Received: 21 December 2018 | Revised: 2 May 2019 | Accepted: 5 June 2019

DOI: 10.1002/da.22937

ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA
WILEY

RESEARCH ARTICLE

Advancing clinical neuroscience through enhanced tools: Pediatric social anxiety as an example

Ashley R. Smith Ph.D.[1] | Katharina Kircanski[1] | Melissa A. Brotman[1] | Quyen B. Do[2] | Anni R. Subar[1] | Jennifer S. Silk[2] | Scott Engel[3] | Ross D. Crosby[3] | Anita Harrewijn[1] | Lauren K. White[4] | Simone P. Haller[1] | Elise M. Cardinale[1] | George A. Buzzell[5] | Tyson Barker[6] | Ellen Leibenluft[1] | Daniel S. Pine[1]

[1]Emotion and Development Branch, National Institute of Mental Health, Bethesda, Maryland

[2]Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania

[3]Center for Bio-Behavioral Research, Sanford Research, Fargo, North Dakota

[4]Lifespan Brain Institute, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[5]Department of Education, University of Maryland, College Park, Maryland

[6]Department of Psychology, University of Oregon, Eugene, Oregon

Correspondence
Ashley R. Smith, Ph.D., Section on Development and Affective Neuroscience, National Institute of Mental Health, 9000 Rockville Pike, Building 15K, Bethesda 20892, MD.
Email: ashley.smith2@nih.gov

Funding information
National Institute of Mental Health, Grant/Award Number: Intramural Research Program

Background: Clinical researchers face challenges when trying to quantify diverse processes engaged during social interactions. We report results from two studies, each demonstrating the potential utility of tools for examining processes engaged during social interactions.

Method: In the first study, youth (n = 57) used a smartphone-based tool to rate mood and responses to social events. A subset (n = 20) completed the second, functional magnetic resonance imaging study. This second study related anxiety to error-evoked brain responses in two social conditions—while being observed and when alone. We also combined these tools to bridge clinical, social-contextual, and neural levels of measurement.

Results: Results from the first study showed an association between negatively-perceived social experiences and a range of negative emotions. In the second study there was a positive correlation during error monitoring between social-anxiety severity and context-specific activation of the pregenual anterior cingulate cortex. Finally, during imaging, the perceived quality of peer interactions as assessed using the smartphone-based tool, interacted with social context to predict levels of activation in the hippocampus and superior frontal gyrus.

Conclusions: By improving measurement, enhanced tools may provide new means for studying relationships among anxiety, brain function, and social interactions.

KEYWORDS
adolescent, anxiety, ecological momentary assessment, neuroimaging, social phobia

1 | INTRODUCTION

Researchers face challenges when attempting to quantify the impact of social experiences on children's anxiety symptoms and brain function. The complexity of children's social experiences creates a need for tools that accurately capture real-time changes in symptoms and that evoke contextual effects on brain function in a controlled, yet ecologically-valid, manner. Adding to this challenge is the complexity of combining multilayered data that bridge aspects of clinical symptoms elicited during real-world social interactions and aspects of brain function influenced by experimental manipulations. This paper describes two tools—ecological momentary assessment (EMA) and a novel neuroimaging paradigm—for beginning to meet these challenges. Together, the two tools assess the impact of social

context on anxiety and associated neural correlates. We illustrate how to use these tools in ways that may allow future studies in larger samples to more definitively bridge data across clinical, contextual, and brain-based domains.

The first study attempts to address how social interactions influence pediatric anxiety symptoms. Most clinical assessments ask patients to report on the previous weeks, often relying heavily on parent report. Such data can be compromised by distortions due to retrospective reporting and/or informant effects (De Los Reyes & Kazdin, 2005). Thus, alternative techniques are needed.

Here we report data from a smartphone-based EMA protocol that collects real-time data on social interactions. EMA addresses children's difficulties in retrospectively reporting aspects of mood (Baltasar-Tello, Miguélez-Fernández, Peñuelas-Calvo, & Carballo, 2018) and anxiety problems (Silk et al., 2018, Tan et al., 2012; for review, see Smyth & Stone, 2003). It capitalizes on the fact that children more accurately rate their current state, compared to average levels of distress over extended periods (McCathie & Spence, 1991). Moreover, EMA also accurately assesses aspects of social contexts, such as peer interactions, that could influence children's emotional state (Morgan et al., 2017; Silk et al., 2011; Tan et al., 2012). Hence, this tool improves assessments by integrating digitally-collected real-time ratings.

EMA may improve researchers' ability to assess subtle differences between mood and anxiety states. This is important given that social anxiety strongly co-occurs with mood problems (e.g., Fehm, Beesdo, Jacobi, & Fiedler, 2008; Grant et al., 2005), and both types of problems co-occur with social difficulties (Barker & Salekin, 2012; Stringaris & Goodman, 2009). Moreover, these associations evolve in complex, context-specific ways (Barker & Salekin, 2012). Youth reports collected in real time can track the unfolding of relations among social encounters, anxiety, and mood symptoms, possibly distinguishing anxious and non-anxious youth's unique experiences.

The second study also assesses relations between anxiety symptoms and social experiences. However, unlike the first study, this second study quantifies changes in brain function that may differentiate socially anxious and non-anxious youth. Social anxiety involves extreme fear of being viewed negatively by peers, which can result in avoidance behaviors, such as reticence to raise one's hand in class, during which errors and associated negative evaluations might occur. Therefore, research on the brain's error-monitoring system provides a particularly rich avenue to extend anxiety-relevant theory (for review, see Meyer, 2017, Weinberg, Dieterich, & Riesel, 2015). Understanding how socially anxious youth might uniquely process errors may elucidate key biological correlates. Indeed, electroencephalography (EEG) studies link anxiety to hypersensitive error monitoring (for review, see Meyer, 2017). However, given the context-specific nature of social anxiety and anxious youth's fear of negative evaluation, it is important to study errors made in socially-relevant contexts, such as in the presence of peers.

At a mechanistic-level, EEG has been widely applied to assess error-monitoring in anxious youth. More recently, this work has examined social interactions' impact on error-monitoring (Barker, Troller-Renfree, Pine, & Fox, 2015). It is important to extend EEG using techniques such as functional magnetic resonance imaging (fMRI) with better spatial resolution, since functioning of two adjacent brain areas can have opposite effects on defensive behaviors (Janak & Tye, 2015). Moreover, work is needed to develop ecologically-valid fMRI paradigms that leverage this improved spatial resolution. The current report describes an fMRI paradigm that assesses error-related brain responses during peer observation.

