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Fear responses to safety cues in anxious adolescents: Preliminary evidence for atypical age-associated trajectories of functional neural circuits

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ABSTRACT

Adolescent anxiety is common and impairing and often persists into adulthood. There is growing evidence that adult anxiety is characterized by abnormal fear responses to threat and safety cues, along with perturbations in fear-related neural circuits. Although some of this work has been extended to adolescents, with promising results, it is not yet clear whether changes in these circuits across developmental age varies between anxious and non-anxious adolescents. Here we used fMRI to examine how age modulates neural responses as adolescents are exposed to threat and safety cues. Participants were 15 anxious and 11 non-anxious adolescents (age 12–17) who completed a fear conditioning paradigm. The paradigm incorporated a threat cue comprising a neutral face which was paired with a fearful, screaming face, a safety cue comprising a different neutral face, and a control stimulus. Across the whole sample, neural activation to the threat cue (relative to the control cue) correlated positively with age in a number of regions, including the dorsal anterior cingulate and bilateral dorsolateral prefrontal cortex (PFC). However, neural activation to the safety cue (relative to the control cue) was modulated differently by age in the two groups: a more positive association between activation and age was observed in the control group compared to the anxious group in various regions including medial and dorsolateral PFC, anterior insula, and amygdala. These findings suggest that maturation of the neural substrates of fear responses to safety cues may be perturbed in anxious adolescents, potentially contributing to the emergence and maintenance of anxiety disorders in adulthood.

1. Introduction

Adult anxiety is characterised not only by behavioural, cognitive, and neural abnormalities in fear responses to threat cues but also inappropriate fear of safety cues. Anxiety disorders often have their onset during adolescence (Pine et al., 1998), and improved understanding of how they emerge could inform early interventions to attenuate their progression. Substantial differences between adults and adolescents in terms of brain structure and function, cognition, and social environment mean that studies of adolescents are crucial. Here we examined how neural responses to threat and safety cues differ between anxious and non-anxious adolescents and in particular how these differences may emerge across development.

Studies using conditioning paradigms, where an initially neutral stimulus becomes a reinforced conditioned stimulus (CS+) through repeated pairings with an aversive unconditioned stimulus (UCS), have established that high anxious adults show exaggerated self-reported and physiological fear responses to threat cues (Lissek et al., 2005). Yet anxious individuals do not only fear cues that predict threat; they also show generalized fear responses to safety cues. *Safety* learning occurs when neutral stimuli which are never followed by the UCS (i.e., non-reinforced conditioned stimuli, CS−) come to signal the *absence* of the threat. Fear responses to safety cues may sometimes be adaptive but can also be costly, because individuals expend energy on unnecessary fear and/or avoidance

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behaviours and cannot benefit from opportunities or resources associated with safety cues.

Healthy adults show a relatively steep drop-off in self-reported and physiological fear as graduated safety cues become less perceptually similar to the threat cue, (Lissek et al., 2008; Lissek et al., 2013b; Dunsmoor et al., 2011b; Dunsmoor and Schmajuk, 2009). In contrast, anxious individuals fear a wider range of safety cues – even those less perceptually similar to threat cues (Dunsmoor et al., 2011b; Haddad et al., 2012; Lissek, 2012; Lissek et al., 2009, 2010; Lissek et al., 2013a).

These difficulties in inhibiting fear responses to safety cues may be driven by anxiety-associated abnormalities in prefrontal-subcortical circuitry (Kim et al., 2011b). Ventromedial prefrontal cortex (vmPFC) activation in healthy adults diminishes as safety cues become more similar to a threat cue. The vmPFC response is less discriminating in anxious patients (Greenberg et al., 2013b), or generally lower (Britton et al., 2013), suggesting deficient vmPFC recruitment in response to safety cues. In contrast, in regions where healthy volunteers show 'positive' generalization gradients (i.e., greater activity as safety cues increase in resemblance to threat, which occurs in the insula, supplementary motor area (SMA), and dorsomedial prefrontal cortex (dmPFC) (Lissek et al., 2013b), as well as anterior cingulate (ACC), and caudate (Greenberg et al., 2013a)), no anxiety-linked differences have been found (Greenberg et al., 2013b). Together these data suggest that at the neural level, generalization abnormalities in anxiety are found in regions that are involved in inhibitory but not excitatory responses.

