

Adolescent anxiety disorders and the developing brain: comparing neuroimaging findings in adolescents and adults

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ABSTRACT

Adolescence is the peak period for the incidence of anxiety disorders. Recent findings have revealed the immaturity of neural networks underlying emotional regulation in this population. Brain vulnerability to anxiety in adolescence is related to the unsynchronised development of anxiety-relevant brain functional systems. However, our current knowledge on brain deficits in adolescent anxiety is mainly borrowed from studies on adults. Understanding adolescent-specific brain deficits is essential for developing biomarkers and brain-based therapies targeting adolescent anxiety. This article reviews and compares recent neuroimaging literature on anxiety-related brain structural and functional deficits between adolescent and adult populations, and proposes a model highlighting the differences between adolescence and adulthood in anxiety-related brain networks. This model emphasises that in adolescence the emotional control system tends to be hypoactivated, the fear conditioning system is immature, and the reward and stress response systems are hypersensitive. Furthermore, the striatum's functional links to the amygdala and the prefrontal cortex are strengthened, while the link between the prefrontal cortex and the amygdala is weakened in adolescence. This model helps to explain why adolescents are vulnerable to anxiety disorders and provides insights into potential brain-based approaches to intervene in adolescent anxiety disorders.

Anxiety disorders are the most common types of mental illnesses in China, and their incidence has been gradually increasing over the past 30 years.¹ Anxiety disorders mainly manifest as excessive fear, worry and avoidance that induce severe emotional distress, somatic diseases, and cognitive and behavioural impairments, and in turn damage normal social functioning and negatively affect quality of life.² With high lifetime prevalence and high risk for recurrence, there is still a lack of effective treatments for anxiety disorders.³ This may be related to the unclarity of the psychopathological mechanisms underlying emotional dysfunction.⁴

Anxiety disorders have an early onset; their incidence among children and adolescents is higher than that among other age groups.⁵ This may be related to the developmental trajectory of the adolescent brain. The brain structure changes significantly from childhood to adolescence in terms of myelination and synapse pruning.⁶ Hormones of puberty, together with pressures from the external environment, reshape the central neural system. These developmental processes and abnormalities may trigger and/or mediate the onset and progression of anxiety disorders in adolescence. In this article, we would review anxiety-relevant abnormalities in the developing brain and attempt to propose a psychopathological model of neural systems underlying anxiety disorders for adolescence, emphasising the differences between adolescents and adults.

BRAIN STRUCTURES ASSOCIATED WITH ANXIETY DISORDERS

Previous studies have shown that the amygdala, prefrontal cortex, bed nucleus of the stria terminalis (BNST), hippocampus, striatum, anterior insula, anterior cingulate cortex and hypothalamus were closely related to anxiety disorders.^{7–9} For instance, the activation in the hippocampus, amygdala and anterior insula during negative emotion processing was enhanced in patients with anxiety disorders.¹⁰ In addition, abnormal thalamic volume is an indicator of social anxiety, especially in children and adolescents.¹¹ The neural networks that regulate social vigilance mainly comprise the bed nucleus of the stria terminalis and prefrontal cortex.¹² Patients with anxiety disorders usually show behavioural avoidance, and the avoidance neural network includes the dorsal anterior cingulate cortex, anterior insula,

sublenticular extended amygdala and temporal pole. Notably, the functional connectivity between the amygdala and the anterior insula is associated with the degree of avoidance.¹³ These structures, which are closely related to anxiety, may play unique roles in the development of cognitive and emotional capabilities among adolescents.

Amygdala

Previous literature supports that the amygdala is related to fear learning and that its pathological increase in volume is a sign of anxiety disorders.¹⁴ As has been shown, scary scenes elicit stronger activations in the amygdala among young people with anxiety disorders than healthy controls.¹⁵ Within the amygdala, the basolateral amygdala participates in processing emotional and somatic responses of anxiety by integrating and transmitting sensory information.¹⁶ Various projections from the basolateral amygdala regulate anxiety-like behaviours after fear extinction.⁹ Amygdala-based neural networks have been observed to be interrupted among adolescents with anxiety disorders.¹⁷

