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Arrested development? Reconsidering dual-systems models of brain function in adolescence and disorders

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Abstract

The dual-systems model of a ventral affective system, whose reactivity confers risks and liabilities, and a prefrontal control system, whose regulatory capacities buffer against these vulnerabilities, is an intuitive account that pervades many fields in the cognitive neurosciences – especially in the study of populations that differ from neurotypical adults, such as adolescents or individuals with affective or impulse regulation disorders. However, recent evidence that is inconsistent with dual-systems models illustrates the complexity of developmental and clinical variations in brain function. Building new models to account for this complexity is critical to progress in these fields, and will be facilitated by research that emphasizes network-based approaches and maps relationships between structure and function, as well as brain and behavior, over time.

The allure of dual-systems models

Over the last decade, a common account of brain functioning has emerged in the cognitive neurosciences. One system in this account, the ventral affective system, is commonly portrayed as indexing risks and liabilities (especially those associated with emotional dysregulation) via heightened reactivity in subcortical regions, such as the amygdala and ventral striatum (VS) [1-4]. A second system in this account, the prefrontal cortex (PFC), acts as a counterpoint to the first because its responses are depicted as reflecting control and regulation of the ventral affective system's reactions [5-8]. This ‘dual-systems’ account has been used to explain patterns in normative neurodevelopment, especially during adolescence [9-11], and also to account for atypical brain function in disorders of affect or impulse regulation (many of which emerge in adolescence, such as depression and addiction) [12-15]. The appeal of straightforward this account has aided in formulating hypotheses and interpreting results, which has undoubtedly helped to advance these fields in years past, although advocates note that these models are necessarily both simplistic and speculative [9,11,15-18]. However, such caveats are all too easily overlooked given the pull of such a strong meme [19] (Box 1). Therefore, in this review we illustrate the complexity of brain function as revealed through studies of adolescent development and disorders, and highlight results that contradict simple dual-systems accounts. Specifically, we focus on evidence that

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is inconsistent with a uniform portrayal of greater ventral affective activity as detrimental to adaptive functional outcomes, and greater prefrontal cortical activity as facilitative of them. We then identify multiple ways in which progress can be achieved in this field, including suggestions for future research that incorporate recent advancements in neuroimaging approaches.

The dual-systems model in adolescent brain-behavior relationships

One domain where the dual systems model has dominated is the study of normative adolescent brain development. An implicit assumption motivating much of this research is that neuroimaging will help explain the significant changes documented in motivated behavior, risk-taking, affect, and peer orientation during adolescence – trends that may increase vulnerability to psychopathology or result in a wide range of adverse outcomes, such as drug and alcohol abuse, smoking, disordered eating, and health-risking behaviors, such as unsafe sex [20-24]. The dual-systems model suggests that teenagers are predisposed towards these new patterns of behavior because of an imbalance between early maturation of limbic motivational and emotional systems and slower or later maturation of prefrontal cortical control [9,11,15,16,20-22,25-28].

Although evidence for the dual-systems model has been elaborated well elsewhere [9,11,20-22,27], itwill be briefly summarized here. One line of support comes from studies of brain function during adolescence. These studies have been largely cross-sectional, and smaller in scope than investigations of developmental changes in brain structure, although the use of longitudinal methods and larger sample sizes has been growing in recent years (reviewed in [29]; see also [30]). Findings relevant to the dual-systems model include multiple reports of heightened subcortical (amygdala or VS) responses in adolescents to affective stimuli, including some emotional expressions and certain phases of reward processing [1-4,31,32]. Other studies contribute demonstrations of diffuse (non-focal) or diminished patterns of activity in PFC during cognitive control tasks, alongside potentially compensatory engagement of additional brain regions to achieve control [5-8,33-35]. However, post-hoc interpretations of these patterns represent a debatable issue that has been under increasing scrutiny in recent years (Box 2). In addition, relatively few of these fMRI studies directly assess both reactivity to rewards (or other affective stimuli) and regulatory control in the same paradigm or sample, or relate brain function to real-world behaviors (assessed via self/parent reports or more sophisticated methodologies) that are presumed to be affected by the interplay between these two systems (but see [1,2,7,28]).

