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## Journal of Affective Disorders

journal homepage: [www.elsevier.com/locate/jad](http://www.elsevier.com/locate/jad)

## Research report

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



Anna J. Watters<sup>a</sup>, Ian H. Gotlib<sup>b</sup>, Anthony W.F. Harris<sup>a</sup>, Philip M. Boyce<sup>a</sup>,  
Leanne M. Williams<sup>a,b,\*</sup>

<sup>a</sup> Discipline of Psychiatry, University of Sydney Medical School, Australia

<sup>b</sup> Stanford Mood and Anxiety Disorders Laboratory, Stanford University, United States

## ARTICLE INFO

## Article history:

Received 21 February 2013

Accepted 26 April 2013

Available online 10 June 2013

## Keywords:

Biomarkers

Depression

Family study

First-degree relatives

Facial expressions of emotion

Brain research and integrative neuroscience network (BRAINnet) facial

## 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.

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## 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,

\* Correspondence to: University of Sydney Medical School, Westmead Millennium Institute, The Brain Dynamics Centre, Acacia House, Hawkesbury Rd, Westmead Hospital, Westmead, Sydney, NSW 2145, Australia.  
Tel.: +61 2 9845 8195; fax: +61 2 9845 8190.

E-mail address: [leawilliams@stanford.edu](mailto:leawilliams@stanford.edu) (L.M. Williams).

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 et al., 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’).

## 2.4. Procedure

After screening, participants proceeded with testing, which involved the 'Web-questionnaire' battery, cognitive tasks including testing of emotion bias ('WebNeuro battery'), and brain and genetic assessments. Assessment order varied depending on the availability of facilities and was occasionally completed in two separate visits in the same week. The study complied with the Declaration of Helsinki and was approved by the Sydney West Area Health Service, Human Research Ethics Committee. Informed consent was obtained after the nature of the proceedings was explained.

## 2.5. Symptom and functional capacity assessments

Assessments of symptoms and functional capacity included the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960) and the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992), administered during the clinical interview. The 'Web-questionnaire' included the 42-item Depression Anxiety Stress Scale (DASS-42) (Lovibond and Lovibond, 1995a, 1995b), the Brain Resource Inventory of Social Cognitions (BRISC), which is a measure of trait Negativity Bias (Williams et al., 2012), Satisfaction with Life Scale (SWLS) (Diener et al., 1985),

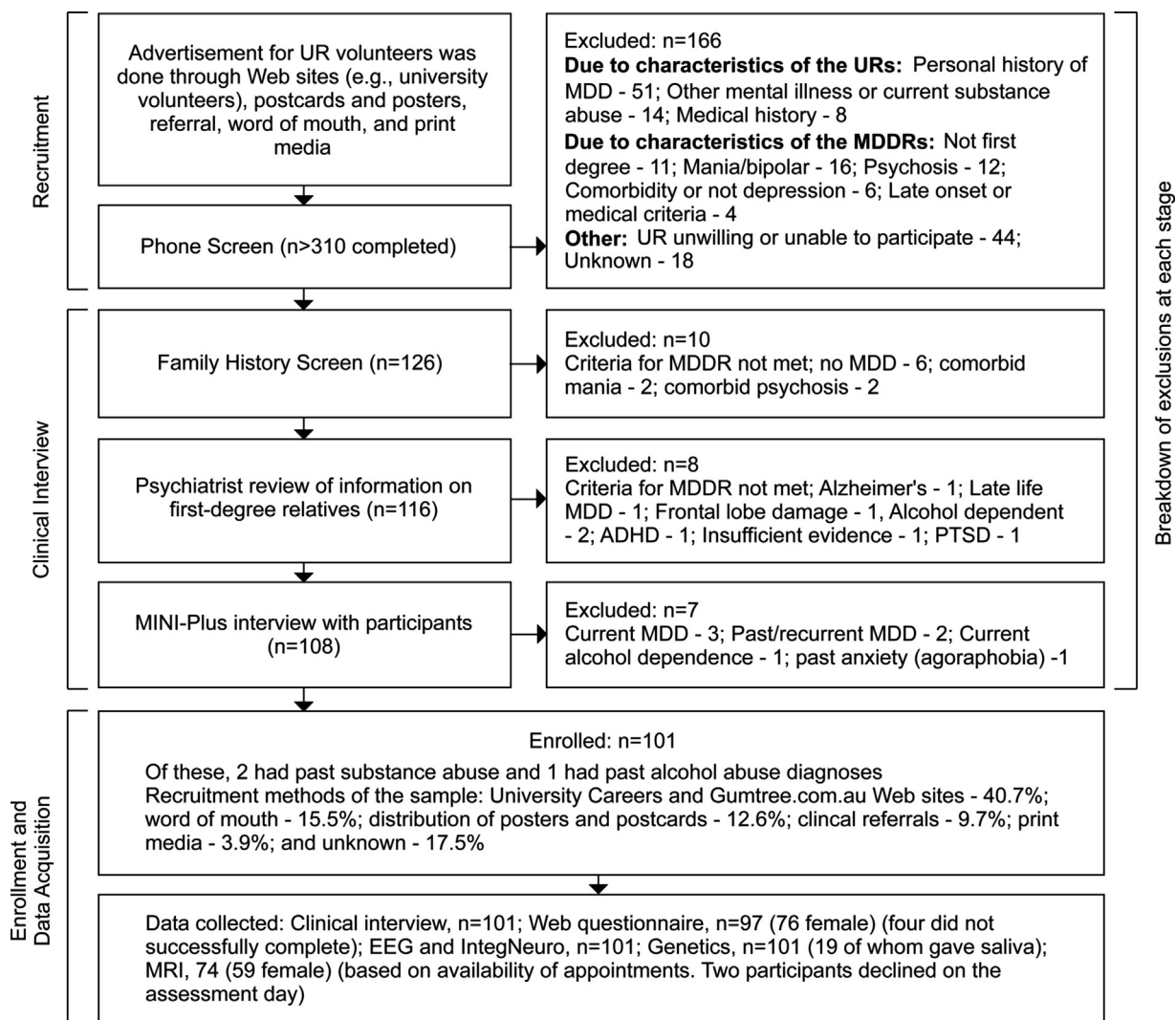
World Health Organization Quality of Life scale (WHOQoL-BREF) (Skevington and McCrate, 2012; The WHOQoL Group, 1998), and the Early Life Stress Questionnaire (McFarlane et al., 2005).

