



## **Offspring at High Risk for Anxiety and Depression**

### **Preliminary Findings From a Three-Generation Study**

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**Numerous studies have** demonstrated the familial transmission of major depressive disorder (MDD) in adult first-degree relatives of depressed patients (Gershon et al. 1982; Klein et al. 2001; Taylor et al. 1980; Weissman et al. 1982; Winokur 1982). Recent comprehensive reviews of controlled family studies of depression reveal that the average risk ratio (RR) for major depression among relatives of probands with major depression compared with control subjects was 2.0, indicating a moderate influence of familial aggregation on nonbipolar mood disorders (Sullivan et al. 2000). A recent meta-analysis of community-based twin studies of major depression yielded a heritability estimate of 0.37 (95% confidence interval [CI] 0.28 to 0.42). These estimates are in the range of estimates for other complex genetic disorders such as diabetes and breast cancer and

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suggest that environmental risk factors also make a substantial contribution (Sullivan et al. 2000). Retrospective data on onset and course from existing family studies indicate that early age of onset and recurrence are associated with increased familial clustering of depression (Wickramaratne et al. 2000). In parallel, studies of offspring of parents with affective disorders reveal an approximately threefold increased risk of depression among child and adolescent offspring (Downey and Coyne 1990; Hammen et al. 1990; Keller et al. 1986; Kovacs et al. 1997; Kutcher and Marton 1991; Lieb et al. 2002; Orvaschel et al. 1988; Puig-Antich et al. 1989; Weissman et al. 1984, 1987; Williamson et al. 1995). However, the results of recent family and twin studies of youth suggest that prepubertal depression may be less heritable than postpubertal depression (Harrington et al. 1997; Kaufman et al. 2001; Merikangas and Angst 1995; Rende and Weissman 1999; Rende et al. 1999; Silberg et al. 1999, 2001). The discrepancy in these findings may be attributable to anxiety as a prodromal form of depression or that prepubertal MDD is diagnostically heterogeneous into adulthood (Avenevoli et al. 2001; Breslau et al. 1995; Cole et al. 1998; Kovacs et al. 1989; Lewinsohn et al. 1994; Pine et al. 1998; Reinherz et al. 1993; Rende et al. 1999; Rohde et al. 1991; Thapar and McGuffin 1997; Weissman 2002; Weissman et al. 1999). There also appear to be differences in both the specificity and risk factors for preadolescent and adolescent-onset depression that will be examined in future analyses of the present study.

The overall aim of this research is to examine the familial aggregation of mood disorders and other psychiatric disorders across the generations. By following the second and third generations of a cohort with well-characterized mood disorders (generation 1) compared with non-psychiatrically ill control subjects, we aimed to understand the stability of risk across the generations, to identify premorbid vulnerability factors (biological markers, early signs), and to apply this information to the development of appropriate and targeted preventive interventions.

This study incorporates a combined family study-high-risk design with a prospective longitudinal follow-up of three generations of families that were initially identified more than 17 years ago. Table 4-1 and Figure 4-1 present a summary of the study design. There are numerous advantages to the combined high-risk and longitudinal design. The potential case yield is increased as is the power to detect risk factor associations, as well as mediating and moderating effects on risk factors (e.g., children of depressed parents with vs. without a divorce). Other important benefits include the ability to identify early patterns and sequence of disease given

**TABLE 4-1** Study design

High-risk	Comparison between individuals with and without risk of parental depression
Longitudinal	Four assessments over 17 years (baseline, 2, 10, and 17 years) from childhood to adulthood in the second generation
Three generations	

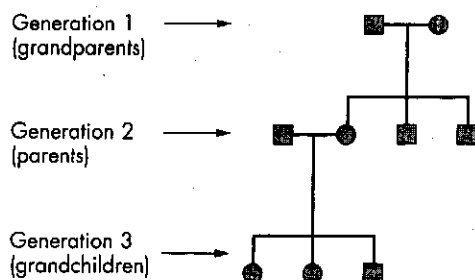
exposure to risk, which in this case is parental depression, and maximization of the reliability of estimates of specificity and stability of transmission (Merikangas et al. 1999).