Prefrontal cortex

The prefrontal cortex contributes to fear conditioning and anxiety symptoms. The activation of the medial prefrontal cortex (mPFC) in adolescents is weakened during extinction recall.¹⁸ The activation of the mPFC of anxious adolescents, however, is stronger than that of the healthy group during negative emotion processing.¹⁹ Trait anxiety is positively correlated with the activation of the right prefrontal cortex.²⁰ High levels of anxiety symptoms are related to delayed development of the neural circuits including the prefrontal cortex in children and adolescents.²¹

Hippocampus

The hippocampus is a crucial area for encoding and retrieving spatial and contextual memories, and its integrity underlies fear conditioning, which is essential for anxiety and defensive behaviours.²² Damages to the hippocampus in non-human primates impair the expression and extinction of fear and thus alter anxiety-related avoidance behaviours.²³ Similarly, in rodent models, lesions in the ventral hippocampus alter anxiety-like behaviours.²⁴ In adolescents, decreased hippocampus volume is one of the risk factors for anxiety disorders.²⁵

Bed nucleus of the stria terminalis

The BNST is the extended part of the amygdala that participates in stress response and anxiety maintenance and is responsible for chronic anxiety.²⁶ The BNST mediates the regulation of anxiety by neural circuits underlying substance abuse. For instance, its plasticity alters in adolescent nicotine users and may in turn produce anxiety-like behaviours.²⁷ In addition, it also mediates the regulation of anxiety by the hypothalamic-pituitary-adrenal (HPA) axis, whose imbalance may result in anxiety disorders.²⁸

Striatum

The striatum includes the nucleus accumbens, caudate nucleus and putamen and is usually considered as a part of the reward circuit. The striatum develops in early adolescence.²⁹ The striatum contributes to anxiety symptoms and anxiety-related bias in emotional, motivational and attentional processes, since it has vital contributions to these processes, and striatum-based functional connectivity differs between anxious adolescents and healthy adolescents.^{7,30}

Hypothalamus

The hypothalamus is a critical structure involved in the anxiety circuit. It is also a central part of the HPA axis responsible for regulating emotions, defensive behaviour, aggression and stress responses. The hypothalamus actively controls aggressive and anxious behaviours by influencing hormone synthesis in adolescence.³¹ Factors that affect HPA axis activities include circadian rhythm disturbances, stress and caffeine, particularly during adolescence.³² The dysregulation of HPA axis activities during adolescence increases the risk of developing anxiety disorders.

NEURAL NETWORKS UNDERLYING ADOLESCENT ANXIETY

Anxiety disorders are not due to deficits of a single brain structure. Instead, there are plenty of studies suggesting anxiety-related neural networks. This section reviews previous findings that link deficits in neural networks to anxiety, especially in adolescents.

Anxiety disorders have abnormalities in many aspects of psychological processes, such as cognitive control, fear conditioning, uncertainty anticipation, motivation bias and stress regulation. Regarding cognitive control, anxiety disorders are characterised by dysfunctional cognitive control of the projection from the prefrontal cortex to the amygdala.¹³ Patients with anxiety disorders show alterations in the fear condition, including abnormalities in the network involving the ventral hippocampus, basolateral amygdala and mPFC.²² Regarding uncertainty anticipation, neural pathways involving the BNST mediate the over-reaction to uncertain anticipations in patients with anxiety disorders.³³ As for motivation, the striatum is associated with unbalanced reward function in anxiety disorders, and the failed regulation of the striatum, amygdala and prefrontal cortex is an important neural underpinning of anxiety disorders.³⁴ Regarding stress, abnormal recruitment of the hypothalamus, amygdala and prefrontal cortex is associated with the failure of stress regulation. Based on the mentioned associations, we assume that psychopathological symptoms of anxiety disorders in adolescence may be underlain with abnormalities in brain structures relevant to cognitive control, fear conditioning, uncertainty anticipation, motivational processing and stress regulation.

