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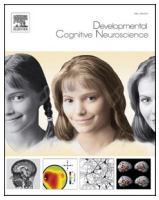

Threat or thrill? the neural mechanisms underlying the development of anxiety and risk taking in adolescence

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ABSTRACT

Anxiety is common in adolescence and has been linked to a plethora of negative outcomes across development. While previous studies of anxiety have focused on threat sensitivity, less work has considered the concurrent development of threat- and reward-related neural circuitry and how these circuits interact and compete during puberty to influence typical adolescent behaviors such as increased risk taking and exploration. The current review integrates relevant findings from clinical and developmental neuroimaging studies to paint a multidimensional picture of adolescent-onset anxiety against the backdrop of typical adolescent development. Ultimately, this paper argues that longitudinal neuroimaging studies tracking approach and avoidance motivations across development are needed to fully understand the mechanisms underlying the development of anxiety in adolescence and to identify and provide effective interventions for at-risk youth.

1. Introduction

Anxiety often manifests in adolescence, with over 31 % of US adolescents reporting symptoms of anxiety (Lee et al., 2006; Merikangas et al., 2010) which have been linked to a pattern of behavioral avoidance in youth (Galván and Peris, 2014; Reniers et al., 2016) and adults (Maner and Schmidt, 2006). Contrasting with this risk-averse phenotype are the typical hallmarks of adolescence such as increased risk taking and exploration, crucial aspects of healthy development (Casey et al., 2008) that can be observed across species (Brenhouse and Andersen, 2011; Steinberg, 2008) and cultures (Duell et al., 2018).

Why does this developmental period give rise to seemingly contrasting phenotypes: an increase in anxiety symptomatology characterized by avoidance and inhibition *and* an increase in risk taking characterized by approach behaviors? Here, we review the current literature and integrate research examining the neural correlates of anxiety and risk taking in an effort to achieve a deeper understanding of the mechanisms underlying anxiety in youth who are afflicted with symptoms at odds with typical adolescent development. We also highlight the adaptive nature of adolescent risk taking as a means of promoting independence, learning, and goal-directed behavior (Casey et al., 2008; Spear, 2000), important facets of adolescent development that are impeded by anxiety and its corresponding patterns of behavioral avoidance.

Ultimately, this paper will argue that the study of adolescent-onset anxiety demands consideration of the concurrent development of approach and avoidance systems and their influence on typical adolescent behaviors (e.g., risk taking). This is a departure from extant research that has studied each of these constructs (approach and avoidance) separately, particularly in the context of anxiety. Future longitudinal studies tracking the interactions between and regulation of approach and avoidance motivations across typical and atypical development are needed to achieve a deeper understanding of the heterogeneity in adolescent anxiety, to identify vulnerable adolescents, and to develop effective interventions for at-risk youth.

2. The development of anxiety

2.1. Background

The experience of anxiety is a normative and evolutionarily adaptive response to stressful environmental stimuli (e.g., potential threats). Rooted in the feeling of fear, anxiety triggers behavioral avoidance, which can promote safety by motivating escape from danger (Beesdo et al., 2009). While avoiding threatening stimuli is adaptive early in development (Shechner et al., 2012), a pattern of behavioral avoidance

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can preclude the opportunity for fear extinction and become reinforcing and habitual (LeDoux et al., 2017), resulting in impaired functioning and increased vulnerability to further anxiety (Arnaudova et al., 2017). This is especially worrisome in adolescence, a period when youth often begin to exhibit increases in risk-taking behaviors and social interaction that are critical for independence in adulthood (Casey et al., 2008).

