Psychiatry Research 205 (2013) 54–58

Contents lists available at SciVerse ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Never-depressed females with a family history of depression demonstrate affective bias

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ARTICLE INFO

Article history:
Received 23 February 2012
Received in revised form
9 July 2012
Accepted 5 August 2012

Keywords:
Emotional Stroop
Endophenotype
Affective processing bias
Major depressive disorder
Family history
Neuropsychology

ABSTRACT

According to cognitive theories of depression, individuals susceptible to depression attend selectively to negative information. The purpose of the study was to examine if such an affective processing bias is present in never-depressed individuals with a family history of major depressive disorder (MDD). Formerly depressed female patients having at least one first-degree relative with a history of MDD ($n=23$), their never-depressed female siblings ($n=21$) and never-depressed female controls ($n=21$) performed a conventional and an emotional Stroop task using negative, positive and neutral words. A significant effect was found of group on negative processing bias; post hoc comparisons indicated that never-depressed siblings showed a larger negative processing bias than never-depressed controls. No significant differences were observed in positive bias or conventional interference between the three groups. Our findings suggest that never-depressed females with a family history of depression, like depressed patients, have more difficulties to inhibit negative material and to direct their attention towards task-specific material. This adds to the existing evidence that affective processing bias is a trait characteristic that contributes to the onset of depression and that could be a useful endophenotype for MDD.

1. Introduction

Major depressive disorder (MDD) causes significant impairment and results in a high disease burden and increased mortality risk. The genetic contribution to MDD is estimated to be in range of 31–42 % (Sullivan et al., 2000). Family members of depressed patients have a two-fold increased risk to develop MDD (Levinson, 2005). The search for specific genes for depression has, however, remained largely unsuccessful, potentially due to the high heterogeneity of MDD and to complex gene–environment interactions in the etiology (Cannon and Keller, 2006). The intermediate phenotype approach (Gottesman and Gould, 2003) promises more successful genetic analyses by studying apparently simpler and less heterogeneous constructs that are linked to clinically observable mental disorders. Besides facilitating genetic analysis, endophenotypes can improve our understanding of the etiology of psychiatric disorders. Gottesman and Gould (2003) stated that endophenotypes for psychiatric disorders must fulfill several criteria in order to be useful. Endophenotypes should be heritable traits that are associated with the disorder, should co-segregate with the disorder within families and should be found in non-affected family members at a higher rate than in the general population.

Biased information processing in attention, memory and interpretation is proposed to be one of the central cognitive dysfunctions found in MDD (Gotlib and Joormann, 2010) and fulfills several of the endophenotype criteria formulated by Gottesman and Gould (2003). Recent cognitive theories of depression posit that depression is caused and maintained by affective processing bias and by deficits in cognitive control when processing negative information (Gotlib and Joormann, 2010). Reduced cognitive control and depressogenic schemas are assumed to engender impaired attentional inhibitory control over negative elaborative processes, such as rumination

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0165-1781/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psychres.2012.08.004

(De Raedt and Koster, 2010). Due to this impaired inhibitory control, depressed patients attend selectively to negative information and also store and retrieve more negative information in memory, resulting in negative thinking, rumination and low mood. Affective processing bias has indeed been frequently demonstrated in depressed patients (Beck, 2008) and in remitted patients (Teasdale and Dent, 1987). Evidence is now emerging that affective processing bias may be heritable, since it has been associated with several variants in candidate genes for depression, like the 5-HTTLPR, *COMT* Val108/158Met (Hayden et al., 2008; Williams et al., 2010; Thomason et al., 2010; Perez-Edgar et al., 2010) and *BDNF* Val66Met (Van Oostrom et al., 2012). Affective processing bias is probably a trait characteristic; it has been observed in patients in remission (Bhagwagar et al.,2004; Joormann and Gotlib, 2007; Ramel et al., 2007) as well as in highly neurotic, never-depressed individuals (Chan et al., 2007), who are at increased risk of depression. There is however also evidence that affective processing bias is activated by mood state and stress and is also state-dependent (Bower, 1981).

To date, knowledge about the presence of affective processing bias in never-depressed family members of MDD patients is limited. Affective processing bias has been studied in never-depressed children of depressed parents (Jaenicke et al., 1987; Joormann et al., 2007; Taylor and Ingram, 1999). These studies have generally reported biased information processing in high risk children, but not always (Mannie et al., 2007). Children of depressed parents also demonstrate increased amygdala and nucleus accumbens activation to fearful faces during unconstrained viewing of emotional expressions on faces (Monk et al., 2008). Children have however not yet reached the peak age of onset in MDD, that is between 20 and 50 years of age (Sadock and Sadock, 2007). Although studying affective processing bias in adult first degree relatives of MDD patients is relevant to determine whether affective bias can be considered a valid endophenotype for depression, it has only been studied in adult first degree relatives of depressed patients in two fMRI studies only (Amico et al., 2012; Lisiecka et al., 2012). First degree relatives demonstrated activation of the right Heschl's gyrus during performance in an emotional dot probe task as well as increased activation of the right middle cingulated cortex and left caudate nucleus during inhibition of negative pictures. To the best of our knowledge, no behavioral studies have been conducted to date.