The present study is unique in examining familial aggregation of mood and anxiety disorders across three generations. Other design features that differentiate the present study from the majority of prior family/high-risk studies include systematic interviewing of both parents regarding not only child psychopathology but also their own psychopathology; prospective follow-up of high- and low-risk groups; inclusion of a demographically comparable control group, which has rarely been incorporated in prior high-risk studies of depression; and measures of potential biological markers for mood and anxiety disorders (i.e., psychophysiological measures, described later).

We hypothesized that the grandchildren of depressed grandparents would have an increased risk of mood disorders. Further, we predicted that multigenerational MDD (i.e., the presence of MDD in both grandparent and parent) would be associated with a significantly greater risk of mood disorders among grandchildren. Finally, in light of the familial links between depression and anxiety disorders, we expected that offspring of parents in both generations would have an increased risk of anxiety disorders, irrespective of parental comorbidity for anxiety and depression. This chapter presents preliminary findings from this three-generation study to illustrate the potential advantages of the design for translational research.

## **METHODS**

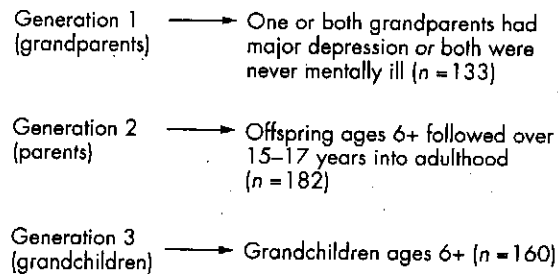
In the original study, probands with major depression were selected from outpatient clinical specialty settings for the treatment of mood disorders (generation 1). The nondepressed probands, who were required to show no lifetime history of psychiatric illness on the basis of several interviews, were selected from a community sample of adults from the same commu-



**FIGURE 4-1** The three generations.

nity, New Haven, Connecticut (for more details see Weissman et al. 1982, 1992, 1997; Warner et al. 1999). The proband, spouse, offspring (generation 2) and grandchildren (generation 3) were interviewed independently. The six families in which either the control proband or spouse in the control group subsequently developed MDD were removed from the study.

The diagnostic interviews across all waves were conducted using a semistructured diagnostic assessment (the Schedule for Affective Disorders and Schizophrenia, Lifetime Version [SADS-L] for adults [Mannuzza et al. 1986], and for subjects between the ages of 6 and 17 the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Epidemiological Version [K-SADS-E] [Orvaschel et al. 1982] modified for DSM-IV [American Psychiatric Association 1994] at wave 4 by Kaufman). The diagnostic assessments were administered by highly trained clinical interviewers who were blind to the clinical status of the parents or grandparents. Multiple sources of information were obtained, including independent assessments of the subjects by direct interview, by parent report, and by direct assessment of both biological parents as often as possible. All final diagnoses (best estimates) were made blindly by experienced psychiatrists or psychologists based on all available information (Leckman et al. 1982). The data presented are based on extensive interviews concerning medical history, psychiatric diagnoses, and social functioning, as well as medical records when available at four waves over 17 years on grandparents and parents, and for grandchildren at the last two waves). The results presented here from the fourth wave are preliminary, based on about 80% of the sample and based on interviews and not best-estimate diagnoses. The response rate for probands, offspring, and grandchildren ranged from 76% to 86% over the previous three waves and did not differ by proband groups. The total sample available for interview and the data collected at wave 4 for these preliminary analyses are described in Figure 4-2.