The average age of onset for most anxiety disorders is in early adolescence (Kessler et al., 2007), with over 31 % of US adolescents meeting clinical threshold for a disorder (Merikangas et al., 2010) and countless others experiencing normative symptoms of anxiety (Beesdo et al., 2009; Siegel and Dickstein, 2011) which have been linked to negative outcomes such as depression, addiction, educational underachievement, and suicide (Chiu et al., 2016; Kendall et al., 2018; Siegel and Dickstein, 2011; Woodward and Fergusson, 2001). Despite a 17 % increase in youth anxiety disorder diagnosis over the past decade (Child Mind Institute, 2018), the majority of anxiety disorders in developing youth remain undiagnosed and untreated (Benjamin et al., 1990; Child Mind Institute, 2018; Green et al., 2019; Merikangas et al., 2010; Siegel and Dickstein, 2011). Instead of cognitive or conscious endorsement of anxiety symptoms, youth often demonstrate behavioral and somatic manifestations of the symptoms themselves (e.g., stomach aches; Siegel and Dickstein, 2011). As routine medical visits often decrease after childhood, ambiguous symptoms can be easy to miss (Siegel and Dickstein, 2011), and data suggest that youth ages 12–17 with anxiety are more likely to have an unmet health need (specifically in mental health care and wellness checkups) than those without anxiety symptoms (Green et al., 2019).

Before noticeable anxiety symptoms emerge, youth often demonstrate attention biases that can manifest as early as infancy and guide learning and behavior, thereby providing a useful marker for the development of anxiety (Shechner et al., 2012). A key predictor of adolescent anxiety is a childhood pattern of behavioral inhibition (BI) that is characterized by fear, wariness, and avoidance of unfamiliar stimuli such as new people or situations (Fox et al., 2005; Broeren et al., 2013; Domschke and Maron, 2013; Henderson et al., 2015). Inhibited children are almost four times as likely as those without BI to develop anxiety disorders in adolescence (Chronis-Tuscano et al., 2009; Essex et al., 2010; Schwartz et al., 1999); however, not all individuals with BI go on to develop anxiety later in life (Henderson et al., 2015). Therefore, a thorough examination of risk and resilience in this high-risk group is crucial for understanding and preventing the development of anxiety in adolescence.

Throughout development, anxiety is thought to affect neural functioning through an atypical modulation of attention by, or an attentional bias towards, threats and fearful stimuli. This is supported by neuroimaging studies in populations with both clinical and non-clinical anxiety that have highlighted atypical functioning of what is generally referred to as the "salience network" of the brain, comprised of regions such as the threat-sensitive amygdala and the regulatory prefrontal cortex (PFC) that together are involved in controlling attention and response to threat (for full review, see Blackford and Pine, 2012). However, altered threat processing is not the only signature of anxiety; a smaller body of research has also documented biased reward processing and atypical functioning of reward-related regions such as the striatum in anxious and at-risk youth (Guyer et al., 2006; Lahat et al., 2018). A closer look at the concurrent development of threat- and reward-processing neural networks in at-risk youth is necessary to understand how, why, and which individuals transition from normative to clinical anxiety in adolescence.

2.2. Puberty and the adolescent brain

The transition from childhood to adolescence represents a high-risk phase for the development of anxiety. The beginning of puberty triggers an overproduction of axons and synapses across the brain, which is followed by a pattern of rapid pruning later in adolescence (Crews et al., 2007). During this period, subcortical regions involved in processing reward and threat such as the ventral striatum (VS) and amygdala are hyperactive in response to stimuli, increasing desire and sensitivity for positive feedback (Galván, 2013). Simultaneously, regulatory systems in the prefrontal cortex (PFC) are still maturing (Casey et al., 2008). The differential developmental trajectories of these dynamic systems is thought to underlie the drive for exploration and risk taking—in addition to the vulnerability for negative outcomes—in adolescence (Casey and Jones, 2010; Galvan et al., 2006).

The neurobiology of adolescent motivated behavior has been explained by the Triadic Model, in which three neural systems—approach, avoidance, and regulatory—interact and compete to influence response to positive and aversive cues (Ernst et al., 2009). This model posits that while adolescents demonstrate increased striatal response to positive stimuli and increased amygdala response to negative stimuli, when appetitive and aversive stimuli are pitted against each other, regulatory systems will bias behavior towards approach responses in adolescents compared to adults (Ernst et al., 2009). This model provides a promising framework for the study of adolescent-onset anxiety, as the reciprocal roles of the striatum and amygdala in decision making is of particular relevance to the development of anxiety in youth. The fact that both reward- and threat-related systems exhibit continued development that often manifests as enhanced excitability in adolescence adds complexity to the behavioral patterns observed during this developmental period.