Figure 1 summarises previous findings regarding the deficits of neural networks underlying anxiety disorders, characterised by the five components. We will further review

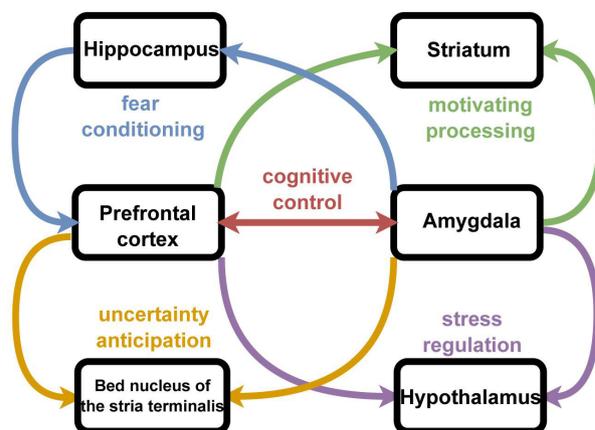
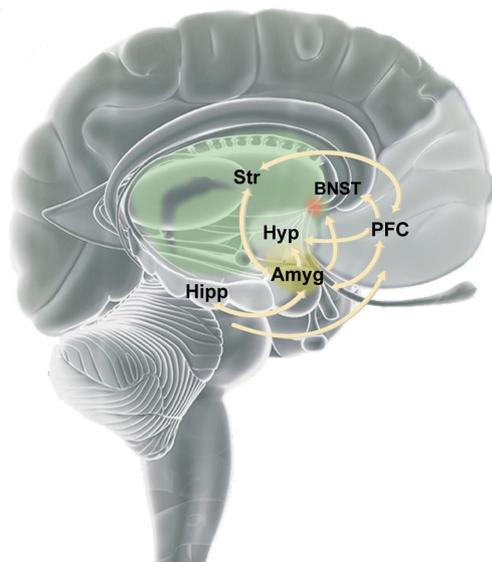


Figure 1 Schematic presentation of anxiety-related functional systems and brain structures. The arrows indicate the neural projections between two brain regions. The pathological interactions of the six critical regions in the anxiety network bring about functional abnormality for patients with anxiety disorders. Amyg, Amygdala; BNST, Bed nucleus of the stria terminalis; Hipp, Hippocampus; Hyp, Hypothalamus; PFC, Prefrontal cortex; Str, Striatum.

the findings relevant to these components in the following subsections.

Cognitive control: amygdala and mPFC

The neural circuit between the mPFC and the amygdala is closely related to cognitive control. The amygdala projects to different areas of the mPFC; specifically, basal amygdala neurons project to the prelimbic and the infralimbic subdivision of the mPFC, completing the fear expression and extinction.³⁵ The activation of this pathway corresponds to an increase in individual anxiety-like behaviours and a decrease in social interaction.³⁶ The mPFC integrates inputs from various areas and projects them back to the amygdala to achieve top-down inhibitory control. The number of basal amygdala neurons projecting to the mPFC tends to become stable during adolescence.⁴ In adolescence, the maturation of the mPFC is later than that of the amygdala, and the ability of top-down regulation is immature and weak.³⁷ Hence, insufficient inhibition of the amygdala neurons may provide a potential neural basis for adolescent anxiety disorders.

Fear conditioning: ventral hippocampus, basolateral amygdala and mPFC

Deficiency in fear extinction is one of the characteristics of anxiety disorders. The ventral hippocampus, basolateral amygdala and the mPFC form an interconnected circuit that plays a vital role in fear learning and extinction.^{38 39} The mPFC receives outputs from the ventral hippocampus. Glutamatergic inputs from the ventral hippocampus enhance the plasticity of mPFC neurons and promote maturation.⁴⁰ When the ventral hippocampus projects to the mPFC, neurons synchronise to the theta frequency (4 to 12 Hz), forming and

maintaining anxiety-like behaviours.^{39 41} In contrast, inhibiting the projections from the ventral hippocampus to the mPFC reduces the synchrony of the theta frequency and reduces the probability of anxiety disorders.³⁹

The ventral hippocampus and the basolateral amygdala rely on each other coding fear-related memories.⁴² Glutamatergic inputs from the basolateral amygdala to the ventral hippocampus pyramidal neurons increase individual anxiety, while inhibition of this projection reduces anxiety-related behaviours.⁴³ The pathway projected from the basolateral amygdala to the ventral hippocampus regulates social interactions as well.^{42 43} The dual function of this pathway in modulating anxiety and social behaviours possibly explains the high comorbidity rate of anxiety disorders and autism spectrum disorders.⁴⁴ The projections from the ventromedial prefrontal cortex to the amygdala inhibit fear expression, and this process is modulated by the hippocampus.⁴⁵

