Journal of Psychiatric Research 64 (2015) 9–18

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Reduced default mode network suppression during a working memory task in remitted major depression

Lucie Bartova [a, 1], Bernhard M. Meyer [a, 1], Kersten Diers [b], Ulrich Rabl [a], Christian Scharinger [a], Ana Popovic [a], Gerald Pail [a], Klaudius Kalcher [c, d], Roland N. Boubela [c, d], Julia Huemer [e], Dominik Mandorfer [a], Christian Windischberger [c, d], Harald H. Sitte [f], Siegfried Kasper [a], Nicole Praschak-Rieder [a], Ewald Moser [c, d], Burkhard Brocke [b], Lukas Pezawas [a, *, 1]

[a] Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria
[b] Department of Psychology, Dresden University of Technology, Dresden, Germany
[c] MR Centre of Excellence, Medical University of Vienna, Vienna, Austria
[d] Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria
[e] Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria
[f] Center of Physiology and Pharmacology, Institute of Pharmacology, Medical University of Vienna, Vienna, Austria

ARTICLE INFO

Article history:
Received 10 September 2014
Received in revised form
14 January 2015
Accepted 26 February 2015

Keywords:
Default mode network
Functional magnetic resonance imaging
Major depressive disorder
Remission
Rumination
Working memory

ABSTRACT

Insufficient default mode network (DMN) suppression was linked to increased rumination in symptomatic Major Depressive Disorder (MDD). Since rumination is known to predict relapse and a more severe course of MDD, we hypothesized that similar DMN alterations might also exist during full remission of MDD (rMDD), a condition known to be associated with increased relapse rates specifically in patients with adolescent onset. Within a cross-sectional functional magnetic resonance imaging study activation and functional connectivity (FC) were investigated in 120 adults comprising 78 drug-free rMDD patients with adolescent- (n = 42) and adult-onset (n = 36) as well as 42 healthy controls (HC), while performing the *n*-back task. Compared to HC, rMDD patients showed diminished DMN deactivation with strongest differences in the anterior-medial prefrontal cortex (amPFC), which was further linked to increased rumination response style. On a brain systems level, rMDD patients showed an increased FC between the amPFC and the dorsolateral prefrontal cortex, which constitutes a key region of the antagonistic working-memory network. Both whole-brain analyses revealed significant differences between adolescent-onset rMDD patients and HC, while adult-onset rMDD patients showed no significant effects. Results of this study demonstrate that reduced DMN suppression exists even after full recovery of depressive symptoms, which appears to be specifically pronounced in adolescent-onset MDD patients. Our results encourage the investigation of DMN suppression as a putative predictor of relapse in clinical trials, which might eventually lead to important implications for antidepressant maintenance treatment.

1. Introduction

Major Depressive Disorder (MDD) constitutes the second leading cause of disability worldwide and is associated with a substantial socio-economic burden (Licinio and Wong, 2011; Vos et al., 2012; Becker and Kleinman, 2013; Ferrari et al., 2013). The sequelae of MDD comprise several emotional as well as cognitive symptoms, which are considered to merely reflect a bias towards negatively-valenced information processing leading to adverse emotional

* Corresponding author. Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Tel.: +43 (1) 40400 35680; fax: +43 (1) 40400 3099.
E-mail address: lukas.pezawas@meduniwien.ac.at (L. Pezawas).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jpsychires.2015.02.025

responsiveness, attention, and dysfunctional executive function (Nolen-Hoeksema, 1991; Beck, 2008; Disner et al., 2011; Elliott et al., 2011; Millan et al., 2012). Imaging studies have provided compelling evidence of altered emotion networks in MDD encompassing the amygdala and the anterior cingulate cortex (Drevets et al., 1997; Pezawas et al., 2005; Price and Drevets, 2012), highlighting the superior role of the cortical midline structures in the pathogenesis of MDD and antidepressant treatment response (Liotti et al., 2002; Lozano et al., 2008; Kupfer et al., 2012). Recently, more attention has been paid to cognitive control mechanisms in patients with concurrent major depressive episodes (MDEs) (Harvey et al., 2005; Rose et al., 2006; Matsuo et al., 2007; Walsh et al., 2007; Fitzgerald et al., 2008; Schlosser et al., 2008; Sheline et al., 2009; Vasic et al., 2009; Davey et al., 2012b; Rodriguez-Cano et al., 2014) demonstrating increasingly converging evidence of less default mode network (DMN) suppression during performance of attention-demanding tasks (Sheline et al., 2009; Disner et al., 2011; Anticevic et al., 2012; Rodriguez-Cano et al., 2014). While the DMN (Gusnard et al., 2001; Raichle et al., 2001) is physiologically activated at rest and deactivated during goal-directed cognition, insufficient DMN suppression has been repeatedly associated with goal-irrelevant functions such as self-referential thought, introspective processing or rumination (Mason et al., 2007; Hamilton et al., 2011; Anticevic et al., 2012; Marchetti et al., 2012; Nejad et al., 2013). Complementary evidence of dysfunctional DMN activation in MDD has also been detected at rest (Greicius et al., 2007; Sheline et al., 2010; Zhang et al., 2011; Davey et al., 2012a; Zhu et al., 2012; Connolly et al., 2013; Guo et al., 2013; Li et al., 2013; Sambataro et al., 2013; Dutta et al., 2014; Ho et al., 2014).