Previous work examining VS function during adolescence has primarily focused on its association with reward. The dopamine (DA) system, which coordinates excitatory and inhibitory neural activity, undergoes changes in the striatum during adolescence (Ernst et al., 2009; Galvan, 2010). Higher dopamine levels and greater dopaminergic response to reward in the VS have been associated with higher sensation-seeking tendencies such as increased risk taking (Derringer et al., 2010; Riccardi et al., 2006; Zuckerman, 1985). Furthermore, adolescents demonstrate heightened VS activity in response to rewards compared to children or adults (Galvan, 2010).

More recently, the role of the striatum has also been implicated in fear processing and anxiety. The striatum becomes sensitized at the same developmental timepoint when anxious symptomatology first manifests. Furthermore, the striatum is closely interconnected with the amygdala, hippocampus, and ventromedial PFC—all key players in adolescent anxiety—and is known to be highly involved in motivation, conditioning/prediction error, and attention (Lago et al., 2017). Pre-clinical animal models have demonstrated that the VS (e.g., nucleus accumbens; NAcc) is necessary for scaling fear to degree of threat: adult rats with NAcc lesions showed specific impairments in rapid uncertainty-safety discrimination, a skill that is necessary for survival and disrupted in clinical anxiety (Ray et al., 2020). While future work is needed to examine whether this association holds in juvenile rats, the striatum has also been linked to anxiety in humans; anxious youth show greater striatal response to low- rather than high-valued outcomes, perhaps due to the relative level of potential risk associated with each option, in addition to demonstrating increased VS activity during feedback anticipation (Benson et al., 2014). Furthermore, an intolerance of uncertainty—a common feature of anxiety (Dekkers et al., 2017; Osmanağaoğlu et al., 2018)—has been positively associated with striatal volume (Kim et al., 2017).

Altered striatal functioning has also been highlighted in studies of at-risk youth. Research examining reward processing in behaviorally inhibited adolescents has found that adolescents with BI—who demonstrate increased amygdala activity during threat processing—also demonstrate increased striatal activity during reward processing (Guyer et al., 2006; Lahat et al., 2018). Similarly, early life adversity has been associated with altered response to both positive and aversive cues across species (Nelson et al., 2009) as well as alterations in both amygdala and striatal development that together affect learning and mental health (Fareri and Tottenham, 2016), rendering a thorough

investigation of both the amygdala and the striatum crucial for the study of anxiety across development.

The adolescent striatum receives input from the amygdala (Haber and Behrens, 2014), allowing it to translate evaluative signals into value-based action (e.g., approach or avoid; Fareri and Tottenham, 2016). The connections between these regions are crucial for affective development and may be disrupted in anxiety, as behaviorally inhibited individuals demonstrate reduced amygdala-striatal resting state connectivity (Roy et al., 2014). Furthermore, animal work suggests that amygdala-striatal communication plays a crucial role in motivated behavior, as flow of information between the amygdala and the NAcc is necessary for active avoidance behavior in rats (Ramirez et al., 2015). While studies of risk taking often focus on the reward-seeking VS and the regulatory PFC, it is imperative to consider how reward-related processes interact with the similarly sensitive threat reactivity of the adolescent amygdala. Conversely, while the increase in adolescent anxiety has been linked to the contrasting developmental trajectories of the threat-sensitive amygdala and the regulatory PFC, it is important to consider how the VS works in tandem with the amygdala to impact adolescent decision making.

2.3. Risk taking and anxiety

While aberrations in approach and avoidance motivations have been linked to both maladaptive risk taking (e.g., substance abuse; Casey and Jones, 2010) and affective disorders (e.g., anxiety; Arnaudova et al., 2017), there is currently a dearth of studies documenting risk taking in anxious adolescents. Furthermore, the extant research has primarily focused on "dangerous" risk taking (e.g., substance abuse) in anxiety, with less emphasis placed on adaptive risk-taking behaviors that might be beneficial for adolescent development (Duell and Steinberg, 2019). While the characterization of anxiety phenotypes often focuses on risk aversion (Sonuga-Barke et al., 2016), the heterogeneity of the disorder and its interaction with typical adolescent development adds complication to this narrative.

