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Review

The emergence of depression in adolescence: Development of the prefrontal cortex and the representation of reward

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Abstract

Adolescent development is accompanied by the emergence of a population-wide increase in vulnerability to depression that is maintained through adulthood. We provide a model for understanding how this vulnerability to depression arises, and why depression is so often precipitated by social rejection or loss of status during this phase. There is substantial remodeling and maturation of the dopaminergic reward system and the prefrontal cortex during adolescence, that coincides with the adolescent entering the complex world of adult peer and romantic relationships, where the rewards that can be obtained (feelings such as belonging, romantic love, status and agency) are abstract and temporally distant from the proximal context. Development of the prefrontal cortex makes it possible to pursue such complex and distal rewards, which are, however, tenuous and more readily frustrated than more immediate rewards. We hypothesize that when these distant rewards are frustrated they suppress the reward system, and that when such suppression is extensive and occurs for long enough, the clinical picture that results is one of depression.

Keywords: Adolescence; Depression; Reward; Prefrontal cortex

Contents

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> Left to itself the future has nothing to offer. We have to make up the future until we get there.
>
> Adam Phillips, *Side Effects*, 2006, p. 97

Adolescence is a time of enormous flux and development, with changes occurring in almost every domain of a young person's life; from the physical, to the psychological, the interpersonal and the sociocultural. Adolescence has been defined as a developmental period that starts with puberty and ends with the assumption of adult roles and responsibilities (Dahl, 2004; Steinberg et al., 2006); a definition that captures the extent to which biologically driven processes shape important social changes during the period. It is the aim of this paper to demonstrate how biological development interacts with social development during adolescence, and how, in particular, the prefrontal cortex becomes able to represent increasingly complex and distant social goals. As the opening quote suggests, the future exists only as it is created in one's mind. We contend that this process of mentally representing the future becomes more sophisticated during adolescence, and enables young people to engage with the more complex social world that emerges during the period. However, we conjecture that a cost of the ability to mentally represent salient goals that are abstract and temporally distant is an increased vulnerability to depression when these more tenuous goals are frustrated. Most neurobiological theories of adolescent psychopathology suggest that the major explanation for vulnerability to mental disorder in the period is the delay in maturation of the prefrontal cortex compared to earlier-maturing limbic areas. The theory we develop here, by contrast, implicates development of the prefrontal cortex itself as central in explaining the rise in vulnerability to depression during the adolescent period and beyond.

1. Depression in adolescence

Of the many changes that occur in adolescence, the one that forms the focus of this article is the increase in the prevalence of clinical depression (principally DSM-IV major depressive disorder; APA, 1994). The prevalence increases almost linearly from puberty: from a 1-month prevalence in late childhood of 2 percent (Costello et al., 2002; Rutter, 1994), to a 1-month prevalence during late adolescence of 6 percent (Blazer et al., 1994), and a lifetime prevalence by the mid-twenties period of about 1 in 4 (Angst and Dobler-Mikola, 1984; Kessler et al., 2001; Lewinsohn et al., 1998). This increased vulnerability compared to childhood is characteristic not only of adolescence, but is sustained for most of adult life, with some decline in the post-menopausal years for women (Jorm, 1987, 2000). The increase occurs particularly among females, and it is from puberty that the preponderance of females in depressed samples emerges (Cyranowski et al., 2000; Piccinelli and Wilkinson, 2000). Various explanations have been offered for this increase in the prevalence of depression, including that it is the result of: (i) the effects of a changing hormonal milieu on the brain (Angold et al., 1999; Brooks-Gunn and Warren, 1989), (ii) the changed experience of the post-pubertal body (Susman et al., 1987), (iii) an increased experience of interpersonal stress (Leadbeater et al., 1995) and (iv) changes in cognitive style and capacity, especially for rumination (Nolen-Hoeksema et al., 1991). Each of these explanations has garnered important evidence in their support, although we argue that they fail to capture the strong interaction between the different domains of adolescent development. In particular, there has been an absence, until recently, of theories that integrate the way that developmental changes in the brain result in cognitive and emotional changes that alter the way adolescents interact with the social environment to give rise to an increased vulnerability to depression.

1.1. Recent models

Recently, three models have appeared in the literature that have sought to explain adolescent vulnerability to depression using more integrative, neuroscientifically principled frameworks.

1.1.1. The "social information processing network"

Nelson et al. (2005) propose that changes in social behavior during adolescence are correlated with the development of a brain system that they refer to as the social information processing network. The three components of the network develop along different trajectories, such that the development of the "affective node", approximately equivalent to the subcortical limbic system, outpaces maturation of the cortically based "cognitive-regulatory node". The mismatch is proposed to create a vulnerability in which strong emotional responses to social stimuli are not tempered by the yet-to-mature regulatory mechanisms. This is said to explain an increase in the rate of depression during adolescence.

1.1.2. The triadic model

Ernst et al. (2006) put forward a triadic model—composed of approach, avoidance and regulatory components—to describe changes in adolescent behavior. They propose that development of the approach system precedes maturation of the avoidance system, and that this mismatch cannot be corrected by the still immature third arm of the triad; the cortically based regulatory system. The authors apply this model to depression, and propose that depression is associated with changes in two of the triadic model's arms—decreased approach and increased risk avoidance—though the mechanism by which this occurs is not elaborated.

1.1.3. The dysregulated positive affect model

A third model, proposed by Forbes and Dahl (2005), examines the relationship between adolescent depression and the development of the neural reward system. They conceptualize depression as a reduction in positive affectivity (a factor that indexes active engagement with the environment), which is a theory that has been proposed previously (Clark and Watson, 1991; Costello, 1973; Watson and Tellegen, 1985) and that will be expanded on in this paper. They make a link between development of the neural systems underlying reward in adolescence, which may become vulnerable to dysregulation as a consequence of their remodeling, and a predisposition to depression.

These three frameworks provide useful heuristics for explaining the neurodevelopmental basis for the affective and behavioral changes observed in adolescence. By demonstrating how the development of regulatory mechanisms lag behind development of affective brain systems, the models seem particularly appropriate for explaining the increased rates of dysregulated behaviors, especially drug use and risk taking, that emerge during adolescence but decline during adulthood when regulatory brain systems have reached adult levels of maturity. None of the models, however, provide specific detail about how, exactly, the changes in regulatory and affective systems give rise to depression as opposed to other forms of emotional and behavioral dysregulation. They are not able to explain the increased rates of depression that *start* in adolescence but *persist* though adulthood, by which time, presumably, the regulatory mechanisms whose delayed development putatively gave rise to affective dysregulation, and as a consequence depression, have matured. Fig. 1 shows graphically how the proposed mismatch between development of the limbic and prefrontal cortical systems makes more sense of the epidemiological data for drug use disorders than it does for depression. Specifically, it shows that the incidence of depression remains elevated beyond the age of 25, by which time prefrontal cortical development has been completed (Giedd et al., 1999; Gogtay et al., 2004; Paus, 2005; Sowell et al., 2003).

