Journal of Psychiatric Research 46 (2012) 181–188

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Altered inhibition of negative emotions in subjects at family risk of major depressive disorder☆

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ARTICLE INFO

Article history:
Received 12 June 2011
Received in revised form
13 September 2011
Accepted 24 October 2011

Keywords:
Major depressive disorder
Vulnerability
High risk
Unaffected first degree relatives
*f*MRI
Inhibition of emotional information

ABSTRACT

Unaffected 1st degree relatives of patients with major depressive disorder (MDD) are more likely to develop MDD than healthy controls. The aim of our study was to establish neuronal correlates of familial susceptibility in the process of inhibition of emotional information. Unaffected 1st degree relatives of patients with MDD ($N = 21$) and matched healthy controls ($N = 25$) underwent a functional magnetic resonance imaging procedure with an inhibition task. Blood oxygenated level dependent signal was evaluated for the two groups during inhibition of positive, negative and neutral information. In a 2×3 ANOVA unaffected relatives of patients with MDD were compared to healthy controls, jointly and separately for all three levels of emotional valence of the information. The interaction between group and emotional valence of the inhibited information was significant, indicating "a negative neural drift" in unaffected relatives of patients with MDD. The unaffected relatives of patients with MDD displayed an increased activation during inhibiting of negative material in the right middle cingulate cortex and the left caudate nucleus ($p < 0.05$, family wise error corrected). There was no difference between the two groups in terms of inhibiting positive or neutral stimuli. Our findings provide the first evidence that unaffected relatives of patients with MDD differ from the standard population in terms of neural correlates of inhibition of negative emotional information. Overactivation of cingulate cortex and caudate nucleus may indicate a learnt strategy aimed at coping with increased susceptibility to negative information schemata and may have future consequences for therapy.

1. Introduction

People who have a 1st degree relative suffering from major depressive disorder (MDD) and yet stay healthy are of major importance in neuroimaging research of MDD. This almost unexplored strand of neuroimaging research is of particular interest, because the 1st degree unaffected healthy relatives of patients with MDD (UHR-MDD) are 3.6 times more liable to develop the disorder than people without family history of it (Fanous et al., 2002). Due to their increased susceptibility to the disease and an absence of acute MDD symptoms, neural susceptibility to MDD can be observed separately from the acute effect that depression has on the brain functioning on their example. Exploring susceptibility separately from the MDD episode helps to understand the process of development of the disorder and may contribute to the establishment of biological risk markers relevant for early detection.

Certain psychological and behavioral traits distinguish the UHR-MDD people from people without family history of MDD. For example, the UHR-MDD react faster to negative stimuli (especially fear) and less quickly to positive information compared to healthy controls (Le Masurier et al., 2007). Moreover, the UHR-MDD tend to have more negative cognitions and beliefs (Giles et al., 1990). Furthermore, healthy monozygotic twins of patients with MDD have cognitive impairments in selective and sustained attention, executive function and working memory, similar in quality but not severity to those observed in MDD patients (Christensen et al., 2006).

However, studies investigating neural correlates of features distinguishing the UHR-MDD group by the use of brain imaging techniques are rare. In one, Wolfensberger et al. (2008) studied healthy monozygotic twins of people suffering from MDD or anxiety using functional magnetic resonance imaging (*f*MRI) of

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doi:10.1016/j.jpsychires.2011.10.010

verbal encoding and retrieval. They discovered that in spite of not demonstrating any negative bias on a behavioral level, twins of patients with MDD showed increased activation in the left inferior frontal gyrus when compared to the healthy controls. This example illustrates that susceptibility can manifest itself without behavioral signals, in face of which using the techniques of neuroimaging is a necessity (Kathmann et al., 2003; Savitz and Drevets, 2009).