While some studies have found that anxious adolescents are at reduced risk for substance abuse due to their risk aversion (Malmberg et al., 2010), others have reported an increased risk in this population (Child Mind Institute, 2018; Kilgus and Pumariega, 2009; Low et al., 2008). Sex and gender differences may contribute to this variability in behavior; female adolescents tend to demonstrate stronger associations between anxiety and drug and alcohol use than males (Cruz et al., 2017; Wu et al., 2010).

Evidence also suggests the existence of anxiety subtypes with distinct behavioral profiles. In one study, researchers identified two subtypes of social anxiety: one characterized by the typical behavioral inhibition and risk avoidance, and the other—deemed the "approach-motivated" subtype—by impulsiveness, reward sensitivity, risk taking, and substance abuse (Nicholls et al., 2014). Another study tested a genetic moderator of loss aversion and impulsivity in anxious adolescents and found that high expression of a specific gene variant was linked to a behavioral profile characterized by low loss aversion and high impulsivity, suggesting a genetic marker of increased proclivity for risk taking in anxious youth (Ernst et al., 2014).

Understanding different behavioral profiles of adolescent anxiety is especially important given the implications of risk taking and mental health for the juvenile justice system. Symptoms of anxiety and depression are common in juvenile offenders (Cauffman, 2004) and may influence offending behaviors in justice-involved youth (Copeland et al., 2007; Hoeve et al., 2013); however, mental health needs in this population are often left unmet (Zajac et al., 2015). Taken together, these results underscore the importance of considering risk-relevant traits such as impulse control and reward sensitivity (in addition to threat sensitivity) in studies of adolescent anxiety.

2.4. Threat vs. thrill

Risky decision-making does not always necessitate the potential for a tangible reward. Instead, the presence of potential threat in a situation may be the very aspect that ignites reward-related circuitry (and the corresponding rewarding feelings) within an adolescent brain. Whether riding a roller coaster, jumping out of an airplane from 12,000 feet in the air, or forgoing your helmet on the last leg of a bike journey, potential threat can evoke strong and exciting sensations that mimic the feelings of reward in individuals of all ages (Spielberg et al., 2014). For example, a program called "Adrenaline Instead of Amphetamine" found that men addicted to stimulating psychoactive drugs such as amphetamine could be effectively treated by engaging in legal and more benign thrills such as sky diving (Makarowski et al., 2016); in other words, the adrenaline produced by potential threat could mimic the rewarding feelings of illicit drug use on the human brain. While the efficacy of this therapy has only been tested in adults, future work might benefit from employing a similar treatment strategy in a younger population.

Due to the disparate development of threat, reward, and regulatory systems, risking danger may be uniquely thrilling in adolescence compared to in other stages of life (Dahl, 2004). The sensation of thrill is involved in many aspects of adolescent risk taking, including romance and sexual experimentation. As the idea of "butterflies in the stomach" suggests, social interaction in adolescence can be as much rewarding as it is acutely terrifying. In order to explore and learn from new and potentially scary experiences, it would greatly behoove the adolescent brain to have a nuanced perception of threat that can perceive danger as both frightening and rewarding. Previous research provides initial support for this theory, as adolescents tend to be more tolerant of uncertainty during risky decision-making than either children or adults (Van Den Bos and Hertwig, 2017) and are more willing to take risks when the risk is ambiguous rather than when risks are clearly stated (Tymula et al., 2012).

