Journal of Affective Disorders 173 (2015) 45–52

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Cortico-limbic network abnormalities in individuals with current and past major depressive disorder

Paul Klauser [a,b,*], Alex Fornito [a,b], Valentina Lorenzetti [a,b], Christopher G. Davey [b,c], Dominic B. Dwyer [b], Nicholas B. Allen [c,d], Murat Yücel [a,b]

[a] Monash Clinical and Imaging Neuroscience, School of Psychological Sciences & Monash Biomedical Imaging, Monash University, Clayton, Australia
[b] Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Australia
[c] Orygen Youth Health Research Centre, Centre for Youth Mental Health, The University of Melbourne, Australia
[d] Melbourne School of Psychological Sciences, The University of Melbourne, Australia

ARTICLE INFO

Article history:
Received 25 June 2014
Received in revised form
17 October 2014
Accepted 20 October 2014
Available online 4 November 2014

Keywords:
Magnetic resonance imaging
Voxel-based morphometry
Major depressive disorder
Uncinate fasciculus
Ventromedial prefrontal cortex

ABSTRACT

Background: Brain abnormalities in fronto-temporal structures have been implicated in major depressive disorder (MDD). This study aims to identify their anatomical distribution and their relation to the time course of the disease.
Methods: A whole-brain voxel based morphometry analysis was conducted to assess gray and white matter alterations in 56 participants with a lifetime history of MDD, including currently depressed (cMDD) and remitted patients (rMDD), and 33 matched healthy controls (HC).
Results: Compared to HC, MDD participants showed increased white matter volume (WMV) in the uncinate fasciculus (UF) and decreased gray matter density (GMD) on the ventromedial prefrontal cortex (vmPFC). The increased WMV in UF was driven by both cMDD and rMDD groups and positively correlated with depression scores. The GMD decrease in the vmPFC resulted mainly from abnormalities in rMDD and was not correlated with depression scores. Finally, temporal UF and vmPFC white matter showed strong structural covariance suggesting functional interactions between these two brain regions.
Limitations: The retrospective and cross-sectional design of the study limits the generalizability of the results. Information concerning ongoing treatment did not allow the exploration of interactions between medication and observed abnormalities. The duration of the remission period could have influenced abnormalities in the subgroup of remitted patients.
Conclusions: Fronto-temporal alterations in MDD consist of alterations in a cortico-limbic network involving the ventromedial prefrontal cortex and temporal white matter tracts. State-like abnormalities in the UF survive remission and persist as trait-like abnormalities together with alteration in the vmPFC.

1. Introduction

Although the biological underpinnings of major depressive disorder (MDD) are not well understood, there is converging evidence in favor of an involvement of frontal and medial temporal brain regions in the pathogenesis of the disease (Price and Drevets, 2012). Neuroimaging studies have played an important role in the identification of structural and functional brain abnormalities in MDD and helped to guide the development of novel therapeutics such as transcranial magnetic stimulation (George et al., 2013) and deep brain stimulation (Mayberg et al., 2005).

The frontal lobe is consistently involved in findings from structural neuroimaging studies, and there is robust evidence of gray matter loss in the anterior cingulate cortex (ACC) from three independent meta-analyses (Bora et al., 2012a; Du et al., 2012; Lai, 2013). The ACC is part of the *medial prefrontal network* that has been shown to be central in emotional processing. This medial prefrontal network encompasses the medial part of the orbito-frontal cortex, also known as ventro-medial prefrontal cortex (vmPFC), and can also be extended to limbic structures as well as to basal ganglia and thalamus to form an *extended* medial prefrontal network (Price and Drevets, 2010). While findings concerning structural abnormalities in these extended cortical and subcortical components are inconsistent (Bora et al., 2012b), most functional neuroimaging studies in MDD report abnormal activation during tasks assessing emotional processing, and increased connectivity in task-free, so-called resting state conditions (Kerestes et al., 2013; Stuhrmann et al., 2011; Wang et al., 2012).

* Correspondence to: Monash Clinical and Imaging Neuroscience, School of Psychological Sciences & Monash Biomedical Imaging, Monash University, 770 Blackburn Road, Clayton, Victoria 3168, Australia. Fax: +61 3 9348 0469.
E-mail address: paul.klauser@monash.edu (P. Klauser).

http://dx.doi.org/10.1016/j.jad.2014.10.041
0165-0327/

Together, these findings raise the idea that MDD could result from abnormalities in an emotion-processing network implicating the medial prefrontal cortex (e.g., vmPFC) and related limbic structures (e.g., amygdala). This theoretical model of abnormalities in the extended medial prefrontal network in MDD is supported by a large body of structural and functional neuroimaging studies using different modalities, including magnetic resonance imaging (MRI) (Drevets et al., 2008), positron emission tomography (PET) (Monkul et al., 2012), single-photon emission computed tomography (SPECT) (Galynker et al., 1998; Nagafusa et al., 2012) and magnetoencephalography (MEG) (Lu et al., 2012). In some brain regions, these abnormalities are also associated with histopathological changes such as reduced cortical thickness and cellular alterations in frontal gray matter (Rajkowska et al., 1999) as all well as alterations of frontal white matter composition (Tham et al., 2011).