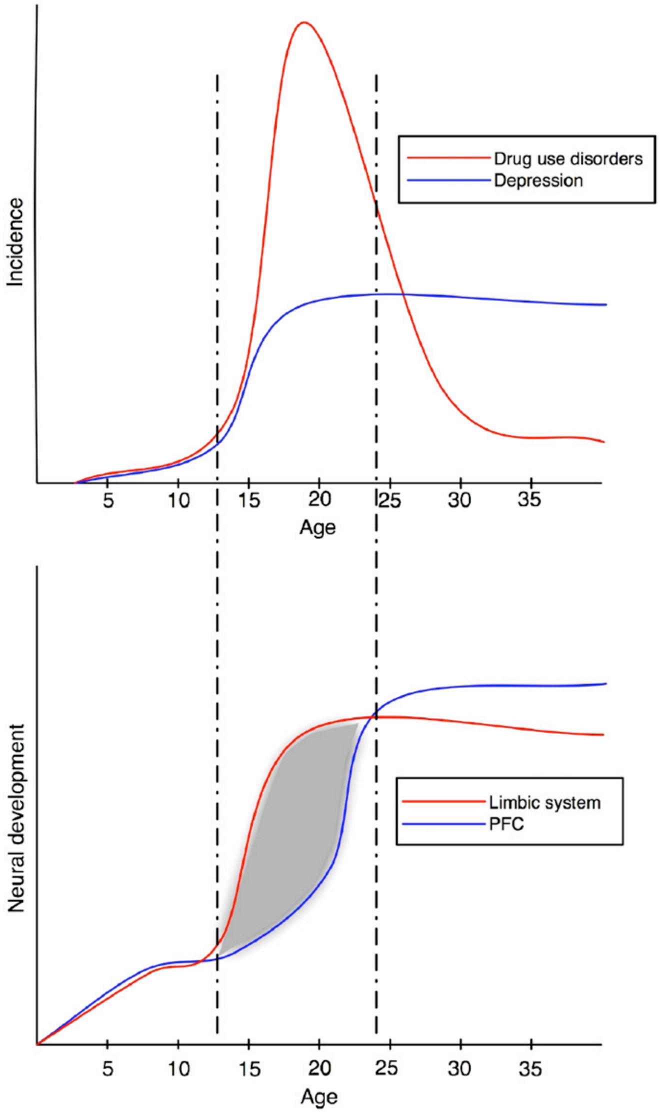

Fig. 1. The top graph schematically describes the ages of onset for depression and drug use disorders across the first four decades of life (adapted from Burke et al., 1990), and the bottom is a graphical representation of the development of the limbic system and prefrontal cortex (PFC) over the same time span. Recent theories have implicated a mismatch between development of the limbic system and PFC (represented by the shaded area in the bottom graph) as being responsible for a heightened vulnerability to mental disorder in adolescence. While this explanation has some validity for externalizing disorders such as drug abuse and dependence, it has less for depression, where vulnerability to the disorder remains evident through adulthood, beyond the time at which prefrontal cortical maturation is complete.

In addition, the theories appear to hold that, in the main, affective and motivational systems exist subcortically, while regulatory systems are cortical, evincing one of Davidson's (2003) "sins" in the study of emotion—there is substantial evidence that the generation of affect involves cortical regions, and that regulatory mechanisms involve subcortical regions (Phillips et al., 2003). Indeed, that affect and affective regulation can even be said to exist as separable processes has recently been brought into question (Campos et al., 2004).

Our own proposal as to why vulnerability to depression increases during adolescence attempts to build on these models. We agree that depression is usefully conceptualized as a reduction in reward sensitivity, and that adolescence is a period where affective experiences become intensified and motivationally enhanced, especially in social contexts. Rather than portray depression as a failure of regulation; however, our theory suggests that vulnerability to depression is increased by the adolescent's enhanced capacity to anticipate different types of rewards to those that dominate childhood: rewards that are more abstract, tenuous and temporally distant, and, therefore, more easily frustrated.

1.2. The emergence of depression post-puberty

Depression that emerges during adolescence is often the forerunner to adult depression, a disorder that because it starts so early, has such a high prevalence, and is so often chronic and recurrent—about 70 percent of people will have a subsequent episode of depression after the first (Kessler and Walters, 1998; Rao et al., 1995)—affects a larger proportion of the total life course than any other chronic condition (Kessler et al., 2001; Mathers et al., 2000). Depression that starts in adolescence appears to be different from childhood depression. Compared to adolescent depression, prepubertal depression is more likely to be associated with an adverse family environment (Harrington et al., 1996) and less likely to be familial (Silberg et al., 2001). When children who have been depressed are followed through adolescence and to early adulthood, they are, in contrast to those with adolescent-onset depression, more likely to have conduct and substance use disorders than they are to have recurrent depression (Harrington et al., 1990; Weissman et al., 1999b). Puberty thus appears to herald not only a greater risk of depression, and the emergence of a substantial gender difference in this risk, but also the start of life-long recurrent depression in many people (Lewinsohn et al., 1999; Rao et al., 1995; Weissman et al., 1999a).

Depressive episodes during adolescence are usually first episodes, and there is substantial research to suggest that life stresses play a more important role in this episode compared to later episodes (Brown and Harris, 1989; Lewinsohn et al., 1999; Monroe and Harkness, 2005; Monroe et al., 1999). The breakup of a romantic relationship is particularly potent, with almost half of all adolescents having their first episode of depression having had a relationship breakup in the preceding year (Monroe et al., 1999). Rejection by peers also has significant salience for adolescent depression (Hecht et al., 1998; Prinstein and Aikins, 2004; Vernberg, 1990), and other failures and disappointments are common (Brown and Harris, 1989). It is important, therefore, for any proposed theory of adolescent depression to account for the role of environmental, and particularly interpersonal, stresses as precipitants. Before we proceed to present our model, however, we need first to demonstrate how depression is related to reward sensitivity, and how interpersonal events assume such an important reward function in adolescence.

2. Reward and depression

One of the difficulties that arises in the study of depression is the heterogeneous nature of its clinical presentation, which has led to a search for more fundamental underlying biological and psychological substrates. Analysis of the factors underlying emotion and motivation more generally has shown that two higher-order dimensions are salient: positive affectivity (other terms include behavioral activation, approach, and reward sensitivity), and negative affectivity (or behavioral inhibition, or avoidance) (Davidson, 2000; Gray, 1973; Whittle et al., 2006). Perhaps counter-intuitively, positive affectivity is the factor that is more specifically related to depression (Clark and Watson, 1991; Depue and Iacono, 1989; Watson and Tellegen, 1985), and, in support of this, reduced positive affectivity is the endophenotype for depression that is most consistently supported in the literature (Hasler et al., 2004). Major depressive disorder is characterized by a number of symptoms that accord with the concept of reduced positive affectivity. Symptoms such as reduced energy, loss of interest in previously enjoyed activities, loss of libido, lowered self-confidence, loss of appetite, hopelessness and social withdrawal are frequently observed in even mild depression; with weight loss due to reduced appetite and psychomotor retardation becoming apparent as depression becomes more severe (Goldberg and Huxley, 1992).

Positive affect is generated by rewarding engagement with the environment (Davidson, 2000; Depue and Collins, 1999; Lazarus, 1991). Rewards, which can be broadly defined as stimuli that an organism will do work, or take action, to approach (Rolls, 2000), act as positive reinforcers to increase behaviors that lead to achievement of goals; and can come to act as goals in their own right (Schultz, 2000). Interpersonal rewards hold particular potency for humans and are important contributors to positive affectivity (Depue and Collins, 1999; Depue and Morrone-Strupinsky, 2005). The higher-order dimension of positive affectivity has two lower-order components—affiliation and agency—that represent the important contribution of interpersonal engagement (Depue and Collins, 1999; Depue and Morrone-Strupinsky, 2005; McCrae and Costa, 2003; Tellegen and Waller, 1994). Affiliative rewards reflect the enjoyment and valuation of close interpersonal bonds, and engender feelings of warmth and affection (Depue and Collins, 1999). They are specifically interpersonal in nature. Agentic rewards are experienced with social dominance and the enjoyment of leadership and potency; they encompass goals that are both social and more broadly reward-related (Depue and Collins, 1999). These interpersonal rewards are perhaps the most salient and anticipated of all human rewards.

