Face-Emotion Processing in Offspring at Risk for Panic Disorder

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ABSTRACT

Objective: Panic disorder (PD) has been linked to perturbed processing of threats. This study tested the hypotheses that offspring of parents with PD and offspring with anxiety disorders display relatively greater sensitivity and attention allocation to fear provocation. **Method:** Offspring of adults with PD, major depressive disorder (MDD), or no disorder (ages 9–19) viewed computer-presented face photographs depicting angry, fearful, and happy faces. Offspring rated (1) subjectively experienced fear level, (2) how hostile the face appeared, and (3) nose width. Attention allocation was indexed by latency to perform ratings. **Results:** Compared with offspring of parents without PD ($n = 79$), offspring of PD parents ($n = 65$) reported significantly more fear and had slower reaction times to rate fear, controlling for ongoing anxiety disorder in the offspring. Offspring with an anxiety disorder ($n = 65$) reported significantly more fear than offspring without an anxiety disorder but not when parental PD was controlled. Social phobia but no other anxiety disorder in offspring was associated with slower reaction times for fear ratings (but not greater fear ratings). Parental PD and offspring social phobia independently predicted slower reaction time. **Conclusions:** Results support an association between parental PD and offspring responses to fear provocation. Social phobia in children may have a specific relationship to allocation of attention to subjective anxiety during face viewing. *J. Am. Acad. Child Adolesc. Psychiatry,* 2005;44(7):664–672. **Key Words:** anxiety, memory, panic disorder, genetics.

The purpose of this study was to identify risks conferred to children by parental panic disorder (PD). Considerable research examines risk factors for PD. Relatives of adults with PD have been shown to exhibit elevated levels of fear when exposed to respiratory stimulation, a feature that characterizes PD (Klein, 1998). This correlate appears specific to PD since it does not occur in adult relatives of patients with MDD (Coryell et al., 2001). Similarly, adults with PD, but not major depressive disorder (MDD), display perturbed attention when exposed to threats. For example, patients with PD allocate more attention than healthy adults to words describing aspects of panic attacks (reviewed in Williams et al., 1996). As with respiratory perturbations, these alterations in attention are thought to index risk of PD specifically (Clark, 1999).

It remains unclear whether the antecedents for PD in juveniles are independent of mood or anxiety disorders in the child or of MDD in parents. Panic attacks and MDD in adolescence each predicts increased rates of PD and MDD in adulthood (Pine et al., 1998, 2001). Moreover, offspring of parents with MDD exhibit elevated rates of both anxiety disorders and MDD, relative to offspring of healthy parents (Weissman et al., 1997). Such findings suggest that pediatric anxiety and MDD represent alternative manifestations of a shared

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vulnerability for adult MDD and PD. Consistent with this view, children at high risk of PD and MDD appear similar on laboratory-based measures of behavioral inhibition, which is similarly elevated in both groups relative to controls (Rosenbaum et al., 2000).

Other findings suggest that specific risk features may occur among children at risk of PD. For example, as in adult PD, childhood anxiety is characterized by respiratory dysregulation (Pine et al., 2000). Similarly, when anticipating exposure to an air puff, children of parents with anxiety disorders exhibit lower fear thresholds, as assessed by startle magnitude, than children of healthy parents (Merikangas et al., 1999). Finally, a recent study found elevated cortisol levels in infants of mothers with PD, although the study did fail to find the expected high rate of behavioral inhibition in these infants (Warren et al., 2003). Regardless, because none of these studies examined offspring of parents with MDD, it remains unclear whether findings reflect a specific risk of PD or a broader risk of both PD and MDD. Of note, studies in adults suggest distinct genetic factors predispose to MDD and PD (Kendler, 2001).

Studies in adult PD have used reaction time to index attention allocation. Reaction time provides an informative link to experimental psychology studies because it is a standard for measuring attention in various contexts. By capturing attention resources in PD, fear-inducing stimuli may slow responses on a competing task. Alternatively, as reviewed elsewhere (Williams et al., 1996), fear-inducing stimuli may slow responses as increasing attention is devoted to the stimulus. PD is hypothesized to involve hypersensitivity and enhanced attention allocation to internal bodily sensations (Clark, 1999). In support of this hypothesis, patients with PD exhibit elevated ratings on the Anxiety Sensitivity Index (ASI), which assesses self-reported concerns about the harmfulness of bodily sensations (McNally, 2002). Although such concerns are hypothesized to influence attention (Clark, 1999), the study of attention to internal sensations in PD has relied exclusively on self-report measures such as the ASI (McNally, 2002) and has not been conducted during remission. In children, we found that elevated scores on the ASI were unrelated to parental PD (Mannuzza et al., 2002). However, there is a need to gather data that go beyond self-report. The concurrent study of self-ratings of fear and reaction time during fear monitoring in individuals at risk of PD may allow a bridging of clinical and experimental research approaches on markers of risk of PD.

