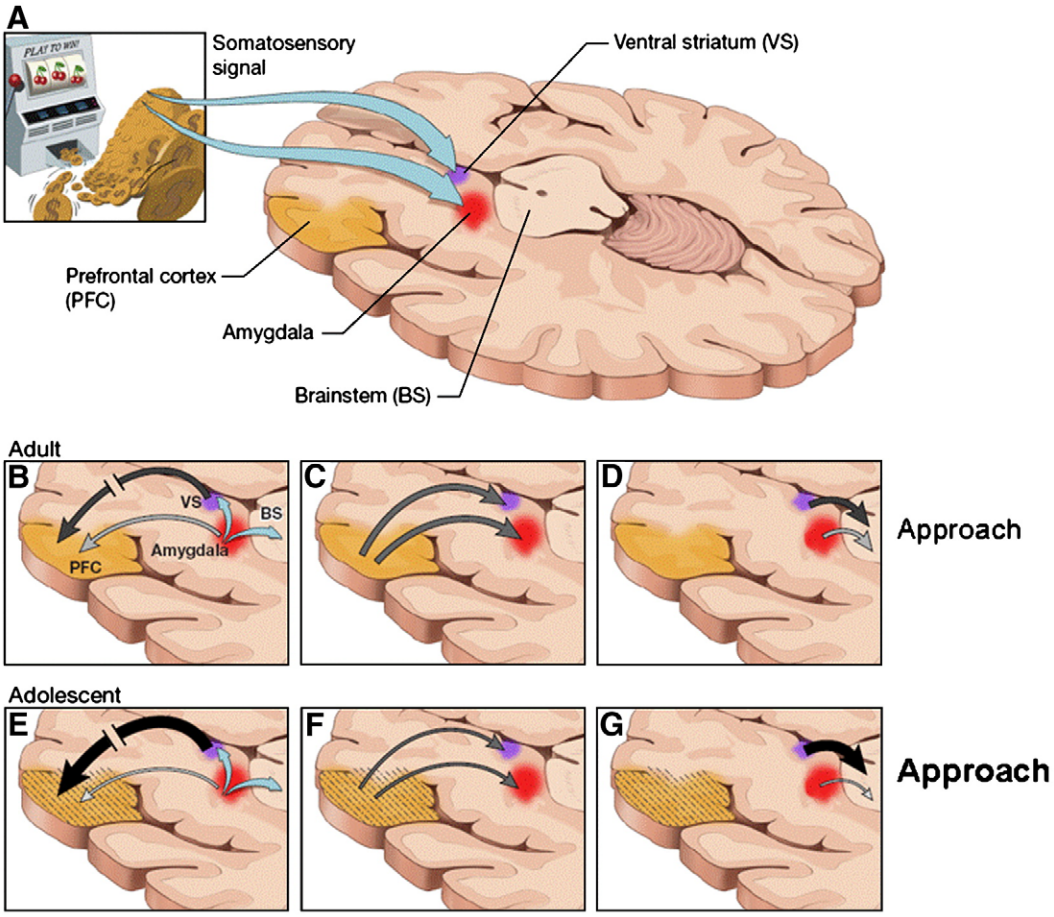

Fig. 2. Representation of the translation of incoming somatosensory signals into the coding of behavioral responses in the context of appetitive stimuli ($ gain at a game of chance). The B, C and D panels represent the adult scenario, and the E, F, and G panels represent the adolescent scenario. The immaturity of the prefrontal cortex is represented by a hatched patterning of the region, and thinner projections back to the amygdala and ventral striatum (F.). A. Somatosensory signals from thalamo-cortical and/or thalamic projections reach the amygdala and striatum. B. The amygdala rapidly processes this information and sends it to brainstem nuclei (BS) for immediate action if necessary (mainly withdrawal) and to prefrontal cortex (PFC) for further evaluation. The striatum (VS) also processes the somatosensory information, which is sent back to the prefrontal cortex through pallido-thalamic cortical loops (interrupted arrow because indirect projections). Given that the environmental stimuli are positive, the message to the brainstem from the amygdala is weak and does not elicit a withdrawal response. C. The prefrontal cortex (here the ventrolateral prefrontal cortex) sends back the processed information to the amygdala and striatum. D. Both striatum and amygdala translate this now modulated signal into motivation to respond towards the appetitive stimuli. In this scenario of appetitive context, the response of the striatum might drive the behavioral response more strongly than the response of the amygdala, as seen by the thickness of the arrows directed to effector systems. E. The striatal output is relatively more active in adolescents than in adults. F. Cortical projections are weaker in adolescents than in adults. G. The differential weight of the projections from the amygdala and striatum to effector systems is greater in adolescents than in adults, suggesting stronger motivation to approach than to avoid in adolescents than in adults in a positive context. This representation, by virtue of being a model, is simplistic and speculative.

towards approach responses in adolescents compared to adults. In this case, the approach system would be hyper-responsive in contrast to the avoidance system, which would be relatively hypo-responsive. These regulatory mechanisms would be partly mediated by prefrontal cortical function.

Medial prefrontal cortex, particularly within the dorsal anterior cingulate gyrus, is engaged when a conflict is present, and a more dorsal, anterior region of the prefrontal cortex (Brodmann Area [BA] 9) is engaged when self-monitoring becomes prominent. In adulthood, these prefrontal cortical controls tend to exert inhibitory influences over behavior, through distinct modulation of amygdala and striatal circuits. In adolescence, the delay in prefrontal maturation relative to other brain structures (Durston and Casey, 2006; Luna and Sweeney, 2004; Yurgelun-Todd, 2007) would support lesser conflictual resolution of decisions and less self-monitoring compared to the adult mature state. This prefrontal immaturity might favor the expression of striatal function, and dampen amygdala response. The exact mechanisms cannot yet be apprehended because of the lack of knowledge on the behavioral translation of what is known of the ontogeny of brain structures and neurochemical function (see hormonal and dopamine sections below). However, following the proposed scheme, adolescents would show a greater preference for the bet (risky) option, be less upset at losing and happier at winning than adults. Accompanying this behavioral pattern, the amygdala would be less involved, the ventral striatum more involved and medial prefrontal cortex less involved than in adults during risky decision making. Although scarce, developmental studies of monetary decision-making seem to be consistent with this scenario (Eshel et al., 2007; Ernst et al., 2005; Galvan et al., 2006b; van Leijenhorst et al., 2006).