The development of depressive symptoms that reflect low positive affectivity and that follow interpersonal rejection or other disappointments make adaptive sense from an evolutionary perspective. Allen and Badcock's (2003) "social risk hypothesis" proposes that depressive symptoms represent a defensive psychobiological response to increased perception of interpersonal risk. When a person perceives that their actions have been unsuccessful in achieving their interpersonal goals, then it may be in their interest to reduce the risk of further deterioration in their social resources by withdrawing from interpersonally risky endeavors, reducing their seeking of rewards, and reflecting on their unsuccessful actions and how they could improve their chances of achieving their goals in the future. It is our contention that the pursuit of interpersonal rewards takes on particular importance during adolescence, and we will outline later how this is related to development of the prefrontal cortex and dopaminergic system, and how this leads to a vulnerability to depression. First, however, we offer a review of the basic functions of the reward system.

2.1. The neurobiology of reward

The major underlying neural substrate of reward is the dopaminergic system, which at its core consists of the nucleus accumbens and dopaminergic projections to this area from the ventral tegmental area (Chambers et al., 2003; Nestler and Carlezon, 2006). It is the release of dopamine into the nucleus accumbens that is the principal event for the translation of motivation into action, and for driving of behaviors that seek to attain goals (Panksepp, 1998). Dopamine release from the ventral tegmental area is initiated by glutamatergic projections from the nucleus accumbens, prefrontal cortex, anterior cingulate cortex and amygdala, and this dopamine release in turn not only modifies the activity of the initiating region, but all the regions to which it projects (a "one-to-many" pattern of influence) (Lewis, 2005). The action of nucleus accumbens neurons is indirect: the region projects GABA-ergic neurons to the ventral globus pallidus, that then project to the thalamus, that in turn influences diverse cortical and subcortical structures associated with motor output (Chambers et al., 2003). The dopaminergic system is demonstrably complex, with multiple connections between brain structures that have sometimes reciprocal and overlapping influences on one another (as illustrated in Fig. 2).

Dopamine has a neuromodulatory function: it induces little change in neuronal basal activity by itself, but potentiates or suppresses responses evoked by other transmitters (Seamans and Yang, 2004). Most research has shown that dopamine suppresses glutamatergic inputs (Hirata et al., 1984; Vives and Mogenson, 1986; Yim and Mogenson, 1982), an action that "chisels away at the diffuse and rather amorphous mass of excitatory action and gives a more specific form to neuronal performance" (McGeer et al., 1978, p. 133). The significance of this is that the dopaminergic system promotes the neuronal representation of salient, relevant stimuli to stand out against the diverse range of stimuli (both internal and external) that could potentially be represented but that are forced into the background by the system's activity. The capacity of dopamine to stabilize activity is important for orienting action toward features of the environment that are relevant to an individual's goals in the face of multiple and ambiguous stimuli; a feature of many social interactions.

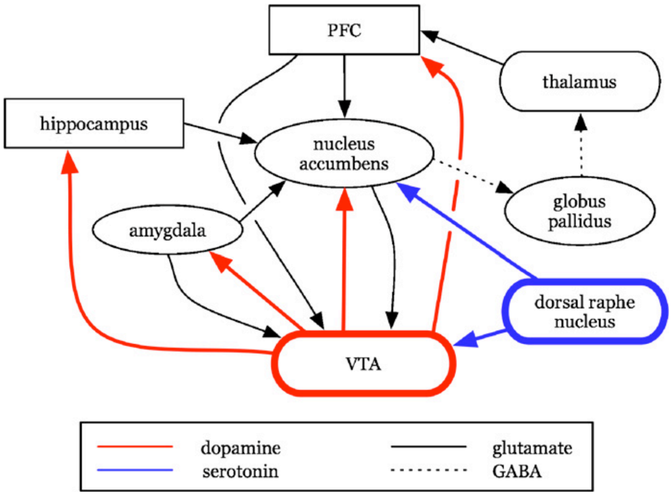

Fig. 2. A schematic representation of the dopaminergic reward-system. Reward-related dopaminergic projections originate from the ventral tegmental area (VTA) and project to subcortical regions and to the prefrontal cortex (PFC). The nucleus accumbens is critically placed for the integration of reward-related information, receiving as it does afferent projections from the VTA and from the regions to which the VTA projects. Dopaminergic output from the VTA is modified by projections arriving from the PFC, amygdala and nucleus accumbens. The major output pathway from the nucleus accumbens is via GABA-ergic projections to the globus pallidus, that then projects to the thalamus, and from there to the prefrontal cortex (and other regions, not illustrated). Serotonergic projections from the dorsal raphe nucleus have an important modulatory influence on dopamine release.

Serotonin, the neurotransmitter most often implicated in the pathogenesis of depression (Stahl, 2000), interacts with the dopaminergic system to further shape reward function. The dorsal raphe nucleus projects serotonergic neurons to both the ventral tegmental area and nucleus accumbens (De Deurwaerdere et al., 1998; Di Mascio et al., 1998), and modulates dopaminergic activity at these sites and at their presynaptic terminals (Benloucif and Galloway, 1991; Parsons and Justice, 1993). Some authors (e.g., Katz, 1999) have suggested that the primary function of the serotonergic system is to reduce impulsive over-responding to proximal affective stimuli. Serotonin acts to inhibit dopaminergically mediated effects on exploratory activity, sensitivity to stimuli, and reactivity to proximal rewards in favor of maintaining affective engagement with long-term goals (Depue and Collins, 1999; Depue and Spoont, 1986; Spoont, 1992).

The monitoring of action is critical if goals are to be reached, especially more complex goals such as occur in a social context. The dorsolateral prefrontal cortex contributes an important monitoring function by maintaining goal-related information in an active state, with evidence that neurons in the region sustain their patterns of firing during the delay between the presentation of a stimulus and the later attainment of reward (Funahashi et al., 1989; Fuster and Alexander, 1971; Goldman-Rakic, 1987; Smith and Jonides, 1999). The ability to maintain a representation of a goal over a period of time, or ''memory for the future'' (Ingvar, 1985), is a part of the dorsolateral prefrontal cortex's function in the temporal organization of behavior. A related function is the sequencing of behavior to attain rewards, and especially, directing changes in behavior according to contingencies (''if now this, then later that; if earlier that, then now this''; Fuster, 2001, p. 323). The anterior cingulate cortex, which has reciprocal connections with both the dorsolateral prefrontal cortex and the orbitofrontal cortex (Barbas, 1992; Petrides and Pandya, 1999), and is itself densely innervated by dopaminergic neurons, is well placed to coordinate the monitoring of actions that are subserved by both regions.

The recognition of rewarding objects is reliant on learning, whereby a previously encountered stimulus becomes rewarding because of its association with a pleasant and desirable outcome. Such reward-related learning is accompanied by neuroplastic changes in nucleus accumbens neurons (Horger et al., 1999), under the influence of afferent prefrontal cortical projections (Karreman and Moghaddam, 1996; Pennartz et al., 1994); and by a similar process of synaptic modification in orbitofrontal neurons (Rolls, 1999). The hippocampus, which is reciprocally connected to the dorsolateral prefrontal cortex and engages with the region in the formation of explicit, conscious memory, shows neuroplastic changes that index the formation of these memories. Dopamine receptor stimulation activates gene transcription and protein synthesis, which are processes that are essential for synaptic plasticity (Huang and Kandel, 1995; Impey et al., 1996). Neuroplastic changes are thus dependent on the activation and integrity of the dopaminergic reward system (Gurden et al., 1999).

Recent research has highlighted features of the reward system that are relevant to an understanding of its role in depression. First, it has become apparent that the dopaminergic reward system is activated by the *anticipation* of rewards rather than their consummation (Berridge and Robinson, 1998), and by stimuli that *predict* rewards, rather than the rewards themselves (Knutson et al., 2000, 2001; O'Doherty et al., 2002; Schultz, 1998). Secondly, and relatedly, the dopaminergic reward system responds to novel, intermittent and unexpected rewards rather than expected rewards where learning has already occurred (Ljungberg et al., 1992; O'Doherty, 2004; Waelti et al., 2001), and is transiently suppressed when an expected reward is omitted (Hollerman and Schultz, 1998; Ljungberg et al., 1992). The significance of these findings lies in the fact that the dopaminergic system has a function beyond mediating pleasure: it energizes the *seeking* of salient rewards, and underlies a more general anticipatory state that engages salient, novel features of the environment (Panksepp, 2005).