The other main source of support for the dual-systems model has been extrapolated from studies of cortical development that have utilized various metrics of structural change in gray matter (GM) or white matter (WM). Developmental changes in GM density or cortical thickness vary significantly by region, with extended and more complex nonlinear trajectories seen in higher-order association areas (such as dorsolateral PFC or inferior parietal lobule), which contrast with early peaks and linear declines in primary sensorimotor areas and other regions with simple laminar structure (such as posterior orbitofrontal cortex, subgenual cingulate cortex, and anterior insula) [17,36]. In addition, WM tracts throughout the brain (including those that connect PFC with the striatum or amygdala) generally exhibit increases in maturational indices from childhood through adolescence – these changes are typically linear with respect to WM volume [37-40] and nonlinear with respect to diffusion parameters [37,39-42]. Many of these pathways do not reach 90% of maximum values until after age 20, particularly those traversing lateral and medial PFC [37,40]. These varied structural metrics are complementary and not necessarily robustly correlated [40], suggesting that GM development is only moderately informative about WM development

and that neither should probably be heavily extrapolated to predict expected functional patterns during adolescence.

In summary, there is substantial evidence that these two systems function differentially during adolescence and that the PFC exhibits a protracted course of structural maturation, although there is somewhat weaker direct evidence that either pattern impacts real-world behavior, despite this connection being frequently inferred or implied. Given the limited empirical demonstrations of links between these neurodevelopmental changes and behavior, especially the lack of studies showing that brain changes over time specifically covary with relevant behavioral change over time, we suggest that the field has sometimes been arguing by analogy – in the sense that conclusions are drawn based on similarities between the pattern of these brain changes (including their hypothesized neuropsychological implications) and folk psychologies of adolescent development [19].

Evidence of complexity in adolescent brain-behavior relationships

In this section we examine recent data that may constitute exceptions to dual-systems accounts of neurotypical adolescent development. This includes empirical studies contradicting the patterns of brain function during adolescence described above, reports suggesting that occasionally the supposed roles of particular brain regions as predisposing towards functional versus dysfunctional outcomes are reversed (with subcortical reactivity appearing protective or PFC responses seeming to confer vulnerabilities), and patterns in structural development that counter dual-systems predictions. Throughout, we remain mindful of recent findings (discussed in Box 2) establishing the limited evidence for focalization effects across development, the potential pitfalls of interpreting patterns across development or disorders by redescribing them as compensatory or inefficient, and our limited understanding or acknowledgement of selectivity (or lack thereof) in brain function.

We begin with the ventral affective system, focusing on the VS and amygdala. First, many researchers observe either hypoactivity or no differences between adolescents and adults in VS responses to some reward conditions or paradigms [1,3,43]. Similarly, recent developmental fMRI studies of emotion reactivity and regulation have not consistently found heightened responses in amygdala during adolescence [31,32,44,45]. Second, studies indicate the VS neither responds solely to rewards [46] nor always biases adolescents towards maladaptive behavior. For example, a recent longitudinal study of the transition from childhood to adolescence found increases in VS response to emotional facial expressions were associated with increases in resistance to peer influence and decreases in risky behavior [31]. Although initially counterintuitive, this makes sense when considering that peers are external regulators of behavior – for most typically-developing teenagers, sensitivity to peers will guide them towards largely positive outcomes. In another recent study , greater VS response during social exclusion was associated with greater reductions in negative affect following social exclusion during adolescence [47]. Both of these studies are therefore consistent with findings that VS activity may index effective emotion regulation [48] and with the more general proposition that some forms of affective variability may be associated with positive adjustment [49]. Two further studies observed that diminished striatal (and heightened prefrontal) responses to reward anticipation and outcome were associated with reports of lower daily positive affect and higher depression in both typically-developing and depressed adolescents [50,51]. Taken together, these studies suggest that occasionally the ventral affective system is not hyperreactive during adolescence and that heightened responses are sometimes associated with adaptive outcomes.

The case of PFC function in adolescent development is perhaps even more complex. The dual-systems model posits that the PFC is still immature relative to the ventral affective

system. But what does that immaturity translate into at the level of function – more or less activity? As noted above, many empirical studies and reviews note that in tasks where cognitive control is required, activations in PFC increase with age [33-35]. Yet, others report decreases in PFC responses with age [8,44,45] or interesting non-linear patterns – less or more activity in adolescence than either adulthood or childhood [25,52,53]. Overall, the literature on neurodevelopmental underpinnings of cognitive control shows bidirectional, complex patterns – both increases and decreases in PFC activations that vary across subregions and tasks – that should be interpreted with caution [8,54-56]. For example, a recent study examining inhibitory control in an antisaccade task found that transient activations in PFC related to inhibitory control during a given saccade decrease with age, whereas sustained set-related activations in PFC increase [6]. Such complex patterns are difficult to reconcile, as both developmental patterns are routinely considered evidence of 'mature' brain function, which can make the literature appear 'inconsistent or opportunistic' ([8], p.109; see also [56]).