For clarification, the model uses the term amygdala to refer to the network that controls avoidance behavior and which consists, in part, of amygdalo-striatal-cortical loops. Similarly, the term ventral striatum refers to the network that controls approach behavior and which consists, in part, of striatal-cortical-amygdala loops. This dynamic scheme of how a salient incoming stimulus engages brain circuits is illustrated in Figs. 2 and 3. Fig. 2 renders the scenario of an appetitive stimulus (making money) and Fig. 3 illustrates the scenario of an aversive stimulus. In both figures, panels B, C and D represent the adult pattern of neural responses, and panels E, F and G represent the adolescent response pattern. Five key points can be made about these

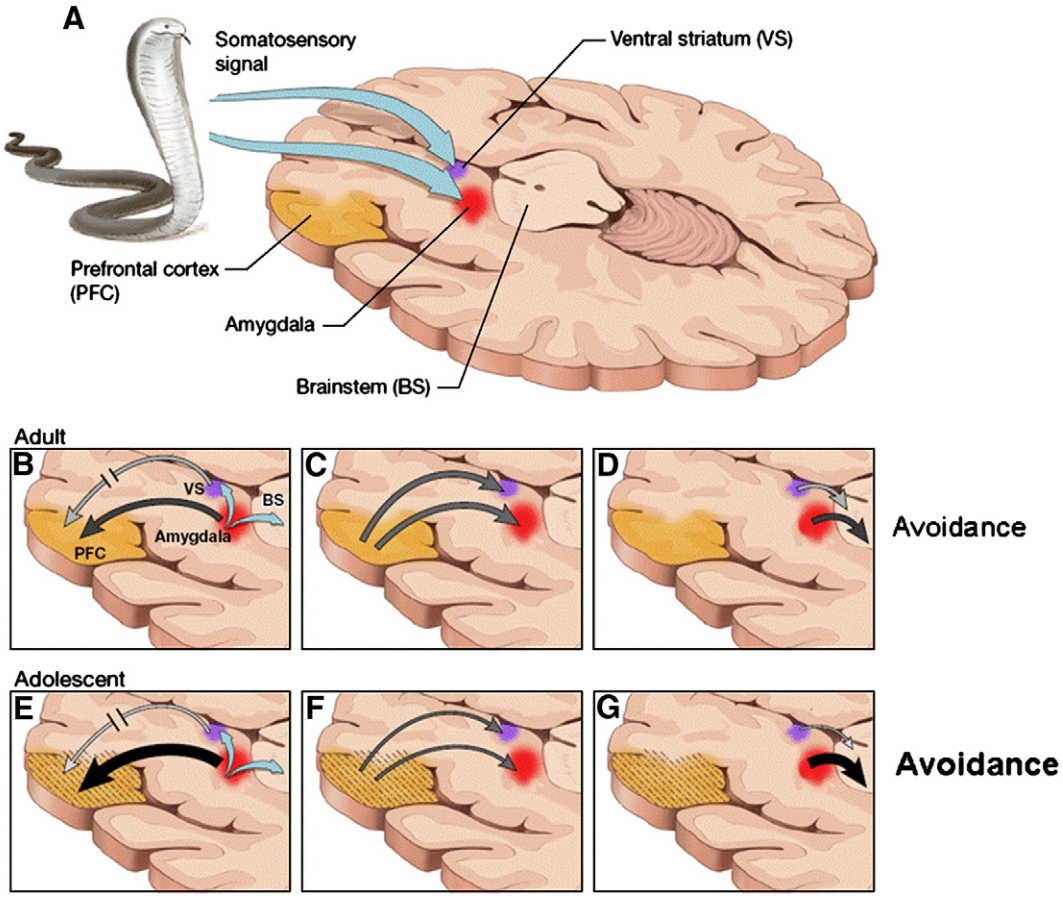

Fig. 3. Representation of the translation of incoming somatosensory signals into the coding of behavioral responses in the context of aversive stimuli snake. The B, C and D panels represent the adult scenario, and the E, F, and G panels represent the adolescent scenario. The immaturity of the prefrontal cortex is represented as a hatched patterning of the region, and thinner projections back to the amygdala and striatum (F.). A. Somatosensory signal from thalamo-cortical and/or thalamic projections reach the amygdala and striatum. B. The amygdala processes rapidly this information and sends it to brainstem nuclei (BS) for immediate action if necessary (mainly withdrawal) and to prefrontal cortex (PFC) for further evaluation. The striatum (VS) also processes the somatosensory information, which is sent back to the prefrontal cortex through pallido-thalamic cortical loops (interrupted arrow because indirect projections). Given that the environmental stimuli are negative, the message to the brainstem from the amygdala is relatively strong and could generate a withdrawal reaction. C. The prefrontal cortex (here the ventrolateral prefrontal cortex) sends back the processed information to the amygdala and striatum. D. Both striatum and amygdala translate this now modulated signal into motivation to respond away from the aversive stimuli. In this scenario of an aversive context, the response of the amygdala might drive the behavioral response more strongly than the response of the striatum, as seen by the thickness of the arrows directed to effector systems. E. The amygdala output is relatively more active in adolescents than in adults. F. Cortical projections are weaker in adolescents than in adults. G. The differential weight of the projections from the amygdala and striatum to effector systems is greater in adolescents than in adults, suggesting stronger motivation to avoid than to approach in adolescents than in adults in a negative context. This representation, by virtue of being a model, is simplistic and speculative.

figures: (1) All three nodes and their projections are engaged in response to either positively or negatively valenced stimuli; (2) The relative recruitment and information transmitted from these nodes differ as a function of valence and context; (3) Adolescents show less modulation of their neural responses reflected as a more differentiated neural coding of positive or negative stimuli; (4) The situation of risk, when positive and negative stimuli co-occur, is coded in favor of positive stimuli in adolescents relative to adults; (5) Finally, this developmental model rests on neural maturation occurring in the structures themselves and their projections. At this point, it is difficult to know precisely how these two components, separately or in interaction, contribute to the characteristics of behavioral responses.

As already mentioned, the pattern of involvement of these systems depends strongly on the context in which the motivated behavior occurs, particularly, whether the context is non-social (e.g., monetary) or social.

2.2.2. The Social Reorientation Model (Social Information Processing Network SIPN)

2.2.2.1. Description. A number of neurobiological models have been proposed to understand the neural processing of social information (Allison et al., 2000; Adolphs, 2001; Haxby et al., 2002; Gallagher and Frith, 2003; Nelson et al., 2005). The Social Information Processing Network (SIPN) formulated by Nelson et al. (2005) offers a neural systems model similar in conception to the triadic model. It comprises three discrete nodes with specific, although overlapping, functions, that collaboratively integrate social information to influence behavior (Fig. 4).