2.2. *The association of depression with reward-based learning*

There is substantial evidence that depression is associated with impaired reward functioning. For example, depressed subjects show reduced response to financial rewards (Henriques and Davidson, 2000; Henriques et al., 1994; Hughes et al., 1985), and subjects with elevated depressive symptoms show a failure to modulate their behavior in response to reward reinforcement (Pizzagalli et al., 2005a). There are, however, only a few neuroimaging studies that have examined the relationship. Epstein et al. (2006) showed reduced ventral striatal response to positive stimuli in depressed compared to normal subjects. Keedwell et al. (2005) also showed reduced ventral striatal activity in depressed participants responding to positive images, and increased activity in the ventromedial cortex; both changes were correlated with severity of anhedonia. A study by Mitterschiffthaler et al. (2003) that examined the response of participants to positive images, demonstrated that, compared to controls, depressed subjects showed decreased activation in the medial prefrontal cortex and increased activation in the orbitofrontal and dorsal anterior cingulate cortices.

Evidence that depression is associated with altered reward functioning has emerged from other experimental paradigms. Electroencephalographic studies have shown that activity in the left dorsolateral prefrontal cortex is correlated with stronger bias to respond to reward-related cues (Pizzagalli et al., 2005b), and that reduction in activity in the left dorsolateral prefrontal cortex is both a key feature of depression and strongly related to disturbance of approach function (Henriques and Davidson, 1991). Tremblay et al. (2005) showed that the dopaminergic reward system is altered in depression by demonstrating that amphetamines have enhanced rewarding effects in depressed subjects, correlated with the severity of anhedonia; a perhaps surprising result that may reflect disinhibition of dopaminergic neurons that are hypoactive at baseline.

Resting-state imaging studies of adult patients with depression concur that reward-related areas are commonly affected. The most consistently reported findings are that activity is increased in the strongly interconnected amygdala, subgenual anterior cingulate cortex and orbitofrontal cortex (though activity in the latter is inversely related to depression severity; Drevets et al., 1992), and decreased in the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex and hippocampus (Davidson et al., 2002; Drevets, 2000; Mayberg et al., 1999). Mayberg (1997) summarizes the resting-state findings as demonstrating increased

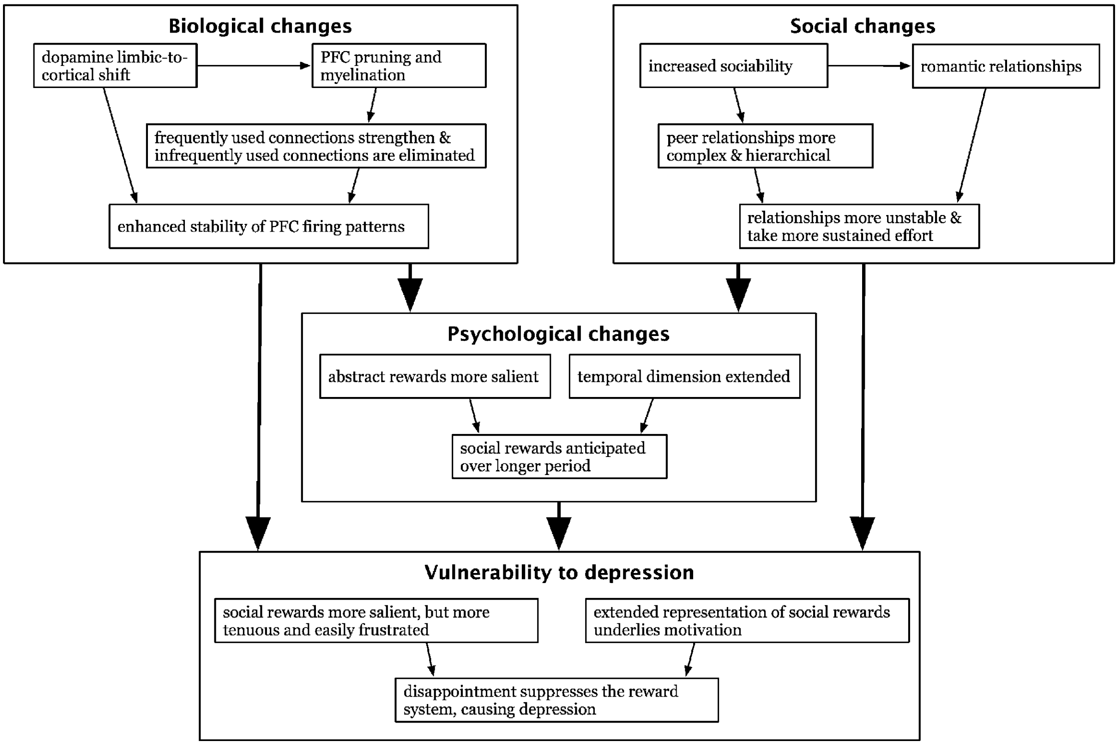

Fig. 3. A schematic overview of the theory. The changes that occur in adolescence allow for the representation of abstract, complex rewards such as found in interpersonal relationships, but at the cost of an increasing vulnerability to depression. Biological changes mean the brain is able to encode more complex rewards, while social changes see adolescents become more sociable and engaged in a more complex social milieu, where relationships, which tend to be unstable, need to be more actively pursued. These changes lead to psychological changes including an increased sense of the importance of social relationships, and the ability to see both the self and its relationships in a more extended temporal context. While these changes are important for pursuing the complex social rewards that become available during adolescence (and underlie a general sense of motivation), frustration and disappointment in achieving the rewards can lead to suppression of the reward system, and hence depression.

arousal in the ventral limbic structures, with concomitant reduction in activity in dorsal structures.

The few functional magnetic resonance imaging studies in child and adolescent depression include a study by Killgore and Yurgelun-Todd (2006) that showed increased activity in the medial orbitofrontal cortex of depressed compared to control subjects viewing fearful faces, and a study by Forbes et al. (2006) that specifically examined reward responsivity in depressed young people, and showed blunted activity in the orbitofrontal and dorsal anterior cingulate cortices (findings that are the inverse of those from adult studies). The neuroimaging study of depression in young people is clearly in its infancy, and awaits further, more focused investigations to clarify the disorder's neurobiological underpinnings.

What *is* clear, however, is that depression and impaired reward functioning have a close relationship. When the findings that have been discussed in the above sections are considered together—that depression often follows interpersonal disappointment; that depression is characterized by low positive affectivity, of which an important contributor is anticipation of interpersonal engagement; that omission of anticipated reward suppresses the reward system; and that this suppression of reward functioning is characteristic of depression—then an integrated theory of depression begins to emerge. Indeed, it is theory that is consistent with Allen and Badcock's (2003) proposal that depressed states have evolved to inhibit social reward seeking when there are perceived threats to a person's social value. In the remainder of the paper, we will describe how development of the adolescent brain and the social environment produces involves a shift towards anticipation of, and motivation toward, abstract future social rewards, and how the possibility of depression is potentiated by developmental processes that result in the reward system being more intimately linked to these types of rewards. Fig. 3 provides an overview of the theory, the components of which will become clearer as the argument develops.

3. Development in adolescence

Adolescence is a critical period for the establishment of an individual's trajectory through adulthood (Steinberg et al., 2006). Fundamental aspects of adult life are determined by an adolescent's engagement in education, vocational achievement and relationships, and an enhanced sense of identity is formed. The period of adolescence takes a person from dependence on his or her parents for most of life's needs to, at the end of adolescence, the ability to live independently and potentially start a family of their own.