It is vital to begin combining these tools so that larger studies might eventually bridge data across multiple domains, including clinical, social-contextual, and neural domains. Given the complex dynamics of children's social experiences (for review see, Nelson, Jarcho, & Guyer, 2016) real-time tracking with EMA provides crucial information. Moreover, manipulating real-world social experiences provides additional key insights by bringing a level of experimental control to complex dynamics (Sequeira, Ladouceur, Jones, & Silk, 2019; Silk, in). Finally, quantifying neural responding is also vital, because comprehensive classifications of behavior may require linked assessments of brain function. Neuroscience shows that behaviors classified as similar based merely on their appearance are reclassified as distinct when they arise from divergent computations and associated neural processes (LeDoux & Daw, 2018). When behaviors reflect clinical problems, distinct behaviors may require distinct treatment approaches. Here we present a preliminary analysis that incorporates data from an EMA assessment into a characterization of brain functions associated with behaviors evoked in social as opposed to non-social contexts.

In summary, the current report describes two tools for quantifying complex, context-specific aspects of pediatric social anxiety. These tools each assess anxiety in social contexts, one targeting clinical manifestations (Study 1) and the other assessing neurobiological correlates (Study 2). Finally, we illustrate one potential approach to integrate these tools to bridge clinical, social-contextual, and neural domains and thereby further elucidate the impact of context on anxiety symptoms in youth (Study 3).

2 | STUDY 1: EMA

2.1 | Objectives

To assess anxiety, irritability, and happiness in the context of peer interactions. To compare real-time anxiety ratings with currently-used assessment measures. And finally, to examine the impact of recent social experiences on affect ratings.

2.2 | Method

All procedures were approved by the National Institute of Mental Health Institutional Review Board. Parents and participants provided written consent/assent. Fifty-seven youth (ages 8–18, $M = 13.55$, $SD = 2.79$) completed a smartphone-based assessment. Thirty-seven youth met DSM-5 criteria for at least one anxiety disorder ("anxious group," 21 females, age $M = 13.43$; $SD = 2.73$) and 20 youth were free of any psychiatric illness ("healthy group," 12 females, age $M = 13.79$, $SD = 2.95$) as assessed via a semistructured clinical interview with a

trained clinician (KSAD, Kaufman et al., 1997). See Table S1 for a full list of diagnoses. Clinicians assessed anxiety symptoms, severity, and impairment using the Pediatric Anxiety Rating Scale (PARS; Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002). In addition, participants and their parents completed the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997) to assess current anxiety symptoms. All measures were collected within 3 months of study participation. All participants were paid for participation. Anxious patients also received treatment following their participation. Full inclusion and exclusion criteria are included in Supporting Information Materials.

All participants completed seven consecutive days of EMA on a lab-provided or personal smartphone. Participants were prompted three times per day (morning, afternoon, evening) to answer a battery of questions about their momentary effect and recent interactions with peers. Prompt times were randomized within 1-hr blocks that participants prespecified based on their waking times, school schedules, and bedtimes. Participants were given 1 hr to complete each prompt; otherwise, that survey expired and data for that prompt were coded as missing. Participants were incentivized to complete as many prompts as possible by receiving a $10 bonus for completing over 75% of prompts (M = 75.86%, SD = 14.26%). There was no difference in prompt completion rate between anxious and healthy youth, $t(54) = 1.24$, $p = .24$ (anxious group: M = 73.52%, SD = 14.81%; healthy group: M = 80.00%, SD = 12.62%, or as a function of self-reported anxiety (SCARED total child-report; $r = 0.12$, $p = .38$). Further, the percentage of prompts completed was not related to age ($r = -0.10$, $p = .47$) or gender ($t(54) = .45$, $p = .65$). Prompt completion differed by timepoint ($F(2,1196) = 3.01$, $p = .05$, $\eta^2_p = .005$): more prompts were completed in the mornings (78.9%) and evenings (76.6%) compared to afternoons (71.5%).

EMA questions assessed emotions both *at* the time of the prompt and *since* the last prompt (e.g., "*At the time of the beep, I felt worried or scared,*" "*Since the last beep, I felt worried or scared;*" see Supplemental Materials Figure 1 for all included items). The current analyses focus on self-reported worry, frustration, grouchiness, anger, unhappiness, and happiness. All affect ratings were on a 5-point Likert scale (1 = *Not at all*, 5 = *Extremely*). Grouchiness was assessed on a 5-point temporal scale (1 = *None of the time*, 5 = *The whole time*). Additional questions probed the context in which the assessment was completed (e.g., with family, friends, home, etc.) and recent interactions with peers (i.e., "*Since the last beep my interactions with other kids have been…*", 1 = *Very positive* to 4 = *Very negative*). All assessments were administered via ReTAINE software (www.retaine.org).

2.2.1 | Data analysis plan

Due to the nested nature of the data (prompts within participants), multilevel modeling was performed in SPSS Version 25 using mixed models (Snijders & Bosker, 2011). All continuous Level-1 predictors were person-centered. All continuous Level-2 predictors were grand-mean centered. All details about specific models are included in the Supporting Information Materials. To validate the EMA measures, group differences and the relations between EMA-rated anxiety and other measures of anxiety were assessed. All method and results for these analyses are included in the Supporting Information Materials.

2.2.2 | Relations between EMA and other measures of anxiety

To explore how in-clinic measures of anxiety symptoms and severity are related to EMA-reported anxiety, we examined the relations of EMA-reported anxiety with self-reported SCARED total scores, parent-rated SCARED total scores, and clinician-rated PARS scores. Each of these measurements (child-reported SCARED, parent-rated SCARED, PARS) was run in a separate model. In each model, the in-clinic anxiety rating was a fixed, continuous predictor and EMA-reported anxiety (*Since the last beep, I felt worried or scared* or *At the last beep, I felt worried or scared*) was the dependent variable. All analyses controlled for time (in days) between completing the clinic assessments (SCARED, PARS) and the start of the EMA session. Each model was first run across all participants and then with the sample constrained to only treatment-seeking patients.

2.2.3 | Impact of peer interactions on affect ratings: At the same prompt

To examine how one's perception of recent peer interactions relates to affect ratings within the same prompt, rating of social interactions was included as a fixed, continuous predictor and affect rating as the dependent variable. Separate models were run for each affect rating (anxiety, frustration, grouchiness, happiness, etc.).

2.2.4 | Impact of peer interactions on affect ratings: At the next prompt (within a day)

Finally, for affect ratings that demonstrated significant associations with social interactions within the same prompt, we tested whether the perception of recent peer interactions also relates to those affect ratings at the next prompt. In these models, we used lagged ($t - 1$) ratings of social interactions as a fixed, continuous predictor and affect rating as the dependent variable. Lagged associations were constrained to the same day and did not cross into the following day. Affect ratings were also lagged and included as an additional predictor variable to examine changes in effect at t.

2.3 | Results

2.3.1 | Relations between EMA and other measures of anxiety (Table 1)

Across all participants, self-reported and parent-rated SCARED total scores and clinician-rated PARS scores (within 3-months) significantly predicted average EMA ratings of anxiety (*Since the last beep*, all $ps < .05$). Similar findings emerged when anxiety ratings AT the time of the beep were examined except clinician-rated PARS scores were not associated with EMA ratings of anxiety ($p = .20$).