The *detection* node identifies the social properties of stimuli. It encompasses visual processing areas, including the inferior occipital cortex, inferior regions of the temporal cortex, particularly the specialized face area of the fusiform gyrus (Haxby et al., 2002; Perrett et al., 1982; Kanwisher and Yovel, 2006), and the intraparietal sulcus. Other regions of the temporal cortex carry functions such as the processing of biological movement within the superior temporal sulcus (STS) (Allison et al., 2000; Vaina et al., 2001; Haxby et al., 2002; Puce and Perrett, 2003; Jellema et al., 2004), and face recognition and episodic memory retrieval within the temporal poles (Adolphs, 2001; Gallagher and Frith, 2003).

The *affective* node serves to attach an affective tag to the social stimuli. It is not specific to the social nature of the stimuli and encompasses the regions that code for reward or punishment, otherwise conceptualized as approach or avoidance. As such, the affective node

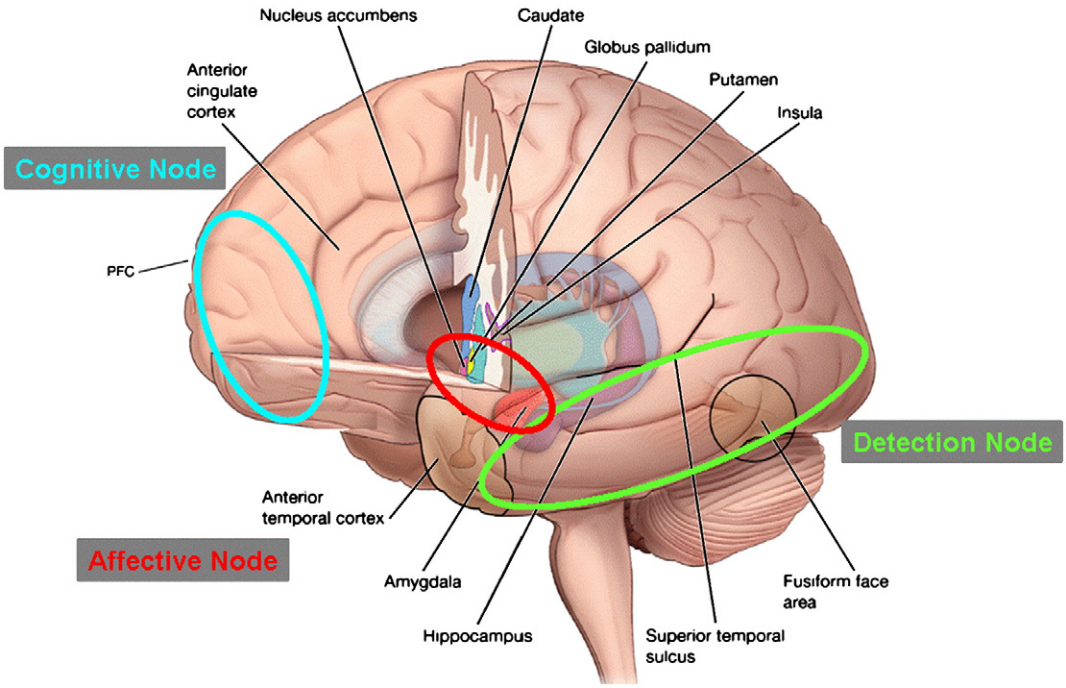

Fig. 4. Cartoon of a saggital view of the brain with the half left anterior hemisphere removed to reveal medial structures of the forebrain. The circles identify the three nodes of the social information processing network (SIPN). The detection node (green circle) includes the fusiform face area, the superior temporal sulcus and the anterior temporal cortex. These regions are involved in basic perceptual processes on social stimuli. The affective node (red circle) includes the amygdala, hypothalamus, nucleus accumbens, and bed nucleus of the stria terminalis. The affective node interacts with the detection node to attach an affective value to social stimuli. The cognitive-regulation node (blue circle) comprises the dorsomedial prefrontal cortex and the ventral prefrontal cortex. This node is involved in inhibitory processes and in understanding self- and other-perspective in social interactions (revised cartoon from Fig. 1 of Nelson et al., 2005). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

maps onto parts of the triadic model. It comprises the amygdala, ventral striatum, septum, bed nucleus of the stria terminalis, and hypothalamus (e.g., Davis, 2006; Wise, 2004; Di Chiara, 2002; Walker et al., 2003).

The *cognitive* node regulates and directs the use of the integrated social signal for present or future behavioral responses, as part of the formation of or the adherence to rules of behavior. Three sets of cognitive processes are identified. The first set is specific to the social domain and concerns the self- and other-perception of mental states (Vogeley et al., 2001). Congruent evidence assigns the paracingulate (BA 9/32) and dorsomedial prefrontal cortex, particularly the rostral extension (frontal pole), to the coding of reflective social processes (see review Gallagher and Frith, 2003; Vanderwal et al., 2008). The second cognitive set serves to inhibit prepotent responses and is subserved by the ventral prefrontal cortex, with a dominance of the right hemisphere (Garavan et al., 2006). The third one organizes the generation of sequences of behaviors at the service of an overarching goal (Blair and Cipolotti, 2000). This function has been attributed to the lateral PFC (ventral BA 47, 45 and 46, and dorsal BA 8 and 9) (for review Tanji and Hoshi, 2008).

2.2.2.2. Application to the neural coding of a social economic decision-making. In this example, we place in a social context the decision-making described above. Individuals are asked to select between betting on a potential gain/loss (approach) or passing (avoidance), while a "neutral" peer (same age, same sex, and unfamiliar) is playing alongside. In this example, the actions of both players are independent, and mimic the situation of individuals playing side-by-side at slot machines. This scenario minimizes issues of complex emotional and cognitive responses associated with social interactions in games of exchange.

We predict that the presence of a social other will be detected and processed through the SIPN, and at the same time, influence the balance of the triadic model. The detection of an unfamiliar social presence is expected to generate a state of alert (Misslin, 2003), whose main function is to prepare the organism for a rapid response to a potential danger. Accordingly, this state of alert should facilitate activation of the threat (avoidance) system, and hinder the engagement of the reward (approach) system. Although social interactions, and thus cognitive processes, are minimized in this example, the cognitive interpretation of the social presence still needs to proceed for generating the appropriate behavioral response.

From a neural perspective, the response to the presence of an unfamiliar other would activate the SIPN detection node, particularly the fusiform gyrus, the superior temporal sulcus (STS), and temporal pole. The initial affective tagging would favor a threat mode through preferential recruitment of amygdala-related circuits relative to striatal-related circuits. Integration of the neural signals associated with the decision-making task and the social context is expected to shift the triadic balance towards a more conservative choice behavior. This balance may be modulated further by prefrontal controls, particularly dorsal and rostral medial PFC, that coordinate rules of behavior.