The use of face-emotion displays may facilitate this effort to bridge clinical and experimental approaches. Although previous research implicates perturbed attention in pediatric anxiety disorders, studies use verbal stimuli. The processing of such stimuli can be influenced by linguistic capacity, culture, or other factors that may complicate efforts to examine the relationship between pediatric anxiety and attention (Vasey et al., 2003). Face-emotion displays, in contrast, produce similar reactions in people from diverse cultures, suggesting that they engage a neural circuit involved in evolutionarily conserved, core aspects of human's emotional experiences (Haxby et al., 2002). This circuit encompasses the amygdala, cingulate gyrus, and orbitofrontal cortex. Thus, the use of evocative faces permits a bridging of clinical and basic research on emotion (Haxby et al., 2002).

This study investigated whether risk of PD involves perturbed attention response to anxiety provocation. Although previous work examined development of face-emotion identification, the current study represents the first computer-based investigation of fear provocation sensitivity to faces in juveniles. To consider whether such perturbations are specific to PD, the study also included as comparisons offspring of parents with MDD but not PD. The study tested the hypothesis that the risk of PD is associated with elevated subjective fear ratings and slow reaction time to report subjective fear during the viewing of mildly threatening pictures. Specifically, we hypothesized that emotionally evocative facial photographs will produce significantly higher self-ratings of fear and significantly slower reaction times for fear ratings in offspring of parents with PD, relative to offspring of parents without PD, independent of the presence of anxiety disorders in offspring. It was also predicted that anxiety disorders in offspring will relate to self-ratings and reaction times for fear ratings. Finally, the study examined the degree to which hypothesized differences are specific to fear ratings as opposed to other rating/instruction sets.

METHOD

Subjects

Offspring (ages 9–19 years) of parents with PD, MDD, or psychiatrically healthy parents were recruited. Exclusion criteria for offspring were lifetime history of psychosis, mania, or pervasive developmental disorder; current use of psychotropic medication; IQ < 70; significant medical conditions; and residence outside the New York Metropolitan area. Comparison parents were identified

using methods previously described (Mannuzza et al., 1992). Briefly, two sources were used. For one source, names of comparison parents were provided by parents with PD and MDD using the acquaintance method (Mannuzza et al., 1992). For the other source, subjects were recruited who were attending a medical clinic for routine health care. Approximately half of comparison parents were recruited from each source. Inclusion and exclusion criteria were the same for probands and comparisons, but comparison parents could not have a lifetime history of mood or anxiety disorders.

Data were collected as part of a 2-hour home-based assessment of emotional reactivity that ended with a CO_2 challenge procedure. Full disclosure was provided, and written informed consent/assent was obtained. This report is based on 144 offspring recruited from 92 families. This study included 24 offspring of 16 families with parents with PD only, 53 offspring of 34 families with parents with MDD only, 41 offspring of 26 families with parents with MDD/PD, and 26 offspring of 17 families with healthy parents.

Diagnostic Assessment of Parents

Parents were administered the Structured Clinical Interview for *DSM-III-R* (Spitzer et al., 1992) by trained clinicians blind to all other information. When one parent was unavailable, the other served as the informant, which occurred for 44% of parents. Interviewers wrote summaries documenting the lifetime *DSM-IV* diagnoses formulated, and interview fidelity was monitored through expert review of these summaries. In previous studies, satisfactory interrater and test-retest reliabilities have been reported for the disorders of interest (κ = 0.50–0.70) (Spitzer et al., 1992). Because interviewers were well-trained clinicians highly familiar with the Structured Clinical Interview for *DSM-III-R*, interrater reliability was not further examined.

To classify offspring risk of PD or MDD, offspring born to either one or two affected parents were considered affected (four offspring had two parents with PD). Familial comorbidity of PD and MDD was defined as either one parent having both disorders or as each disorder occurring in different parents, a scheme used previously (Rosenbaum et al., 2000). Beyond the diagnosis of PD, 11 families had a parent with social phobia. In analyses not shown here, parent social phobia exhibited no association with offspring anxiety diagnosis or face-processing performance. As a result, parent social phobia is not considered further.