## 2.6. Cognitive tests of emotion biases

Stimuli consisted of 96 photographs of four males and four females showing facial expressions of six kinds of emotions: happy, sad, fear, disgust, anger, and neutral. The photographs were selected from a previously established set (Gur et al., 2002) and were standardized according to size, luminance and central alignment of the eyes; this set is normed for ages 6–92 years (Mathersul et al., 2009; Williams et al., 2009a, 2009b). The photographs were presented on a touch-screen computer monitor in a pseudorandom order for 2 s each. Participants were instructed to identify the emotion depicted on each face by selecting the corresponding emotion label from six options presented in the same order.

## 2.7. Analyses

We began by describing the characteristics of the MDDR sample and psychopathology in all participants as assessed with the FHS. We compared the UR and control groups with respect to



**Fig. 1.** CONSORT Diagram for the enrollment (right side) and exclusion (left side) of  $n = 101$  URs in the study. *Abbreviations:* ADHD: attention deficit hyperactivity disorder, EEG: electroencephalogram, MDD: major depressive disorder; MDDR: UR relatives with MDD, MINI: mini-international neuropsychiatric interview, MRI: magnetic resonance imaging, PTSD: post-traumatic stress disorder and UR: unaffected relative.

symptom levels (DASS-42), Negativity Bias measures, and functioning capacity (SOFAS, SWLS and WHOQoL scales), using *t*-tests with a family-wise error rate (FWER) of 0.01. The contribution of ELS was examined by regressing family history, ELS, and their interaction on each symptom and function measure in turn. We examined bias to each emotion in terms of correct identification and response speed relative to neutral in URs relative to controls, again using *t*-tests with a FWER of 0.01. We then computed the correlations between negative emotion bias markers and each of our symptom and functioning measures.

### 3. Results

Of the 310 URs who volunteered for this study, 101 (77 females; mean age  $30.8 \pm 13.3$  years, range 18–68) met UR criteria and participated (Fig. 1). The matched control sample consisted of 101 individuals (77 females; mean age  $30.7 \pm 13.0$  years, range 18–65). The two groups did not differ with respect to age or years of education (Table 1; see Supplement Section 1. for a summary of group differences with respect to ethnic origin and marital status).

#### 3.1. Defining high-risk status according to the convergence of self-reported history and clinician ratings

UR participants had an average of 4.2 (SD=1.69) first-degree relatives, including two parents, 1.8 siblings (SD=1.28) and 0.4 children (SD=0.88). Psychiatrist review confirmed that all URs had a first-degree relative with a lifetime diagnosis of MDD. UR participants had an average of 1.5 MDDRs (SD=0.6). Sixty-three URs had at least one family member with the highest confidence rating of three; 20 had a rating of two, and 18 had a rating of one. Controls reported no family history of MDD on the Mental Status Examination items (Trzepacz and Baker, 1993).

The mean age of MDDRs (total  $n=154$ ; 87 female) was  $45.5 \pm 17.4$  years (range=17–92), or age at death ( $n=12$ ) was  $74.8 \pm 9.9$  years. The most frequent age of onset for MDDRs was during adolescence (30%), followed by their 20s (27%) and 30s (13%); 22% had their first episode after age 40. Most URs ( $n=80$ ,

79%) had at least one parent with MDD (11 had both parents affected); 46 (46%) had at least one MDDR sibling (eight had more than one), and six (6%) had an MDDR child. See Supplement Section 2 for further MDDR details.