Uncertainty anticipation: BNST, amygdala and prefrontal cortex

The neural networks that include the BNST, amygdala and prefrontal cortex participate in the anticipation of uncertain threats.^{33 46 47} There is a functional separation between the basolateral amygdala and the BNST. The basolateral amygdala mediates immediate responses to threats and is related to panic disorder and specific phobia in anxiety disorders. The BNST, in contrast, mediates sustained responses to unpredictable threat information and is related to generalised anxiety disorder and post-traumatic stress disorder.⁴⁸ The excessive and

persistent anxiety response of patients with anxiety disorders to uncertain information may be underlain with neural projections from the basolateral amygdala to the BNST.³³ The BNST receives the inputs from the mPFC.⁷ The nerve connection between the mPFC and the BNST has a modulating effect on anxiety.⁴⁹

Motivation processing: striatum, amygdala and prefrontal cortex

The nucleus accumbens of the striatum evaluates stimuli in terms of motivational values, and the dorsal striatum integrates and transmits information to the prefrontal and motor cortices.⁵⁰ Reward representations are available to the ventral striatum that participates in forming motivational and goal-oriented behaviours. The amygdala actively regulates the striatum. The direct projection from the amygdala to the striatum supports 'fight or flight' motor responses, as well as avoidance learning.³³ In addition, the ventral striatum participates in emotion and motivation processing, driving action outputs from the basal ganglia.⁵¹ The projection from the prefrontal cortex to the striatum contributes to cognitive functions, such as decision-making.⁵² The mPFC achieves a balance between anxiety-like and motivated behaviours by the inputs to the amygdala and the striatum.⁵³

Stress regulation: hypothalamus, amygdala and prefrontal cortex

The hypothalamus is sensitive to stressors and plays a regulatory role. Under stressful conditions, amygdala-to-hypothalamic outputs maintain anxiety behaviours.⁵⁴ The neurotransmissions from the hypothalamus to the amygdala build fear expression and generalisation, and the deactivation of hypothalamic orexin neurons alleviates excessive fear.⁵⁵ The direct projection from the prefrontal cortex to the hypothalamus involves regulating emotional stress, emotional arousal and control of aggressive behaviours.⁵⁶ In anxiety-inducing situations, the prefrontal cortex inputs dopamine to the amygdala, which further excites the hypothalamic neurons and initiates the HPA axis, triggering a somatic response of sympathetic excitation.⁵⁷ In patients with anxiety disorders, overactivation of the amygdala leads to overexpression of corticotropin-releasing factors, promoting HPA axis hyperactivity and manifesting as an over-reaction to stress.⁵⁸

Differences in brain networks across subtypes of anxiety disorders

Morphologically, patients with social anxiety disorder (SAD) have a larger grey matter volume in the dorsal striatum.⁵⁹ They have reduced frontal lobe volume and increased amygdala volume relative to healthy controls.⁶⁰⁻⁶¹ Patients with generalised anxiety disorder (GAD) have reduced ventromedial prefrontal cortex volume and hypothalamus volume.⁶²⁻⁶⁴ Patients with panic disorder (PD) have smaller grey matter volumes

in the amygdala, the hippocampus, the prefrontal cortex and the bilateral striatum.⁶⁵⁻⁶⁶

During emotion-related tasks, the amygdala and the parahippocampal gyrus are overactive in patients with SAD, with enhanced functional connectivity between the amygdala and the prefrontal cortex.⁶⁷⁻⁶⁸ In contrast, patients with GAD have insufficient activation in the prefrontal cortex and weak functional connectivity between the amygdala and the prefrontal cortex.⁶⁹ In gambling games, BNST activity is increased while amygdala activity is suppressed in patients with GAD, where anxiety experience is triggered by high uncertainty.⁷⁰ In fear conditioning, patients with PD have hyperactivation in the hypothalamus and abnormal recruitments of the hippocampal-prefronto-amygdala network with hippocampal excitation, manifesting as excessive fear learning.⁶⁷⁻⁷¹