Complexities are also beginning to emerge in the literature on adolescent structural development. In one study, contrary to dual-systems predictions, increased WM maturity was associated with increased engagement in risky behaviors, adjusting for known age-related increases in both measures [57]. Another recent investigation that mapped structure-behavior changes through adolescence using a cohort-sequential design observed that VS (specifically, nucleus accumbens) actually volumetrically increased over a two-year period across three age groups ranging in initial age from 9-23 years, and that this was correlated with increased drive in the behavioral approach system (BAS [58]). Initial levels of VS and medial OFC volumes, on the other hand, were correlated with increases in BAS reward responsiveness [59]. The effects of individual differences in volumes across these regions on facets of reward sensitivity did not vary by age group. This study is notable for addressing the lack of data linking longitudinal change in behavioral indices of reward sensitivity to relevant brain structure (as noted above). At the same time, it also reveals complexities that may be inconsistent with dual-systems models. Specifically, the VS exhibited a clear nonlinear trajectory with a peak in 13-17 year-olds (defined as late-adolescents), rather than the linear patterns of volumetric decreases and peak functional responses typically cited as evidence of early 'maturity' in the ventral affective system [9,11,20-22,27]. In addition, there was no evidence for age-related variation in the magnitude of correlations between VS or medial OFC structure and reward sensitivity.

It should also be noted in closing this section that other key factors besides development are known to influence patterns of activity across prefrontal and subcortical regions. These include (i) task performance [60], (ii) task design, including transient-event versus sustained-set paradigms [6] or different baseline and timing conditions [28,61], and (iii) various data analysis techniques. For example, researchers recently discovered that some functional connectivity analyses interpreted as demonstrating developmental increases in long-range connections during rest (i.e., independent from any task) were spurious effects of greater motion in younger participants [62,63], which were eliminated with appropriate controls for motion-induced artifacts. Similar effects could be at work in the empirical studies that show developmental increases in task-dependent functional connectivity between prefrontal and subcortical regions [2,31].

Complex brain-behavior relationships in depression and its development

Although dual-systems models are prevalent in proposals about the neural foundations of many clinical disorders, we focus here on major depressive disorder (MDD). This condition is frequently described as resulting from heightened limbic reactivity (especially in the amygdala) that overwhelms PFC control capacities, and/or deficient top-down control

(particularly by medial PFC) over limbic regions [64]. However, the empirical evidence in adult and adolescent samples is equivocal. Although many studies have shown patterns of hyperactivity in the amygdala in depressed samples [65,66], recently recent study demonstrated amygdala hyperactivity in response to rewards amongst depressed samples, a finding that fits less well with the idea that amygdala hyperactivity is responsible for the negative affect associated with depression [67]. Yet, many other studies have found no significant differences in amygdala reactivity between depressed individuals and various other subgroups, including healthy controls [68-70]. There is similar disagreement about patterns of activity in PFC. One recent review of brain function in depression [71] concluded that depression is typified by hypoactivation in dorsolateral PFC (including dorsal ACC), as well as hyperactivation in ventromedial PFC (including subgenual ACC). This distinction is accompanied by the premise that dorsolateral regions are associated with adaptive processes, such as cognitive control, executive function, and emotion regulation, whereas ventromedial regions either generate negative emotions or maladaptively heighten self-reflection and self-awareness. However, this recasting of roles is also subject to disagreement, as other researchers have suggested that ventromedial PFC plays a central role in the downregulation of amygdala responses [2,72].