The most frequent diagnosis in MDDRs after MDD was anxiety ( $n=42$  family histories of URs), followed by alcohol abuse/dependence ( $n=24$ ) and substance abuse/dependence ( $n=9$ ). Controls reported no MDD and little other psychopathology in their families, less than that in UR families (Supplement Section 2; Supplemental Table 2d).

#### 3.2. Defining high-risk status by the profile of current depressive and anxiety symptoms, functional status, and other contributing risk factors

For the UR and control groups, average scores on self-report symptom and functioning scales were well within the normal ranges (Table 1) (norms for the scales are presented in Supplement Section 3) (Diener et al., 1985; Lovibond and Lovibond, 1995a, 1995b; Skevington and McCrate, 2012; The WHOQoL Group, 1998; Williams et al., 2012). Despite these low levels of symptoms, URs reported significantly higher levels of depression, anxiety, and stress on the DASS-42 than did controls. URs also had a greater trait Negativity Bias than did controls, representing a greater sensitivity to stress and expectation of negative outcomes. Most participants fell in the range of 80–89 on the SOFAS, indicating good functioning in all areas and being occupationally and socially effective. On the SOFAS, URs had significantly lower functioning than did controls, who bordered on the superior functioning range. URs had significantly lower satisfaction with life than did controls. The lower functioning of URs relative to controls was also evident on the overall WHOQoL, and specifically on the Physical, Psychological, and Social subscales.

#### 3.3. The relation between high-risk status and early life stress

URs reported a higher occurrence of ELS than did controls (Table 1). To reduce covariance between ELS and family history status, participants with three or more ELS events were grouped as “high ELS” and those with two or fewer were categorized as “low

**Table 1**

Differences between the UR and control groups on demographic, symptom, functioning, and early life stress measures (M  $\pm$  SD).

Categories	Measures	Characteristic	Group		Significance			Effect Size
			UR	Control	<i>t</i>	<i>df</i>	<i>p</i>	<i>r</i>
Demographics		Age	30.8 $\pm$ 13.3	30.7 $\pm$ 13.0	-0.038	200	0.970	0.004
		Education (yrs)	15.2 $\pm$ 2.1	15.2 $\pm$ 2.0	-134	200	0.894	0.000
Symptoms	DASS-42:	Depression	1.5 $\pm$ 1.8	0.5 $\pm$ 1.0	-4.50	144.7	0.000 <sup>a</sup> ***	0.325
		Anxiety	1.1 $\pm$ 1.6	0.4 $\pm$ 0.8	-3.78	135.0	0.000 <sup>a</sup> ***	0.267
		Stress	3.3 $\pm$ 3.0	1.8 $\pm$ 1.7	-4.56	152.7	0.000 <sup>a</sup> ***	0.294
		Total score	5.9 $\pm$ 5.2	2.7 $\pm$ 2.5	-5.46	136.2	0.000 <sup>a</sup> ***	0.365
	Negativity bias		-0.8 $\pm$ 0.7	-1.2 $\pm$ 0.4	-5.07	151.5	0.000 <sup>a</sup> ***	0.869
Functioning	SOFAS		85.4 $\pm$ 7.7	90.9 $\pm$ 7.0	5.25	199	0.000 <sup>a</sup> ***	0.350
			24.6 $\pm$ 5.9	26.8 $\pm$ 5.3	2.78	194	0.006 <sup>a</sup> **	0.192
	WHOQoL:	Total score	300.0 $\pm$ 42.5	318.7 $\pm$ 31.1	3.47	174.2	0.001 <sup>a</sup> ***	0.244
		Physical	82.5 $\pm$ 11.4	86.4 $\pm$ 7.7	2.81	166.0	0.006 <sup>a</sup> **	0.197
		Psychological	71.5 $\pm$ 11.9	77.6 $\pm$ 9.3	3.91	189	0.000 <sup>a</sup> ***	0.275
		Social	69.0 $\pm$ 19.2	75.9 $\pm$ 15.0	2.75	179.2	0.007 <sup>a</sup> **	0.196
Environmental	77.0 $\pm$ 12.8	78.8 $\pm$ 9.1	1.13	171.5	0.262	0.081		
Early life stress		ELS total	2.2 $\pm$ 2.4	1.3 $\pm$ 1.7	-2.81	171.0	0.006 <sup>a</sup> ***	0.211

Abbreviations: DASS-42: 42-item depression anxiety stress scale, ELS: early life stress, SOFAS: social and occupational functioning assessment scale, SWLS: satisfaction with life scale, UR: unaffected relative, WHOQoL: World Health Organization quality of life scale.

<sup>a</sup> Unequal variances according to Levene's test and conservative statistics reported.

\*\* Alpha < 0.01.

\*\*\* Alpha < 0.001.