Brain network differences exist in different subtypes of anxiety disorders and are reflected differentially in various brain structures. Notably, current treatments for anxiety disorders also have different efficacy for different subtypes; for example, cognitive-behavioural therapy to treat patients with SAD tends to be less effective for other anxiety disorders.⁶¹ Possible neural underpinnings are that the aberrance patterns of the anxiety network are different for different subtypes of anxiety disorders: hypersensitivity to emotional stimuli in patients with SAD, inadequate top-down control in patients with GAD and excessive fear learning in patients with PD. With future verifications of this hypothesis, changes in the anxiety network may help to predict the efficacy of treatments.⁷²

UNIQUE FEATURES OF THE ADOLESCENT ANXIETY-RELATED NETWORKS

Based on the above review, we further propose that the imbalance in the developmental progress of these five systems during adolescence provides an essential basis for the high incidence of anxiety disorders during this period. From adolescence to adulthood, the neural connections in anxiety neural networks change dramatically. For example, the intensity of connections between subcortical structures decreases with age⁷³; the long and extensive cortical connections gradually dominate and the regulation to subcortical regions is enhanced, forming the neural basis for the gradual improvement in emotional processing.⁷⁴ As shown in figure 2, the anxiety network of adolescents and adults differs in regional activations and structural and functional connectivity within the anxiety network.

Insufficient cognitive control in adolescence

During emotion processing, amygdala activation shows a non-monotonic change with age, with reduced amygdala activation more in adults than in adolescents.⁷⁵ During adolescence, the activation of the prefrontal cortex in performing cognitive tasks becomes more focal with age, and adults show stronger prefrontal activation than