While an abundance of imaging research on cognitive control or functioning was conducted in patients with concurrent major depressive episodes (MDEs), studies dedicated to remitted MDD (rMDD) are relatively sparse and inconclusive (Walsh et al., 2007; Okada et al., 2009; Schoning et al., 2009; Kerestes et al., 2012a, 2012b; Nixon et al., 2012; Li et al., 2013; Norbury et al., 2013; Smoski et al., 2013; Jacobs et al., 2014; Young et al., 2014). Nonetheless, rMDD is of significant clinical interest since it often represents a euthymic state with increased relapse risk (Bhagwagar and Cowen, 2008; Kendler and Gardner, 2010) and, together with information on the number of previous MDEs, guides clinical recommendations for antidepressant maintenance treatment (APA, 2013). Apart from providing complementary evidence to disease concepts of symptomatic MDD, the study of rMDD raises the possibility to elucidate the neurobiological and psychological mechanisms underlying maintenance of remission as well as determinants of relapse (Marchetti et al., 2012). While the majority of above-mentioned rMDD studies focused on possible alterations in task-positive networks, the involvement of task-negative DMN regions gains increasing attention (Jacobs et al., 2014; Li et al., 2013). Specifically, the extent of DMN suppression, which has been shown to be crucial for goal-directed cognition and to be dysfunctional in symptomatic MDD (Disner et al., 2011; Hamilton et al., 2011; Anticevic et al., 2012; Nejad et al., 2013; Leech and Sharp, 2014), has yet to be thoroughly studied in this specific patient group (Marchetti et al., 2012). Additionally, several limitations present in previously published rMDD studies such as concomitant antidepressant treatment (Walsh et al., 2007; Schoning et al., 2009; Nixon et al., 2012; Li et al., 2013), moderate sample size (Okada et al., 2009; Norbury et al., 2013), or incomplete remission (Walsh et al., 2007; Schoning et al., 2009) make it difficult to draw final conclusions.

Hence, we conducted a cross-sectional functional magnetic resonance imaging (fMRI) study in a large sample of adult fully remitted and drug-free MDD patients as well as adult healthy controls (HC) without any previous psychiatric life-time diagnosis. Additionally, we investigated possible behavioral and neural differences with respect to age of MDD onset, because adolescent-onset MDD contrasts clinically with its adult-onset counterpart with regard to chronicity, severity, vulnerability, and stress-sensitivity (Harrington et al., 1990; Klein et al., 1999; Weissman et al., 1999; Aalto-Setala et al., 2002; Gilman et al., 2003; Zisook et al., 2007; Kendler et al., 2009; Pajer et al., 2012; Schosser et al., 2012; Ramirez et al., 2015). The main goal of this study was to assess both task-positive (Cole et al., 2014) and task-negative (Anticevic et al., 2012) differences of neural networks that are engaged or suppressed during working-memory (WM) performance. Based on recent findings demonstrating a relationship between reduced DMN suppression and increased rumination in symptomatic MDD (Hamilton et al., 2011), we hypothesized to observe similar deficits in full remission, a condition, where maladaptive self-referential processing has been associated with onset of depressive symptoms (Nolen-Hoeksema, 1991; Michl et al., 2013). Moreover, we expected that adolescent-onset rMDD patients would be more severely affected than those with adult-onset given the more deleterious course of adolescent-onset MDD.

2. Methods and materials

2.1. Participants

Study volunteers recruited by online advertisements, announcements on bulletin boards or word of mouth were invited to the outpatient clinic of the Department of Psychiatry and Psychotherapy, Medical University of Vienna (MUV), Vienna, Austria, to participate in this cross-sectional fMRI study. Study procedures were approved by the Ethics Committee (EC) of the MUV (EC Number: 11/2008) according to the Declaration of Helsinki (WMA, 2013). All participants, who were adult and fully capable to give written informed consent, were considered and financially compensated for their expenditure of time.

After a comprehensive clinical assessment comprising previous history, neurological and medical examinations involving electrocardiography, blood pressure measurement and routine laboratory testing, all subjects underwent a thorough psychiatric examination. Diagnoses were evaluated according to the German version of the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (Wittchen et al., 1997). Depressive symptoms were assessed by the 21-item version of the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). Only healthy participants without any previous or concurrent Axis I disorder were enrolled in this study, whereas previous single or multiple MDEs without any other present or previous axis I disorders were mandatory for inclusion of rMDD patients. In order to exclude cases with questionable clinical significance, only patients reporting previous antidepressant treatment (antidepressant medication, psychotherapy, or both) were included. Only rMDD patients who remitted and discontinued any antidepressant treatment at least three months prior to study enrollment were considered. Based on recent recommendations for considering remission and normal levels of functionality (Romera et al., 2011) a total HAM-D score $\leq$5 was required for all subjects. A complete list of further inclusion- and exclusion criteria is available in the Supplemental Information. Consecutively, 78 adult rMDD patients were enrolled in this study. With respect to age of onset, adolescent-onset was defined as $\leq$19 years and adult-onset as >19 years (Pajer et al., 2012). 42 adult HC chosen from a larger sample were automatically age- and gender-matched for both adult rMDD subgroups comprising 42 adolescent- and 36 adult-onset patients using an optimal full matching procedure (Hansen and Olsen Klopfer, 2006).