A large number of neuroimaging findings from our group (Lorenzetti et al., 2010; Takahashi et al., 2009, 2010a), and others (for review, see Koolschijn et al. (2009)), as well as post-mortem observations, which support the involvement of the cortico-limbic network have used region of interest (ROI) analyses. ROI studies are limited towards areas that can be easily anatomically delimited and manually traced (e.g., amygdala, hippocampus) or regions of theoretical importance, which intrinsically depends on results from previous studies (Bora et al., 2012a). These limitations could be addressed using a broader investigation that is not regionally biased and in which gray and white matter changes associated with the cortico-limbic system (and possibly other networks) are identified via a whole-brain analysis. In addition, it is important to evaluate whether cortico-limbic abnormalities reflect an acute change associated with the experience of a depressive episode, or whether they reflect a more enduring, trait-like characteristic.

Here we first hypothesized that a whole-brain comparison between participants with a lifetime history of MDD and healthy controls would reveal structural abnormalities in core regions of the extended medial prefrontal network, namely, the medial prefrontal cortex and the limbic system. Second, we predicted that the severity of these abnormalities would correlate with the level of depressive symptoms. Finally, we anticipated that the distinction between current (cMDD) and remitted (rMDD) depression would allow us to further distinguish between abnormalities present only during acute illness (state markers) and those that persist throughout periods of remission, representing putative trait markers.

This study aimed to comprehensively investigate brain abnormalities underlying depression and their relation to symptom expression, as well as, to the time course of the illness. Accordingly, we conducted a whole-brain voxel-based morphometry analysis of the gray and white matter in individuals with a lifetime history of major depressive disorder, including those who are currently depressed and those in remission.

2. Material and methods

This study was approved by the Mental Health Research and Ethics Committee of Melbourne Health, Melbourne, Australia.

2.1. Participants

Ninety-five participants were recruited in Melbourne from mental health clinics or from the general community through advertisement in the local media. They received reimbursement for their participation in the study. Among all participants, 31 had a current diagnosis of MDD, 31 were in remission from a previous MDD episode and 33 were healthy controls. Six participants were excluded from the analysis due to the presence of gross brain abnormalities (two were currently depressed and 4 were remitted patients), leaving a final sample of 29 currently depressed participants, 27 participants with remitted depression and 33 healthy controls. Inclusion criteria were age between 18 and 50, English as a main language, IQ > 70 and normal vision (or corrected to normal). General exclusion criteria were history of head trauma, impaired neuroendocrine function or steroid use, neurological condition or electro-convulsive therapy within the past 6 months. Patients with any current Axis I psychiatric disorder other than an anxiety disorder were also excluded. Healthy controls did not have any current or lifetime history of psychiatric disorder.

Among the 56 MDD patients (29 currently depressed and 27 remitted), 33 had been prescribed an antidepressant and 19 were medication-naive for the 6 months preceding their assessment. 17 received selective serotonin reuptake inhibitors (SSRIs), 4 serotonin-norepinephrine reuptake inhibitors (SSNRIs), 3 noradrenergic and specific serotonergic antidepressants (NaSSAs), 2 tricyclic antidepressants (TCAs), 2 monoamines oxidase inhibitors (MAOIs), one lithium and one norepinephrine reuptake inhibitor (NRIs).

Participants with a lifetime history of MDD and healthy controls were comparable concerning age, gender, intelligence, alcohol use and intracranial volume (Table 1). As expected, depression scores were the highest in the MDD group, and their positive affect score was the lowest. Within the MDD group, currently depressed participants had the highest depression scores (except for high positive affect), the earliest age of onset, and the highest rates of current anxiety disorder and medication (Table 1). The depression scores were higher in the remitted group than in the control group, suggesting residual depressive symptoms.

Five ROI manual-tracing studies from this cohort have already been published (Takahashi et al., 2009, 2010a, 2010b; Lorenzetti et al., 2010; Lorenzetti et al., 2009), but the present study is the first whole-brain analysis on this sample.

2.2. Clinical and neuropsychological data

All participants underwent general screening with the Structured Clinical Interview for DSM-IV-TR (SCID-IV-TR) and the Alcohol Use Disorders Identification Test (AUDIT) (Bush et al., 1998). Depressive symptoms were measured using a series of questionnaires including the Beck's Depression Inventory-II (BDI-II) (Beck et al., 1996) and the Mood and Anxiety Symptom Questionnaire (MASQ) (Watson et al., 1995b, 1995a). Premorbid and current intelligence were also measured using The Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) and the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) respectively.

2.3. MRI data acquisition

T1-weighted structural MRI data were obtained from a 1.5 T Siemens MAGNETOM Avanto scanner (Siemens, Erlangen, Germany) at St. Vincent's Hospital, Melbourne. Images were acquired with the following parameters: time to echo = 2.3 ms, time repetition = 2.1 ms, flip angle = 15°, matrix size = 256 × 256, giving an isometric voxel dimension of 1 mm^3.

2.4. MRI data preprocessing

Each scan was visually checked to exclude the presence of artefacts or gross anatomical abnormalities that could impact image preprocessing. Voxel-wise analysis of brain gray and white matter volume or density differences was conducted using the DARTEL (Diffeomorphic Anatomical Registration Through