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Research report

Using multiple methods to characterize the phenotype of individuals with a family history of major depressive disorder

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ABSTRACT

Background: Unaffected relatives (URs) of individuals with major depressive disorder (MDD) are biologically more vulnerable to depression. We compare healthy URs and controls at the level of phenotype (symptoms and functioning) and endophenotype (negative emotion bias), and further investigate the interrelation between these and the contribution of environmental early life stress.
Methods: URs ($n=101$), identified using Family History Screen interview methods and matched controls completed written and interview questions assessing symptoms of depression and anxiety, negative cognitive style, life functioning and early life stress. Biases in emotion processing were measured using a facial expression of emotion identification paradigm.
Results: Compared to controls, URs reported higher levels of depression and anxiety, a stronger negative cognitive bias, and poorer functioning and lower satisfaction with life. URs were slower to correctly identify fear and sad facial expressions. A slower response time to identify sad faces was correlated with lower quality of life in the social domain. Early life stress (ELS) did not contribute significantly to any outcome.
Limitations: The methodology relies on accurate reporting of participants' own psychiatric history and that of their family members. The degree of vulnerability varies among URs.
Conclusions: A family history of depression accounts for subtle differences in symptom levels and functioning without a necessary role of ELS. A negative emotion bias in processing emotion may be one vulnerability marker for MDD. Biological markers may affect functioning measures before symptoms at the level of experience.

1. Introduction

Major Depressive Disorder (MDD) is one of the most prevalent psychiatric disorders and is associated with considerable suffering and impairment (Blazer et al., 1994). Genetic risk for MDD contributes up to 37% of the variance in depressive symptoms (Muglia et al., 2010; Sullivan et al., 2000). Similarly, having a first-degree relative with depression increases the likelihood of MDD onset by an estimated 2.84 times (Sullivan et al., 2000). Identifying biological markers (or endophenotypes—expressions of genes within the body) for depression is critical to understanding vulnerability to this disorder (Hasler et al., 2004). Endophenotypes may be easier to identify as vulnerability factors than are genes themselves, given that they are closer to the observed symptoms in terms of mechanisms (Gottesman and Gould, 2003).

Cognitive neuroscience models of depression and of risk for depression highlight the importance of biases in emotion processing (Beck, 2008; Gotlib and Joormann, 2010; Williams et al., 2009a, 2009b), and of identifying endophenotypic markers of emotional bias and the functional dysregulation they produce (Beck, 2008; Hasler et al., 2004). Using facial identification paradigms, investigators have shown the responses of depressed patients to be consistent with a shift in the perception of faces toward more sadness and less happiness (Gollan et al., 2008; Rubinow and Post, 1992; Venn et al., 2006; Yoon et al., 2009). Reflecting the enduring nature of this bias, remitted depressed patients demonstrate a negative bias in the perception of happy faces (LeMoult et al., 2009) and a heightened perception of fear faces (Merens et al., 2008). Whereas some studies have found that URs more quickly identify fear faces (Le Masurier et al., 2007), others have found no differences in reaction time or accuracy (Mannie et al., 2007). Using a slightly different identification task,

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URs have been found to demonstrate a 'positive emotion bias,' requiring higher intensities of sad facial expressions for correct identification, and a lower accuracy for identification of anger. Other studies have found evidence for a negative emotion bias in URs using different paradigms (Feder et al., 2011). URs have also been found to make negative interpretations of ambiguous words and stories more often than do controls (Dearing and Gotlib, 2009), and young UR daughters have been shown to give more attention to sad faces and less attention to happy faces than to neutral faces (Joormann et al., 2010). Participants at high risk for depression, defined psychometrically (e.g., the presence of sub-clinical symptoms or negative cognitive bias), tend to misperceive emotions less positively and more negatively than do controls (Arce et al., 2009; Chan et al., 2007; Csukly et al., 2008). Complementary findings in functional magnetic resonance imaging of neural circuitry have shown URs to have reduced activity in dorsolateral prefrontal cortex and increased activation of the amygdala and nucleus accumbens for fear (Mannie et al., 2011), and reduced activity in the nucleus accumbens for happy faces (Monk et al., 2008). These studies of URs and other high-risk groups suggest that a negative bias in emotion processing precedes depression and is related to risk for MDD at the genetic and symptom levels.

We conducted a high-risk family study to identify candidate markers for depression that are present before the onset of disorder (Talati et al., in press). The study also tested a first marker: a behavioral measure of negative emotion bias. High-risk family studies are useful for examining vulnerability markers in heritable illnesses. In this design, the presence of markers is assessed in URs of individuals affected by depression (MDDRs) and in healthy non-relative controls to provide evidence for the criterion that a biomarker be more prevalent in relatives of depressed individuals than in non-relative controls due to their genetic association with their depressed relative (Gottesman, et al., 2003). To address this criterion, the first aim of this study was to establish the family history status of URs.