The aim of the current study was to establish neuronal correlates for the MDD susceptibility in unaffected healthy 1st degree relatives of patients suffering from MDD. Cognitive-emotional inhibition was chosen as a candidate to probe cerebral networks which may be important for development of MDD for a few reasons. Patients with MDD have deficient inhibition of negative stimuli (Goeleven et al., 2006; Lau et al., 2007). The deficit is accompanied by changes in functioning of dorsolateral prefrontal and cingulate cortex (Eugene et al., 2010; Gotlib and Joormann, 2010), that are a part of the circuitry involved in executive control (Vogt et al., 1992; Wagner et al., 2001). Alterations connected with the deficit are also observed in subcortical regions such as amygdala and HPA axis (De Raedt and Koster, 2010; Gotlib and Joormann, 2010). Furthermore, emotional inhibition is a crucial factor in efficient mood regulation which is disturbed in MDD (Beauregard et al., 2006; Joormann et al., 2007). Some cognitive strategies of coping with stress such as positive refocusing or refocusing on planning are based on the ability to inhibit certain emotional reactions and change the course of information processing (Garnefski and Kraaij, 2007). The emotional inhibition is a process indispensible in attention switching, executive function and working memory which were previously named as impaired in symptoms of MDD liability (Brunel and Wang, 2001). Furthermore, cognitive-emotional inhibition has a potential to activate the frontal-posterior-cingulate network (Brunel and Wang, 2001; Houghton and Tipper, 1996; Machens et al., 2005) which is a part of the limbic-frontal circuitry disturbed in MDD (Seminowicz et al., 2004). Finally, the endophenotypes clinically relevant to MDD risk are alterations in neuropsychological measures of cognitive function and neuroticism (Hall and Smoller, 2010). That implies a pattern of superfluous emotional reaction and its disturbed inhibition.

Our hypothesis was that the UHR-MDD differ from healthy controls in terms of inhibition of emotional information. Some of their cortical areas involved in inhibiting e.g. cingulate cortex or prefrontal cortex (Shafritz et al., 2006) may be more activated to compensate for increased emotional activation.

2. Materials and methods

2.1. Participants

Twenty one unaffected healthy 1st degree relatives of patients suffering from MDD and twenty five healthy control subjects without family history of any psychiatric disease participated in the study. The UHR-MDD participants were recruited among 1st degree healthy relatives of patients attending local psychiatric outpatient clinics as well as psychiatric wards of The Adelaide and Meath Hospital Incorporating the National Children's Hospital, St. James's Hospital in Dublin and Health Service Executive psychiatric services in Dublin South-West and Middle Leinster. The patients, amongst whose relatives we recruited the UHR-MDD participants, were diagnosed with MDD by a consultant of psychiatry and a psychiatrist and did not have any psychiatric comorbidity. The healthy control subjects were volunteers recruited via advertisements.

2.2. Depression measures and participants' eligibility for the study

Participants' health and eligibility for the study was verified by a consultant of psychiatry (with the means of psychiatric interview, Structured Clinical Interview for DSM-IV (First et al., 1997), Hamilton Depression Rating Scale (HDRS) (Hamilton, 1959), Montgomery–Asberg Depression Rating Scale (MDRS) (Montgomery and Asberg, 1979) and Beck Depression Inventory (BDI II) (Beck et al., 1996), the last one self-rated) and a psychologist (an interview and the task training). The exclusion criteria of the study were: a previous or present head injury, a current and past psychiatric or neurological disease, a current medical disease influencing central nervous system, alcohol and drug dependency, current abuse of drugs, inability to read and see stimuli presented on the screen. Also an extensive interview about family history of MDD was conducted with each participant to ensure that they were appropriately classified as UHR-MDD or healthy subjects. The two groups, as indicated by p values, were balanced in relation to age, gender, handedness and education (Table 1). All the participants scored within the norm interval in HDRS and MDRS characteristic of healthy individuals. The mean ratings of both groups were below the level characteristic for MDD.

After an extensive description of the study, written informed consent was obtained from all study participants. The study protocol was approved by the local ethics committee of the Trinity College Dublin, the University of Dublin, Ireland and prepared in accordance to the ethical standards laid down in the Declaration of Helsinki.

2.3. Design

The study was a two sample design with UHR-MDD and the control subjects as compared groups. After the ascertainment procedure presented above participants were assigned to one of the two groups. A cognitive-emotional inhibition task was designed to record subjects' brain activity with the means of an event-related *f*MRI experiment.

Table 1
Demographic variables and clinical results for unaffected healthy 1st degree relatives of patients with major depressive disorder (UHR-MDD) and healthy controls without family history of major depressive disorder.

	Unaffected relatives of patients with major depressive disorder (UHR-MDD) ($N = 21$)	Healthy controls without family history of major depressive disorder ($N = 25$)	p values
Age (SD)	38.6 (14.5)	36.3 (11.9)	0.55
Gender (F/M)	11/10	13/12	0.607
Handedness (right/left)	21/0	25/0	
Years of education (SD)	16.56 (3.26)	17.32 (2.43)	0.383
Hamilton Depression Rating Scale	3.71 (3.1)	1.78 (1.93)	0.016[a]
Montgomery–Asberg Depression Rating Scale	3.14 (4.03)	0.52 (1.73)	0.01[a]
Beck Depression Inventory	3.67 (5.72)	2.04 (2.6)	0.226

[a] Significant differences between the unaffected healthy relatives of patients with major depressive disorder and healthy controls ($p < 0.05$).