In adolescence, the influence of a social context on motivated behavior is expected to be magnified relative to either childhood or adulthood. This proposition is supported by the dramatic changes in social behavior, as described above. These changes manifest as an intensification of emotional responses to social situations, enhanced primacy of peer interactions in the adolescent social life, and hypersensitivity to peer evaluation. The translation of these effects at the behavioral level with respect to decision making depends on parameters of the social context, such as degree of familiarity, number of peers, gender, or age. Both enhanced avoidance or enhanced approach of the adolescent behavior compared to the adult behavior can be elicited by a social context. Back to our example, we can speculate the following effects associated with the presence of a peer during a gambling game in adolescents relative to adults: exaggerated recruitment of the structures underlying social detection (fusiform gyrus, STS and temporal lobe); tilted choice pattern towards either avoidance or risk-taking, reflected as

stronger mobilization of either amygdala or striatal circuits, depending, for example, on the positive or negative state that the presence of the unfamiliar peer generates; lesser modulation by cognitive control evidenced as attenuated recruitment of prefrontal structures. These hypotheses can be tested using functional neuroimaging tools. How these changes are affected by psychopathology, or conversely, how psychopathology can be triggered by these changes is of primary interest.

In summary, adolescence is a period of neural remodeling that affects the functional pattern of networks that collaboratively shape behavior. These effects are amplified in a social context (e.g., enhanced risk taking or enhanced avoidance in a social vs. nonsocial context). However, individual differences in the manifestations of adolescent behavior are huge and provide a unique platform for the study of the modulatory factors of motivated behaviors (e.g., genetics, physiological, hormonal, environmental factors).

One such modulatory factor is sex. Gender differences in choice behavior and in social responses support the importance of hormonal influences. Substantial literature addresses hormonal influences on affiliative behavior (Bartz and Hollander, 2006; McCormick et al., 2005). Puberty, a keystone of adolescence, is obviously an active contributor to the adolescent behavioral shifts. Both physical maturation and hormonal changes affect behavior. The following section will focus on hormonal changes, and more specifically on the evidence supporting hormonal contribution to the adolescent pattern of motivated behaviors.

3. Hormonal systems in adolescence

3.1. Pubertal changes in hormonal secretion

Puberty is marked by fundamental modifications in both the hypothalamic–pituitary–gonadal (HPG) and hypothalamic–pituitary–adrenal (HPA) axes (Romeo, 2005). The HPG axis controls the secretion of sex hormones and the HPA axis controls the secretion of stress hormones. These pubertal shifts in HPG and HPA function result in very different levels of gonadal and adrenal steroid hormones during puberty relative to childhood. That is, the adolescent nervous system is exposed to significant and sustained increases in gonadal steroids such as androgens, estrogens and progestins (HPG axis), while pubertal alterations in stress reactivity can lead to changes in exposure to adrenal steroids such as cortisol and corticosterone (HPA axis).

Steroid hormones are potent modulators of neuronal function. For instance, gonadal and adrenal steroids have been shown to influence factors such as neuronal survival (Gould et al., 1991; Nordeen et al., 1985), neurogenesis (Cameron and Gould, 1994; Montaron et al., 1999; Tanapat et al., 1999), neurite outgrowth (Toran-Allerand, 1976; Wellman, 2001), synaptogenesis (Woolley, 1998), receptor expression (Handa et al., 1996), neurotransmitter synthesis (Luine et al., 1977), and neuronal excitability (Mermelstein et al., 1996). Thus, it is tempting to speculate that some of the major changes occurring in the structure and function of the adolescent nervous system are, at least in part, mediated by the marked changes in hormonal secretion during puberty. Importantly, the key structures involved in the triadic model of motivated behaviors, namely the mesolimbocortical pathway, amygdala and medial prefrontal cortex (Ernst et al., 2006), demonstrate relatively high levels of receptors for the gonadal and/or adrenal steroids (de Kloet, 1984; McEwen, 1981). Thus, the equilibrium achieved within the triadic system is likely to be influenced by hormonal changes during adolescence.

3.2. Pubertal maturation of the hypothalamic–pituitary–gonadal (HPG) axis

The hypothalamic–pituitary–gonadal (HPG) axis controls the secretion of gonadal steroids. The rise in gonadal steroids signalling the onset of puberty is mediated by increased secretion of gonadotropin-releasing hormone (GnRH) into the median eminence from neurosecretory cells located throughout the forebrain and hypothalamus (Ojeda and Urbanski, 1994; Plant, 1994). GnRH, in turn, signals the pituitary to release luteinizing hormone (LH), which then acts on the testes and ovaries to produce androgens, and estrogens and progestins, respectively.

Prior to puberty, the HPG axis is inhibited by relatively small amounts of gonadal steroids through a neuroendocrine negative feedback loop, and thus, androgen, estrogen, and progestin levels remain low before puberty. During pubertal development, the HPG axis becomes progressively less sensitive to the inhibitory feedback provided by gonadal steroids (Richardson et al., 2004; Sisk and Turek, 1983) (Fig. 5A). Interestingly, activation of the HPG axis actually begins before the onset of pubertal development, indicating that the change in HPG sensitivity to negative feedback is independent of the pubertal rise in gonadal steroids.

In addition to pubertal changes in negative feedback, recent attention has focused on two novel neuropeptides associated with GnRH secretion and puberty onset: kisspeptin and gonadotropin-inhibitory hormone (GnIH) (Dungan et al., 2006; Kriegsfeld, 2006). Kisspeptin stimulates GnRH secretion through a G-protein-coupled receptor (GPR54) expressed on GnRH neurons (Kauffman et al., 2007), and has been implicated in the onset of puberty (Navarro et al., 2007). Conversely, GnIH appears to inhibit GnRH neurons (Bentley et al., 2006; Kriegsfeld, 2006), suggesting that a reduction in GnIH activity may contribute to the rise of GnRH secretion observed around the onset of puberty. Together, the decreased negative feedback on the HPG axis and interaction of stimulatory and inhibitory neuropeptides on the function of GnRH neurons results in the pubertal rise in gonadal steroids, termed gonadarche, and commencement of fertility and sexual behavior (Kauffman et al., 2007; Ojeda and Urbanski, 1994). The extent to which these neurobiological changes contribute to the social re-orientation shift occurring during adolescence needs to be further examined.