Diagnostic Assessment of Offspring

All parents of offspring and offspring themselves were administered a semistructured clinical interview, the Parent as Respondent Informant Schedule, by trained clinicians blind to all other information. Like other standardized semistructured clinical interviews, such as the Schedule for Affective Disorders and Schizophrenia for School-Age Children, this interview generates psychiatric diagnoses in a child based on criteria endorsed by an informant who can be either the child him- or herself or a parental informant concerning symptoms in the child. Different interviewers conducted the child and parent informant assessments. Previous studies demonstrate the interview to exhibit acceptable interrater and test-retest reliability (Kentgen et al., 1997). Reliability was also examined in the current study.

Interview fidelity was monitored through audiotapes and preparation of narrative summaries documenting *DSM-IV* diagnoses formulated; these were blindly reviewed by expert clinicians. Final diagnoses were assigned by considering any child or adolescent to be affected if an ongoing anxiety disorder was identified in the interview with the parent or child. The fidelity of this procedure was monitored by best estimate review of all available diagnostic information in 45 cases independently by two experts. Agreement between experts was satisfactory for all disorders of interest, as was the agreement between experts and the final diagnoses (κ > 0.65), including the two specific disorder-related classifications used in the current report: any anxiety disorder (κ = 0.89) and social phobia (κ = 0.92).

Face-Emotion Viewing Paradigm

The paradigm included 24 different faces, each presented three times for 4 seconds on an IBM laptop computer. To standardize presentation and response recording, the task was programmed in the e-prime software package.

Photographs expressed high-intensity "happy," "fearful," or "angry" expressions (eight each). To minimize habituation, 24 different individuals were randomly selected from two standard sets, with eight individuals depicting a specific emotion (happy, fearful, and angry) (Ekman and Friesen, 1976). The 72 trials were divided into three eight-trial blocks administered as part of a single "run"; three three-block runs were completed, producing 72 trials (eight faces × three blocks × three runs). Order of face presentation and block was randomized. For individual faces, ordering of presentation was completely random, such that each subject used a different random order of presentations. Different instructions accompanied each block; blocks were separated by a series of fixation stimuli and instructions. In other versions of this task, "neutral" faces were included (Monk et al., 2003; Nelson et al., 2003). However, the focus of the current study is on effects of instruction-set manipulations during high-valence face viewing, not on response to different facial expressions. Therefore, the inclusion of neutral faces was not deemed relevant.

The face-emotion viewing paradigm was administered by a technician blind to the psychiatric status of parents and offspring. Before data collection, subjects were trained until they demonstrated appropriate performance. Training began with an explanation of all study procedures by the technician. Subjects were then shown facial stimuli not used in the task and were asked to explain the way in which they would rate these pictures for each of the instruction sets. Finally, subjects were presented with "practice trials" on the laptop computer during which time they again viewed novel faces. To proceed to the actual test, subjects had to demonstrate their ability to make their ratings within the 4-second time window for each face. Practice was repeated until subjects could comfortably perform the ratings in the allotted viewing time. This usually required relatively few replicates, such that the entire training procedures required no more than 5 minutes.

During one block, subjects were told to rate the degree to which they felt afraid or anxious at the moment that they viewed a face (a "how afraid" rating). During another block, subjects were told to rate the degree to which a face appeared hostile (a "how hostile" rating) by imagining how threatening the individual might seem if "encountered on a street corner" (Adolphs, 2002). In a third block, subjects were told to rate the degree to which the nose on each face appeared wide or narrow (a "how wide" rating). The "how hostile" condition was included to address the possibility that groups might differ in perceptions of negative emotion in general rather than perception of internally experienced fear in particular. The "how wide" rating controlled for group differences in rating behavior, irrespective of emotional set.

Ratings were made on a 5-point scale, and reaction times were automatically recorded in milliseconds by having subjects record their responses on the keyboard of the IBM laptop. Subjects indicated their ratings by using two hands that were placed on the laptop keyboard numbers, from 1 to 5, with the index finger of the left hand on the ''1'' key and the index through fifth finger of the right hand on the ''2–5'' keys. Subjects' hands remained on the keys for the duration of the task, and subjects fixated on the pictures as they appeared on the laptop screen. With this procedure, subjects did not have to manually search for the appropriate key to indicate their response.