**FIGURE 4-2** Descriptions of the three generations.

## RESULTS

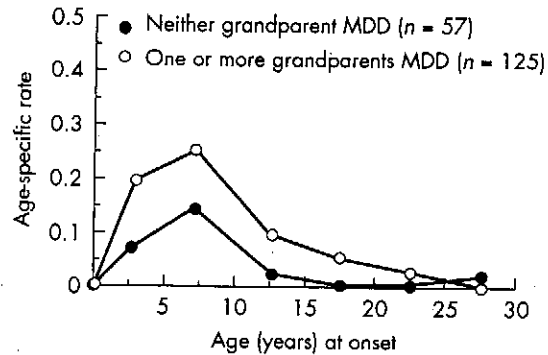
### Sequence of Onset and Age-Specific Rates of Anxiety Disorder and MDD

Figures 4-3 and 4-4, respectively, show the age-specific rates of anxiety and MDD in the second generation stratified by the MDD status of the grandparents (generation 1). The peak incidence of an anxiety disorder, at ages 5 to 10 (Figure 4-3), is much earlier than that for MDD, which occurs between the ages of 15 and 20 (Figure 4-4).

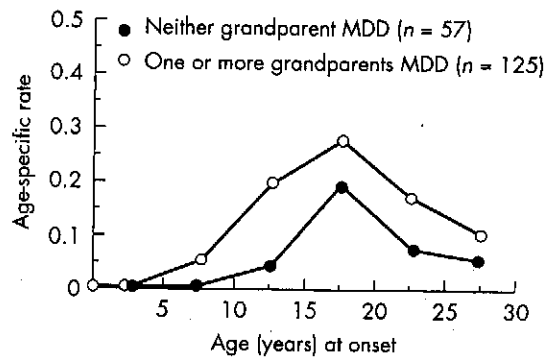
The age-specific rates in the third generation follow a similar pattern as in the second generation, with the exception that the second generation had a longer period of follow-up (Figures 4-5 and 4-6). Not shown here is the finding that grandchildren with a diagnosis of anxiety (prior to the onset of MDD) had a 2.4-fold increase in risk for MDD compared with grandchildren without a prior diagnosis of anxiety. These findings are consistent with the hypothesis that anxiety may act either as a predisposition or temporal antecedent to recurrent, early-onset MDD. This form of MDD is characteristically the most severe and has the poorest treatment outcome. The observation that anxiety disorder also was a precursor of MDD in the second generation in wave 4 led us to examine psychophysiological indicators of anxiety in youth based on prior research demonstrating increased startle response among offspring of parents with anxiety disorders compared with those of probands with substance use disorders and control subjects (Grillon et al. 1997a, 1997b, 1998; Merikangas et al. 1999).

### Effect of Parent and Grandparent MDD on Grandchildren

Grandparent MDD has a strong impact on the risk of mood disorders in the grandchildren. The grandchildren in the high-risk group (i.e., those with at least one depressed grandparent) have higher rates of mood disorders



**FIGURE 4-3** Age-specific rates of any anxiety disorder in parent (generation 2) by major depressive disorder (MDD) status of grandparent (generation 1).

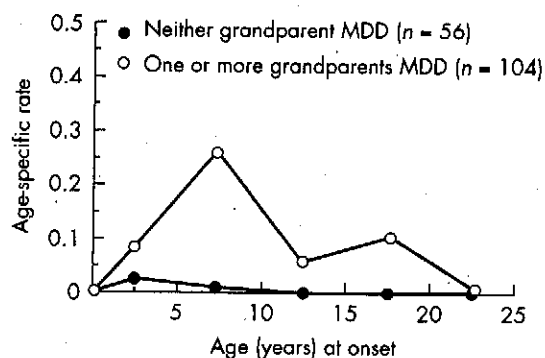


**FIGURE 4-4** Age-specific rates of major depressive disorder (MDD) in parent (generation 2) by MDD status of grandparent (generation 1).