3.3. The hypothalamic–pituitary–adrenal (HPA) axis

Prior to gonadarche and to the pubertal increase in gonadal hormones, the adrenal glands begin to secrete increasing amounts of androgenic steroids such as dehydroepiandrosterone (DHEA). This endocrinological harbinger of puberty is termed adrenarche. Adrenarche is thought to be specific to humans and nonhuman primates (Papadimas, 1997; Smail et al., 1982), but recent research indicates a similar process may occur in rats (Pignatelli et al., 2006). In addition to DHEA, the adrenals are also the primary source of the corticosteroids (e.g., cortisol in primates and corticosterone in most rodent species). Though both human and animal studies show slight increases in the secretion of corticosteroids during puberty (Apter et al., 1979; Spinedi et al., 1997; Walker et al., 2001), large amounts of corticosteroids are only typically released in response to physical and/or psychological stressors (Sapolsky et al., 2000).

The major neuroendocrine axis that controls stress-induced secretion of adrenal steroids is the hypothalamic–pituitary–adrenal (HPA) axis (Herman and Cullinan, 1997). The HPA axis is driven by the release of corticotropin-releasing hormone (CRH) from the hypothalamus into the portal system of the pituitary, which in turn causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH then stimulates the synthesis and release of the corticosteroids from the adrenal cortex. Similar to the HPG axis, the corticosteroids secreted by the HPA axis control their own release through a neuroendocrine negative feedback loop, such that high levels of corticosteroids suppress further CRH and ACTH release (Herman and Cullinan, 1997).

It is important to note that many brain regions outside the hypothalamus modulate HPA reactivity. For instance, the hippocampus

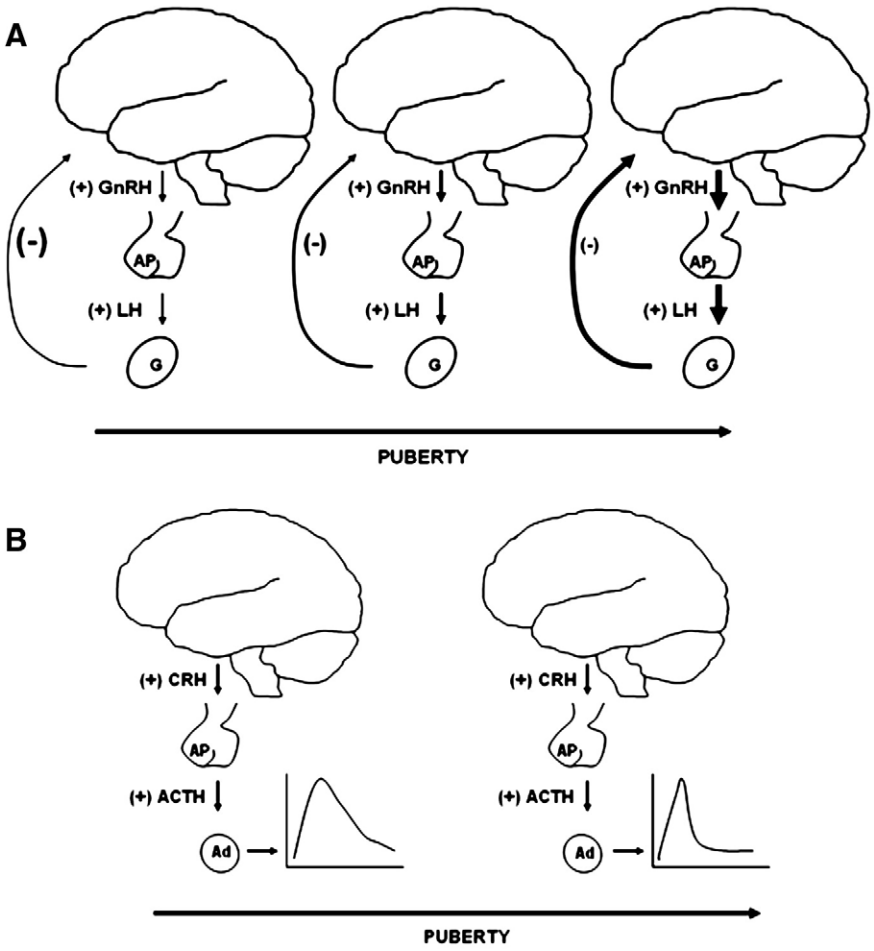

Fig. 5. Maturation of the HPG and HPA axis over puberty. A. The upper panel depicts changes in the hypothalamic–pituitary–gonadal (HPG) axis. In pre-puberty, small amounts of gonadal steroids (light arrow from gonads to brain) exert a relatively strong feedback. With puberty, larger amounts of gonadal steroids are required to maintain the negative feedback (larger arrow from gonads to brain), while androgen, estrogen and progestin levels rise. B. The lower panel depicts changes in the hypothalamic–pituitary–adrenal (HPA) axis. Puberty is characterized by a slight increase in the secretion of corticosteroids. However, the most significant change occurs in the release of corticosteroids in response to stress. The hormonal stress response appears to be protracted in prepubertal animals relative to adult animals.

and medial prefrontal cortex play important roles in corticosteroid-dependent negative feedback, while projections from the central nucleus of the amygdala can stimulate CRH release from the hypothalamus (Herman et al., 2003). Thus, maturation of these brain areas during adolescence may have important implications in HPA function and stress responsiveness (Romeo and McEwen, 2006).

The magnitude and duration of stress-induced corticosteroid responses change dramatically during puberty. For instance, prepubertal animals show an extended hormonal stress response compared to adults (Fig. 5B). Specifically, when male or female rats are exposed to an acute stressor (e.g., foot shock, ether vapors, restraint), corticosterone levels in prepubertal animals take at least 45 to 60 min longer to return to baseline compared to adults (Goldman et al., 1973; Romeo et al., 2006a,b, 2004a,b; Vazquez and Akil, 1993). Experience with stressors also influences the HPA response differently in prepubertal and adult animals, in that adults exposed to a repeated stressor demonstrate reduced ACTH and corticosterone responses, while prepubertal animals exhibit heightened responses (Romeo et al., 2006a). The physiological and behavioral implications of such altered responses in adolescent and adult animals are unknown.

It is presently unclear if similar shifts in HPA reactivity occur during adolescence in humans. However, as brain regions important in HPA function, such as the hypothalamus, hippocampus, amygdala and prefrontal cortex, all continue to mature well into adolescence, it appears likely that human adolescence will also be marked by changes in HPA responsiveness. Future studies will need to consider the role of puberty on HPA function and what interactions corticosteroids may have on brain regions implicated in the triadic model of adolescent emotional development. An interesting proposition is that hormonal changes during adolescence could sensitize structures to incoming stimuli, leading to sharper shifts in the triadic system equilibrium in adolescence relative to childhood or adulthood. These effects can be direct or modulated by neurotransmitter systems, such as the dopamine system.

