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Forgetting the best when predicting the worst: Preliminary observations on neural circuit function in adolescent social anxiety

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ABSTRACT

Social anxiety disorder typically begins in adolescence, a sensitive period for brain development, when increased complexity and salience of peer relationships requires novel forms of social learning. Disordered social learning in adolescence may explain how brain dysfunction promotes social anxiety. Socially anxious adolescents ($n = 15$) and adults ($n = 19$) and non-anxious adolescents ($n = 24$) and adults ($n = 32$) predicted, then received, social feedback from high and low-value peers while undergoing functional magnetic resonance imaging (fMRI). A surprise recall task assessed memory biases for feedback. Neural correlates of social evaluation prediction errors (PEs) were assessed by comparing engagement to expected and unexpected positive and negative feedback. For socially anxious adolescents, but not adults or healthy participants of either age group, PEs elicited heightened striatal activity and negative fronto-striatal functional connectivity. This occurred selectively to unexpected positive feedback from high-value peers and corresponded with impaired memory for social feedback. While impaired memory also occurred in socially-anxious adults, this impairment was unrelated to brain-based PE activity. Thus, social anxiety in adolescence may relate to altered neural correlates of PEs that contribute to impaired learning about social feedback. Small samples necessitate replication. Nevertheless, results suggest that the relationship between learning and fronto-striatal function may attenuate as development progresses.

1. Introduction

The drive for social acceptance can promote a corresponding fear of rejection that, if extreme, may manifest as social anxiety (Klapwijk et al., 2013). Since prediction error signaling supports learning, altered signaling may contribute to some of the hallmarks of social anxiety disorder. Specifically, altered prediction error signaling could lead to deficient recall of positive past social experiences, which in turn could promote the negative social expectation and interpretation biases that are common to patients with social anxiety (Clark and McManus, 2002; Rapee and Heimberg, 1997). Such deficits may be particularly detrimental during adolescence, a sensitive developmental period that is marked by heightened salience of social acceptance and rejection (Brown and Larson, 2009) and the establishment of complex, peer-focused patterns of behavior and learning (Blakemore, 2008; Crone and Dahl, 2012; Nelson et al., 2005; Steinberg and Morris, 2001). These shifts coincide with peak onset rates of social anxiety, and occur in conjunction with significant changes in brain function (Casey et al., 2000; Nelson et al., 2014; Ordaz et al., 2013; Pfeifer et al., 2013; Rubia et al., 2006; Satterthwaite et al., 2013). Adolescence begins with hormonal changes of puberty, followed by the physical expression of pubertal maturation over subsequent years (Grumbach, 2002); its conclusion is culturally constrained by the assumption of adult roles (Blakemore and Mills, 2014). This transition involves acquiring skills needed for peer-based relationships (Blakemore and Mills, 2014), which thereby promotes novel patterns of peer-focused behavior and learning (Blakemore, 2008; Crone and Dahl, 2012; Nelson et al., 2005; Steinberg and Morris, 2001). A Prediction Error (PE) model may explain how brain

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Table 1
Demographics.

	Adults				Adolescents			
	Anxious *n*		Non-anxious *n*		Anxious *n*		Non-anxious *n*	
Sample size	19		32		15		24	
Female/male	15/4		17/15		9/6		9/15	
% White non-Hispanic or Latino	52.63		44.75		66.67		83.33	
Current primary diagnosis								
SAD	5		–		7		–	
GAD	4		–		2		–	
SAD + GAD	10		–		6		–	
Current secondary diagnosis								
MDD	1		–		1		–	
ADHD	0		–		3		–	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Age (years)	27.86	*7.82*	26.17	*5.16*	12.79	*3.39*	13.68	*2.39*
Tanner Score	–		–		2.92	*1.16*	3.36	*1.36*
IQ	112.78	12.58	119.13	11.38	104.80	*12.45*	112.63	*11.69*
FNE	22.07	*8.07*	9.81	*4.92*	21.08	*8.27*	6.91	*4.97*
	Min	Max	Min	Max	Min	Max	Min	Max
Age range (years)	18.25	49.58	21.00	44.83	8.00	17.42	9.42	17.17

SAD, social anxiety disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; ADHD, attention deficit hyperactivity disorder; IQ, intelligence quotient; FNE, fear of negative evaluation.

dysfunction during adolescence, a sensitive period of brain development (Casey et al., 2000; Nelson et al., 2014; Ordaz et al., 2013; Pfeifer et al., 2013; Rubia et al., 2006; Satterthwaite et al., 2013), fosters maladaptive social responding. However, limited research uses PE models to assess adolescent psychopathology.