TABLE 1 Relations between EMA-rated anxiety and other measures of anxiety

	Predictors			
	Self-reported SCARED total	Parent-rated SCARED total	Clinician-rated PARS (3-month)	Clinician-rated PARS (1-week)
All participants (N = 57)				
Anxiety SINCE				
Coeff	0.03	0.02	.03	–
SE	0.01	0.01	.02	–
t	5.90***	2.50*	2.08*	
β	.49	.27	.24	–
SE	.08	0.10	.10	
Anxiety AT				
Coeff	0.02	.01	.01	–
SE	.004	0.01	.01	–
t	4.65***	2.09*	1.29	–
β	0.32	0.17	.12	–
SE	0.07	0.08	.08	
Treatment-seeking anxious participants (N = 37)				
Anxiety SINCE				
Coeff	.03	0.01	−0.02	−0.006
SE	0.01	0.01	.03	0.04
t	3.87***	0.38	−0.52	−0.14
β	0.48	.09	−0.02	−0.03
SE	0.12	0.17	.17	0.17
Anxiety AT				
Coeff	0.02	0.005	−0.02	−0.01
SE	0.005	.01	.02	0.02
t	3.77***	0.60	−1.11	−0.61
β	0.36	0.10	−0.14	−0.03
SE	0.10	0.14	0.17	0.17

Note: The left hand column indicates the variable that is being predicted. Abbreviations: EMA, ecological momentary assessment; PARS, pediatric anxiety rating scale; SCARED, screen for child anxiety related emotional disorders; SE, standard error.
*p < .05.
**p < .01.
***p < .001.

When the sample was constrained to anxious participants only, self-reported SCARED scores were still associated with EMA-rated anxiety (p < .05; *Since* and *At the time of the beep*, Figure 1a). However, neither parent-rated SCARED scores (Figure 1b) nor clinician-rated PARS scores (Figure 1c) predicted either EMA rating of anxiety in anxious participants (ps > .05). An additional analysis was run on the subset of anxious participants who had clinician ratings within 1-week of completing the EMA protocol (n = 25). Again, clinician-rated PARS scores did not significantly predict either EMA rating of anxiety for the exact same measurement period (p > .05, Figure 1d).

2.3.2 | Impact of peer interactions on affect ratings: at the *same* prompt (Table 2)

The model examining the relation between ratings of recent peer interactions and anxiety (*At the time of the beep*) at the same prompt was significant (p < .05). Specifically, rating peer interactions since the last prompt more negatively were associated with higher ratings of anxiety at the time of the prompt. This pattern was consistent across other negative emotions—frustration, grouchiness, and unhappiness (all ps < .05). The model examining happiness was also significant, but in the opposite direction; rating peer interactions more negatively was associated with lower ratings of happiness over the same time period (p < .05). Models examining anger (*At the time of the beep*) and anxiety (*Since the last beep*) were not significant (ps > .05).

2.3.3 | Impact of peer interactions on affect ratings: At the next prompt (within a day) (Table 2)

Interestingly, the model predicting grouchiness at the current prompt (t), based on ratings of peer interactions at the previous prompt (t-1), was significant (p < .05). Specifically, rating peer interactions more negatively at the previous prompt predicted higher ratings of grouchiness at the current prompt, above and beyond the previous rating of grouchiness. Models examining the impact of previous peer interactions on subsequent ratings of anxiety, frustration, unhappiness, and happiness were not significant (all ps > .05).

3 | STUDY 2: fMRI PARADIGM

3.1 | Objective

To quantify the impact of peer observation and social anxiety on error-related brain responses in youth.

3.2 | Method

All procedures were approved by the National Institute of Mental Health Institutional Review Board. Parents and participants provided written consent/assent. In the current analysis, 20 youth (9–18 years old; M = 13.75; SD = 2.66) completed a modified version of the Eriksen Flanker task during fMRI (Eriksen & Eriksen, 1974). Nine youth met DSM-5 criteria for at least one anxiety disorder (age M = 13.68; SD = 3.13; see Table S1 for a list of full diagnoses) and 11 youth were free of any psychiatric illness (M = 13.85; SD = 2.12) as assessed by a semistructured clinical interview with a trained clinician. Full inclusion and exclusion criteria are included in Supporting Information Materials.

All participants and their parents completed the SCARED within 3 months of the imaging visit to assess current anxiety symptoms. The SCARED Social Anxiety subscale (averaged across child and parent reports) was used in all analyses to examine the impact of individual differences in social anxiety on task performance and brain response to errors. In the current sample Social Anxiety scores did not correlate with age (r = −0.05; p = .84) or IQ (r = 0.12; p = .67) and were well-distributed across both anxious and healthy participants (See Supporting Information Materials). Data collection is ongoing. All participants were paid for participation. All anxiety patients also received treatment following participation.