4. Dopamine system in adolescence

4.1. An overview of dopamine system development

Synapses (Huttenlocher, 1984) and receptors (Andersen et al., 2000; Lidow et al., 1991; Seeman et al., 1987) are generally overproduced and pruned to match the needs of the environment (Andersen, 2003; Jacobson, 1973; Stewart and Cygan, 1980). These dramatic rearrangements occur primarily during adolescence across all mammalian species (Andersen et al., 2000; Lidow et al., 1991; Seeman et al., 1987), although regional variations exist in this process. As discussed below, the striatum, including the nucleus accumbens (ventral striatum), undergoes this process during puberty onset

(Teicher et al., 1995), whereas pruning within the medial prefrontal cortex (mPFC) is delayed relative to most other brain regions (Huttenlocher, 1979; Andersen et al., 2000).

Environmental events sculpt the immature system within specific windows of development, which are known as sensitive periods (e.g., Crews et al., 2007). The outcome is unique to any given sensitive period and therefore not necessarily predictable based on exposure to a similar inciting event at other stages. One such sensitive period may occur during the process of overproduction in adolescence (e.g., Andersen et al., 2008). The influence of sensitive periods on corticolimbic circuitry is particularly important, because of the pivotal role that this circuitry plays in psychopathology.

4.2. Neuroanatomy of the dopamine system

The dopamine pathway is discretely localized within specific regions, and is distributed along three paths, i.e., mesocortical, mesolimbic, and nigrostriatal. The mesocortical and mesolimbic systems receive dopamine input from cell bodies located in the ventral tegmental area (A10), while the nigrostriatal system is innervated by the substantia nigra (A9). The mesolimbic system projects to the nucleus accumbens, the amygdala, and the olfactory bulbs. The mesocortical system projects to the prefrontal cortex, including the orbital, medial (infralimbic and prelimbic regions in the rodent), and dorsolateral regions. Finally, the nigrostriatal system innervates the caudate, putamen, and globus pallidum. Dopaminergic cell bodies emanating from A8 into the retrorubral area also exist, but will not be discussed further here.

Dopaminergic innervation is typically measured by immunoreactivity to the catecholamine biosynthetic enzyme tyrosine hydroxylase (TH-IR), although the density of the dopamine transporter (DAT) is also used. TH-IR or DAT concentrations reach adult levels early in life in the dorsal striatum and ventral striatum, with no significant changes during the adolescent period, and decrease gradually with age (Haycock et al., 2003; Moll et al., 2000; Andersen and Teicher, 2002; Meng et al., 1999). However, the ventral striatum is a complex structure, with multiple subregions that extend beyond the core and shell dichotomy (Heimer et al., 1997). Dopamine innervation within these subregions is likely to evolve along distinct trajectories during adolescence. Some evidence of such subregional differentiation is presented below. Similarly, ontogenic dopaminergic changes have been well documented in the prefrontal cortex across the adolescent period (Rosenberg and Lewis, 1995; Benes et al., 2000; Huttenlocher, 1979). For example, during this period, dopamine innervation reaches the deep layers V and VI of the prefrontal cortex (Benes et al., 2000), where it modulates target structures.

4.3. Changing signaling mechanisms that uniquely drive individual microcircuits within these dopaminergic systems

Dopamine receptor subtypes were initially defined as D1 and D2, based on their actions on the cyclic AMP second messenger system (Kebabian and Calne, 1979). With advances in technology, this simple dichotomy has expanded to D1 and D2 families. The D1 family is composed of D1 and D5 receptors (Bergson et al., 1995). D1 and D5 are more excitatory in nature, are linked to stimulatory G proteins, and classically increase the activity of the second messenger cAMP. D1 and D5 share common locations of expression, but D5 expression has a greater distribution based on study of the non-human primate. The D2 receptor family is subdivided into D2, D3, and D4 receptors and is widely distributed. These receptors are inhibitory in nature, couple with inhibitory G proteins, and reduce cAMP activity, protein kinases, and the inositol triphosphate (IP3) system.

Functions attributed to these receptors are diverse and are too broad to be adequately covered here. Briefly, D1 receptors play a vital role in working memory and are associated with disorders that show deficits in this function (e.g., schizophrenia, depression, attention-deficit hyperactivity disorder). D2 receptors have gained notoriety for their role in antipsychotic action, and are often linked to schizophrenia. In addition, these receptors are thought to modulate novelty-seeking and impulsivity.

A neurocomputational model of the role of dopamine in reinforcement learning (Frank et al., 2005) has been formulated on the basis of the functional dichotomy of the D1 and D2 receptors and the established coding of dopamine flux for learning contingencies (Schultz, 2007). This model attributes a "Go" function (approach of positive stimuli) to D1 receptors in response to phasic increases of dopamine, which signal the receipt of unexpected rewards, and a "NoGo" function (avoidance of negative stimuli) to D2 receptors in response to dopamine dips, which signal the absence of expected rewards. This model was extended from selectively involving the basal ganglia to including the orbitofrontal cortex as the site of object value representations (Frank and Claus, 2006). Such work is singularly important as it provides quantitative measures of mechanisms that can predict behavior. As knowledge on neurodevelopment accumulates, the incorporation of the dimension of ontogenic changes into such models could help in the formulation of the first neurocomputational formulation that can predict developmental changes in motivated behavior. The hope is that neural systems models, such as the triadic model, could be useful for the elaboration of new mathematically-based models.

At present, most of our knowledge on ontogenic molecular changes comes from animal studies. Here, we will review findings in rodents. With the usual caveats related to inter-species differences, we characterize the juvenile period as postnatal (P) day 20 through day 28, a period that precedes pubertal changes; the adolescent period as P28 through P50; and the adult period as beyond P90. These stages are subject to debate and definitions vary across laboratories. An additional caveat is that most studies have been conducted selectively in male animals, which raise the issue of sex differences.

4.3.1. Prefrontal cortex

Dopamine projections from the VTA form synapses on both pyramidal and GABAergic interneurons (reviewed by Gonzalez-Burgos et al., 2007). Rather than by direct dopamine modulation of these neurons, non-specific dopamine synaptic release sites seem to work by volume transmission, i.e., overall levels of extracellular dopamine (Gonzalez-Burgos et al., 2007). In the cortex, extracellular dopamine concentration closely reflects neuronal activity, because of the low expression of DAT in this region.