To address the second biomarker criterion of latency—the presence of biomarkers in URs who have no history of MDD—we first established the healthy status of URs and controls through clinical interview. We then investigated group differences in depressive symptoms, anxiety, trait negativity bias, social and occupational functioning, satisfaction and quality of life, as well as the relation between these and our candidate biomarker, emotion bias. Showing that the biomarkers are evident before the onset of depression will clarify whether changes associated with depression are a consequence of the illness or whether they exist as part of a vulnerable predisposition. Previous studies have found that URs have higher levels of baseline depressive symptoms or lower levels of psychosocial functioning compared to controls (Bruder et al., 2007; Joormann et al., 2007; Lauer et al., 1997). Moreover, these symptoms have been related to the presence of biomarkers (e.g., cortical thinning) (Peterson et al., 2009), suggesting that there are differences in symptom and functioning levels associated with genetic vulnerability and the presence of biomarkers even in healthy URs.

In addressing the aims of this study, we considered an additional environmental risk factor that has been shown to compound genetic risk for depression: early life stress (ELS). Studies have demonstrated ELS to be related to increased symptoms and the onset and severity of both depression and anxiety disorders in adulthood (Kendler et al., 1993; Kessler and Magee, 1993). ELS may affect depression through its long-lasting impact on the neurobiological systems that generate emotional biases (Gatt et al., 2010a, 2010b; Heim and Nemeroff, 1999; Heim etal., 2008; Goldman et al., 1992). In the current study, we assessed the presence of ELS in URs and controls, and assessed the contribution of ELS as a moderator of the relation between emotion bias markers and symptoms.

Our hypotheses were: (i) family history of MDD is related to higher levels of symptoms of anxiety and depression, and lower scores on function scales; (ii) URs show a negative bias in processing facial emotion relative to controls, particularly toward sad and fear faces; and (iii) stronger emotion bias will be related to higher levels of depressive and anxiety symptoms and to lower functioning scores.

2. Methods

2.1. Participants

Participant URs were required to have no history of MDD and at least one first-degree relative (i.e., parent, sibling, child) with a history of MDD. UR volunteers were recruited via advertisement and screened in a semi-structured phone interview prior to clinical interviews to assess personal and family history of mental illness. URs were interviewed by trained research assistants using the Mini-International Neuropsychiatric Interview (MINI) (Goldman et al., 1992; Rush et al., 2000) and were excluded from participation if they had current MDD or a history of MDD or Axis I disorders according to DSM-IV criteria, with the exception of a past Alcohol or Substance Use Disorder. Additional exclusion criteria included any impediment (e.g., vision, movement, comprehension in completing study tasks) or any general medical condition or head injury that would interfere with measurement of biological markers.

2.2. Screening for family history

All first-degree relatives of URs were assessed for MDD and other psychopathology, including mania and psychosis, using the Family History Screen (FHS) (Weissman et al., 2000), which uses the UR participant as the informant (Hardt and Franke, 2007; Thompson et al., 1982). MDDRs had MDD as their primary lifetime psychiatric diagnosis with no history of mania or psychosis. MDDRs had experienced at least one episode of depression before age 60 that had no known organic cause (e.g., substance abuse, brain injury or comorbid with a genetic illness). MDDR depression symptoms, episodes, and treatment were assessed using semi-structured questions based on the family history method diagnostic criteria (Andreason et al., 1986). Final diagnoses of first-degree relatives, including MDDRs, were confirmed by two psychiatrists based on all information obtained, and diagnoses of MDDRs were given confidence ratings from one to three. The highest rating of three was given when all FHS symptoms were reported and for a biological treatment and treatment by a psychiatrist, or if direct contact was made with the MDDR relative and their MINI-Plus indicated MDD. A confidence rating of two indicated that the MDDR screened positive for MDD on both screening criteria and a confidence rating of one was given for less complete evidence (e.g., symptoms reported without biological treatment). There were no criteria applied to participants' first-degree relatives who were not classified as MDDR.

2.3. Controls

Data for a matched convenience sample were available through the Brain Resource International Database (overseen by the non-profit BRAINnet Foundation). Controls were screened for personal history of mental illness using the same criteria and methodology as UR participants and differed from URs only in having no first-degree relative with MDD. Family psychiatric history was obtained from controls using items from the Mental Status Examination (Trzepacz and Baker, 1993), administered as part of the self-report Web-based questionnaire ('Web-questionnaire').