Whereas risk-taking behaviors have been associated with a tolerance of uncertainty (Blankenstein et al., 2016), symptoms of anxiety are often linked to an *in*tolerance of uncertainty (Dekkers et al., 2017; Osmanağaoğlu et al., 2018). In a study of unmedicated anxious adults, researchers tested whether risk avoidance in anxiety was driven by risk aversion—an intolerance of uncertain outcomes—or an attentional bias towards potential loss. Risk avoidance was linked to increased risk sensitivity, while loss sensitivity was equivalent across anxious and control groups (Charpentier et al., 2017). This suggests that, regardless of likelihood of loss, perhaps the very aspect of risk that is thrilling for healthy adolescents—that inherent uncertainty of the outcome—is interpreted as threat in anxious adolescents. Future studies documenting risk taking in anxious youth are necessary to understand how adolescent changes in tolerance of uncertainty influence trajectories of anxiety development.

In an attempt to test whether threat becomes uniquely rewarding during puberty, Spielberg and colleagues found that increased amygdala response to threat over time was associated with higher sensation seeking and lower anxiety in individuals who also demonstrated increased VS response to threat over time (Spielberg et al., 2014). Another study providing evidence for the potentially rewarding aspects of threat in adolescence examined learning and neural response in conditions involving evaluation threat. In this study, striatal activity during learning under evaluation threat tracked performance such that adolescents demonstrating increased striatal activity also demonstrated increased learning, a unique pattern that was not seen in adults (Depasque and Galván, 2019). These findings add nuance to a seminal study of reward processing and anxiety that found that adolescents with a history of BI demonstrated increased striatal response during decisions in which the outcome was contingent on participant response (Bar-Haim et al., 2009). How might anxiety impact striatal response to evaluation threat—and would this brain response be conducive or detrimental to learning?

Understanding the influence of amygdala-striatal interactions on adolescent behaviors and mental health across development holds great promise for tailored and effective intervention in adolescence. Perhaps amygdala reactivity can promote approach over avoidance behaviors when combined with VS activity, and promoting positive risk taking by linking threat to reward could help prevent the manifestation of anxiety in adolescence. Previous research suggests that reward-based training may be effective in reducing anxiety and—importantly—has lower risk of exacerbating future anxiety than threat-related treatments (Dandeneau and Baldwin, 2009). If the hyperactive striatum in adolescence is driving adolescents to engage and persevere in learning under threat, perhaps it works in tandem with the amygdala in a similar fashion to reinterpret threat and encourage learning during risky decision-making. An examination of the development of both reward and threat systems simultaneously—and their contributions to risk taking and learning—is imperative.

3. Measuring meaningful change

3.1. A need for longitudinal studies

While neural signatures of both clinical and non-clinical anxiety have been examined in youth, research has yet to capture the transition from normative to clinical anxiety in adolescence from a neurobiological perspective. Cross-sectional studies in childhood and adolescence have helped the field identify which neural regions underly typical anxiety phenotypes and have provided snapshots of neural development across different individuals at varying ages. However, in order to examine the interactions between fronto-amygdala-striatal circuits across adolescence and their relevance for normative and clinical anxious trajectories, longitudinal studies in youth across the anxiety continuum are crucial for accurately tracking developmental change.

Longitudinal studies also allow researchers to track the development of parallel processes in adolescence that may be bidirectionally associated with the development of anxiety. For example, sleep difficulties—which are common in adolescence—are often a precursor of anxious symptoms, can prospectively predict worsening anxiety, and may be especially impactful to mental health in early adolescence (McMakin and Alfano, 2015). Similarly, poor sleep has been associated with increases in both symptoms of anxiety (Kelly and El-Sheikh, 2014) and risk-taking behaviors (Baker et al., 2020; Telzer et al., 2013). Tracking the interactions between sleep difficulties and symptoms of anxiety as youth enter adolescence would provide valuable insight into the development of anxiety and potential interventions for at-risk youth.

3.2. Neuroimaging methods

3.2.1. Dynamic causal modeling (DCM)

The majority of current knowledge regarding brain development and neural signatures of anxiety disorders in youth focuses on correlational associations (e.g., heightened amygdala activity correlating with anxiety severity or reduced PFC functioning in anxious youth during the viewing of emotional images). However, this precludes identification of how these brain regions influence each other to affect adolescent behavior and mental health. Is it an overactive threat response in the amygdala, constant over-regulation in the PFC, or competing influences of the amygdala and VS that drive the feeling of anxiety?