D1 and D2 receptors are differentially activated by the level of dopamine volume transmission. D1 receptors are more likely to respond to low dopamine levels, and D2 receptors to high dopamine levels (Durstewitz et al., 2000). Functionally, lower concentrations of dopamine are hypothesized to be associated with more focused, goal-directed activity. Higher concentrations of dopamine are believed to reduce this focus, and in turn, facilitate the integration of multiple environmental inputs that are involved in learning and behavioral flexibility (Floresco, 2006; Berridge 2007). As mentioned above, other formulations of the role of dopamine on reinforcement have been proposed based on the complementary functions of the D1 and D2 dopamine receptors (Frank and Claus, 2006). During adolescence, ontogenic changes in dopamine levels and receptor density serve to maximize learning about the environment, but can also lead to highly focused (and sometimes pathological) behaviors.

Unique characteristics of dopamine function within the prefrontal cortex during adolescence include tight autoregulation of dopamine synthesis and release (Andersen et al., 1997a; Teicher et al., 1991), and changes in a number of indices such as firing rate of dopamine neurons, (Marinelli, unpublished observation), dopamine receptor density (Andersen et al., 2000; Tarazi and Baldessarini, 2000), and second messenger system activity (Andersen, 2002). These features culminate in enhanced prefrontal dopamine drive during adolescence (Spear, 2000). The functional significance of this uniquely strong dopaminergic

drive during adolescence may be to facilitate the learning of new associations between stimuli/action and outcome. Much more is to be learned about the relevance of this phenomenon to adolescent behavior.

The triadic model predicts that adolescents are biased towards rewarding events/activities that can be amplified within a social context. Simultaneously, adolescents may experience a diminished impact of aversive consequences in the context of potential rewards, which would contribute to elevated risk-taking and impulsivity. Increased dopamine activity within the prefrontal regions would suggest greater, and not lesser, modulation over behavior, which is in contrast to the theoretical models of reduced cognitive regulatory control in adolescence (Yurgelun-Todd, 2007; Galvan et al., 2006a; Durston et al., 2006; Dahl, 2004; Ernst et al., 2006). However, the complex nature of dopamine signaling changes within the microcircuitry of the developing prefrontal regions suggests that changes in receptor distribution, and not overall dopamine activity, influences a number of these adolescent behaviors.

An example of this complexity is illustrated by the differential maturation trajectories of dopamine receptors during adolescence. Overall, dopamine receptors within the prefrontal cortex rise and fall across adolescence. Both D1 and D2 receptors increase by 20–35% and reach a peak density during adolescence before pruning (Andersen et al., 2000). However, these receptors demonstrate differential rates of pruning, with D1 receptors pruning earlier than D2 receptors.

In addition, age-related changes in dopamine receptors are not uniform within the cellular pools of the prefrontal cortex. Instead, the overproduction of D1 receptors occurs selectively on glutamatergic pyramidal cells that project to the ventral striatum (Brenhouse et al., 2008; Gorelova et al., 2002; Tseng and O'Donnell, 2005). Specifically, only 2% of these glutamatergic projections are D1 immunoreactive in juvenile rats, rising to 44% at P40, and falling down to 6% with maturity at P100. This D1 receptor population is associated with highly focused behavior and motivational responses to environmental events (Kalivas et al., 2005), perhaps making it more difficult for adolescents to modulate pre-potent responses to appetitive stimuli (Brenhouse et al., 2008). Consistent with the incentive salience model of Berridge (2007), adolescents are more likely to show behaviors similar to those observed in addiction: novelty-seeking, impulsivity, and a bias towards appetitive stimuli.

In contrast, D2 receptors excite the activity of fast-spiking GABA interneurons after puberty (Tseng et al., 2007). These neurons are important for efficiently integrating multiple inputs in real-time. However, whether the overproduction of D2 receptors during adolescence (Andersen et al., 2000) is selective for GABA or glutamate neurons is not yet known. Overall, D2 receptors in the PFC allow for more flexibility by allowing multiple inputs to modulate glutamatergic output.

The triadic model predicts that adolescent patterns of motivated behaviors result from greater influence of striatal circuits, lesser contribution of amygdala circuits, and immature cognitive controls relative to adult dynamics. Data from rodents suggest that immature prefrontal function reflects stronger D1-driven, prepotent responding rather than overall weaker prefrontal dopaminergic control. The particular effect of stress on the triadic model is worth considering. Similarly to addictive drugs, stress increases extracellular levels of dopamine. This increase is typically larger in the prefrontal cortex relative to the ventral striatum and the dorsal striatum (Abercrombie et al., 1989). However, this regional pattern of stress-related extracellular dopamine elevation emerges with age (Lyss et al., 1999). Stress-induced changes in dopamine release and HPA-related effects (reviewed above) peak within the prefrontal cortex during adolescence (Andersen and Teicher, 2008; Leussis and Andersen, 2008; Pryce, 2008). Thus, age-related changes in dopamine prefrontal activity are now well documented not only at baseline but in different contexts (e.g., stress, exposure to addictive drugs), and suggest distinct context-dependent modulation of the triadic balance during adolescence. Ultimately, the optimal balance between D1 and D2 prefrontal cortical systems would be expected to facilitate motivational drive for appetitive stimuli (D1 receptors), and permit a wider range of stimuli to be processed (D2 receptors). This scheme would enhance both motivational drive and the capacity to attend to co-incidental information, which, in turn, would concur to promote learning/experiencing about a wider array of stimuli and situations (Berridge, 2007). Finally, the strengthening of these functions in adolescence should help individuals to separate from the familial safety and move towards new social environments, while at the same time learning about novel situations in preparation for the adult life.

4.3.2. Striatum

Early animal developmental studies of dopamine activity within the striatum have suggested a linear increase in presynaptic markers such as dopamine content, dopamine transporter binding, and TH-IR up to the onset of adolescence (Broaddus and Bennett, 1990; Coyle and Campochiaro, 1976). More recent works go beyond the preadolescent period and include adolescent periods. These studies have documented important changes during this time in pre-synaptic, intra-synaptic and post-synaptic functions of the dopamine system.

4.3.2.1. Presynaptic regulation of dopamine activity. The striatum regulates dopaminergic activity through both inactivation by the DAT (dopamine reuptake into pre-synaptic afferent cells) and autoregulatory processes (dopamine synthesis), in contrast to the PFC, which relies mainly on autoregulatory processes. Levels of the DAT rise and fall over the course of adolescence (Moll et al., 2000). Autoreceptors that regulate dopamine synthesis, but not release (Andersen and Gazzara, 1993), gradually desensitize as puberty approaches (Andersen et al., 1997a), but remain present in the striatum throughout adulthood. Of note, blockade of the DAT by cocaine is not associated with differential changes in extracellular dopamine levels between adolescents and adults (Frantz et al., 2007).