Although this emerging evidence sheds light on the nature of fear learning difficulties in anxious adults, extending conclusions from adults to adolescents is not straightforward and the few studies of fear generalization in youth have mainly focussed on younger children. What has been shown in anxious adolescents is that, like anxious adults, they may have elevated self-reported fear of both threat and safety cues (Lau et al., 2008) and at the neural level, they may have reduced subgenual ACC activity across a range of safety stimuli (Britton et al., 2013). The vmPFC may show a more subtle pattern: anxious adolescents in this study had higher vmPFC activation for the extreme ends of the gradient (CS+ and CS−) and lower activation for intermediate stimuli, which may reflect heightened sensitivity to both threat and safety.

Studies of the *age trajectory* of these responses in anxious and non-anxious adolescents are, however, lacking. Yet adolescence is a period of protracted neurocognitive maturation of key brain circuits involved in fear regulation, and so anxiety-associated differences are likely to emerge gradually as a perturbation of these age-typical changes. Age-related changes have been observed in emotional processing in general through normal adolescence (Cohen Kadosh et al., 2012; Deeley et al., 2008; Glenn et al., 2012; Moore et al., 2012; Somerville et al., 2011; Van Den Bulk et al., 2013; Vink et al., 2014; Yurgelun-Todd, 2007). With regard to fear learning specifically, studies of rodents suggest greater sensitivity in the acquisition of fear associations during adolescence compared to other developmental stages (Den and Richardson, 2013). An inability to attenuate these fear responses through a process of new (extinction) learning has been reported as well (Kim et al., 2011a) (McCallum et al., 2010), a finding that extends to humans (Pattwell et al., 2012). In relation to safety learning, one study found stronger fear of safety cues in older than younger adolescents (Glenn et al., 2012). Some studies have investigated the neural substrates of these age-associated changes, and have found correlations between adolescents' age and activation in key areas including hippocampus, amygdala, ventrolateral PFC, dorsomedial PFC, thalamus, and caudate while viewing emotional pictures or faces (Vink et al., 2014; Deeley et al., 2008). This indicates that patterns of emotional processing in general, and perhaps fear responding in particular, change through childhood and early adolescence, lending credibility to the idea that the emergence of anxiety could be due to perturbed age-associated changes in fear responses at the behavioural and/or neural level.

1.1. This study

In this study, we sought to examine this idea by investigating age trajectories in neural responses during fear responding in anxious and non-anxious adolescents. We employed a threat/safety learning paradigm based on the "screaming lady" task (Lau et al., 2008). During fMRI, participants viewed a threat cue (CS+, neutral face) that was paired with an unconditioned stimulus (UCS, fearful face and scream), a safety cue (CS−, different neutral face), and a control cue (oval). Conditioning studies often compare CS+ and CS− responses directly. However, we expected that anxious adolescents would show elevated fear of the CS− (Lau et al., 2008) as well as perturbed neural responses to both threat and safety (Britton et al., 2013). Directly comparing CS+ and CS− responses would not allow us to consider elevated fear of threat and elevated fear of safety separately. We therefore considered responses to each CS separately in order to probe group and age-related differences in fear of threat (i.e., CS+ relative to control) and fear of safety (i.e., CS− relative to control). One potential difficulty of this approach is that both comparisons could merely index face processing, because both involve comparing a neutral face with an oval. We checked whether this was plausible by comparing the pattern of findings for the two contrasts; regions active due solely to face processing should elicit the similar responses for both contrasts. Based on previous studies, we expected anxiety-associated differences and age-related changes across the whole group during fear of threat and safety in hippocampus, amygdala, and PFC. We also explored a new hypothesis: that anxious and non-anxious groups show age-related divergence in these patterns of neural activation.

2. Method

2.1. Participants and procedure

The final sample consisted of 26 participants aged 11–17 recruited through the community. Fifteen were anxious (2 males; mean age = 15.2 ± 1.5 years, range 154–212 months) and 11 were healthy (5 males; mean age = 15.6 ± 1.3 years, range 168–212 months). The group-by-gender interaction was not significant, Fisher's exact test $p = .095$.

Data from nine other participants were excluded: three withdrew prior to or during scanning; three had excessive movement during scanning (>3 mm in any direction) or gross structural abnormalities; one reported seeing only one face; and two showed no behavioural evidence of conditioning (no increase in CS+ ratings from pre-acquisition to acquisition and no elevated ratings of CS+ above CS− during acquisition).

Based on Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS), 11 of the anxious participants met criteria for one or more anxiety disorders and 4 had subclinical symptoms. Seven had concurrent major depression. Non-anxious participants had no current or past psychological disorders. Exclusion criteria included IQ < 70; current psychotropic medication; and conditions that would increase the risks of MRI. The local ethics committee approved the study and we obtained written informed consent/assent from parents and participants respectively. Participants completed the KSADS and measures of IQ and trait anxiety at an initial visit and completed scanning procedures during a second visit at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). Participants and parents were reimbursed for their participation.