ELS.” The URs (22%) and control (34%) groups did not differ with respect to the percentage of high ELS participants ( $X^2 [1, n=191]=3.212, p=0.073$ ). Regression analyses confirmed the contribution of family history to variance in symptom scales; however, ELS and ELS by family history did not significantly contribute to any outcome (Supplement Section 4).

### 3.4. Comparing URs to controls on the candidate marker of emotion bias

Compared with controls, URs were significantly slower to respond to correctly identified facial expressions of fear and sadness than to a correctly identified neutral face (Table 2). The two groups did not differ with respect to the correct identification of any facial expression (Table 2). Group biases in terms of misidentification errors were therefore not explored.

### 3.5. Associating candidate behavioral emotion bias markers to current symptoms and functional status

Response times to sad facial expressions were negatively correlated with the WHOQoL social scale ( $r[n=191]=-0.16, p=0.027$ ; this approached significance at a FWER of 0.01), indicating that increased response time to identify sad faces was related to decreased quality of life in the social domain. No other correlations of RT to sad and fear with symptom or functioning scales reached significance (Supplement Section 5).

## 4. Discussion

Our results indicate that biological vulnerability to depression is accompanied by overt symptoms and affects functioning and quality of life. ELS had no effect on symptoms or functioning. URs had a slower response time to sad and fear facial expressions than did controls. There may be negative emotion biases associated with familial risk for depression. Emotion bias did not relate to overt symptoms.

To test our first hypothesis, we examined the effects of family history on our measures at the phenotype level. URs had higher symptom levels of depression, anxiety and stress, and higher Negativity Bias self-report measures. Negativity Bias is a measure of cognitive bias toward negative appraisal of oneself and situations. It is a stable measure of risk for depression, relating to genetic and brain markers (Williams et al., 2012; Watters and Williams, 2011). This group difference in Negativity Bias confirms that URs are at greater

risk for depression than are controls. Family history vulnerability was related to level of functioning, satisfaction with life, quality of life including physical, psychological and social, and observer-rated social and occupational functioning (SOFAS). These findings support a model of depression in which biological vulnerability is not completely latent but is accompanied by overt symptoms and affects functioning and quality of life. We may, however, expect URs to score more closely to MDD patients on these scales to support a continuum between risk and depression. Contrary to our expectations, there was no effect of ELS on symptoms or functioning for either group. It is proposed that ELS impacts vulnerability through the emotion processing pathways; therefore, the effect on symptoms may be subtle and more measurable on latent biomarkers.

Regarding our second hypothesis, our findings indicate that compared to controls, URs had a slower response time to correctly identify sad and fearful facial expressions. As previously reported in depression, slowed response time for identification of facial expressions, in addition to accuracy and bias behavioral performance measures, is mostly found for sad (Gollan et al., 2008; Watters and Williams, 2011) and less commonly for fear (Pine et al., 2004). Brain measures confirm unique patterns of activation for both fearful (Sheline et al., 2001) and sad facial expressions in depression (Surguladze et al., 2005). Few studies conducted with URs have shown increased response time for fear (Le Masurier et al., 2007) and increased activation of limbic regions for fear (Mannie et al., 2011; Monk et al., 2008). While response time is implicated in performance outcomes of emotion bias tasks, it has not been specified exactly what the slower response time signifies. It is generally taken as an indicator of poorer performance, and may indicate greater engagement of the participant with the facial expression, as demonstrated in attention tasks (Joormann et al., 2007), or decreased information processing ability (Cooley and Nowicki, 1989). Our results are consistent with these findings for sad and fear as stimuli relevant to emotion processing, and with the possibility that negative emotion biases are associated with familial risk for depression.

With respect to our third hypothesis, our findings did not provide evidence in support of emotion bias relating to overt symptoms. Symptom indicators of risk have previously been found to predict outcomes in emotion identification (Chan et al., 2007; Csukly et al., 2008; Watters and Williams, 2011). However, in the current study, participants were not selected as being at risk according to symptom scales and were mostly clustered in the ultra-healthy range. We found a tendency only for slow response time to sad faces to be related to lower quality of life in the social domain. This finding fits well with the social cognitive theories of depression that posit that depression is associated with lower social functioning due to negative biases in

**Table 2**  
Family history and emotion identification; reaction time (ms±SD) and accuracy (%±SD).

Test	Expression	Group		Significance			Effect Size
		UR	Control	T	df	p	r
Reaction time (emotion—neutral)	Sad	992.4±760.9	790.1±569.7	-2.14	200	0.034*	0.149
	Anger	796.9±702.4	720.5±565.5	-0.85	199	0.397	0.060
	Disgust	898.4±805.7	821.1±873.0	-0.65	196	0.518	0.046
	Fear	1336.4±799.9	1005.9±602.8	-3.32	200	0.001**	0.227
	Happy	-198.1±385.0	-159.1±401.4	0.70	200	0.482	0.032
Reaction time to neutral		1569.2±451.4	1512.5±437.7	-0.91	200	0.366	0.064
Accuracy	Sad	72.9±23.1	71.7±21.8	-0.39	200	0.696	0.027
	Anger	61.4±15.5	64.7±15.3	1.54	200	0.126	0.107
	Disgust	51.1±16.9	50.6±17.5	-0.20	200	0.839	0.015
	Fear	82.6±15.6	78.8±16.6	-1.68	200	0.095	0.117
	Happy	98.8±4.5	98.6±3.9	-0.21	200	0.835	0.024
	Neutral	91.7±10.8	92.5±10.5	0.44	200	0.659	0.038

\* Alpha < 0.05.