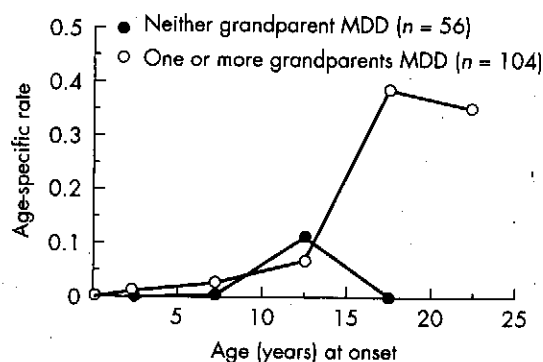
than those in the low-risk group (22.1% vs. 3.6%, RR 4.5 [95% CI 1.1 to 15.2]) after adjusting for age and gender of grandchild, using Cox proportional hazard regression models. These results support the use of the original high- and low-risk classification.

The following results are preliminary.

We further categorized the grandchildren by grandparent and parent depression status. Grandparents without MDD (groups 1 and 2) were defined as low risk and grandparents with MDD (groups 3 and 4) as high risk (Figure 4-7). We found that grandchildren with a depressed grandparent, regardless of their parents' depression status, were at increased risk for mood disorder. This may be because the majority of the depressed grandparents were originally selected through a depression treatment clinic.



**FIGURE 4-5** Age-specific rates of any anxiety disorder in grandchild (generation 3) by major depressive disorder (MDD) status of grandparent (generation 1).



**FIGURE 4-6** Age-specific rates of major depressive disorder (MDD) in grandchild (generation 3) by MDD status of grandparent (generation 1).

Their depression may have been of a more severe or chronic form, which also tends to be more familial. The grandchildren from groups 2 and 4 had the poorest overall functioning (not shown). These findings were independent of grandparent depression status, suggesting that parental MDD also has an impact on offspring.

Group 2 (grandparent not depressed, parent depressed) is of considerable interest. Our previous findings in the offspring (generation 2) of depressed grandparents showed, both cross-sectionally and over a 10-year follow-up, that these offspring were at a threefold increased risk for MDD. We also found that some of the offspring (generation 2) with nondepressed parents (generation 1) developed MDD (group 2). However, Fendrich et al. (1990), in an analysis of the second wave of these data, showed that they

had a lower rate of MDD, a later age of onset, and more family environment risk factors (discord between parents and children, poor parental bonding, etc.) compared with control subjects. These findings were replicated by Nomura et al. (2002) in the same sample at 10-year follow-up (the third wave), when the second generation were all adults. These findings raised questions about the transmission of depression to the third generation (grandchildren in group 2). We hypothesized that cases of parental depression in group 2 may be nonfamilial phenocopies that will not result in transmission of MDD to the grandchildren. Our findings in the grandchildren (third generation in group 2) are consistent with this hypothesis (see Figure 4–7). The rate of MDD in grandchildren did not differ between low-risk groups (groups 1 and 2). When the full-sample and best-estimate diagnoses are completed, we will examine the nature, severity, and onset of the mood disorders in the grandchildren in the four groups. We will also assess the transmission of familial risk factors across the generations and the range of disorders in the grandchildren.