3.1. Adolescent social experience

A description of the social world that adolescents encounter illustrates how much more complex their worlds become. Adolescents are substantially more sociable than younger children (Steinberg and Morris, 2001)—they spend up to a third of their waking hours in their company of their peers (Hartup and Stevens, 1997). This sociability, and more effortful and deliberate formation of relationships, is at least in part driven by the increased affective salience of socially related events (Larson and Richards, 1994; Steinberg and Morris, 2001).

Peer relationships become more complex and hierarchical during adolescence (Brown, 2004). One-on-one relationships include the individual friendships that adolescents will have started engaging in during childhood, though they now become more intimate and trusting (Steinberg and Morris, 2001), with the addition during adolescence of romantic relationships. Small groups of between three and ten members become important, and compared to childhood groups, are more likely to evolve from the efforts of the adolescents than from adult organization (Brown and Klute, 2003). Adolescents start to associate with larger crowds consisting of people who have established the same basic identity as each other (e.g., goths, nerds, skaters), even though they may not actually know each other. Membership of particular crowds is dependent on the reputation that an adolescent has among his or her peers (Brown, 2004). The significance of these layers of interaction, in which dyadic relationships are nested in dynamic group structures that are themselves nested in broader crowd structures, is what they tell us about the complexity of adolescent relationships compared to those in childhood.

Romantic relationships emerge during adolescence, prompted by new motivational systems, sexual development and cultural imperatives (Steinberg et al., 2006). The relationships often evolve out of a friendship group, and are more likely to occur if the group is composed of males and females (Connolly et al., 2000). The relationships shift from being more public relationships in the context of friendship groups in early adolescence, to later become more private affiliations with deeper feeling and commitment (Brown, 2004; Connolly and Goldberg, 1999).

The types of relationships that adolescents engage in change throughout the adolescent period. Dunphy (1963, 1969) proposed that adolescents proceed through a sequence of relationships: from small same-sex groups early in adolescence, to the formation of groups with both sexes, to larger crowds, and finally to dissolution of crowds into a loose association of couples. Dunphy's proposed sequence of relationships stood untested for many decades. However, recent research has validated its basic tenets, while demonstrating that the sequence unfolds over a longer time span than proposed by Dunphy, not ending for most young people until they are in their mid-twenties (Connolly et al., 2000; Richards et al., 1998; Smetana et al., 2006). Interestingly, this is the same age at which maturation of the prefrontal cortex is completed (which we will discuss shortly).

Adolescent relationships are inherently unstable; especially so for girls (Brown, 2004; Hardy et al., 2002). Fewer than half of adolescent friendships endure over the period of a year (Connolly et al., 2000; Degirmencioglu et al., 1998), and romantic relationships are similarly short-lived, especially in early adolescence (Connolly and Goldberg, 1999; Connolly et al., 2000; Feiring, 1996). If the criteria for group cohesion is that half of its original members remain intact, then between a third and a half of groups will dissolve over the course of a year (Cairns and Cairns, 1994; Degirmencioglu et al., 1998; Ryan, 2001). There is extensive antagonism both between and within groups. Higher-status members often ridicule lower-status members, and group members tend to make fun of those outside the group (Adler and Adler, 1998). The reputation that adolescents have among their peers is also unstable: comparison of data on popularity of an adolescent among his or her classmates over a period of 6 months shows there is considerable fluctuation (Rubin et al., 1998). The tenuousness of adolescent relationships is accompanied by an increased sensitivity to acceptance and rejection by peers (Brown, 2004; Larson and Richards, 1994; Nelson et al., 2005; O'Brien and Bierman, 1988), making adolescence a period of particularly high interpersonal stress, associated especially with the establishment and maintenance of the kind of social reputation that will enhance social acceptance and reduce the likelihood of rejection and ostracism. Adolescent relationships as a whole are marked by an increase in depth and complexity. Compared to childhood relationships, they take more effort, and are nested in more complicated social structures that make them less stable and necessitate the development of important new skills to navigate them.

3.2. Brain development

Biological change is the *sine qua non* of adolescence. Puberty starts in the brain—with the release of gonadotrophin-releasing hormone from the hypothalamus under the influence of neural mechanisms that are still opaque (Sisk and Foster, 2004). In recent years, the protracted course of brain development has become apparent, with imaging studies showing that adolescents' brains continue to develop until they are in their mid-twenties (Giedd et al., 1999; Gogtay et al., 2004; Paus, 2005; Sowell et al., 2003). It is the prefrontal cortex, in particular, that demonstrates this prolonged period of development, especially compared to regions such as the primary motor and sensory cortices (Bourgeois et al., 1994; Huttenlocher, 1979). The two most marked changes in the prefrontal cortex during adolescence are a pruning of synapses, correlated with a reduction in gray matter, and an increase in myelination that is correlated with an increase in white matter (Giedd et al., 1999).

There is a proliferation of prefrontal synapses that occurs firstly during early childhood and then later at puberty (at which time gray matter volume peaks; Giedd et al., 1999), followed by reorganization and pruning of synapses after puberty (Huttenlocher, 1984; Zecevic and Rakic, 2001). The dorsolateral prefrontal cortex is the last area for the process to be completed (Paus, 2005). Accompanying the synaptic pruning, though starting earlier in childhood (Toga et al., 2006), is a linear increase in myelination of cortico-cortical neuronal connections that occurs particularly for connections between the different prefrontal regions (including via the corpus callosum), and between the dorsolateral prefrontal cortex and occipital, temporal and parietal association areas (Fuster, 2002; Gogtay et al., 2004; Paus et al., 1999; Sowell et al., 1999). The myelination has the effect of increasing the efficiency of conduction and communication by up to a hundred-fold (Casey et al., 2005; Toga et al., 2006). The parallel processes of synaptic pruning and myelination strengthen frequently used connections and eliminate infrequently used connections. This increases the stability of firing patterns of prefrontal cortical neurons (Rutherford et al., 1998) that are able to fire in a more concerted, sustained pattern (Lewis, 1997; Miller, 1996). It has been observed that activity in the prefrontal cortex becomes less diffuse and more focal during adolescence (Durston et al., 2006), which is consistent with the improved efficiency of prefrontal connectivity.

Adolescence sees substantial development of the dopaminergic system. There is an increase in dopaminergic input to the prefrontal cortex, indexed by an increase in the density of dopaminergic fibres (Kalsbeek et al., 1988; Verney et al., 1982) and in the density of dopamine transporters (Spear, 2000), which is partially offset by developmental decline in dopamine synthesis and turnover after early adolescence (Andersen, 2003; Teicher et al., 1993). Dopamine receptors are overproduced in early adolescence, followed by pruning that is more evident in subcortical than prefrontal regions (Spear, 2000). The net effect of increased dopaminergic projection to the