This study aimed at examining affective processing bias in remitted depressed patients with a family history of depression, in their non-affected female siblings and in never-depressed controls selected from the general population. Only female participants were included in view of the female preponderance in depression that may suggest sex-specific etiologic pathways (Kendler et al., 2002). We hypothesized affective processing bias to be present in remitted depressed patients and never-depressed female siblings at a higher rate than in a matched control group. Adopting the emotional Stroop paradigm to assess affective processing bias, we expected remitted depressed patients and non-affected female siblings to show longer color naming latencies when naming the color of negative words than neutral or positive words (Williams et al., 1996). Furthermore, we expected affective processing bias and depression to co-segregate within families and hypothesized that remitted depressed patients would demonstrate stronger affective processing bias, and thus longer color naming latencies when naming the color of negative words, as compared to their non-affected female siblings. Finally, we expected no interference effects in general selective attention in remitted depressed patients or their female siblings using the traditional Stroop paradigm, since studies using neuropsychological tasks have found little empirical support for cognitive deficits in remitted depressed patients (Gotlib and Joormann, 2010).

2. Methods

2.1. Participants

Women aged 18–65 years from European Caucasian origin were invited to participate in a clinical study of the genetics of MDD, GenMood (Verhagen et al., 2008), through psychiatric treatment settings and advertisements. All participants were screened before inclusion for current and lifetime diagnosis of MDD and other psychiatric diagnoses and for family history of depression.

Formerly depressed female patients ($n=23$) had a history of MDD, at least one first-degree relative with a history of formerly diagnosed and treated MDD, MDD in remission at enrollment and no history of alcohol abuse, manic or psychotic episodes. Never-depressed female siblings ($n=21$) were sisters of the participants in the patient group, without either a current or lifetime history of depression. Never-depressed siblings who participated in the study thus had a sibling and another first degree relative with a lifetime history of MDD. Unaffected female controls ($n=21$) had no personal or family history of current or lifetime psychiatric disorder. They were matched for age and education to resemble the patient and family member groups as closely as possible. The study was approved by the Dutch central medical ethics review board.

2.2. Materials

2.2.1. Diagnostic instruments

The Dutch version of the Composite International Diagnostic Interview (CIDI), version 2.1, was used to examine depressive and other psychiatric diagnoses. The following CIDI sections were used: lifetime presence of mood disorders, anxiety disorders, schizophrenia and other non-affective psychotic disorders, alcohol abuse and dependence. The family history of depression was examined using an adapted version of the Family Interview for Genetic Studies (Maxwell, 1992) and the Family History Research Diagnostic Criteria (Endicott et al., 1975) following the method described for the GenMood project (Verhagen et al., 2008).

2.2.2. Stroop tasks

The *emotional Stroop task* (Williams et al., 1996) was administered to assess processing bias for negative and positive information. Words were generated with negative, positive and neutral content and were rated for valence by psychology students. Subsequently, 10 words per affective category were selected based on the valence ratings and matched for word frequency and length (see Table 1). The task consisted of three blocks with 100 presentations each. One block contained the selected negative words, one block the positive words and one block the neutral words. Words appeared one by one in the middle of a computer screen for 1997 ms. Participants were asked to name the ink color of the words as fast as possible by speaking it into a microphone. Reaction times (RTs) were registered using computer software (Voogd, 2005). The experimenter used a button box to register incorrect or invalid answers (like "uhh").

The *conventional Stroop task* was used to assess impairments in attention, especially cognitive interference from automatic responses, and consisted of a computerized version of the original Stroop (1935) task. The task consisted of three blocks with 100 items each, that appeared one by one in the middle of a computer screen for 1997 ms. The first block consisted of color words printed in black ink; participants were asked to read aloud the words as fast as possible into a microphone. The second block consisted of colored bars; the participants were asked to name the colors as fast as possible. The third block consisted of color words printed in inconsistent colors; participants were asked to name the color of the ink as fast as possible, ignoring the meaning of the words. Reaction times were registered and the experimenter registered incorrect and invalid responses.

2.3. Statistical analysis

Invalid and incorrect responses were removed from the data. To minimize the influence of outliers, we also deleted the RTs that were longer than two standard deviations from the mean. Negative and positive affective processing bias scores were calculated using the difference in RTs between neutral and negative or neutral and positive blocks, respectively. Higher scores indicated greater negative or positive affective processing bias. General interference was calculated as the main outcome variable of the cognitive Stroop task, by subtracting the mean RT from the inconsistent word color condition from the colored-bars condition. Normality of distribution of the affective processing bias variables was examined using a Kolmogorov–Smirnov test and yielded non-significant results, indicating a normal distribution of the bias scores. Participants made very few errors ($<1\%$).

The differences with regard to negative and positive processing bias and general interference between remitted patients, never-depressed female siblings and controls were analyzed using one-way ANOVAs with group as the between-subjects factor. To account for potential familial clustering between patients and siblings, the analyses were repeated using Generalized Estimating Equations with a linear regression model, family identity link and robust estimators. Negative bias