Data Analysis

Subjects made three ratings during face viewing (afraid, hostile, nose- width). Differences between offspring at risk of PD and offspring with and without anxiety disorders on fear ratings exclusively would support the hypothesis that risk of PD and ongoing anxiety disorders in children are associated with selective perturbation in anxiety-state monitoring. The main study hypotheses on face-rating measures were tested using two sets of mixed linear models in SAS PROC-MIXED using the autoregressive covariance structure as an estimation method, given that the response to a given picture may be influenced by the response on the preceding picture. Means of dependent measures were normally distributed, based on results from Kolmogorov-Smirnov tests. One set of models treated reaction time data as dependent; the other treated self-rated fear as dependent. The explanatory variables comprised fixed effects (gender, age, diagnosis in parents or offspring, face-emotion type [happy, fearful, angry], instructions [afraid, hostile, width]) and random effects (family and subjects). The use of mixed linear models, in which family and subjects are treated as random effects, allows statistical tests to account for the fact that multiple offspring from a single family contribute data. Results from the mixed models revealed significant intrafamilial correlation, both for reaction times ($Z = 4.8$, $p < .001$) and for self-ratings ($Z = 4.5$, $p < .001$).

Associations between parental and offspring diagnoses were analyzed using SAS GEE/GENMOD, treating current anxiety diagnosis in the offspring as dependent. Explanatory variables included both fixed effects (offspring gender, parental PD, parental MDD, parental PD × MDD interaction) and random effects (family and subjects). As with the use of mixed linear models, the use of GEE allows statistical tests of associations between parent and child diagnoses to account for the fact that multiple offspring from a family contribute data. In this analysis, compound symmetry was specified as a covariance matrix.

Analyses examining associations between fear ratings and anxiety diagnosis in offspring considered two diagnostic indicators. One set of analyses considered offspring with any ongoing anxiety disorder as ''affected''; another selected only offspring with social phobia as ''affected.'' To reduce collinearity, one set predicted face-rating performance from either parent or child diagnosis, treated individually, while controlling for gender and age. Another more comprehensive set included both parent and child diagnoses as well as offspring gender and age.

The primary hypotheses were tested through two-way interactions between parental PD diagnosis and face-rating instructions. Models also included two-way interaction terms between instruction set and both parental MDD and offspring anxiety diagnoses (two-tailed a priori $p = .05$ for all tests). Although no associations with MDD were expected, parental MDD was included as a predictor to evaluate specificity. To maximize statistical power, the initial analysis did not directly contrast offspring of parents with PD and MDD. A supplementary analysis directly compared these groups.

Repeated observations on individuals across time and separate observations on individuals are not independent observations. Other studies have relied on a mixed analysis of variance statistical model to adjust statistical tests by modeling within-family aggregation and repeated-measure effects (Rosenbaum et al., 2000; Slattery et al., 2002; Verbeke and Molenberghs, 1997; Wolfinger, 1997). This method was used in the current study, implemented in SAS, to derive nonbiased estimates of degrees of freedom for effects and their interactions (Littell et al., 1996).

RESULTS

Table 1 presents the groups' demographic characteristics, revealing no significant group differences.

Anxiety Diagnosis in Offspring and Diagnosis in Parents

Offspring born to parents with either MDD or PD had significantly higher rates of current anxiety disorders (42%–61%) than offspring of parents without MDD or PD (19%). Table 1 presents rates of specific offspring anxiety disorders. There were significantly more females among offspring with a current anxiety disorder (67%) than among those without an anxiety disorder (44%) ($\chi^2 = 6.5$, $p < .01$). Offspring with and without anxiety disorders did not differ on other potentially confounding characteristics.

In a multivariate logistic model predicting the presence of an anxiety disorder in offspring, both parental PD ($\chi^2 = 3.9$, $p < .05$) and parental MDD ($\chi^2 = 7.3$, $p < .01$) predicted an increased rate of offspring anxiety, as did offspring female gender ($\chi^2 = 7.3$, $p < .01$). The interaction between parental MDD and PD was not significant ($\chi^2 = 0.2$, $p > .2$).

Face-Viewing Responses: Descriptive Data

Table 2 presents raw means for reaction times and ratings for each face-type (happy, fearful, angry) in each instruction set (afraid, hostile, nose width). Table 3 statistically compares ratings and reaction time responses across the three instruction sets and three face types. Significant face type by instruction interactions were found for reaction time (Table 3, row nine; $F = 38.5$, $p < .001$) and for emotion ratings (Table 3, row nine; $F = 246.1$, $p < .001$), indicating, as expected, that subjects altered rating behavior and reaction times across instruction sets and face types. Happy faces received the highest ratings for nose width but the lowest ratings on ''afraid'' and ''hostile.'' Happy faces also required the longest