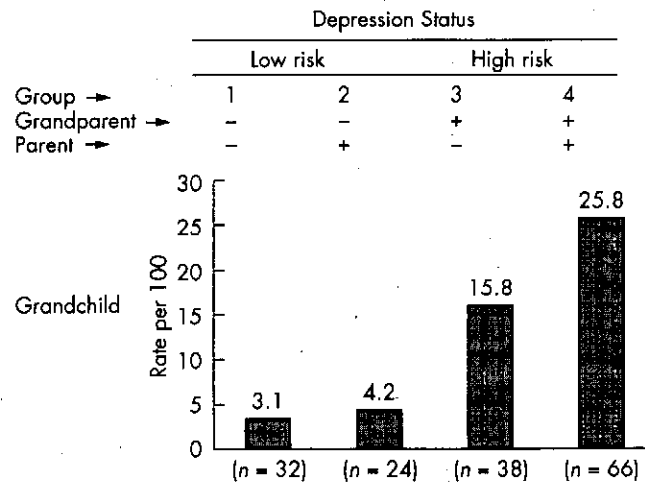
## **DISCUSSION**

### **Summary of Findings**

The preliminary data confirm our major hypotheses. First, there was a strong degree of familial aggregation across the three generations investigated in the present study. Mood disorders in the grandparents were associated with mood disorders in the grandchildren, irrespective of parental mood disorder. We also confirmed our second hypothesis, that multigenerational depression was associated with the greatest level of depression in offspring. In addition, we found that the third generation was at increased risk for anxiety disorders in childhood, followed by MDD in adolescence. This increased risk of MDD preceded by anxiety was stable across the three generations in high-risk samples. If confirmed in the full sample, this finding could provide a powerful index of genetic risk.

The findings illustrate the potential importance of collecting family history data beyond the first generation for research studies that involve children. Although the offspring of depressed parents without a grandparent history of depression may represent phenocopies, they did not appear to differ clinically from the offspring with both a depressed parent and a depressed grandparent. However, the risk for depression in the next generation of these groups may be quite different. Alternatively, depression-free adults with a depressed parent may confirm an increased risk of depression in the third generation.





**FIGURE 4-7** Mood disorder rates in grandchildren, by major depressive disorder (MDD) status of grandparents and parents.

### **Psychophysiological Measures**

A convergence of evidence suggests that psychophysiological measures, which are noninvasive, cost-effective, and easily obtained in children, are good candidates for biological markers of vulnerability to depressive or anxiety disorders. This includes electroencephalogram (EEG) findings from 1) studies in infants or young children who are at risk for depressive or anxiety disorders by virtue of family history of depression (Dawson et al. 1997; Field et al. 1995), 2) studies of behaviorally inhibited and uninhibited children (Davidson and Fox 1989; Fox et al. 1992), and 3) studies in adults and adolescents with depressive or anxiety disorders (Bruder et al. 1997; Davidson 1992; Kentgen et al. 2000). Davidson (1992) reviewed evidence that frontal brain asymmetry, as measured by EEG alpha asymmetry, identifies a diathesis predisposing individuals to respond with predominantly negative or positive affect, which may relate to the risk for depression or anxiety. Reduced left frontal activation is hypothesized to be associated with a deficit in approach-related behaviors and right frontal activation with withdrawal-related behaviors. In several studies, infants of depressed mothers exhibited reduced left frontal activity compared with infants of nonsymptomatic mothers (Dawson et al. 1997; Field et al. 1995). Similarly, behaviorally inhibited children showed an EEG alpha asymmetry indicative of right frontal activation, whereas uninhibited children showed the opposite asymmetry (Davidson 1992). Depressed adults have

been reported to show greater left than right frontal alpha asymmetry (Davidson et al. 1987; Gotlib et al. 1998; Henriques and Davidson 1991), but not all studies have found this frontal asymmetry (Reid et al. 1998).

Some studies have found the opposite alpha asymmetry at posterior sites in depressed adults, indicative of reduced right relative to left posterior activity (Davidson et al. 1987; Reid et al. 1998), but other studies have not found this asymmetry (Henriques and Davidson 1991). Heller et al. (1995) suggested that the failure of some studies to find evidence of reduced right posterior activation in depression may be due to the opposing effects of anxiety on parietotemporal activity. This is supported by EEG findings of less right than left posterior activation in adults and adolescents having MDD without an anxiety disorder, but not in those with a comorbid anxiety disorder (Bruder et al. 1997; Kentgen et al. 2000). Remitted depressed patients who were normothymic during EEG testing displayed evidence of both reduced left frontal and right posterior activity, which supports the hypothesis that these EEG alpha asymmetries may represent state-independent trait markers (Henriques and Davidson 1991).