\*\* Alpha < 0.01.

interpretations of situations. In the absence of overt symptoms, one's functioning may still be less than optimal. In healthy populations, the presence of biological markers for MDD may have an effect on functioning before giving rise to symptoms.

The current study contributes to our understanding of familial risk for MDD (Gotlib and Goodman, 1999; Mannie et al., 2011; Talati et al., *in press*) by using multiple methods to establish family history status. Error in the reporting of MDDRs was minimized by first using the FHS—which has good sensitivity with most errors made in underreporting (Milne et al., 2009)—and a final review by psychiatrists of all information collected. In this process, we gained further details regarding MDDRs which can be used to increase confidence in the familiarity of the MDD for the UR (Kendler et al., 1999). The FHS has also shown that MDD is the most prevalent mental illness among MDDRs, with little occurrence of mania or psychosis, and that mental illness overall is greater in the relatives of URs than in relatives of controls. The current study has built up a multifaceted profile of participants that includes symptoms, functioning scales and ELS history, and a broadly-defined study population in terms of age, gender and kind of first-degree relationship. This will enable the further stratification of participants according to multiple risk markers (e.g., age (Hankin et al., 1998), gender (Gater et al., 1998), type of ELS (Kessler et al., 2010)) to learn more about the mechanisms that underlie these risk factors and further integrate them with a biological model.

#### 4.1. Limitations

High-risk family studies are limited by the accurate self-reporting of participants regarding their mental health history and that of their first-degree relatives. We used a more complex family history screen for URs that was not available to controls, which left greater room for misreporting in controls. Inherently, degree of vulnerability will differ between URs based on the individual heritability of the MDD; however, we are able to say that risk for depression is higher across the UR group (Talati et al., *in press*).

#### 4.2. Future research

A next step is to consolidate candidate markers and integrate multiple measures to gain a more comprehensive understanding of how they work together (e.g., the INTEGRATE framework (Williams et al., 2008) and Research Domain Criteria (Morris and Cuthbert, 2012)). Examining multiple measures across several domains of functioning in the same group of family participants will increase the depth of our understanding of the mechanisms through observing different aspects of cognition and emotion with outcomes at different levels of measurement. In the UR cohort described in this study, we aim to integrate genetic, brain and behavioral measures in the domains of emotional, cognitive and self-regulatory functioning.

Identification of biomarkers will enable the early identification and screening of those at highest risk in order to target interventions, making interventions more successful and cost-effective. For example, a study targeting young people at risk due to family history demonstrated a 20% increased efficiency in reducing depression compared to a general population (Stice et al., 2008). Screening tools based on biological markers could be developed to complement established methods. Further, a brain-based understanding of vulnerability for depression could inform the development of new approaches to therapy such as those used in neurotherapy, the development of brain training games, and objective measurements of therapy outcome.

## 5. Conclusion

The family study design has great potential for identifying biomarkers of vulnerability for depression. Our first analyses confirm that family history of depression accounts for clinically subtle differences between those with and without a family history of depression regarding overt symptom levels and more evident differences in functioning, with little direct role for ELS. Negative emotion bias in the processing of fear and sadness may be a marker of vulnerability for depression.

#### Role of funding source

This study was funded by an Australian Research Council; Discovery Project Grant #DP0773994.

#### Conflict of interest

LMW has received consulting fees (Brain Resource Ltd.). LMW is a stockholder and has stock options in Brain Resource Ltd. She has received Advisory Board fees from Pfizer. IHG has received Advisory Board fees from Bristol-Meyers Squibb.

#### Acknowledgments

We would like to acknowledge the editorial support of Jon Kilner, MS, MA.

## Appendix A. Supporting information

Supplementary information associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2013.04.042>.