TABLE 1
Characteristics of Offspring by Parent Diagnosis

Characteristic	PD Only (n = 24)	MDD Only (n = 53)	PD & MDD (n = 41)	Nonill (n = 26)
Mean age	14.5 ± 3.2	15.2 ± 3.1	14.6 ± 2.8	15.5 ± 2.2
Female, no. (%)	13 (54)	32 (59)	24 (59)	12 (46)
IQ[a]	104 ± 10	102 ± 12	102 ± 10	104 ± 10
Social class (range 0–5)	2.6 ± 0.6	2.7 ± 1.0	3.1 ± 1.0	2.5 ± 0.7
Face Accuracy,[b] (range 28–52)	43.6 ± 4.6	45.4 ± 5.1	45.8 ± 3.8	44.4 ± 3.7
Lifetime major depression,[c] no. (%)	2 (8)	9 (17)	4 (10)	1 (4)
Current Anxiety Disorder,[d] no. (%)	10 (42)	25 (47)	25 (61)	5 (19)
Social phobia	2 (8)	11 (21)	10 (24)	3 (12)
Separation anxiety	2 (8)	6 (11)	7 (17)	0 (0)
Generalized anxiety	2 (8)	1 (2)	4 (10)	0 (0)
Specific phobia	5 (21)	11 (21)	15 (37)	3 (12)

Note: PD = panic disorder; MDD = major depressive disorder.
[a] Composite from verbal and design portion of Kaufman Brief Intelligence Test.
[b] Score on the Benton Test of Facial Recognition. Data are available only for a subset of the 144 subjects (n = 97).
[c] Occurrence of at least one MDD episode at some point during lifetime. Only two subjects met criteria for current MDD.
[d] Occurrence of at least one current/ongoing anxiety disorder; specific disorders are listed in rows below.

time to rate for the "nose width" rating but the shortest time for the "afraid" and "hostile" ratings. Similarly, "afraid" ratings differed from "hostile" ratings in both reaction time and levels. These results suggest that rating performance in offspring reflected the engagement of distinct psychological processes across instruction sets.

Correlations were examined between rating responses and reaction times. There was a significant correlation between level of fear and reaction time to make fear ratings (r = 0.49, p < .001). However, reaction times and rating levels were uncorrelated for ratings of hostility (r = 0.02) or nose width (r = 0.13). These findings suggest that reaction time and fear levels assess a common underlying construct specific to the emotion of fear. Moreover, as with the distinct face-emotion orderings for ratings and reaction times across the three instruction sets, these distinct patterns of correlations suggest that performance of the task reflects engagement of distinct psychological processes during each rating set as opposed to factors such as motor coordination or training that are likely to similarly influence each of the three rating sets.

Table 3 presents relationships (F and p values in row 13, Table 3) between responses to faces (reaction time, fear ratings), age, and gender as well as parental PD, parental MDD, current offspring anxiety disorder, and their interactions. The main hypotheses are addressed in the two instruction set by parent PD interactions as well as the instruction set by offspring anxiety disorder interactions. Specifically, differences were expected during the "afraid" but not the "hostile" or "nose width" rating sets.

Face-Viewing Responses as a Function of Parental PD

As predicted, reaction times differed across the three instruction sets in offspring at high compared with low risk of PD (Table 3, row 13, parental PD by instruction

TABLE 2
Offspring Reaction Times and Ratings to Angry, Fearful, and Happy Faces (Means ± SD)

	Instruction Set Across All Faces					
	How Afraid Are You?		How Hostile Is the Face?		How Wide Is the Nose?	
Face Type	Reaction Time (ms)	Fear Rating[a]	Reaction Time (ms)	Hostility Rating[a]	Reaction Time (ms)	Width Rating[a]
Angry faces	1,640 ± 495	2.4 ± 1.1	1,840 ± 339	3.7 ± 0.6	1,788 ± 328	2.5 ± 0.5
Fearful faces	1,601 ± 506	2.0 ± 1.0	1,911 ± 365	2.8 ± 0.9	1,817 ± 330	2.5 ± 0.6
Happy faces	1,194 ± 381	1.1 ± 0.4	1,367 ± 318	1.2 ± 0.4	1,849 ± 342	3.2 ± 0.6

[a] Each emotion face rated 1–5, 1 = low level, 5 = high level of fear, hostility, or nose width.