Because of the preceding findings, an additional aim of this study was to evaluate the potential of EEG alpha asymmetry measures as biological markers of a phenotype of depression characterized by early onset of anxiety and familial loading for MDD. It was hypothesized that frontal alpha asymmetry will vary as a function of familial loading of MDD and will be associated with risk for MDD alone and MDD comorbid with anxiety. Resting EEG is measured in both parents (generation 2) and grandchildren (generation 3) who are at high or low risk for depression by virtue of their family history. Both grandchildren and parents who come from high-risk families in which a grandparent had MDD show EEG alpha asymmetries indicative of greater right than left frontal activation, whereas offspring from low-risk families do not show this pattern of alpha asymmetry. Moreover, based on findings of abnormal posterior alpha asymmetries in adult and adolescent depression, high-risk offspring are expected to differ from low-risk offspring in showing evidence of less right than left activation at posterior sites. Offspring with both parents depressed or who have both a parent and a grandparent who are depressed, show the greatest difference in the alpha asymmetries compared with low-risk offspring. Data collection and analysis are ongoing.

The startle reflex was also included in this study and is a relatively new approach to investigating emotions. Since the early 1990s, the startle reflex has provided unique and integrative ways of probing aversive states and psychopathology in adults and children. Startle presents several advantages that make it an ideal tool to identify vulnerability markers for mood

and anxiety disorders. It is sensitive to aversive states. It is also a translational methodology that not only links neuroscience to psychological sciences, but also permits cross-generational research in humans.

The startle reflex is a cross-species response to an intense and surprising stimulus. In animals, startle is measured by assessing the whole-body reflex. In humans, the "startle pattern" consists of a forward thrusting of the head and a descending flexor wave reaction, extending through the trunk and knees (Landis and Hunt 1939). The amplitude and the latency of the startle reflex can be measured by recording the eyeblink reflex, the most consistent and persistent component of the startle pattern. Although a startle response can be elicited with visual and tactile stimuli as long as the stimuli are sufficiently intense and have a fast rise time, most startle studies use acoustic stimuli (e.g., brief bursts of white noise at 90 to 115 dBA).

One appealing characteristic of startle is its extreme sensitivity to aversive emotional states in both humans and animals. Brown et al. (1951) first reported that startle was increased or potentiated by conditioned fear in animals. Since this seminal study, the so-called fear-potentiated startle effect has been replicated many times using different procedures in different laboratories. Thus, startle is increased or sensitized following administration of shocks (Davis 1989). It is also increased upon reexposure to aversive contexts in which shocks have been previously administered (Gewirtz et al. 1998). Finally, it is facilitated by innately aversive stimuli such as bright lights. Despite the fact that Brown et al.'s (1951) initial study was prompted by the anecdotal clinical observations that anxious people show an exaggerated startle response to loud sounds, it is only recently that the startle reflex methodology has been used to study fear and anxiety in humans. Several studies have documented potentiated startle during aversive states in humans. Grillon et al. (1991) reported a robust and highly reliable increase in startle when subjects were verbally informed to expect unpleasant aversive stimuli such as shocks. Similar results were obtained for aversive expectation following learned fear (i.e., fear conditioning) (Grillon and Davis 1997; Hamm et al. 1993). Startle is also increased during the processing of unpleasant stimuli (e.g., aversive pictures) (Lang et al. 1990). Finally, anxiogenic situations such as darkness facilitate startle (Grillon et al. 1997b). Grillon et al. (1997b) suggested that the facilitation of startle in the dark in humans and the facilitation of startle in rodents exposed to bright light have similar evolutionary bases. Rodents are nocturnal animals and are vulnerable in bright spaces, whereas humans are diurnal and are more vulnerable in the dark. In general, threatening environments facilitate startle in both species. Experiments with changes in lighting conditions illustrate another advantage of startle as a translational

tool of investigation. Because very similar experiments can be conducted in two species, human and animal research can inform each other.