## References

- Andreason, N.C., Scheftner, W., Reich, T., Hirschfeld, R.M., Endicott, J., Keller, M.B., 1986. The validation of the concept of endogenous depression. A family study approach. *Archives of General Psychiatry* 43, 246–251.
- Arce, E., Simmons, A.N., Stein, M.B., Winkelman, P., Hitchcock, C., Paulus, M.P., 2009. Association between individual differences in self-reported emotional resilience and the affective perception of neutral faces. *Journal of Affective Disorders* 114, 286–293.
- Beck, A.T., 2008. The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry* 165, 969–977.
- Blazer, D.G., Kessler, R.C., McGonagle, K.A., Swartz, M.S., 1994. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *American Journal of Psychiatry* 151, 979–986.
- Bruder, G.E., Tenke, C.E., Warner, V., Weissman, M.M., 2007. Grandchildren at high and low risk for depression differ in EEG measures of regional brain asymmetry. *Biological Psychiatry* 62, 1317–1323.
- Chan, S.W., Goodwin, G.M., Harmer, C.J., 2007. Highly neurotic never-depressed students have negative biases in information processing. *Psychological Medicine* 37, 1281–1291.
- Cooley, E.L., Nowicki Jr., S., 1989. Discrimination of facial expressions of emotion by depressed subjects. *Genetic Social and General Psychology Monographs* 115, 449–465.
- Csukly, G., Czobor, P., Simon, L., Takács, B., 2008. Basic emotions and psychological distress: association between recognition of facial expressions and symptom checklist-90 subscales. *Comprehensive Psychiatry* 49, 177–183.
- Dearing, K.F., Gotlib, I.H., 2009. Interpretation of ambiguous information in girls at risk for depression. *Journal of Abnormal Child Psychology* 37, 79–91.
- Diener, E., Emmons, R.A., Larsen, R.J., Griffin, S., 1985. The satisfaction with life scale. *Journal of Personality Assessment* 49, 71–75.
- Feder, A., Skipper, J., Blair, J.R., Buchholz, K., Mathew, S.J., Schwarz, M., Doucette, J.T., Alonso, A., Collins, K.A., Neumeister, A., Charney, D.S., 2011. Tryptophan depletion and emotional processing in healthy volunteers at high risk for depression. *Biological Psychiatry* 69, 804–807.
- Gater, R., Tansella, M., Korten, A., Tiemens, B.G., Mavreas, V.G., Olatuwura, M.O., 1998. Sex differences in the prevalence and detection of depressive and anxiety disorders in general health care settings: report from the World Health Organization collaborative study on psychological problems in general health care. *Archives of General Psychiatry* 55, 405–413.
- Gatt, J.M., Nemeroff, C.B., Schofield, P.R., Paul, R.H., Clark, C.R., Gordon, E., Williams, L.M., 2010a. Early life stress combined with serotonin 3A receptor and brain-derived neurotrophic factor valine 66 to methionine genotypes impacts emotional brain and arousal correlates of risk for depression. *Biological Psychiatry* 68, 818–824.
- Gatt, J.M., Williams, L.M., Schofield, P.R., Dobson-Stone, C., Paul, R.H., Grieve, S.M., Clark, C.R., Gordon, E., Nemeroff, C.B., 2010b. Impact of the HTR3A gene with