4.3.2.2. Extracellular dopamine. Overall, ontogenic changes in striatal dopamine regulatory processes seem to maintain extracellular dopamine at a lower level across the adolescent period compared to adult levels. In addition, these levels show some variability within distinct sub-periods of adolescence, i.e., early vs. middle vs. late adolescence, reflecting a transient increase in mid-adolescence (45 days) (Badanich et al., 2006). This transient increase in extracellular dopamine levels, without a change in regulation, is consistent with neuronal bursting activity at the level of dopamine cell bodies (Marinelli, unpublished observation).

4.3.2.3. Dopamine post-synaptic receptors. Similar to the prefrontal cortex, the striatum demonstrates a heightened dopaminergic state at the receptor level. D1 and D2 dopamine receptor striatal populations are over-expressed and pruned following approximately the same time course as dopamine innervation (as indicated by DAT binding) (Teicher et al., 1995). These maturational trajectories have been found to differ by regions (ventral vs. dorsal striatum) and also by receptor type (D1 vs D2 dopamine receptors).

In the rat ventral striatum, D1 receptor density increases dramatically by 156% between 25 and 40 days in males and declines modestly (25%) by 80 days of age. In the dorsal striatum, however, the adolescent rise in receptor density is more transient. Here, D1 receptor density increases 67% between 25 and 40 days in the rat, but declines sharply by 54% of 40 day-old values in adulthood.

D2 receptors follow a different pattern of expression. D2 receptor density steadily increases and reaches its peak in adolescence. In both ventral and dorsal striatum, D2 receptors are pruned and remain stable from 60 days of age (late adolescence) and onward (Teicher et al., 1995).

Age-related changes in receptor expression levels will produce varying degrees of activity post-synaptically. For example, immediate

early genes, such as *c*-fos, show differential levels of activity as a function of age in response to stimulants (Cao et al., 2007; Andersen et al., 2001). However, the net effect of the pre- and post-synaptic ontogenic changes in the striatum has not been clearly assessed at the level of appetitive or aversive drive, in contrast to the adult literature (e.g., Frank et al., 2007; Everitt and Robbins, 2005). The regulation of extracellular dopamine, which reduces dopamine levels in the synapses, undergoes ontogenic changes responsible for the transient increase in mid-adolescence period. However, the excess of post-synaptic dopamine receptors might mitigate the consequences of such lower dopamine levels.

Finally, as a general caveat, the findings reviewed above all originate from rodent studies and their generalization to humans is only speculative. Another limitation is that these studies were conducted solely in males. Since a few studies show sex differences in the ontogeny of dopamine, as described below, the full picture of the maturation of the dopamine system awaits significantly more work.

4.3.3. Sex differences

Sex-dependent changes in signaling mechanisms occur in the striatum and the prefrontal cortex, although the knowledge gained so far is patchy. Interestingly, these changes do not seem to be influenced by the pubertal gonadal hormonal rise as shown by studies of castration and ovariectomy (Andersen et al., 2002).

Contrasting with significant pruning in the male striatum, females fail to demonstrate pruning of D1 or D2 receptors during the adolescent/adult transition. This may be partly due to the observation that females, in contrast to males, do not show overexpression of these receptors during adolescence.

In adulthood, sex differences in the expression of D1 receptors vary in function of the striatal region. The dorsal striatum shows similar pattern of D1 receptor expression in males and females (Andersen et al., 1997b). However, the ventral striatum exhibits an excess of ~58% D1 receptor density in males compared to females. The functional consequence of this sex difference may be mitigated by sex differences in cyclic adenosine monophosphate cyclase activity (cAMP), which also undergoes developmental changes during adolescence (Andersen, 2002).

Finally, adolescent females have been shown to be more sensitive to changes in motor activity in response to dopamine manipulations (Stewart and Cygan, 1980) and to drugs of abuse (Walker et al., 2006) compared to adolescent males (Andersen et al., 2002). These sex differences in vulnerability to dopamine perturbations might eventually be explained by a better understanding of ontogenic changes in the dopamine system.

5. Summary

This review was focused on the neurobiology of motivated behaviors from a developmental perspective. Although far from being exhaustive, this review moves from a global to a molecular framework, revealing huge gaps in knowledge. Our main goal was to provide a foundation against which hypotheses about mechanisms underlying changes in motivated behaviors during adolescence could be formulated.

Based on a global approach, two neural systems models were presented that provide a simplistic neural architecture of the neural underpinnings of motivated behavior (fractal triadic model) and social information processing (SIPN). These models show how neural changes, developmental or pathological, can affect behavioral outputs. In a nutshell, the fractal triadic model proposes three functional systems that support approach, avoidance and behavioral regulation. Each of these systems involves the same three neural nodes, striatum, amygdala and prefrontal cortex. However, these nodes exhibit a functional dominance towards approach, avoidance or regulation, respectively, that can be used as a starting point to understand changes in behavior.

Adolescence is characterized by a propensity towards approach behavior in situations of incentives. However, huge individual differences moderate this generic statement, and the study of these individual differences can provide a unique opportunity to examine the factors that modulate motivated behavior. Psychopathology presents specific alterations in motivated behaviors that can be captured by a neural systems approach, like the fractal triadic model. For example, anxiety disorders are typically characterized by the primacy of avoidant behavior. Addiction is defined by abnormal approach behavior towards a set of specific stimuli.

The second theme covered in this review addresses pubertal changes. Puberty, with its cascade of hormonal alterations, is expected to influence the overall function of the neural systems model. This is quite an open area of research, as relatively little work, so far, has been conducted to systematically evaluate these effects. We hope that this review will foster such lines of research, and help strategize this endeavor.

The last section addressed one aspect of molecular changes (dopamine) across development that can directly impact motivated behavior. The central role of dopamine in motivated behavior is well recognized. This role was not covered here, but a number of excellent reviews are available (e.g., Wickens et al., 2007; Di Chiara and Bassareo, 2007b; Nicola, 2007; Floresco and Magyar, 2006). Ontogenic changes in dopamine function seem to facilitate the responding to multiple stimuli and, at the same time, enhance the intensity (salience) of appetitive stimuli. This effect on salience is also probably true for aversive stimuli, but, in this case, it may be more susceptible to context than in the case of rewarding stimuli. The influence of context may explain the discrepancies in the literature with respect to enhanced or diminished sensitivity to punishment in adolescents. This last statement is highly speculative, but opens the door to important research questions to be added to the many more issues that are raised in this review.

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