Perhaps the most compelling feature of the startle reflex is the abundant basic research that informs its underlying anatomic and functional basis, thereby shedding light on the biological pathways involved in fear and anxiety states. Clinicians have long recognized that anxiety is not a unitary phenomenon but can take several forms (Barlow 2000). An accepted distinction is that between fear, a phasic response associated with an identifiable threat, and anxiety, a more sustained state of apprehension not obviously associated with a specific cue. Davis (1998) described two separate pathways mediating fear-potentiated startle that may be associated with these two aversive states (i.e., fear and anxiety). The first pathway is responsible for the phasic potentiation of startle during anticipation of an aversive event (e.g., a shock) signaled by a cue (e.g., a light). This pathway, which appears to activate cue-specific fear, is critically dependent on the central nucleus of the amygdala. Another structure, the bed nucleus of the stria terminalis (BNST), is involved in a second type of aversive response more indicative of generalized anxiety than fear. For example, under certain conditions, baseline startle reflex shows a gradual elevation over the course of aversive conditioning that may reflect a response to chronic stress (Gewirtz et al. 1998). This elevation is blocked by lesions of the BNST, but not by lesions of the amygdala (Gewirtz et al. 1998). Further evidence of a functional dissociation between the amygdala and the BNST is presented by the fact that lesions of the BNST, but not lesions of the amygdala, block the facilitation of startle by bright light (Walker and Davis 1997a, 1997b). Systemic injections of the stress hormone corticotropin-releasing hormone produce a sustained elevation in baseline startle that is blocked by lesions of the BNST, but not by lesions of the amygdala (Lee and Davis 1997). Based on this result, it has been suggested that the symptom of aversive anticipation that characterizes anxiety may be mediated by a sustained activation of the BNST via corticotropin-releasing hormone (Davis 1998).

There is an emerging literature suggesting that the latter pathway (i.e., BNST) may be implicated in the pathophysiology of anxiety disorders. Empirical evidence from startle studies suggests that anxious patients are overly sensitive to threatening contexts but show fairly normal response to cued fear. Grillon et al. (1994a) showed that patients with panic disorder and posttraumatic stress disorder (PTSD) exhibit increased baseline startle but normal fear-potentiated startle when anticipating signaled shocks. Similarly, Cuthbert et al. (1994) reported normal affective modulation of startle during aversive imagery procedures in patients with various anxiety

disorders (simple and social phobia, PTSD, and panic disorders). However, startle stimuli presented during intertrial periods were significantly elevated in these patients. These elevated baseline levels seem specific to aversive contexts because patients with anxiety disorders do not show increased startle in nonthreatening environments (Grillon et al. 1994b). These results are consistent with the hypothesis of greater contextual fear in anxious patients. There is preliminary evidence that this sensitivity to threatening experimental contexts could constitute a marker for anxiety disorders. Grillon et al. (1997b, 1998) reported that children at high risk for anxiety disorders because of a parental history of these conditions exhibited increased baseline startle.

One important issue in high-risk research on anxiety is to ensure that experiments are developmentally appropriate and that they lead to comparable results across generations. Procedures in which electric shocks are anticipated are obviously unethical for research in children. Recently, Grillon and Ameli (1998) developed a procedure that substituted intense jets of air (air blasts) directed at the neck at the level of the larynx for electric shocks. Anticipation of air blasts activates the amygdala (Pine et al. 2001a, 2001b) and yields robust and reliable startle potentiation in children (Grillon et al. 1999) and in adults of all ages (C. Grillon, unpublished observations). Other procedures, such as testing subjects in the dark, also facilitate startle in children and adults (Grillon et al. 1999), providing additional ways of assessing startle potentiation as a vulnerability marker in high-risk studies.