TABLE 3
Offspring Reaction Times and Face Ratings by Parental and Offspring Diagnosis

	Reaction Time		Face Ratings	
Main Effects	*F*, *df*	*P* Value	*F*, *df*	*P* Value
Age	$F_{1,1181} = 0.9$	≤.34	$F_{1,1181} = 24.1$	≤.001
Gender	$F_{1,1181} = 0.1$	≤.91	$F_{1,1181} = 9.0$	≤.002
Parent diagnosis				
PD	$F_{1,1181} = 4.2$	≤.03	$F_{1,1181} = 2.1$	≤.14
MDD	$F_{1,1181} = 0.1$	≤.84	$F_{1,1181} = 1.8$	≤.19
Offspring diagnosis				
SOPH	$F_{1,1811} = 16.8$	≤.001	—	—
Any anxiety disorder	—	—	$F_{1,1181} = 0.1$	≤.76
Within-subject factors				
Instruction set	$F_{2,1181} = 25.7$	≤.001	$F_{2,1181} = 197.5$	≤.001
Face type	$F_{2,1181} = 54.2$	≤.001	$F_{2,1181} = 291.6$	≤.001
2-Way Interactions				
Instruction by face type	$F_{2,1181} = 38.5$	≤.001	$F_{2,1181} = 246.1$	≤.001
Gender by face type	$F_{2,1181} = 2.1$	≤.11	$F_{2,1181} = 4.6$	≤.01
Gender by Instruction set	$F_{2,1181} = 1.6$	≤.21	$F_{2,1181} = 2.7$	≤.06
Parent diagnosis				
PD by face type	$F_{2,1181} = 0.1$	≤.69	$F_{2,1181} = 3.4$	≤.04
PD by instruction set	$F_{2,1181} = 8.4$	≤.001	$F_{2,1185} = 6.1$	≤.002
MDD by face type	$F_{2,1181} = 0.8$	≤.44	$F_{2,1181} = 2.0$	≤.14
MDD by instruction	$F_{2,1181} = 0.6$	≤.56	$F_{2,1181} = 0.3$	≤.77
Offspring diagnosis				
SOPH by face type	$F_{2,1181} = 0.34$	≤.70	—	—
SOPH by instruction	$F_{2,1181} = 15.6$	≤.001	—	—
Any anxiety by face type	—	—	$F_{2,1181} = 1.8$	≤.17
Any Anxiety by Instruction	—	—	$F_{2,1181} = 2.2$	≤.10

Note: Outcome of analyses are presented for reaction time data and for fear ratings across the three instruction sets. The association of each of the two dependent measures is examined with age, gender, instruction set, face type, diagnosis in parent (PD, MDD) and offspring (any anxiety, social phobia). For offspring diagnosis, separate models are fit either with any anxiety or social phobia. All possible two-way interactions are also examined. Tests of the main study hypotheses are based on significance of diagnosis by instruction set interactions, as indicated by bolding in the first column. PD = panic disorder; MDD = major depressive disorder; SOPH = social phobia.

set interaction [$F = 8.4$, $p < .001$]). Similarly, fear-rating levels were related to offspring risk status (Table 3, row 13, parental PD diagnosis by instruction set [$F = 6.1$, $p = .002$]). These results appear in Table 3 as two-way interactions with instruction set. Post hoc analyses decomposed these interactions. Because our main hypothesis concerned between-group differences during the "afraid" rating, means are presented for these ratings in Table 4. Table 4 also presents statistical tests for between-group differences in this rating set.

Table 4 presents results from models predicting responses only in the "how afraid are you?" instruction set for the three face types (happy, fearful, angry). As hypothesized, significant interactions in Table 3 reflect the association between parental PD and offspring responses during the "afraid" instruction set. Table 4 presents reaction time data in subjects with and without social phobia as well as in subjects with and without parental PD. As shown in the first set of columns in Table 4, for the "afraid" instruction set, parental PD predicted prolonged reaction times ($F = 10.9$, $p < .001$). Table 4 presents rating data for subjects with and without any anxiety disorder as well as in subjects with and without parental PD. Similarly, as shown in the second set of columns, parental PD also predicted higher fear ratings ($F = 7.0$, $p = .008$).