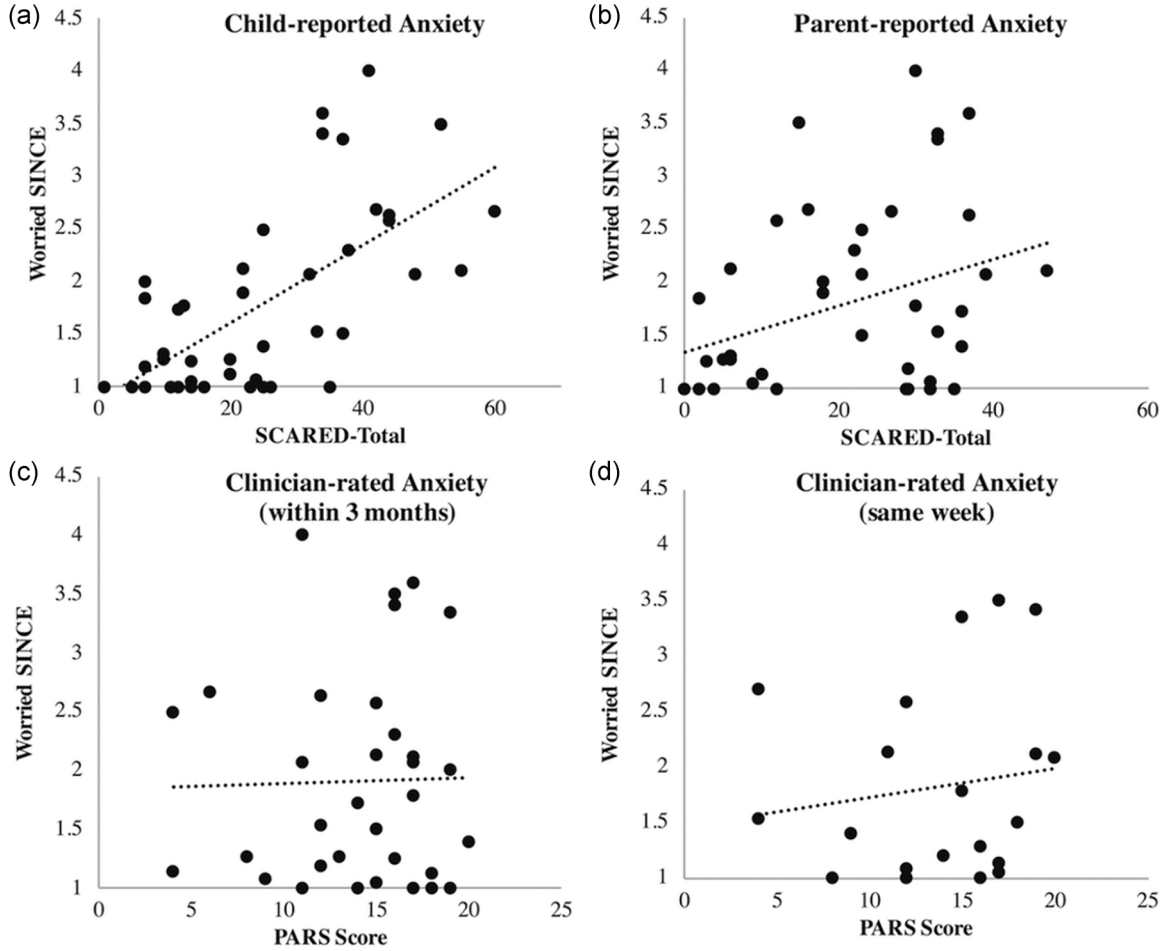

FIGURE 1 Relations between EMA-rated anxiety in treatment-seeking anxious patients (Since the last beep, I felt worried or scared) and self-reported anxiety (a), parent-rated anxiety (b), clinician-rated anxiety (c), and clinician-rated anxiety within the same measurement week (d). EMA, ecological momentary assessment

3.2.1 | Paradigm

Participants completed a modified Erikson Flanker task. See Supporting Information Materials for full task details. Participants completed two, 6-min runs of the task alone (alone condition) and two, 6-min runs while they believed they were being observed by a same-age, same-sex peer (peer condition). In the peer condition, participants were told that another participant was observing them during the task and would be making predictions about their task performance based on information they would exchange at the beginning of the scan (e.g., first name, age, favorite color). In reality, no other participant was present and all communication between "participants" were prerecorded audio files (Smith, Chein, & Steinberg, 2014). Order of the social context manipulation was counterbalanced across participants. All participants were debriefed following the scan.

3.2.2 | Data analysis

See Supporting Information Materials for behavioral data analyses. Neuroimaging analyses focused on responses to errors during incongruent trials (error) compared to correct responses on incongruent trials (correct). All imaging analyses were conducted using Analysis of Functional NeuroImages (AFNI; Cox, 1996). Standard preprocessing procedures were used (afni.proc.py) including despiking, slice-time correction, coregistration, spatial smoothing with a 6-mm smoothing kernel (full width at half maximum, FWHM), and warping to standardized Talaraich space. TRs with greater than 1-mm of movement were censored. All participants included in the analyses had less than 10% of TRs censored (average percentage of censored TRs: $M = 1.74$; $SD = 2.36$). Individual-subject GLMs included six regressors in each social condition (peer, alone): a) correct responses for each trial type (correct congruent, correct incongruent), and b) errors for each trial type (congruent commissions, congruent omissions, incongruent commissions, incongruent omissions). Regressors were time-locked to the onset of each event.

Group-level data were analyzed using mixed-effects models with SCARED Social Anxiety scores as the continuous, between subject variable and social context (peer, alone) and task condition (incongruent error, incongruent correct) as repeated, within-subject variables. All analyses covary for age. Significance for all output maps was determined based on 10,000 Monte Carlo simulations in AFNI's

TABLE 2 Impact of recent peer interactions on affect ratings

	Predictors		
	At the time of the prompt	At the next prompt	
	Peer interactions	Prior peer interactions	Prior mood rating
Mood rating SINCE the last beep			
Anxiety			
Coeff	.05		
SE	.03		
t	1.69		
β	.13		
SE	.05		
Grouchiness			
Coeff	.12	.19	.14
SE	.04	.09	.12
t	2.43*	2.22*	1.17
β	.21	.12	.08
SE	.04	.06	.08
Frustration			
Coeff	.16	.04	−0.04
SE	.04	.10	.09
t	3.64***	0.38	−0.48
β	.27	.02	−0.04
SE	.05	.06	.08
Mood rating at the last beep			
Anxiety			
Coeff	.06	−0.09	−0.08
SE	.03	.08	.07
t	2.06*	−1.15	−1.18
β	.16	−.07	−0.08
SE	.06	.07	.08
Annoyed/angry			
Coeff	.04		
SE	.02		
t	1.68		
β	.06		
Unhappiness			
Coeff	.07	.01	.06
SE	.03	.07	.13
t	2.25*	0.18	0.46
β	.22	.002	.03
SE	.05	.05	.11
Happiness			
Coeff	−0.14	.12	.04
SE	.03	.13	.09
t	−4.30***	0.96	0.43
β	−0.15	.04	.09
SE	.04	.09	.09

Note: The left hand column indicates the variable that is being predicted.
*$p < .05$.
**$p < .01$.
***$p < .001$.

3dClustsim program. The spatial autocorrelation function (two-sided thresholding) was utilized to give an accurate estimate of spatial smoothing across the brain (Cox, Chen, Glen, Reynolds, & Taylor, 2017). With a voxel-wise probability threshold of $p < .005$ and the family-wise error rate of $\propto = .05$, the data set resulted in a cluster contiguity threshold of 1391 mm^3.

3.3 | fMRI results

Overall, there was significant activation in regions previously found to underlie error-related processes (i.e., anterior cingulate, insula, prefrontal regions) when participants made errors, compared to correct responses (Table 3). The full omnibus interaction (social anxiety × social context × trial type) revealed a significant cluster in the pregenual anterior cingulate cortex (pgACC; Figure 2a). Follow-up tests on data extracted from this cluster revealed that this interaction was driven by greater activation during the peer, compared to alone, a condition when participants made errors. This relationship correlated positively with social anxiety scores ($r = 0.73$; $p < .001$; Figure 2b) There were no relations among brain response, social context, and social anxiety following correct responses ($r = -0.26$; $p = .29$; Figure 2c).

4 | STUDY 3: COMBINING EMA AND fMRI

4.1 | Objective

To provide an example of combining EMA-reported social experiences with the social neuroimaging paradigm. In particular, examining

TABLE 3 Study 2: fMRI whole brain results: Social anxiety × social context × trial type

Region	Cluster size mm^3	Talairach coordinates		
		x	y	z
SA × social context × trial type				
Pregenual ACC/ BA 10	1578	11	54	4
SA × social context	–	–		
SA × trial type	–	–		
Social context × trial type	–	–		
ME SA	–	–		
ME social context (peer > alone)	–	–		
ME trial type (error > correct)				
Supramarginal gyrus	11766	49	−49	36
Insula	11578	39	14	−1
Cingulate gyrus	8422	6	21	31
Inferior parietal lobule	8094	−34	−46	39
Medial frontal gyrus	7953	4	61	11
Insula	7719	−31	6	14
Posterior cingulate gyrus	7250	9	−56	24
Middle frontal gyrus	5938	34	41	24
Superior frontal gyrus	4422	−36	36	31
Precuneus	2313	14	−76	44

Note: Cluster contiguity threshold = 1309 mm^3
Abbreviations: fMRI, functional magnetic resonance; SA, social anxiety.