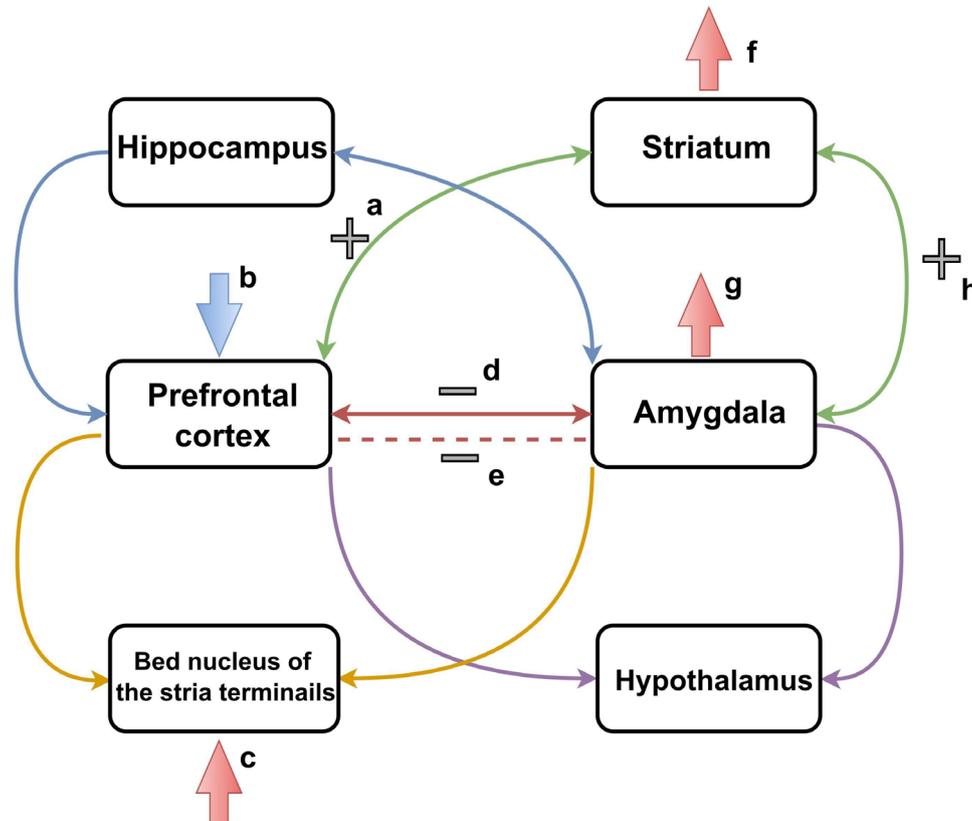


Figure 2 Schematic of the differences between adolescence and adulthood anxiety networks. ‘↑’ or ‘↓’ indicates that the activation of the marked brain region in adolescents is higher or lower than that in adults; ‘+’ or ‘-’ indicates that the connection of this pathway is stronger or weaker in adolescents compared with that of adults. Solid lines indicate functional connections, and dashed lines indicate structural connections. a, DePasque & Galvan, 2017;⁹⁸ b, Casey *et al.*, 2008;⁷⁶ c, Saalfeld & Spear, 2019;⁹² d, Silvers *et al.*, 2017;⁸⁴ e, Lebel & Beaulieu, 2011;⁷⁸ f, Galvan, 2010;⁹⁵ g, Hare *et al.*, 2008;⁷⁵ h, Heller *et al.*, 2016.⁷⁴

adolescents.⁷⁶ Compared with adolescents, adults are able to exert cognitive control of the prefrontal cortex in anxious situations and are less affected by emotional interference.⁷⁵

Functional and structural connections between the prefrontal cortex and the amygdala are reorganised during adolescent development.⁷⁷ The structural connectivity between the amygdala and the prefrontal cortex increases, in terms of fractional anisotropy, with age.⁷⁸ Importantly, reduced integrity of this structural connection in adults and adolescents is associated with anxiety disorders.⁷⁹ In addition, delayed maturation of amygdala-prefrontal connections during adolescence may be one of the neural bases for abnormalities in emotional behaviours.⁸⁰ The number of dendritic spines in mPFC neurons and basolateral amygdala neurons is larger in adolescence than in adulthood due to dendritic remodelling and pruning. However, the later the dendritic remodelling and pruning are completed, the higher the risk of developing anxiety disorders.⁸¹ The signalling endocannabinoid that impacts cognitive control in the prefrontal cortex is enhanced in adolescence, while weaker signalling is found in adolescents with anxiety disorders.⁸²

The functional connectivity between the amygdala and the prefrontal cortex during emotion-related tasks shifts from positive to negative from early childhood to

adolescence, which may be related to the development of the capacity to deal with separation anxiety.⁸³ From adolescence to adulthood, the amygdala-prefrontal functional connectivity shifts from negative to more strongly negative, reflecting the increased regulation of emotions for adults.⁸⁴ Therefore, reduced functional connectivity between the amygdala and the prefrontal cortex indicates failure of top-down control in the prefrontal cortex, which is a potential pathological factor for anxiety disorders in both adolescents and adults.^{85 86}

Ineffective fear extinction in adolescence

Hippocampal volume increases and then decreases from adolescence to adulthood.⁸⁷ During adolescence, the structural connections between the amygdala and the mPFC develop, which is related to fear conditioning.⁸⁸ Relative to adults, even mentally healthy adolescents are ineffective at fear extinction.⁸⁹ Negative functional connectivity in adolescents between the prefrontal cortex and the hippocampus and between the prefrontal cortex and the amygdala is related to deficits in extinction recall and with state anxiety.⁴⁵ In addition, the ventral hippocampus has an ineffective inhibitory effect on the functional connectivity between the basolateral amygdala and the mPFC in adolescents, thereby impacting fear extinction. Disruption of these processes

may lead to pathological emotional responses in psychiatric disorders.^{4 40} For adolescents, excessive functional connectivity between the prefrontal cortex, the amygdala and the hippocampus is associated with a higher risk of anxiety disorders. For adults, the lack of hippocampal inhibition of the prefrontal cortex, which is common in typically developing adolescents, may increase the risk of mood disorders in adults.⁹⁰

Increased response to anticipating uncertainty

The BNST is activated in an environment with unpredictable threats.⁹¹ The reaction of the BNST in adolescents tends to be stronger than in adults.⁹² This may partially explain the high susceptibility of adolescents to anxiety disorders. After all, during adolescence, hyperactivation of the BNST and the basolateral amygdala accompanies increment of anxiety-like behaviours in individuals.⁹³

For adults with social anxiety disorder, the BNST responds more strongly to unpredictable emotional faces. This may be a consequence of weakened functional connectivity between the BNST and the amygdala.⁹¹ The mPFC promotes the activity of the BNST and enhances negative emotions and behaviours.⁴⁹ The functional connectivity between the BNST and the prefrontal cortex is negatively correlated with anxiety severity in patients with anxiety disorders but positively correlated in healthy controls.⁹⁴ However, the relationship between the development of the BNST and anxiety disorders in adolescents, as well as the neural connections of the BNST and their functions during adolescence, is underdocumented and needs further investigation.