- early life trauma on emotional brain networks and depressed mood. *Depression and Anxiety* 27, 752–759.
- Goldman, H.H., Skodol, A.E., Lave, T.R., 1992. Revising axis V for DSM-IV: a review of measures of social functioning. *American Journal of Psychiatry* 149, 1148–1156.
- Gollan, J.K., Pane, H.T., McCloskey, M.S., Coccaro, E.F., 2008. Identifying differences in biased affective information processing in major depression. *Psychiatry Research* 159, 18–24.
- Gotlib, I.H., Goodman, S.H., 1999. Children of parents with depression. In: Silverman, W.K., Ollendick, T.H. (Eds.), *Developmental Issues in the Clinical Treatment of Children*. Allyn & Bacon, Massachusetts, pp. 415–432.
- Gotlib, I.H., Joormann, J., 2010. Cognition and depression: current status and future directions. *Annual Review of Clinical Psychology* 6, 285–312.
- Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry* 160, 636–645.
- Gur, R.C., Sara, R., Hagendoorn, M., Marom, O., Hughett, P., Macy, L., Turner, T., Bajcsy, R., Posner, A., Gur, R.E., 2002. A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *Journal of Neuroscience Methods* 115, 137–143.
- Hamilton, M., 1960. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 23, 56–62.
- Hankin, B.L., Abramson, L.Y., Moffitt, T.E., Silva, P.A., McGee, R., Angell, K.E., 1998. Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology* 107, 128–140.
- Hardt, J., Franke, P., 2007. Validity, reliability and objectivity of the family history method in psychiatry: a meta analysis. *European Psychiatry* 22, 49–58.
- Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. *Neuropsychopharmacology* 29, 1765–1781.
- Heim, C., Nemeroff, C.B., 1999. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry* 46, 1509–1522.
- Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* 33, 693–710.
- Joormann, J., Gilbert, K., Gotlib, I.H., 2010. Emotion identification in girls at high risk for depression. *Journal of Child Psychology and Psychiatry* 51, 575–582.
- Joormann, J., Talbot, L., Gotlib, I.H., 2007. Biased processing of emotional information in girls at risk for depression. *Journal of Abnormal Psychology* 116, 135–143.
- Kendler, K.S., Gardner, C.O., Prescott, C.A., 1999. Clinical characteristics of major depression that predict risk of depression in relatives. *Archives of General Psychiatry* 56, 322–327.
- Kendler, K.S., Kessler, R.C., Neale, M.C., Heath, A.C., Eaves, L.J., 1993. The prediction of major depression in women: toward an integrated etiologic model. *American Journal of Psychiatry* 150, 1139–1148.
- Kessler, R.C., Magee, W.J., 1993. Childhood adversities and adult depression: basic patterns of association in a US national survey. *Psychological Medicine* 23, 679–690.
- Kessler, R.C., McLaughlin, K.A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Aguilar-Gaxiola, S., Alhamzawi, A.O., Alonso, J., Angermeyer, M., Benjet, C., Bromet, E., Chatterji, S., de Girolamo, G., Demyttenaere, K., Fayyad, J., Florescu, S., Gal, G., Gureje, O., Haro, J.M., Hu, C.Y., Karam, E.G., Kawakami, N., Lee, S., Lepine, J.P., Ormel, J., Posada-Villa, J., Sagar, R., Tsang, A., Ustun, T.B., Vassilev, S., Viana, M.C., Williams, D.R., 2010. Childhood adversities and adult psychopathology in the WHO world mental health surveys. *British Journal of Psychiatry* 197, 378–385.
- Lauer, C.J., Bronisch, T., Kainz, M., Schreiber, W., Holsboer, F., Krieg, J.C., 1997. Pre-morbid psychometric profile of subjects at high familial risk for affective disorder. *Psychological Medicine* 27, 355–362.
- Le Masurier, M., Cowen, P.J., Harmer, C.J., 2007. Emotional bias and waking salivary cortisol in relatives of patients with major depression. *Psychological Medicine* 37, 403–410.
- LeMoult, J., Joorman, J., Sherdell, L., Wright, Y., Gotlib, I.H., 2009. Identification of emotional facial expressions following recovery from depression. *Journal of Abnormal Psychology* 118, 828–833.
- Lovibond, P.F., Lovibond, S.H., 1995a. *Manual for the Depression Anxiety Stress Scale*. Psychological Foundation, Sydney.
- Lovibond, P.F., Lovibond, S.H., 1995b. The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the beck depression and anxiety inventories. *Behaviour Research and Therapy* 33, 335–343.
- Mannie, Z.N., Bristow, G.C., Harmer, C.J., Cowen, P.J., 2007. Impaired emotional categorisation in young people at increased familial risk of depression. *Neuropsychologia* 45, 2975–2980.
- Mannie, Z.N., Taylor, M.J., Harmer, C.J., Cowen, P.J., Norbury, R., 2011. Frontolimbic responses to emotional faces in young people at familial risk of depression. *Journal of Affective Disorders* 130, 127–132.
- Mathersul, D., Palmer, D.M., Gur, R.C., Gur, R.E., Cooper, N., Gordon, E., Williams, L.M., 2009. Explicit identification and implicit recognition of facial emotions: II. Core domains and relationships with general cognition. *Journal of Clinical and Experimental Neuropsychology* 31, 278–291.
- McFarlane, A., Clark, C.R., Bryant, R.A., Williams, L.M., Niaura, R., Paul, R.H., Hitsman, B.L., Stroud, L., Alexander, D.M., Gordon, E., 2005. The impact of early life stress on psychophysiological, personality and behavioral measures in 740 non-clinical subjects. *Journal of Integrative Neuroscience* 4, 27–40.
- Merens, W., Booij, L., Van Der Does, A.J., 2008. Residual cognitive impairments in remitted depressed patients. *Depression and Anxiety* 25, E27–E36.