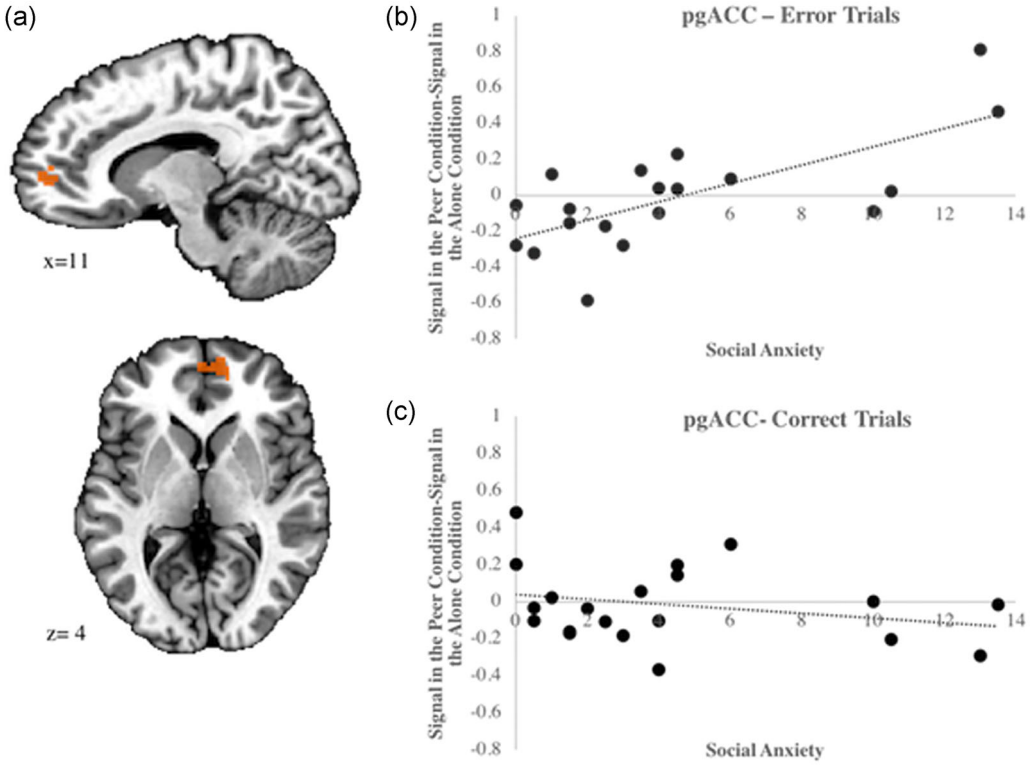

FIGURE 2 A significant social anxiety × social context × trial type interaction emerged in the pgACC (11, 54, 4) (a). When extracted data from this cluster revealed greater activation during the peer, compared to alone, a condition when participants made errors. This relationship correlated positively with social anxiety scores (b). There were no relations among brain response, social context, and social anxiety following correct responses (c). pgACC, pregenual anterior cingulate cortex

how the perceived quality of real-world peer interactions impacts neural responses to errors in the presence of peers.

4.2 | Method

A subset of the participants ($n = 18$) in Study 2 also completed the EMA paradigm from Study 1. To examine the association between individual differences in how real-world peer interactions are perceived and error-related brain responses, the mean rating of recent peer interactions across all prompts ($M = 1.52$, $SD = 0.44$) was included in the imaging model (i.e., "*Since the last beep have my interactions with other kids have been…*", 1 = *Very positive* to 4 = *Very negative*). Higher scores on this measure indicate more negative peer interactions. Ratings of recent peer interactions were not associated with age ($r = 0.05$; $p = .84$) or self-reported social anxiety (SCARED-Social Anxiety subscale; $r = 0.29$; $p = .24$).

4.2.1 | Data analysis

All individual-subject analyses were performed exactly as described in Study 2. Group-level data were analyzed using mixed-effects models with mean peer interaction scores as the continuous, between-subject variable and social context (peer, alone) and task condition (incongruent error, incongruent correct) as repeated, within-subject variables. All analyses covary for age, self-reported social anxiety, and days between EMA and imaging paradigms ($M = 61.9$, $SD = 83.4$). Significance for all output maps was determined based on 10,000 Monte Carlo simulations in AFNI's 3dClustsim program. The spatial autocorrelation function (two-sided thresholding) was utilized to give an accurate estimate of spatial smoothing across the brain (Cox et al., 2017). With a voxel-wise probability threshold of $p < .005$ and the family-wise error rate of $\propto = 0.05$, the data set resulted in a cluster contiguity threshold of 1308 mm^3.

4.3 | fMRI results

Overall, no regions emerged for the full omnibus interaction (peer interaction rating ×social context × task condition). However, peer ratings × social context interactions did emerge, reflecting the average neural responses to correct and incorrect trials (Table 4). These interactions involved large clusters in the hippocampus and superior frontal gyrus (SFG). Follow-up tests indicated positive associations between brain response and rating of peer interactions, indicating greater activation in the peer (hippocampus: $r = 0.44$, $p = .07$; Figure 3a; SFG: $r = 0.37$; $p = .13$; Figure 3b), compared to alone (hippocampus: $r = -0.12$; $p = .63$; Figure 3c; SFG: $r = 0.19$;

TABLE 4 Study 3: fMRI whole brain results: EMA-rated peer interactions × social context × trial type

Region	Cluster size mm³	Talairach coordinates x	y	z
Peer interaction × social context × trial type				
	–	–		
Peer interaction × social context				
Hippocampus	3266	24	61	21
Superior frontal gyrus	2141	−26	−11	−9
Peer interaction × trial type				
	–	–		
Social context × trial type				
	–	–		
ME peer interaction				
Precuneus	2797	4	−41	41
ME social context (peer > alone)				
Thalamus	1531	−4	−14	16
ME trial type (error > correct)				
Orbitofrontal cortex	26859	1	59	1
Insula	8297	34	14	−4
Inferior parietal gyrus	8188	46	−46	39
Precuneus	7438	9	−56	24
Insula	6719	−34	16	6
Inferior parietal lobule	5109	−34	−46	39
Middle frontal gyrus	4031	36	44	21
Anterior cingulate gyrus	3328	6	21	31
Occipital gyrus	3328	−41	−66	26
Superior parietal gyrus	3172	11	−76	44
Thalamus	2141	4	−4	1
Middle frontal gyrus	1938	−36	39	34
Cerebellum	1922	44	−74	−34
Middle temporal gyrus	1891	−59	−11	−14

Note: Cluster contiguity threshold = 1308 mm³.