Furthermore, it has been conjectured that the increased vulnerability to depressive disorders observed during the teenage years is mediated by protracted maturation of the prefrontal regulatory system when compared to the brain networks associated with sensitivity to affective and social stimuli [16,73]. Such proposals utilize an explanatory framework to understand the developmental epidemiology of depression that is very similar to the dual-systems models used to explain the broader range of affective and behavioral changes observed in adolescence, such as with respect to risk taking and drug use. However there is a fundamental difference between these latter behaviors and depression in that, although risk taking and substance use become more common during adolescence, they decline during early adulthood, when regulatory brain systems have usually reached adult levels of maturity [11,27]. The developmental epidemiology of depression, on the other hand, shows that, although increased rates of depression start in adolescence, they persist though adulthood – well past the period when prefrontal regulatory mechanisms have presumably matured [74].

This observation constrains the hypotheses that can explain the epidemiology of depression in neurodevelopmental terms. According to an alternative hypothesis [74], depression does not represent a failure of prefrontal regulation. Instead, vulnerability to depression may actually be increased by the development of prefrontally mediated capacities, such as the adolescent's enhanced ability to anticipate abstract and distal rewards (or punishments; Figure 1). This model predicts that the PFC, rather than exclusively functioning in ways such that maturation constrains vulnerability to depression, may in part also function in ways such that its development is permissive of increased rates of depression in vulnerable individuals. Consistent with this proposition, as noted above, greater depressive symptoms and lower daily positive affect have been associated with heightened PFC responses in adolescence [50,51]. This does not imply that PFC development is pathogenic *per se*, but rather that, along with important new capacities and abilities, it ushers in a new ‘adult’ suite of problems for the developing individual to confront.

New directions

In order to move beyond the limitations of dual-systems models, new conceptual and methodological tools will be needed. Here we highlight three relevant strategies that we believe have the potential to better deal with the complexities of brain function in adolescent development and clinical disorders of affect and impulse regulation. One approach that is gaining momentum is to switch the level of analysis from isolated regions to coordinated

networks. Another approach encourages greater collaboration across historically independent methodological approaches in the cognitive neurosciences (i.e., mapping brain structure versus function). A final useful direction is to foster greater integration of theories and empirical findings from developmental and clinical research conducted outside the cognitive neurosciences.

Early fMRI studies primarily constituted basic mappings of functions, pursuing the question of 'where' to localize a given process in the brain. It is now clear that simple one-to-one mappings between mental processes and brain regions are rare – instead, entire networks of regions interactively support a given function [75]. Many important insights about networks have emerged from researchers investigating structural and task-independent functional connectivity between brain regions. For example, studies of low-frequency oscillations in the BOLD signal during 'rest' helped to identify multiple networks whose response profiles were coordinated in absence of tasks [76]. These functional networks map on to the structural connections between regions illuminated by techniques such as diffusion tensor imaging [77] and there are similarities between resting-state and structural estimates of regional connectivity across development [78] and disorders [79], although the two methodologies are not completely redundant [80,81]. A related trend is the classification of mental states or group membership based on multivoxel pattern analysis (MVPA) techniques, which utilize machine-based learning algorithms to analyze multivariate data in a manner that is typically more consistent with a network-based approach, although this methodology is still rare in developmental and clinical populations [82]. Investigating and conceptualizing brain function in terms of real-time multi-region networks will help mitigate the tendency to parcel human brain function in a phrenological manner, by illuminating how these regions work together to solve challenges such as regulating impulsive behavior or experiencing healthy levels of affect.

Next, significant gains are likely to result from pairing methodologies that in the past have proceeded independently, as it may allow researchers to 'triangulate' concepts and questions of interest. This approach would include studies mapping relations not only between brain structure and function as mentioned above, but also, critically, between behavior and brain structure or function (or both). However, as noted above, there is as yet relatively little empirical research that directly links developmental changes in adolescent brain function or structure to developmental changes in behavior, cognition, or affect [55] – and a particular paucity of truly longitudinal studies that have tracked changes in brain and behavior or clinical symptomatology over time within individuals across adolescence (with notable recent exceptions) [31,59,60,83-85]. To the extent that these structure-function, structure-behavior, or function-behavior studies can be coordinated in large-scale studies of development or disorders [30], significant advances in our understanding may be possible. More generally, studies of these types should reduce the frequency of analogical reasoning about trajectories in development or disorders based on piecemeal studies of structure, function, or behavior in isolation.