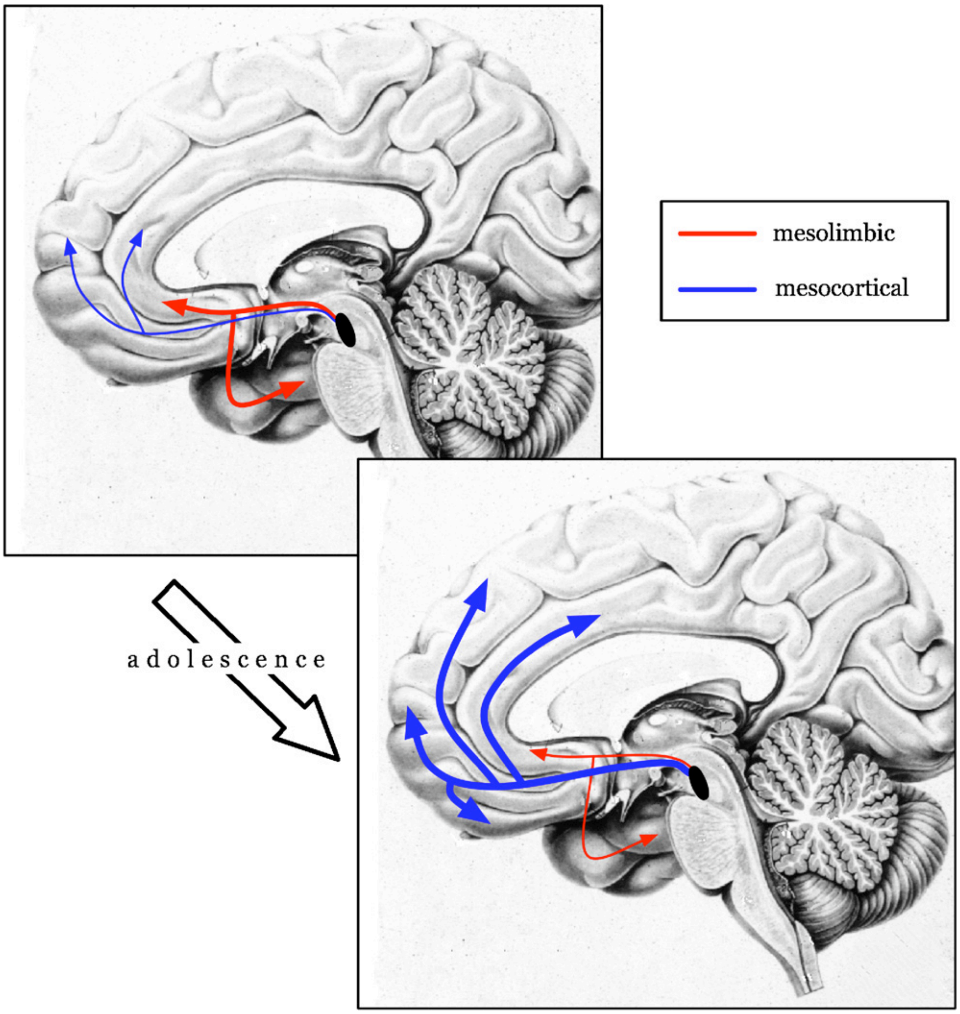

Fig. 4. The figure, which shows the limbic and cortical dopaminergic projections from the ventral tegmental area, illustrates the development of the dopaminergic reward system during adolescence. There is an increase in the number of dopamine fibers projecting to the prefrontal cortex, and an overproduction of dopamine receptors followed by pruning that is more evident in limbic than in cortical regions. The net effect is a shift to relative dominance of the mesocortical dopaminergic system from adolescence.

prefrontal cortex, which shows less pronounced receptor pruning, is a shift in the relative balance between subcortical and cortical dopaminergic systems, with dominance, from adolescence, of the mesocortical dopaminergic system (see Fig. 4).

The development of the dopamine system during adolescence is likely to have an influence on the pruning of prefrontal cortical neurons. As described earlier, dopamine acts to modulate synaptic plasticity. Dopaminergic input to the prefrontal cortex, then, likely contributes to the coupling of salient cortico-cortical connections, and concomitantly to the pruning of connections that do not have significant salience, thereby influencing the important adolescent neurodevelopmental process of prefrontal pruning and myelination. The functional significance of the dopaminergic system's more extensive integration with the prefrontal cortex, which it has a role in shaping, is that the nature of the rewards that can be represented becomes more sophisticated, and thus an adolescent is able to be motivated by, and to respond to, rewards that are more distal and complex. Such rewards are frequently encountered in the increasingly complicated social milieu that emerges during adolescence. Indeed, it may be part of the evolved design of the human brain that the capacity to be increasingly motivated and engaged by distal and abstract rewards emerges during a phase of life when the successful negotiation of such rewards, particularly in the context of success in peer and romantic relationships, is a critical determinant of inclusive fitness (Weisfeld and Janisse, 2004).

3.3. Cognitive development

The pronounced changes in the prefrontal cortex and dopaminergic system during adolescence, both of which are central components of learning, are not surprisingly correlated with significant cognitive changes. Adolescents develop the ability to think in more sophisticated ways: thought becomes more logical and abstract, and less reliant on grounding in actual concrete experience. Adolescents become better able to create hypothetical scenarios and abstract propositions, and better able to reason about the products of their thought. They are able to imagine alternative outcomes to different scenarios, and understand the consequences of those outcomes (Baird and Fugelsang, 2004). These are skills that are essential for navigating their more complex social worlds.

Performance on executive function tasks—such as inhibitory control, processing speed and working memory—improve steadily from middle childhood (Gathercole et al., 2004; Leon-Carrion et al., 2004; Luciana et al., 2005; Luna et al., 2004). In comparison, decision making in the face of ambiguous and abstract data does not show substantial improvement until puberty, with evidence that it is served by the integration of somatic and affective information from the ventromedial cortex (Damasio, 1994; Hooper et al., 2004; Overman et al., 2004). Damasio's (1994) "somatic marker hypothesis" was formulated on the basis of his observations of patients with lesions in the ventromedial prefrontal cortex, who typically perform normally on most cognitive tasks, though have pronounced deficits in everyday social skills and perform badly on tasks that probe complex decision making (e.g., the Iowa Gambling Task; a laboratory experiment in which the optimal strategy for the task is not readily ascertained). This suggests that that the marked improvement of adolescents on performance in the Iowa Gambling Task compared to children (Hooper et al., 2004), and their continued improvement into adulthood (Overman et al., 2004), may be accompanied by improved decision making in complex social situations; a decision making that is better informed by affective information.

Adolescence is commonly held to be a period in which identity is established (Erikson, 1968). This is reflected in changes in cognition, especially with development of the ability of adolescents to reflect on their own thoughts and perspectives, and with an emerging concern with their reputation among their peers. This sense of identity is associated with an emerging sense of the self as it exists across time; with a clearer perspective on patterns of consistency across one's past and the development of plans for the future. Indeed, both an understanding of the life story, via development of autobiographical memory (Habermas and Bluck, 2000), and prospective memory—the ability to hold in mind an intention to carry out an action at a future time (Ellis and Kvavilashvili, 2000)—have been shown to improve during adolescence. The ability to ruminate, a core feature of depressive and anxiety disorders (Nolen-Hoeksema, 2000), also increases during adolescence. Rumination relates to changes in cognitive style, with the emerging ability to consider alternative outcomes ("what if?"), and growing concern with social reputation. It has been suggested that the appearance of rumination is a significant vulnerability factor for the onset of depression (Park et al., 2004; Spasojevic and Alloy, 2001), and as such, is an important factor to consider in attempting to understand the emergence of depression in adolescence.

The development of these important cognitive skills is coincident with maturation of the prefrontal cortex and the region's tighter integration with the dopaminergic system, and with the adolescent's engagement in an increasingly complex social world. The conjunction of these developmental events suggests that the prefrontal cortex assumes a central role in motivating the seeking of the more complex rewards that emerge in this social milieu.

4. The representational function of the prefrontal cortex

The rewards that are sought in adolescence—linked to concepts such as love, belonging, status and agency—are more abstract and often more distant from the present context, and thus require more sustained, coordinated and flexible efforts to achieve them. The prefrontal cortex has, according to theories to be discussed, a specific role in representing these social rewards and the actions required to achieve them in an increasingly complex social environment.

The prefrontal cortex plays a critical role in many higher cognitive functions, including reasoning, planning, social behavior, conceptual thought, and abstraction, though an integrative theory that can explain the region's underlying cognitive architecture remains elusive (Grafman, 2002). While the human prefrontal cortex is relatively large compared to other mammals, it is not disproportionally large compared to some other primates (Semendeferi et al., 2002). The frontal pole (Brodmann's area 10), however, *is* comparatively larger in humans compared to other primates (Semendeferi et al., 2001), and this area appears to be related to human abilities such as the capacity to represent events that occur in the more distant future (Bechara and Damasio, 2005), and the holding in mind of primary goals over an extended period of time while secondary goals are explored (Koechlin et al., 1999). These features are important for the development in adolescence of the ability to represent social rewards.