In general, PE models specify that predictions are elicited by cues that precede motivationally-salient outcomes; discrepancies between predicted and actual outcomes result in updated predictions (Pessiglione et al., 2006; Schonberg et al., 2007). PEs associated with unexpectedly positive and negative outcomes, respectively, heighten or diminish activity in the striatum (Schultz et al., 1997), a subcortical structure that guides reward-related behavior and learning (O'doherty, 2004; Yin et al., 2009). Functional connectivity between the striatum and medial prefrontal cortex (mPFC) is implicated in updating both predictions and the value ascribed to outcomes (Haber et al., 2006; O'doherty, 2004). However, such connectivity may reach functional maturity relatively late in development (Forbes and Dahl, 2012; Gogtay et al., 2004; Sowell et al., 2002). In fact, recent studies find PE-related developmental differences in the striatum (Cohen et al., 2010) and/or striatal-mPFC connectivity (van den Bos et al., 2012) as well as evidence of deficient mPFC-based connectivity in youths (Britton et al., 2013; Fitzgerald et al., 2011; Roy et al., 2013). Failure to establish normative striatal-MPFC connectivity during adolescence, when peer acceptance becomes a much more motivationally-salient outcome, may have a negative impact on PE-based social learning. This may be one mechanism that contributes to the particularly high onset rate of adolescent social anxiety disorders. However, the same mechanism may be less critical for maintaining symptoms among anxious adults, who have moved beyond a critical phase of development when behavior may be more easily shaped by social learning.

The neural correlates of PE are typically investigated using paradigms in which participants learn how arbitrary stimuli predict positive or negative outcomes. Such paradigms are well suited for examining general aspects of PE learning but may be less well suited for studying socially anxious adolescents, who have unimpaired performance on most such paradigms (Dickstein et al., 2010). The present study uses a paradigm known to elicit biased responding in socially anxious adolescents (Guyer et al., 2008) as a preliminary investigation of the relationship between age, social anxiety, and the neural correlates of PE in a social context. Relative to traditional PE paradigms, this novel approach may be better suited for capturing between-group differences in PE, but less well suited for examining general aspects of PE learning. Given past work, we hypothesized that striatal-mPFC engagement would be uniquely altered among socially anxious adolescents. To test this hypothesis, brain activity was assessed with functional magnetic resonance imaging (fMRI) as participants predicted, and then received, expected (accurately predicted) or unexpected (inaccurately predicted) positive and negative feedback from high and low-value peers. Brain activity was then related to performance on a surprise memory task in which participants were asked to recall feedback valence. Socially anxious and non-anxious adolescents and adults were studied to directly compare associations among these groups.

2. Methods and materials

2.1. Participants

Participants included 90 medication-free, anxious and non-anxious adolescents and adults (see Table 1 for demographics and Supplemental Materials for recruitment methods and exclusionary criteria). All patients met DSM-IV criteria for clinical anxiety and all expressed clinically significant fear of social situations during diagnostic interviews and on the Fear of Negative Evaluation (FNE; Watson and Friend, 1969) scale, although only 82% of cases patients met full criteria for social anxiety disorder. However, consistent with dimensional perspectives (Insel et al., 2010), patients with generalized anxiety disorder and sub-threshold social anxiety were also studied. Non-patients were free of psychopathology; all participants were medication free (see Supplemental Materials for full exclusion criteria). Some parents withheld consent to administer the Tanner stage of pubertal development scale, thus developmental stage reflects data from a subset of adolescents (Anxious $n = 12$, Non-Anxious $n = 22$). Anxious and non-anxious participants in each age group did not differ on age, IQ, or self-reported Tanner stage; FNE scores were higher for anxious than non-anxious groups ($t = 8.99$, $p < .001$), but did not differ by age group. Sex was not explicitly used as a matching variable across