Based on the preceding evidence, one would expect that the magnitude of startle in grandchildren and parents will increase as a function of familial loading for anxiety and will be associated with increased risk for anxiety alone and anxiety comorbid with MDD. In those high-risk families in which MDD is comorbid with an anxiety disorder, the magnitude of the startle response should be greater in grandchildren and parents compared with both high-risk families with MDD not comorbid with anxiety and low-risk families. Data collection and analyses are ongoing.

### **Implications for Prevention**

The ultimate aim of this research is to develop appropriate and targeted preventive interventions based on familial and individual risk factors. At least two intervention studies are suggested by our findings. The finding that anxiety disorder is an early precursor of MDD across the generations suggests that treatment of primary anxiety may lead to the prevention of secondary depression (Kessler et al. 1996). Furthermore, these findings

indicate that it may be fruitful to implement early intervention efforts to reduce the severity and recurrence of mood disorders in susceptible youth as they proceed through adolescence.

Finally, the application of prevention efforts among youth of parents with MDD, prior to its onset in the youth, may actually reduce the incidence of depression in a high-risk cohort. This could be accomplished by treatment of parental depression to reduce its impact on the familial environment of exposed youth. For example, Beardslee et al. (1993, 1997) developed a program for offspring of depressed parents. A psychoeducational approach was compared with a purely educational approach among 36 parents, largely middle-class and Caucasian, with a lifetime history of MDD and at least one child age 8 to 15 ( $N=52$ ). These parents were randomly assigned to a psychoeducational intervention, consisting of 6 to 10 sessions, or a control condition, consisting of two 1-hour standardized group lectures on depression. Parental depression was not treated. Parents receiving psychoeducation reported better communication with their children than those in the control group. Their children, compared with children in the control condition, experienced higher levels of overall functioning, as measured by the Children's Global Assessment Scale (CGAS), and gained an increased understanding of their parents' illness. There were no group differences between children in the psychoeducational group and those in the control condition in the amount of change observed on various symptom scales (Beardslee et al. 1993, 1997). Future studies employing more aggressive treatment strategies of either the affected parent or child may address the relevance of this strategy in reducing the impact of depression in youth.

There are three ongoing studies of the impact of treatment of depressed mothers on their children that may inform future treatment efforts among high-risk youth. Garber and colleagues at Vanderbilt University are conducting a study focusing on the impact of treating parental MDD on children's (age 8 to 16) socioemotional adjustment. Their study includes three groups receiving 16 weekly sessions of cognitive-behavioral therapy (CBT), pharmacotherapy, or placebo, with approximately 60 patients per group, as well as a comparison group of 90 nondepressed mothers. Patients are recruited from psychiatric settings. Riley and colleagues at Johns Hopkins targeted 150 depressed women and their children (75 mothers receiving 16 weekly group CBT sessions and 75 receiving paroxetine) and a comparison group of 50 nondepressed mothers and their children, recruited from a family planning clinic.

A third study by Weissman and Pilowsky, ancillary to the multisite Sequential Treatment Alternatives to Relieve Depression (STAR\*D) study, is

examining the impact of remission of maternal MDD on the psychiatric and social functioning of children ( $N=320$ ). The STAR\*D study will compare the effectiveness of different treatment options for MDD, focusing on the common clinical question of what to do when patients fail to respond to standard treatment with an antidepressant medication. STAR\*D will define which subsequent treatment strategies are acceptable to patients and provide the best clinical results. Children are being followed over the course of the depressed mother's treatment.

## CONCLUSIONS

The major findings are the stability of depression across generations and the role of anxiety disorder as a precursor to the development of depression. These findings are consistent with those of numerous previous studies based on retrospective reports or investigations of only two generations. Our results, although preliminary, suggest the stability of the findings across generations. Whether biological markers can be found that can further strengthen the risk predictions awaits the final results. Regardless of these results, findings thus far suggest several opportunities for early intervention.

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