- Milne, B.J., Caspi, A., Crump, R., Poulton, R., Rutter, M., Sears, M.R., Moffitt, T.E., 2009. The validity of the family history screen for assessing family history of mental disorders. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 150B, 41–49.
- Monk, C.S., Klein, R.G., Telzer, E.H., Schroth, E.A., Mannuzza, S., Moulton 3rd, J.L., Guardino, M., Masten, C.L., McClure-Tone, E.B., Fromm, S., Blair, R.J., Pine, D.S., Ernst, M., 2008. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *American Journal of Psychiatry* 165, 90–98.
- Morris, S.E., Cuthbert, B.N., 2012. Research domain criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues in Clinical Neuroscience* 14, 29–37.
- Muglia, P., Tozzi, F., Galwey, N.W., Francks, C., Upmanyu, R., Kong, X.Q., Antoniadis, A., Domenici, E., Perry, J., Rothen, S., Vandeleur, C.L., Mooser, V., Waeber, G., Vollenweider, P., Preisig, M., Lucae, S., Muller-Myhsok, B., Holsboer, F., Middleton, L.T., Roses, A. D., 2010. Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. *Molecular Psychiatry* 15, 589–601.
- Peterson, B.S., Warner, V., Bansal, R., Zhu, H., Hao, X., Liu, J., Durkin, K., Adams, P.B., Wickramaratne, P., Weissman, M.M., 2009. Cortical thinning in persons at increased familial risk for major depression. *Proceedings of the National Academy of Sciences of the United States of America* 106, 6273–6278.
- Pine, D.S., Lissek, S., Klein, R.G., Mannuzza, S., Moulton 3rd, J.L., Guardino, M., Woldehawariat, G., 2004. Face-memory and emotion: associations with major depression in children and adolescents. *Journal of Child Psychology and Psychiatry* 45, 1199–1208.
- Rubinow, D.R., Post, R.M., 1992. Impaired recognition of affect in facial expression in depressed patients. *Biological Psychiatry* 31, 947–953.
- Rush, A.J., Carmody, T., Reimnitz, P.E., 2009. The inventory of depressive symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. *International Journal of Methods in Psychiatric Research* 9, 45–59.
- Sheline, Y.I., Barch, D.M., Donnelly, J.M., Ollinger, J.M., Snyder, A.Z., Mintun, M.A., 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological Psychiatry* 50, 651–658.
- Skevington, S.M., McCrate, F.M., 2012. Expecting a good quality of life in health: assessing people with diverse diseases and conditions using the WHOQOL-BREF. *Health Expectations* 15, 49–62.
- Stice, E., Rohde, P., Seeley, J.R., Gau, J.M., 2008. Brief cognitive-behavioral depression prevention program for high-risk adolescents outperforms two alternative interventions: a randomized efficacy trial. *Journal of Consulting and Clinical Psychology* 76, 595–606.
- Sullivan, P.F., Neale, M.C., Kendler, K.S., 2000. Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry* 157, 1552–1562.
- Surguladze, S., Brammer, M.J., Keedwell, P., Giampietro, V., Young, A.W., Travis, M.J., Williams, S.C., Phillips, M.L., 2005. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological Psychiatry* 57, 201–209.
- Talati, A., Weissman, M.M., Hamilton, S.P., 2013. Using the high-risk family design to identify biomarkers for major depression. *PLoS Trans R Soc Lond B Biol Sci* 368 (1615):20120129. <http://dx.doi.org/10.1098>
- The WHOQoL Group, 1998. Development of the World Health Organization WHOQoL-BREF quality of life assessment. *Psychological Medicine* 28, 551–558.
- Thompson, W.D., Orvaschel, H., Prusoff, B.A., Kidd, K.K., 1982. An evaluation of the family history method for ascertaining psychiatric disorders. *Archives of General Psychiatry* 39, 53–58.
- Trzepacz, P.T., Baker, R.W., 1993. *The Psychiatric Mental Status Examination*. Oxford University Press, NY, USA.
- Venn, H.R., Watson, S., Gallagher, P., Young, A.H., 2006. Facial expression perception: an objective outcome measure for treatment studies in mood disorders? *Int. Journal of Neuropsychopharmacology* 9, 229–245.
- Watters, A.J., Williams, L.M., 2011. Negative biases and risk for depression; integrating self-report and emotion task markers. *Depression and Anxiety* 28, 703–718.
- Weissman, M.M., Wickramaratne, P., Adams, P., Wolk, S., Verdelli, H., Olfson, M., 2000. Brief screening for family psychiatric history: the family history screen. *Archives of General Psychiatry* 57, 675–682.
- Williams, L.M., Cooper, N.J., Wisniewski, S.R., Gatt, J.M., Koslow, S.H., Kulkarni, J., DeVarney, S., Gordon, E., Rush, A.J., 2012. Sensitivity, specificity, and predictive power of the “Brief Risk-resilience Index for Screening,” a brief pan-diagnostic web screen for emotional health. *Brain and Behaviour* 2, 576–589.
- Williams, L.M., Gatt, J.M., Hatch, A., Palmer, D.M., Nagy, M., Rennie, C., Cooper, N.J., Morris, C., Grieve, S., Dobson-Stone, C., Schofield, P., Clark, C.R., Gordon, E., Arns, M., Paul, R.H., 2008. The integrate model of emotion, thinking and self regulation: an application to the “paradox of aging”. *Journal of Integrative Neuroscience* 7, 367–404.
- Williams, L.M., Gatt, J.M., Schofield, P.R., Olivieri, G., Peduto, A., Gordon, E., 2009a. ‘Negativity bias’ in risk for depression and anxiety: brain-body fear circuitry correlates, 5-HTT-LPR and early life stress. *Neuroimage* 47, 804–814.
- Williams, L.M., Mathersul, D., Palmer, D.M., Gur, R.C., Gur, R.E., Gordon, E., 2009b. Explicit identification and implicit recognition of facial emotions: I. Age effects in males and females across 10 decades. *Journal of Clinical and Experimental Neuropsychology* 31, 257–277.
- Yoon, K.L., Joormann, J., Gotlib, I.H., 2009. Judging the intensity of facial expressions of emotion: depression-related biases in the processing of positive affect. *Journal of Abnormal Psychology* 118, 223–228.