Motivational processing bias in adolescence

In reward tasks, peak striatum activation occurs in adolescence relative to childhood and adulthood. Adolescents are more sensitive to rewards as the reward stimuli of the same intensity elicit stronger ventral striatal activation in adolescents.⁹⁵ In contrast, patients with anxiety disorders, who tend to be risk-avoidant, show overactivations at the striatum, which may be one of the neural bases of anxiety disorders.^{7 96}

The functional connectivity between the amygdala and the striatum in response to emotional cues is declining during development, and is associated with enhanced cognitive control.^{74 97} Similarly, the functional connectivity between the prefrontal cortex and the striatum also declines with age.⁹⁸ Adolescents with GAD show increased functional connectivity between the striatum and the amygdala, accompanying higher sensitivity to reward-related stimuli.⁹⁹ Patients with anxiety disorders also show altered prefrontal-striatal functional connectivity.⁵⁰ The prefrontal-striatum connectivity in adults with anxiety disorders is increased,¹⁰⁰ whereas that in adolescents with anxiety disorders may decrease in response to unexpected positive feedback.³⁰ The abnormal development of dopaminergic neurons in the amygdala, the prefrontal cortex, the hippocampus and the striatum during adolescence alters one's exposure

to hormonal influences, which may increase the risk of mental illness.¹⁰¹

Hypersensitivity to stress in adolescence

For adolescents, experiencing stress leads to overexpression of corticotropin-releasing factor receptor 1 in the hypothalamus, the amygdala and the prefrontal cortex, causing abnormalities in the HPA axis that will persist into adulthood.¹⁰² Significantly increased responses to stress in adolescents compared with adults, as evidenced by prolonged hormonal exposure, are possibly responsible for the increased vulnerability to psychiatric disorders seen during adolescence.¹⁰³

CONCLUSIONS

Adolescents are immature in terms of emotional regulation. During adolescence, the emotional control system tends to be hypoactivated, echoing the insufficient cognitive control in adolescents; the fear conditioning system is immature, echoing the ineffective fear extinction; and the reward system and the stress response system are both hypersensitive, echoing the biased motivational processing and the aberrant stress regulation when facing circumstances with potential threats, respectively. These unique features of adolescent brains may partially explain the vulnerability of adolescents to anxiety disorders.

While there has been a large body of literature on the differences of separate anxiety-related functional circuits between adolescents and adults, studies on whether and how the separate functional circuits integrate to represent the vulnerability of adolescents to anxiety are still rare. The anatomical connections and the functional relevance of the five circuits reviewed in the paper are apparent, suggesting the high likelihood of interactions among the functional circuits. Future research should develop and apply advanced methodologies, such as functional network connectivity and multivariate pattern analyses, to reveal the relationships between the interactions of the functional circuits and the risk of adolescent anxiety.

Furthermore, the adolescent-specific brain abnormalities have some clinical implications for adolescent anxiety. The neuroimaging markers for diagnosis and early detection of anxiety in adolescents may differ from those found in adult studies and therefore require further investigations and verifications in the adolescent population. In addition, brain abnormalities in adolescents suggest potential targets for brain-based therapies such as brain modulations. The links between different brain systems and various symptoms and subtypes have implications for individualised brain-based treatments.

This review focused on comparing neuroimaging findings on the anxiety-related brain circuits between adolescents and adults, providing a macro-scale model connecting the adolescent-specific brain features with vulnerability to anxiety. It should be noted that

the essential drives of the functional circuits, such as neuronal properties and neural transmitters, are the bases of the macro-scale observations. Future theoretical and experimental work is expected to reveal theories and findings regarding adolescents' vulnerability to anxiety.

Correction notice The article has been corrected since it was first published online. Figure 2 and its caption have been updated.

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