Future studies would benefit from consideration of methods such as Dynamic Causal Modeling (DCM), which allow inference of causal architecture between related brain regions (e.g., amygdala, PFC, and VS) by measuring effective connectivity between brain regions to estimate how neuronal changes in one region influence activity in another region. This method is promising for developmental samples, as it has the potential to capture complex associations of competing brain networks that are continuously reshaped over development (Goldenberg and Galván, 2015). With this approach, one can answer targeted questions regarding the dynamic chain of events underlying adolescent decision making.

3.2.2. Reliability

Despite the promise of longitudinal neuroimaging research for tracking developmental change, it is important to consider the *test-retest reliability*—or the consistency of an assessment tool to produce stable results with each use (Khoo et al., 2007)—of neuroimaging methods in developmental and at-risk populations (for full review, see Herting et al., 2018). Without establishing reliability, delineating true developmental change from changes based on extraneous factors such as noise or artifact becomes difficult. Imaging modalities vary in their reliability; for example, structural indices of brain maturation such as grey matter measurements, white matter volume, and diffusion tensor imaging (DTI) have been shown to be highly reliable across scans in youth (Drobinin et al., 2020), while task-based fMRI demonstrates good reliability for some regions (e.g., occipital lobe) and lower reliability in subcortical areas such as the amygdala and the VS (Vetter et al., 2017). The chosen analysis method can also influence reliability; in addition to its analytic benefits, DCM demonstrates relatively high reliability between scan sessions (Frässle et al., 2015; Schuyler et al., 2010).

Tangible steps towards improving reliability in developmental samples include reducing motion in the scanner (e.g., by prioritizing participant comfort and offering breaks), structuring additional test-retest scans into the protocol with minimal time between measurements, and utilizing multiple imaging modalities in acquisition, processing, and analysis (Herting et al., 2018). For example, studies combining anatomical and functional markers of neural connectivity (e.g., DTI and fMRI, respectively) have elucidated crucial information regarding the development and maturation of brain networks in children (Supekar et al., 2010), and brain-based age prediction has been shown to improve when using multimodal neuroimaging data (Liem et al., 2017). Overall, utilizing multimodal imaging provides a rich and multidimensional view into the developing brain, while the combination of various sources of measurement mitigates risk for spurious, noise-based findings.

Finally, a strong strategy for increasing replicability and generalizability of findings is to recruit a large, diverse participant sample. Smaller sample size increases the chance of spurious or non-generalizable findings, and even a minimum of 100 participants can fall short of perfect reliability (Turner et al., 2018). A thorough and well-powered examination of individual differences in the developmental risk for anxiety requires adequate sampling from a diverse pool of youth across a continuum of anxiety.

4. Conclusion

Anxiety is common among many developing youth, greatly impairs functioning, and only tends to worsen in severity following adolescence (Beesdo et al., 2009; Bittner et al., 2007; Broeren et al., 2013; Kessler et al., 2007; Merikangas et al., 2010). Furthermore, the threat-related brain processes identified in anxiety directly conflict with typical adolescent behaviors such as increased risk taking and exploration (Casey et al., 2008). How does the simultaneous development of fronto-amygdala and fronto-striatal circuits affect attention and anxiety in adolescence? Are anxious youth who demonstrate concurrent activity in the amygdala and the VS during risk taking more prone to risky behavior, thereby achieving a more normative functioning in adolescence? Examination of this adolescent paradox—the rise of both sensation seeking and anxiety in adolescence—is crucial for answering the open questions regarding how anxiety manifests in adolescence, and for identifying targeted and effective methods and timepoints for treatment. A prospective longitudinal study of youth at risk for anxiety that tracks approach and avoidance motivations, risk taking, and mental health in the journey through puberty is necessary to answer these crucial questions regarding risk and resilience and to aid adolescents tormented by clinical anxiety.

Declaration of Competing Interest

The authors report no declarations of interest.

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