One approach to describing the function of the prefrontal cortex is to assume that it stores representations analogous to those stored in other cortical areas (Grafman, 1995). A representation is a mental entity that stands for something in the outside world (Frith et al., 1999), and is a term used most often in the psychological literature to describe how different areas of the sensory association cortices encode the properties of objects—such as their size, shape and type—and act in concert to "represent" the object as a unified entity in mental space. Recent research has demonstrated that the motor cortex also has a role in object representation, particularly when the object has a function or can be acted on. For instance, viewing a photograph of a hammer activates the ventral premotor cortex (Chao and Martin, 2000); and when a monkey views any object that is capable of being grasped, or watches as someone grasps it, a region of the premotor cortex comparable to Broca's area is activated (Gallese and Lakoff, 2005; Rizzolatti and Arbib, 1998). If the representation of simple objects involves premotor areas, then the prefrontal cortex, which is the association cortex of the motor and premotor areas (Fuster, 2001), should have a role in the representation of more complex concepts that involve action of some type. We have seen already that rewards, which by definition are anticipated and require motivated action in order that they are consummated, activate the dorsolateral prefrontal and orbitofrontal cortices. Furthermore, the very fact that the representation of reward requires a concept of the future implicates the prefrontal cortex, as we shall discuss shortly.

The particular properties of reward that the prefrontal cortex encodes would be expected to include the ways in which the rewards can be approached, and where in extended time they exist. Miller and Cohen (2001) suggest that the prefrontal cortex stores the *rules* for tasks that are undertaken to achieve goals, and coordinates activity in other brain areas appropriate to the present context (the region represents "context information"; Braver et al., 2002). The rules, which are established by repeated associations of action sequences, sensory inputs and affects, are activated by situations that are ambiguous, and where alternative responses can be made. The rules act to guide behavior by promoting the active representation of longer-term goals, and by inhibiting strong prepotent responses that may give immediate gratification but thwart the achievement of the more distal goals. In a similar propsal, Rolls (1999) suggests that the prefrontal cortex encodes a *syntax*, or language system (not necessarily verbal), to work out multi-step plans in order to obtain deferred rewards. These ideas of rules and syntax are particularly apt for an understanding of social interactions. An exchange between two people involves a delicate interplay of facial expressions, bodily postures and the almost limitless utterances of language; and has a complexity that makes achieving social goals (such as who to trust or who to compete with in order to enhance one's reputation) dependent on allowing a syntax to guide behavior.

More than simply encoding rules, Grafman (1995, 2000a, 2002) proposes that the prefrontal cortex activates representations of structured events; events that compose a particular type of goal-directed activity, such as eating at a restaurant, going to a football game or starting a relationship, where from previous experience a person has a script for how events are likely to unfold, and how they should behave. An understanding of these structured events emerges during adolescence (Grafman, 1995), and allows the nesting of short-term (or secondary) goals (e.g., engaging a person in conversation) within overarching primary goals (e.g., establishing a romance with them). Koechlin et al. (1999) have demonstrated that activity in the frontal pole, the cortical area that is phylogenetically most recent and relatively large in humans (Semendeferi et al., 2001), mediates this ability to hold in mind primary goals while secondary goals are explored. It is this same area that Grafman (2000b) proposes stores the more abstract, generalized representations of structured events. He proposes that these representations incorporate the more specific, episodic representations of structured events that are stored in more posterior prefrontal regions. This hierarchical structure suggests a developmental sequence, with the ability to generalize across similar events emerging during adolescence. This capacity is important for navigation of the more complex social interactions that are encountered during adolescence, and for the successful attainment of the social rewards that become available.

The prefrontal cortex has, according to these representational models, a role in representing an extended temporal dimension. Nichelli (2000) proposes that time perspective (or prospective memory), which is indexed by activity in the dorsolateral cortex (Fuster, 1995), emerges out of the representation of structured events that have a typical duration of action, some of which occur over periods of weeks and months (e.g., the school week, sports seasons, the planning of social events). Evocation of such events also activates the ventromedial cortex and the representation of an associated somatic state (Bechara and Damasio, 2005). Human lesion studies have shown that representations of outcomes that are near in time recruit more posterior ventromedial areas, compared to distal representations that activate anterior ventromedial areas that are phylogenetically more recent (Damasio, 1994). Similarly, representations that are tangible activate posterior ventromedial areas, compared with more abstract rewards that activate anterior areas (Bechara and Damasio, 2005). The relationship between the ability to represent outcomes that are both abstract and temporally distant lies in the fact that abstract goals usually require multiple steps before they can be reached, and it is perhaps the perception of this delay, and the steps required, that creates the concept of extended time.

5. Suppression of the reward system and depression

We propose that the initial episodes of clinical depression during adolescence will often result from the frustration, or omission, of a highly anticipated social reward: a reward such as romantic love, belonging to a social group or social agency. Such rewards do more than engage a person when they are encountered; they motivate an active state of arousal that seeks them out (Panksepp, 2005). If rewards are hierarchically arranged such that abstract and distant rewards are represented at a higher level than tangible immediate rewards—consistent with findings from anatomic phylogeny (Bechara and Damasio, 2005) and Grafman's (1995) theory of structured event complexes—then motivation and arousal may be similarly nested, so that higher-order representations underpin the motivation for lower-order rewards, and motivation for the former must be present for the latter to have salience. This account is speculative, but is proposed in order to explain how disappointment in the social realm can lead to the pervasive reduction in reward responsiveness that is observed in depression. Evidence for this proposition arises from analogy with experiments that show that when an anticipated reward is omitted, it has the effect of transiently suppressing the neural reward system (Hollerman and Schultz, 1998; Ljungberg et al., 1992; Schultz, 1998). These experiments examined responses to immediate tangible rewards, where suppression of the reward system occurred for mere seconds. Our hypothesis is that omission of rewards that are extended in their representation into the more distant future will cause a correspondingly prolonged suppression of the reward system, and that when this effect is combined with other vulnerability factors (such as environmental, cognitive and genetic factors) the clinical picture that emerges is consonant with depression.

5.1. *A hypothetical vignette*

An extended example may be useful to illustrate the hypothesis. Imagine a 15-year-old boy, a high-school student, who is eager to become a member of a group of popular boys. He believes that membership of the group will enhance his reputation among his peers, and is motivated by this belief and by the sense of belonging and status that he anticipates he will gain by being a part of the group. He knows one of the boys and engages in conversation with him in class, attempting to form a friendship that will lead to an invitation to join the group outside of the class (goals that are subsidiary to his main goal). It is likely that at this stage his dopaminergic reward system will be engaged by social stimuli related to this endeavor—the sight of the boys in the group, having them talk to him—and will motivate him to actively seek out such rewards. The internal representation of his primary goal, the temporal dimension of which is extended into the more distant future, will underlie a general sense of motivation and well-being: one that is enhanced as he encounters indications that he is approaching his goal.

The young man's efforts with his key friend are sustained over some weeks: with persistence he makes progress, and after school one day, by strategically waiting in the carpark where he knows the group often congregate, he gets his invitation to join them at a party that Saturday night. He arrives at the party to find that none of the boys pay him much attention, including his supposed friend; he makes an effort to ingratiate himself, but makes no progress and leaves feeling let down and disappointed. When on Monday at school he attempts to converse with this friend, the friend tells him that the others think he is a loser and do not want him hanging around. This rejection is devastating for our young man, who not only feels its pain, but has now lost the extended internal representation of this affectively rich future goal. With the loss of this goal, there is a loss of the general sense of motivation and anticipation that the goal was providing. All of the reward-seeking behaviors that were subsidiary to the goal are inhibited. He withdraws socially: he sees no point in engaging in activities such as attending social functions, seeking out the company of friends, or interacting with others more generally. His dopaminergic reward system, especially as it is engaged by the anticipation of social rewards, is suppressed. As this generalizes his appetite diminishes, he has no energy, feels hopeless and finds little enjoyment in any activities (i.e., previously rewarding stimuli have lost their salience); as this state is maintained his symptoms become recognizable as those of a major depressive disorder.