$p = .45$; Figure 3d), condition in youth who rated their peer interactions more negatively.

5 | DISCUSSION

The current manuscript describes two techniques for assessing the impact of social context on anxiety and associated neural correlates. Together, the two techniques highlight the importance of evoking and quantifying relevant social experiences to understand the clinical presentation and biological correlates of pediatric anxiety. The first study used digital assessments to demonstrate the impact of social interactions on symptom reports. Findings demonstrate utility in repeated, simultaneous assessments of social experiences and symptoms proximal to social interactions. This chronometrically-sensitive tool capitalizes on youth's ability to accurately recall recent events; as such, it can dissociate mood and anxiety symptoms in the context of social interactions. The second study demonstrates the impact of social context and social anxiety on brain activity during error monitoring in youth, demonstrating anxiety-related differences in pgACC function.

These two tools provide a unique insight into the ways that social context, and more specifically social stress, impacts youth. Importantly, both tools quantify real-time, child-specific social experiences that might be overlooked or imprecisely quantified by clinicians and researchers relying on current methods. Thus, value is demonstrated for both tools.

The EMA findings showed that when recent interactions with peers were rated as negative, youth reported higher negative affect (anxiety, depression, irritability) compared to more positively-rated peer interactions. However, only irritability symptoms (grouchiness) showed a relative increase at the next prompt following more negatively-rated peer interactions. This nuanced relationship would be difficult, if not impossible, to assess via retrospective reporting. First, it is unclear if children can report emotional symptoms accurately from experiences that occurred several days before any assessment. This may be particularly important in pediatric anxiety, which involves cognitive biases regarding social events (Jarcho et al., 2015). In addition, being able to accurately recognize, report, and connect lingering emotional symptoms to events is difficult for any individual, much less youth. Finally, had our approach focused solely on anxiety ratings rather than simultaneously measuring multiple affective states, the association between social experiences and persistent irritability would have been missed. By capitalizing on repeated measurements, collected within hours of social interactions occurring, we were able to tease apart relations among affective states and social experiences that would be challenging for a clinician or researcher to quantify otherwise.

Findings from the EMA study also highlight the lack of consensus among self-reported, parent, and clinician-rated anxiety symptoms. Informant discrepancies impact treatment, especially among anxious youth (De Los Reyes & Kazdin, 2005). Indeed, in the present sample, informant discrepancies were particularly notable in the anxious youth. Relative to other methods, anxious patients may feel more comfortable using real-time, digital ratings to report embarrassing or anxiogenic social experiences. Moreover, given the relatively low correlations with clinician ratings, individuals providing treatment may be unaware of these patient's feelings. Incorporating such data could become a useful component of measurement-based care for pediatric anxiety (Lewis et al., 2019). One might integrate this methodology into cognitive behavioral therapy (CBT) for treatment-seeking anxious youth in ways that would allow therapists to capitalize on more accurate, in-vivo assessments of symptoms and treatment adherence (e.g., Pramana, Parmanto, Kendall, & Silk, 2014). Such tools could facilitate treatment by deepening dialog between anxious youth and their therapists whereas also providing details regarding context-specific effects and their impact on treatment-related decisions (e.g., Forbes et al., 2012; Wallace et al., 2017).

Functional neuroimaging research has long suffered from a lack of ecologically-valid tasks to probe the neural circuitry associated with social anxiety, thus motivating our second study. Previous research on social context and error-related neural responses has used EEG (Barker et al., 2015; Barker, Troller-Renfree, Bowman, Pine, & Fox, 2018). However, fMRI provides better spatial resolution for identifying error-related processes. Whereas social anxiety is clearly a context-specific disorder, creating this context within the

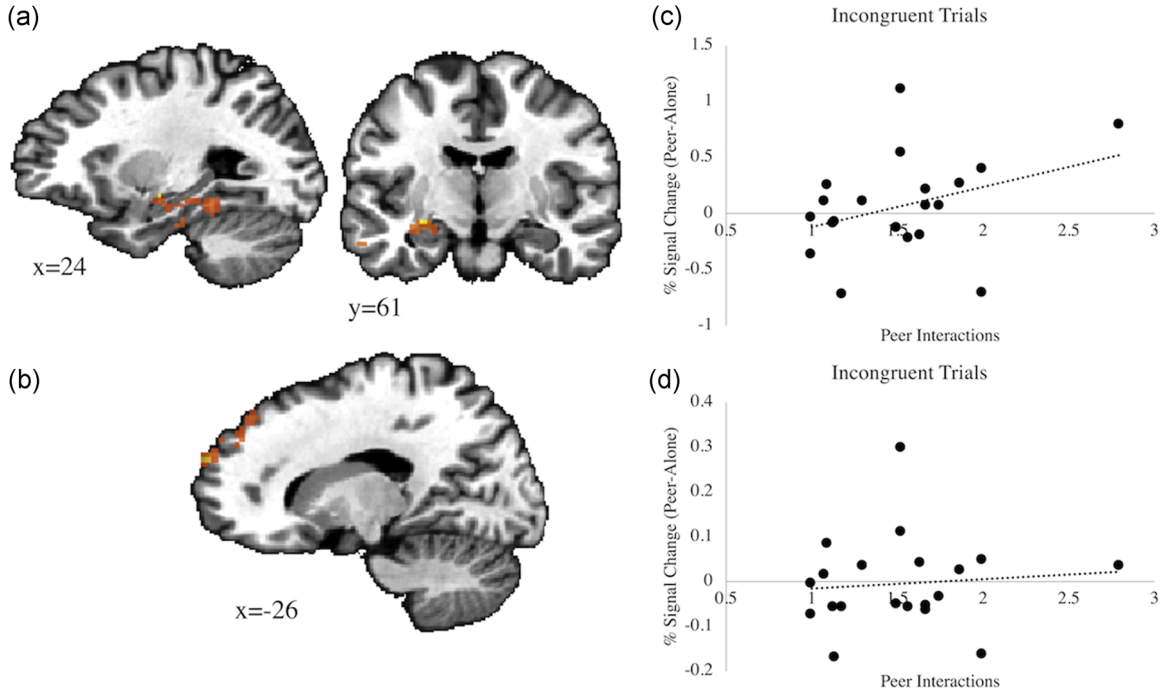

FIGURE 3 A significant peer interaction × social context interaction emerged in the (a) hippocampus (24, 61, 21) and (b) superior frontal gyrus (-26, -11, -9). Data from these clusters revealed greater activation during the peer, compared to alone, a condition in participants who perceived their real-world peer interactions as more negative (c/d). This relationship was not related to task performance

constraints of the imaging environment can be difficult. Past fMRI studies have been successful in eliciting anxious states using peer rejection paradigms (e.g., Guyer et al., 2008; Jarcho et al., 2016). However, naturalistically, social anxiety is not always a result of negative peer interactions but rather stems from the fear or anticipation of negative peer evaluations. In Study 2, we employed a social manipulation in which the participant believed a peer was watching them, without feedback concerning performance. We found a context-specific association between social anxiety severity and error processing in the pgACC, a region implicated in cognitive-emotional interactions (de la Vega, Chang, Banich, Wager, & Yarkoni, 2016; Etkin, Egner, & Kalisch, 2011). This may suggest a heightened emotional response, or increased error monitoring when socially anxious youth make errors in the presence of a peer, relative to errors made in the absence of peers. Importantly, no brain regions exhibited anxiety-related effects to a greater extent when participants completed the task alone, compared to during peer observation. It is important to point out that, without considering social context, the study would have failed to find an association between aberrant error processing and social anxiety—highlighting the importance of considering ecologically-valid contexts, such as the presence of peers, when probing the impact of anxiety on brain response.