Finally, embracing the new developments in neuroimaging approaches described above should not mean abandoning well established methods in developmental and clinical sciences. Many important conceptual and theoretical advances have resulted from more traditional methods of inquiry in psychology, ranging from observational data collection to interviews. It is time to ensure that neuroimaging investigations connect better with developmental or clinical data and theories [55]. Just as neuroscientists believe the fruits of their research will help constrain, refine, or refute theories of developmental and clinical variations in affect and behavior [13,86], such an arrangement would be most beneficial if it were bidirectional.

Concluding remarks

Given all the counterevidence and caveats summarized above, it seems clear that caution is warranted before applying dual-systems models to adolescent development and disorders. This is not because dual-systems models are fundamentally flawed. Rather, overreliance on these models for *post hoc* interpretations of patterns in functional or structural data will tend to reify them, repeating the history of other strong memes in neurodevelopment and disorders discussed in Box 2. In addition, the functions and response profiles exhibited within and between regions addressed in these models are numerous and complex, and their relationships with real-world behavior do not result in a consistent pattern of risks conferred by only one system or region, and protections conferred only by others. Acknowledgment of our limitations is gradually growing, particularly the lack of selective structure-function mappings and brain-behavior mappings [18,56,75], as well as the contradictory use of neuroscience and other psychological research to argue both for and against adolescent capacities for mature behavior [18], the tendency to misinterpret differences as deficiencies [11], the oversimplification of structure-function mappings between subcortical structures and approach or avoidance motivation [9], and the lack of appreciation for the dynamic interplay between limbic and cognitive systems during adolescence [9,11,17]. Nevertheless, this is a very important message to convey and to focus our research efforts on remedying. Indeed, given that the dual-systems interpretations of adolescent, clinical, and forensic behavior have been so enthusiastically adopted by the legal, educational, and journalistic consumers of behavioral science (Box 1), it is especially important that the developmental and clinical cognitive neurosciences do not simply become co-opted into another long-standing meme about human mental life and functioning being defined by a battle between reason and regulation, on the one hand, versus the emotions, on the other. Rather, scientific research should rigorously hew to its vital role to not only confirm our prior conceptions, but also to shock and surprise, no matter how counterintuitive or complex the answers may be (Box 3).

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Box 1. Why are dual-systems models so potent?

Current dual-systems models likely derive significant power from their foundation in the intuitive appeal of interpreting mental life as a balancing act between emotions/passions and reason/logic [87,88], a dichotomy traceable back to Plato and Aristotle). In addition, these models may resonate with early theoretical conceptualizations of adolescence as a period biologically inclined to be stormy and stressful [89]. Dual-systems accounts are prominently featured in cover stories from major international magazines (e.g., Time, National Geographic) on topics like ‘what makes teens tick’ [90,91]. There are also many articles dealing with the political and legal ramifications of ‘adolescent brain science’ [19,92,93], and even recent Supreme Court cases dealing with juveniles directly cite adolescent neuroscience. As written by Justice Kennedy from the U.S. Supreme Court, citing to amicus briefs from the APA/AMA, ‘developments in psychology and brain science continue to show fundamental differences between juvenile and adult minds... parts of the brain involved in behavior control continue to mature through late adolescence’ ([92], p. 766). Unfortunately, the metaphors used in these varied contexts inappropriately suggest that the neurobiology of adolescent development and disorders is already quite well understood, hence constraining future attention and priorities in science, funding, policy, media, justice, and parenting [19].

Box 2. Updating the interpretive toolkit

A critical overarching factor to consider is that there are new fundamental issues in the cognitive neurosciences that need to be resolved, many of which are directly relevant to the way that patterns of brain function are interpreted. The neurosciences still lack well-defined cognitive ontologies – that is, mappings between mental processes and brain function [56], in part because of the emphasis on old brain-mapping strategies (e,g., 'where' does X get processed, 'what' does region Y do). A critical next step is to focus on the specificity of functional response profiles within regions and decrease reliance on reverse inferences [75,94]. Another important direction is to emphasize network-wide patterns rather than activity in isolated regions of interest [95,96]. Without validated cognitive ontologies, we are likely to make and perpetuate oversimplified assumptions about the functions of regions in networks across development (or disorders).

Three additional familiar concepts that have been relied upon in *post hoc* interpretations of neuroimaging data, applicable to both development and disorders, warrant reconsideration: focalization, efficiency, and compensatory activity. The focalization hypothesis [33] argues that, with increasing age, patterns of brain activation mature from being diffuse and weak to focal and strong. In other words, magnitude (and extent) of activation decrease with development in regions considered tangential to the task, and increase (in magnitude but not extent) in regions considered task-central. The related concept of neural efficiency is used to explain decreased responses in task-central regions with development, whereas compensatory activity refers to neural activation that is observed in regions during stages of development (or disorders) when individuals are not exhibiting peak functioning.