Face-Viewing Responses as a Function of Current Anxiety Disorders in Offspring

In a model not shown in Table 4, current anxiety disorders in offspring predicted elevated reports of fear

TABLE 4
Relationship Between Offspring Reaction Times and Fear Ratings With Parent and Offspring Diagnosis

Predictor[b] Variables	Reaction Time[a] Happy Faces	Fearful Faces	Angry Faces	*F, df;* *P* Value	Fear Ratings[a] Happy Faces	Fearful Faces	Angry Faces	*F, df;* *P* Value
Panic disorder								
Absent	1,216 ± 62	1,592 ± 62	1,669 ± 62	$F_{1,335}$ = 10.9;	1.1 ± 0.1	1.9 ± 0.1	1.1 ± 0.1	$F_{1,331}$ = 7.0;
Present	1,483 ± 68	1,788 ± 66	1,871 ± 66	$P < 0.001$	1.1 ± 0.1	2.2 ± 0.1	2.7 ± 0.1	$p = 0.008$
MDD								
Absent	1,276 ± 81	1,706 ± 81	1,707 ± 81	$F_{1,335}$ = 0.3;	1.1 ± 0.2	1.9 ± 0.1	2.4 ± 0.1	$F_{1,331}$ = 1.2;
Present	1,332 ± 58	1,652 ± 59	1,793 ± 59	$P < .59$	1.1 ± 0.1	2.1 ± 0.1	2.5 ± 0.1	$p = .27$
Social phobia								
Absent	1,145 ± 41	1,560 ± 41	1,579 ± 41	$F_{1,335}$ = 17.8;				
Present	1,453 ± 94	1,821 ± 94	1,960 ± 94	$P < 0.001$				
Any anxiety								
Absent					1.1 ± 0.1	1.9 ± 0.1	2.4 ± 0.1	$F_{1,331}$ = 2.3;
Present					1.1 ± 0.1	2.2 ± 0.1	2.6 ± 0.1	$p = .13$

Note: MDD = major depressive disorder.

[a]Adjusted mean values for reaction time to rate level of fear experienced or for overall level of fear experienced across the eight viewings of each face type, adjusted for all predictor variables in the statistical model (see Table 3 age, gender, face type, gender by face type interaction). Values are presented as adjusted means ± SE for estimate of adjusted mean. Latency is expressed in milliseconds. Fear ratings range 1–5.

[b]Associations between dependent measure and diagnosis in parent (PD, MDD) and diagnosis in offspring (any anxiety, social phobia) are estimated in one model, adjusting for all variables shown in the table as well as all other variables in Table 3 (age, gender, face type, gender by face type interaction).

($F = 4.5$, $p < .05$). However, this relationship was no longer present when parental PD was covaried ($F = 2.3$, $p = 0.13$) in the model shown in Table 4. In contrast, for reaction time, a significant interaction was obtained between offspring social phobia and instruction set (see Table 3; $F = 15.6$, $p < .001$), such that social phobia was positively associated with reaction time for fear ratings (Table 4; $F = 15.3$, $p < .001$), even when controlling for parental PD, which also predicted reaction time ($F = 10.9$, $p < .001$). However, in an analysis not shown in Table 4, fear ratings were not affected by social phobia in offspring ($F = 0.9$, $p = .35$).

Face-Viewing Responses as a Function of Parental MDD

No main effect or interaction with instruction set emerged for parental MDD in the models shown in Tables 3 (rows 14 and 15) and 4 (row 2, *F* values). A further secondary analysis, not presented in Table 4, was conducted. This analysis directly contrasted rating performance in two groups: offspring of parents with MDD but not PD ($n = 53$) versus offspring of parents with PD ($n = 65$), either with ($n = 41$) or without ($n = 24$) comorbid MDD (the latter two groups exhibited similar face-rating performance). Unlike the analyses in Table 4, these two analyses combined offspring of parents with PD into a single group to maximize statistical power for direct comparisons between MDD-positive/PD-negative and PD-positive groups. These analyses revealed offspring at risk of PD to have significantly longer reaction times ($F = 5.9$, $p = .01$), but nonsignificant elevations in fear ratings ($F = 2.9$, $p = .08$) than offspring of parents with MDD but not PD.

DISCUSSION

This study examines emotional regulation in offspring of adults with and without PD. It tests whether offspring of parents with PD display different emotional responses to experimental stimuli designed to evoke fear compared with offspring of parents with MDD and those of controls. Offspring of parents with PD as well as offspring of parents with MDD had elevated rates of current anxiety disorders compared with children of normal comparisons. This finding is consistent with previous reports, suggesting that childhood anxiety and MDD may represent alternative manifestations of a shared vulnerability (Beidel and Turner, 1997; Weissman et al., 1997).

As predicted, when viewing evocative faces, offspring at high risk of PD reported more fear and exhibited

longer latencies to report their fear level relative to offspring at low risk of PD. Prolonged latency is taken as evidence of greater attention allocation. Only parental PD predicted patterns of responding to facial photographs; in a direct contrast, offspring of parents with PD exhibited longer latencies for fear ratings than offspring of parents with MDD.