5.2. *The concept of time*

Representations of complex abstract rewards, as illustrated in the vignette, have inherent in them a concept of extended time, which suggests that the diminution of reward-representation in depression should also cause dysfunction in the appreciation of time. There is ample evidence that depression *does* involve an alteration in the way that time is perceived. Depressed patients often describe that the future holds no enticement and that time passes slowly (Kitamura and Kumar, 1982). The latter idea has been validated in a recent study by Bschor et al. (2004) that demonstrated that not only was the subjective experience of time extended for depressed patients, but they systematically overestimated time on objective assessment as well. Wyrick and Wyrick (1977) studied the attitude towards time of depressed patients, and showed that compared to controls they were more preoccupied with past events, and much less focused on future events (although they were more focused on the *imminent* future), and similarly to Bschor and colleagues they showed that depressed people experienced time as passing more slowly, and overestimated passing time. With a diminished ability to represent abstract future rewards, time loses some of its essential features.

A person's relationship with time may also explain the frequently observed presence of rumination in depression. Depressive rumination involve the repetitive going-over of events in the past, or of events that may occur in the future, especially where they involve some perceived or feared injury to reputation. Perhaps this occurs as a consequence of the foreshortening of time in depression: a confidence in an individual's sense of self cannot be sustained when the self, and its relationship with social reward, cannot be effectively represented. Extended time collapses into the present, so that anxieties about the future cannot be allayed, and neither can the past be kept at bay. The increased vulnerability to depression in adolescence develops during the same period that a sense of the self as it exists across time emerges. Our hypothesis is that this concept of extended time is dependent on an individual's capacity to represent the future (and future rewards); an ability that carries with it the cost of depression when this anticipation is frustrated.

6. Individual differences in development and vulnerability

An important question that arises at this point is this: if interpersonal disappointments such as relationship break-ups and peer rejection are such common experiences during adolescence, then why is it that only a portion of people who have these experiences develop a major depressive disorder? There is no doubt that depression has a significant heritable component; and more so for depression starting post-puberty than in childhood (Rice et al., 2002). It may be, for instance, that the stability of a person's dopaminergic reward system, and its susceptibility to suppression following disappointment, is dependent on the inheritance of particular alleles for genes that encode neuronal receptors and transporters. This thesis is bolstered by studies that show that alleles for the D_3 and D_4 dopamine receptors (Dikeos et al, 1999; Lopez Leon et al., 2005) are associated with vulnerability to depression. A large cohort study analyzed by Caspi et al. (2003) showed an association between an allele of the serotonin transporter gene and depression, but only for people who had suffered significant recent life stresses; an elegant illustration of the interaction between genetic inheritance and the social environment. The nature of a person's family and social environment will provide an important source of variance for their vulnerability to depression, both through the likelihood of interpersonal disappointment inherent in their social environment, and in the ability of close, confiding relationships in that environment to buffer and support the person following disappointment. If a person's internal representations include multiple extended interpersonal goals, then disappointment in one realm will less likely cause generalized suppression of their reward system.

It was noted earlier that the gender difference in rates of depression also emerges at puberty, and while our model has not addressed this issue directly, it is consistent with the proposal by Cyranowski et al. (2000) that this difference emerges because of the heightened "affiliative need" of women that is driven by social and hormonal influences that operate from puberty. The suggestion is that affiliative rewards have more salience for women, who are subsequently more likely to be disappointed by the frustration of these needs (Allen and Badcock, 2003; Allen et al., 2006). Interestingly, there is evidence that the prefrontal gray matter changes that occur in adolescence begin earlier for females (Giedd et al., 1999), which may account for some of the difference in vulnerability between the genders.

There is a qualitative change in the nature of reward from puberty, and we contend that vulnerability to depression is brought about not by neural instability resulting from yet-to-mature developmental processes, but by the unstable nature of the rewards that are encoded. Vulnerability to depression starts from the time at which the nature of reward changes and persists through adulthood because the same types of affiliative and agentic rewards maintain their salience. Thus we contend that depression can occur and recur once the qualitative change in the nature of reward has taken place. In addition, the biochemical changes that accompany the first episode of depression may leave residual effects that increase vulnerability to subsequent episodes even further (Post, 1992; Zeiss and Lewinsohn, 1988). While we contend that vulnerability to depression remains heightened beyond the adolescent years because of the changed nature of reward, it is possible that experiences in adolescence may lay the foundation for first episodes of depression that start later. For instance, onset of depression after adolescence may occur in brains that have been 'scarred' by earlier subclinical depressive responses to interpersonal disappointments that were not severe enough to engender a major depression episode. This scenario remains consistent with our theory that it is the development of the ability to represent abstract distal rewards that creates the vulnerability to depression, though leaves open the possibility that adolescence is a time of particularly heightened vulnerability.

7. Hypotheses and future directions

The aim of this paper has been to develop a model that integrates findings from epidemiology, adolescent ethnography, phenomenology, descriptive psychopathology and the developmental, cognitive and affective neurosciences to explain why recurrent depression in adulthood often first emerges during adolescence, and why these early episodes so often follow interpersonal stressors that threaten one's reputation or social value (Allen and Badcock, 2003). The key changes that occur in adolescence are the development of the prefrontal cortex, and its tighter integration with the dopaminergic reward system, and the profound social changes that mediate the passage from childhood dependence to adult independence. It is the thesis of this paper that the two are intimately intertwined, and that development in one realm cannot happen without development in the other. Indeed, one of the driving forces behind the development of the prefrontal cortex, both ontogenetically and phylogenetically, is increased social complexity (Dunbar, 2003).

The prefrontal cortex is consistently implicated in the pathophysiology of depression, and the coincidence of the significant prefrontal cortical development in adolescence with the dramatic developmental increase in the prevalence of depression suggests that the region should be at the center of any proposed theory of depression. Our model implicates the region by extending recent theories about the role of the prefrontal cortex in the representation of complex goals to explain the emergence of depression post-puberty, at a time that social rewards become much more salient and motivating. Where previous models have implicated the delayed development of the prefrontal cortex compared to limbic areas as being responsible for the increased vulnerability to depression in adolescence, our model suggests that it is the development of the prefrontal cortex itself that is responsible. Prefrontal cortical development brings with it enormous advantages, including the ability to make decisions in complex social environments that take into account the consequences of decisions into the future. However, one of the costs of this ability, we propose, is a heightened vulnerability to depression when anticipated future rewards are disappointed.

A good theory must generate hypotheses that can be tested (Popper, 1959), and our theory does suggest at least some novel lines of investigation. Studies could examine the ability of patients with a first episode of depression to respond to social rewards that are presented as being available in the future, and more specifically, use neuroimaging paradigms to examine the brain regions that are activated. Imaging studies could also examine the way depressed patients process temporal information, and how their brains are activated by tasks that require multiple steps to achieve rewards. While studies of these types may demonstrate dysfunction in patients with depression, they will not differentiate epiphenomena from pathogenetic processes. More information would be gleaned by examining brain response to the above paradigms in participants who at risk of a first episode of depression (e.g., by having a first-degree relative with depression, subclinical symptoms, a high-risk temperament, or recent major life stress) and observing similar dysfunction. Elucidating the mechanisms that underlie the emergence of depression during adolescence will be an important step in understanding, with the hope of eventually preventing, recurrent depression into adulthood.

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