Although these intuitive ideas have prevailed for years, empirical reports and reviews are increasingly calling them into question. Several key points were recently raised in this debate [56], foremost among them being that focalization, efficiency, and compensatory activity are primarily ways of describing the observed patterns of data. They create the illusion of explanation, but under close scrutiny tend to suffer from circular logic. The focalization hypothesis in particular lacks neurobiological plausibility [97], statistical tests of it are rare, and informal observations of this pattern may be spurious consequences of more variable spatial normalization in children and adolescents than adults.

Furthermore, new studies have tended not to support the focalization hypothesis. For example, one study examined responses in a decision-making task, controlling for important confounding variables, such as head motion and interindividual variability in anatomy and functional organization [98]. Across three strict age bands (13, 17, and 21 years), only magnitude increased with age – extent did not decrease with age, and there were no regions that went off-line, suggesting a lack of qualitative shifts in the underlying neural networks. Other recent studies have showed patterns of increasing spatial extent or engagement of a more distributed network with age, such as in response to emotional and cognitive challenge [99]. Finally, a three-year longitudinal fMRI study of task-switching recently found that there was greater variability over time in the magnitude (but not extent) of children's responses across key regions of interest, but not adolescents or adults [60].

Box 3. Questions for future research

- What are the consequences of the two best documented developmental changes in brain structure, cortical thinning and increased white matter maturity (as reflected in volume, density, diffusion parameters), for brain function and relevant behavior? We expect direct measurement of behavior 'outside the scanner,' using observational methodologies or other types of verifiable and more ecologically valid data, to become essential.
- Given that neuroimaging research has tended to support the existence of significant sex differences in the neurobiological bases of affective functioning [100] and that many of the notable sex differences in rates of mental disorders also emerge during adolescence [101], to what extent does differential brain development mediate these effects? A focus on aspects of structural or functional development that are affected by gonadal hormones will be of central importance. Additionally, very little is known about how other facets of pubertal development that are known to widely impact adolescent outcomes (such as timing and velocity of pubertal changes [102]) impact brain development and brain-behavior relationships.
- In terms of clinical disorders where affect is a strong feature of the symptomatology, how can we achieve a more nuanced understanding of the relations between different phenomena (e.g., affective temperament, emotional responses, and mood), as well as the way in which they interact, both during development and in the context of mental disorders? A better understanding of core affect [103] and emotional convergence (or lack thereof [104]) would help constrain future neurobiological models of affective disorders [105], as current models wherein reactions by ventral affective systems are poorly regulated by PFC control systems may not even address the primary affective phenomena underlying these disorders (which may involve deficits as well as excesses in affective reactivity, for example).
- How do environments influence neurobiological development, and subsequent risk for disorders? For example, early life experiences such as institutionalization, child abuse, and stress affect brain development in ways that likely confer vulnerabilities [106-108], but how do neurodevelopment and environmental effects interact over the lifespan? Such investigations offer hope by informing prevention approaches grounded in neurobiology and will ultimately provide a more sophisticated understanding of neural plasticity and which modifiable environmental risk factors offer the most promising means of intervention to encourage the development of healthy brains and individuals.

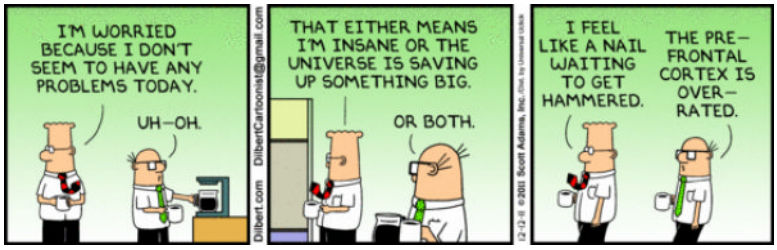

Figure 1.

Dark sides of PFC function. This cartoon aptly illustrates how development of PFC function during adolescence may increase vulnerability to depression via the ability to anticipate abstract and distal rewards or punishments, or set goals and realize disappointment at one's failure to meet them.