Finally, these two tools were combined in an additional analysis. This illustrates the complexity of bridging data across social context, anxiety symptoms, and brain function. As the complexity of an analysis increases, the need for large samples also increases, so that the effects of multiple factors can be isolated. Whereas all of our results are limited by sample sizes, some potentially interesting results did emerge. Namely, we found that youth who perceived their real-world peer interactions more negatively, as reported through EMA, exhibited greater activation in the hippocampus and SFG when they performed the cognitive task whereas believing that a peer was observing their performance. The neural response did not vary as a function of task accuracy, possibly reflecting the limited power of the small sample size. These results might encourage other researchers to examine how biases manifesting in real-world encounters and quantified through EMA influence biases and associated neural correlates manifesting in the MRI scanner. As such, this analysis highlights the need to integrate participants' real-world experiences into laboratory paradigms, particularly when examining the impact of social context on adolescent brain response.

The current studies are not without limitations. First, as noted above, the sample sizes in both studies are moderate, particularly in the imaging study and in the final set of analyses that attempted to bridge data from the two studies. As such, results might best be viewed as illustrating the promising aspect of each technique considered on its own and as a call for larger studies using these tools. Sample size further impacted analyses, because the presence of multiple anxiety disorders in a small sample precluded analyses focused on differences among particular diagnoses. Whereas this heterogeneity is common in pediatric anxiety, ideally, these studies would be completed either in a very large sample or in a smaller sample with patients possessing only social anxiety with little to no comorbid anxiety diagnoses. Second, the social context manipulation used in the imaging study did not elicit context-specific behavioral differences. Whereas we predicted an association

between anxiety symptoms and the number of errors in the peer condition, it is not uncommon that tasks, and specifically the Flanker task, fail to elicit proposed behavioral differences (Barker et al., 2015; Buzzell et al., 2017). Because this study contains a small number of participants, we anticipate that anxiety-related differences will emerge in a larger sample. Yet, the ability to detect neuroimaging relations in the absence of behavioral differences speaks to the sensitivity of neuroimaging as an assessment tool. Finally, the present manuscript served as an introduction to two enhanced tools for studying the impact of social context in pediatric anxiety. Future studies would benefit from comparing these methods to other methods currently used by researchers studying context-specific effects.

Whereas not necessarily limitations, there are several methodological difficulties inherent to these tools that should be addressed. For instance, EMA studies can have high attrition, particularly across data collection. In the current study, we were able to maintain high levels of engagement with our participants by offering a monetary bonus for completing a certain number of assessments (75%) and by allowing participants to choose hours where they were available to complete the assessment (the prompt was then randomized within that hour). Further, many of our younger participants did not own their own smartphones and thus used study-provided devices. Younger participants did not have issues using the device or completing the assessments; however, it may impact the feasibility of data collection in younger children. Part of our motivation for Study 2 was that implementing ecologically-valid social experiences that are relevant to pediatric anxiety in the neuroimaging environment is difficult. One problem researchers face is making the social manipulation both believable and salient to all participants, particularly in a large age range. However, this peer paradigm has been successful in deceiving similarly-aged adolescents (Smith et al., 2014) and young adults/college undergraduates (Sherman et al., in)-and increasing risky decision-making in both studies.

Despite these limitations and difficulties, these studies support the need for tools aimed at quantifying the impact of social experiences in pediatric social anxiety at multiple levels—from clinical presentation in one's natural environment (i.e., social anxiety in the classroom) to more mechanistic tools (fMRI). Here we presented data from two enhanced tools that we think demonstrate the benefit of such techniques for testing interactions between social experiences and the presentation of social anxiety in youth. By enhancing tools for studying complex psychiatric issues, such as social anxiety, we hope to more effectively detect, quantify, and inform treatment plans for pediatric anxiety patients.

ORCID

Ashley R. Smith http://orcid.org/0000-0002-2909-8756

REFERENCES

Baltasar-Tello, I., Miguélez-Fernández, C., Peñuelas-Calvo, I., & Carballo, J. J. (2018). Ecological momentary assessment and mood disorders in children and adolescents: A systematic review. *Current Psychiatry Reports*, *20*(8), 66.

Barker, E. D., & Salekin, R. T. (2012). Irritable oppositional defiance and callous unemotional traits: Is the association partially explained by peer victimization? *Journal of Child Psychology and Psychiatry*, *53*(11), 1167–1175.

Barker, T. V., Troller-Renfree, S., Pine, D. S., & Fox, N. A. (2015). Individual differences in social anxiety affect the salience of errors in social contexts. *Cognitive, Affective, & Behavioral Neuroscience*, *15*(4), 723–735.

Barker, T. V., Troller-Renfree, S. V., Bowman, L. C., Pine, D. S., & Fox, N. A. (2018). Social influences of error monitoring in adolescent girls. *Psychophysiology*, *55*, e13089.

Birmaher, B., Khetarpal, S., Brent, D., Cully, M., Balach, L., Kaufman, J., & Neer, S. M. (1997). The screen for child anxiety related emotional disorders (SCARED): Scale construction and psychometric characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(4), 545–553.

Buzzell, G. A., Troller-Renfree, S. V., Barker, T. V., Bowman, L. C., Chronis-Tuscano, A., Henderson, H. A., … Fox, N. A. (2017). A neurobehavioral mechanism linking behaviorally inhibited temperament and later adolescent social anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(12), 1097–1105.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, *29*(3), 162–173.

Cox, R. W., Chen, G., Glen, D. R., Reynolds, R. C., & Taylor, P. A. (2017). FMRI clustering in AFNI: False-positive rates redux. *Brain Connectivity*, *7*(3), 152–171.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*(1), 143–149.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*(2), 85–93.

Fehm, L., Beesdo, K., Jacobi, F., & Fiedler, A. (2008). Social anxiety disorder above and below the diagnostic threshold: Prevalence, comorbidity and impairment in the general population. *Social Psychiatry and Psychiatric Epidemiology*, *43*(4), 257–265.