Studies in juveniles have relied on varied procedures to document hypersensitivity to threat probes in offspring of PD versus healthy parents. Threats include startling air blasts, mere exposure to a laboratory environment, or presentation of novel social scenarios (Merikangas et al., 1999). When combined with results from the current study, available data suggest that childhood offspring of PD parents, relative to offspring of either parents with MDD or healthy parents, exhibit hypersensitivity to an array of threats.

The use of facial photos extends previous findings, given data suggesting that evocative faces can engage a distributed neural circuit involved in social threat or fear evaluation, a core aspect of human emotional experiences (Haxby et al., 2002). In a recent functional magnetic resonance imaging study using the same task as the current study, engagement of specific brain regions, encompassing a distributed "fear circuit," varied across the three specific instruction sets used in the current study (Monk et al., 2003). The observed differences in fear levels and reaction time for the current study may reflect underlying perturbations in the same neural circuitry, manifest during specific attention states. Given the findings in the current study, we would expect between-group differences in neural engagement for healthy and anxious youths to appear particularly strong when patients attend to an internally experienced fear state.

The association between anxiety disorders in offspring and greater fear during face viewing was accounted for by parental PD. Thus, we did not obtain support of the hypothesis of a simple relationship between pediatric anxiety disorders and perturbed processing of fear provocation. It is difficult to reconcile positive findings with risk status for PD and negative findings for actual anxiety disorders in offspring. However, independent of their risk status, offspring with social phobia specifically had prolonged latency to rate fear, yet they did not report greater fear severity.

The dissociation between risk status and anxiety disorders with regard to fear responses is puzzling, in view of previous studies (Pine et al., 2000). On the other hand, the finding is not without precedent: A family-based study found a similar dissociation in which the parental but not offspring anxiety diagnosis predicted startle reactivity (Merikangas et al., 1999). Other investigations have not controlled for parental psychopathology, and it may be that, among children with anxiety disorders, those with a parental history of anxiety disorders are the ones who are deviant.

The current results suggest some continuities across development in the psychological correlates of anxiety disorders. Using reaction time to index attention allocation, the current study documents perturbations in attention to internal sensations of fear among children and adolescents at risk of PD. However, these same perturbations in offspring with anxiety disorders were not significant when the influence of parental PD was taken into consideration. Multiple explanations could account for such continuity. For example, genetic factors influence engagement of brain regions during face-emotion processing, possibly contributing to continuity (Hariri et al., 2002). Alternatively, parenting behavior could influence offspring responses, given previous findings on the rearing practices of parents with PD (Warren et al., 2003).

Limitations

The current findings should be considered in light of limitations. First, the study recruited at-risk offspring through parents seeking treatment. Although this sampling strategy characterizes studies of familial risk (Merikangas et al., 1999), it is vulnerable to referral biases. Second, small sample sizes limit conclusions on subgroups of specific anxiety diagnoses. Third, because we present no data on genetic factors or brain function, only indirect inferences can be made concerning factors that contribute to the observed differences in behavior; multiple possible explanations could be put forth to account for our findings. Finally, severity of diagnosis in the offspring may be relatively mild compared with cases encountered in clinical settings.

Clinical Relevance

Study results suggest that children and adolescents at risk of PD may differ from other children and adolescents in terms of their rating behavior and attention allocation while viewing evocative facial photographs.

Studies are needed to establish the degree to which perturbed attention to evocative faces predicts the onset of anxiety disorders in general or PD in particular among healthy but at-risk youths. Similarly, studies might examine whether perturbed attention predicts the longitudinal course of anxiety in children with ongoing disorders.

If subsequent studies demonstrate a relationship between face-rating performance and risk of future anxiety, the identification of children and adolescents at high risk of clinically significant anxiety disorders will be considerably facilitated. For example, it may be possible to develop standardized measures of face-emotion processing that could be used to identify children and adolescents who perform below expected norms on face-processing tasks. Such children might eventually be monitored particularly closely so that interventions could be rapidly deployed should these children exhibit initial signs of increases or persistence in anxiety. Similarly, the current data may carry implications for anxious children receiving treatment. Effective treatments may minimize anxiety by reducing inappropriate allocation of attention to internal fear states (Clark, 1999). Evaluations of treatment effects on perturbed attention in pediatric anxiety currently rely solely on self-reported measures, such as the ASI. If the current findings are replicated, this may facilitate the development of observational measures that quantify perturbed attention allocation. Such measures may provide clinicians with objective, tractable indices useful in monitoring the success of treatment.

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