Forbes, E. E., Stepp, S. D., Dahl, R. E., Ryan, N. D., Whalen, D., Axelson, D. A., … Silk, J. S. (2012). Real-world affect and social context as predictors of treatment response in child and adolescent depression and anxiety: An ecological momentary assessment study. *Journal of Child and Adolescent Psychopharmacology*, *22*(1), 37–47.

Grant, B. F., Hasin, D. S., Blanco, C., Stinson, F. S., Chou, S. P., Goldstein, R. B., … Huang, B. (2005). The epidemiology of social anxiety disorder in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of Clinical Psychiatry*, *66*, 1205–1215.

Guyer, A. E., Lau, J. Y., McClure-Tone, E. B., Parrish, J., Shiffrin, N. D., Reynolds, R. C., … Ernst, M. (2008). Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Archives of General Psychiatry*, *65*(11), 1303–1312.

Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature*, *517*(7534), 284–292.

Jarcho, J. M., Davis, M. M., Shechner, T., Degnan, K. A., Henderson, H. A., Stoddard, J., … Nelson, E. E. (2016). Early-childhood social reticence predicts brain function in preadolescent youths during distinct forms of peer evaluation. *Psychological Science*, *27*(6), 821–835.

Jarcho, J. M., Romer, A. L., Shechner, T., Galvan, A., Guyer, A. E., Leibenluft, E., … Nelson, E. E. (2015). Forgetting the best when predicting the worst: Preliminary observations on neural circuit function in adolescent social anxiety. *Developmental Cognitive Neuroscience*, *13*, 21–31.

Kaufman, J., Birmaher, B., Brent, D., Rao, U. M. A., Flynn, C., Moreci, P., … Ryan, N. (1997). Schedule for affective disorders and schizophrenia

for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980–988.

LeDoux, J., & Daw, N. D. (2018). Surviving threats: neural circuit and computational implications of a new taxonomy of defensive behaviour. *Nature Reviews Neuroscience*, *19*(5), 269.

Lewis, C. C., Boyd, M., Puspitasari, A., Navarro, E., Howard, J., Kassab, H., … Simon, G. (2019). Implementing Measurement-Based Care in Behavioral Health: A Review. *JAMA psychiatry*, *76*(3), 324–335.

McCathie, H., & Spence, S. H. (1991). What is the revised fear survey schedule for children measuring? *Behaviour Research and Therapy*, *29*(5), 495–502.

Meyer, A. (2017). A biomarker of anxiety in children and adolescents: A review focusing on the error-related negativity (ERN) and anxiety across development. *Developmental Cognitive Neuroscience*, *27*, 58–68.

Morgan, J. K., Lee, G. E., Wright, A. G. C., Gilchrist, D. E., Forbes, E. E., McMakin, D. L., … Silk, J. S. (2017). Altered positive affect in clinically anxious youth: The role of social context and anxiety subtype. *Journal of Abnormal Child Psychology*, *45*(7), 1461–1472.

Nelson, E. E., Jarcho, J. M., & Guyer, A. E. (2016). Social re-orientation and brain development: An expanded and updated view. *Developmental Cognitive Neuroscience*, *17*, 118–127.

Pramana, G., Parmanto, B., Kendall, P. C., & Silk, J. S. (2014). The smartcat: An m-health platform for ecological momentary intervention in child anxiety treatment. *Telemedicine Journal and e-Health*, *20*(5), 419–427.

Research Units on Pediatric Psychopharmacology Anxiety Study Group (2002). The pediatric anxiety rating scale (PARS): Development and psychometric properties. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*(9), 1061–1069.

Sequeira, S.L., Ladouceur, C.D., Jones, N.P., & Silk, J.S. (2019, March). *Interactions between neural activation to social reward and experiences of social threat in adolescent girls*. In T. M. Chaplin (Chair), Neural reward reactivity and adolescent psychopathology and substance use: fMRI and ERP studies. Symposium conducted at the 2019 Biennial Meeting of the Society for Research in Child Development, Baltimore, MD.

Sherman, L. E., Rosenbaum, G. M., Smith, A. R., Botdorf, M. A., Fettich, K., Patrianakos, J. L., … Chein, J. M. The interactive effects of peers and alcohol on functional connectivity in young adults. *NeuroImage*, *197*, 264–272.

Silk, J. S. (in press). Context and dynamics: The new frontier for developmental research on emotion regulation. *Developmental Psychology*.

Silk, J. S., Forbes, E. E., Whalen, D. J., Jakubcak, J. L., Thompson, W. K., Ryan, N. D., … Dahl, R. E. (2011). Daily emotional dynamics in depressed youth: A cell-phone ecological momentary assessment study. *Journal of Experimental Child Psychology*, *110*(2), 241–257.

Silk, J. S., Tan, P. Z., Ladouceur, C. D., Meller, S., Siegle, G. J., McMakin, D. L., … Ryan, N. D. (2018). A randomized clinical trial comparing individual cognitive behavioral therapy and child-centered therapy for child anxiety disorders. *Journal of Clinical Child & Adolescent Psychology*, *47*(4), 542–554.

Smith, A. R., Chein, J., & Steinberg, L. (2014). Peers increase adolescent risk taking even when the probabilities of negative outcomes are known. *Developmental Psychology*, *50*(5), 1564–1568.

Smyth, J. M., & Stone, A. A. (2003). Ecological momentary assessment research in behavioral medicine. *Journal of happiness studies*, *4*(1), 35–52.

Snijders, T. A. B., & Bosker, R. (2011). *Multilevel analysis: An introduction to basic and advanced multilevel modeling* (2nd ed.). Thousand Oaks, CA: Sage.

Stringaris, A., & Goodman, R. (2009). Three dimensions of oppositionality in youth. *Journal of Child Psychology and Psychiatry*, *50*(3), 216–223.

Tan, P. Z., Forbes, E. E., Dahl, R. E., Ryan, N. D., Siegle, G. J., Ladouceur, C. D., & Silk, J. S. (2012). Emotional reactivity and regulation in anxious and nonanxious youth: A cell-phone ecological momentary assessment study. *Journal of Child Psychology and Psychiatry*, *53*(2), 197–206.

de laVega, A., Chang, L. J., Banich, M. T., Wager, T. D., & Yarkoni, T. (2016). Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization. *Journal of Neuroscience*, *36*(24), 6553–6562.

Wallace, M. L., McMakin, D. L., Tan, P. Z., Rosen, D., Forbes, E. E., Ladouceur, C. D., …Silk, J. S. (2017). The role of day-to-day emotions sleep, and social interactions in pediatric anxiety treatment. *Behavioral Research and Therapy*, *90*, 87–95.

Weinberg, A., Dieterich, R., & Riesel, A. (2015). Error-related brain activity in the age of RDoC: A review of the literature. *International Journal of Psychophysiology*, *98*(2), 276–299.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Smith AR, Kircanski P, Brotman MA, et al. Advancing clinical neuroscience through enhanced tools: Pediatric social anxiety as an example. *Depress Anxiety*. 2019; 36:701–711. https://doi.org/10.1002/da.22937