NeuroImage: Clinical 17 (2018) 786–793

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Risk for affective disorders is associated with greater prefrontal gray matter volumes: A prospective longitudinal study

Julian Macoveanu[a,b,*], William Baaré[b], Kristoffer H. Madsen[b,c], Lars Vedel Kessing[a], Hartwig Roman Siebner[b,d], Maj Vinberg[a]

[a] Psychiatric Centre Copenhagen, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[b] Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
[c] Section for Cognitive Systems, Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kgs. Lyngby, Denmark
[d] Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark

ARTICLE INFO

Keywords:
Affective disorders
Structural MRI
Anterior cingulate cortex
VBM

ABSTRACT

Background: Major depression and bipolar disorders aggregates in families and are linked with a wide range of neurobiological abnormalities including cortical gray matter (GM) alterations. Prospective studies of individuals at familial risk may expose the neural mechanisms underlying risk transmission.
Methods: We used voxel based morphometry to investigate changes in regional GM brain volume, over a seven-year period, in 37 initially healthy individuals having a mono- or di-zygotic twin diagnosed with major depression or bipolar disorder (high-risk group; mean age 41.6 yrs.) as compared to 36 individuals with no history of affective disorders in the index twin and first-degree relatives (low-risk group; mean age 38.5 yrs.).
Results: Groups did not differ in regional GM volume changes over time. However, independent of time, high-risk twins had significantly greater GM volumes in bilateral dorsal anterior cingulate, inferior frontal gyrus and temporoparietal regions as compared to low-risk twins. Further, individuals who developed an affective disorder at follow-up (n = 12), had relatively the largest GM volumes, both at baseline and follow-up, in the right dorsal anterior cingulate cortex and right inferior frontal cortex compared to high- and low-risk twins who remained well at follow-up.
Conclusion: This pattern of apparently stable grater regional GM volume may constitute a neural marker of an increased risk for developing an affective disorder in individuals at familial risk.

1. Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) have consistently been linked with neurophysiological impairments related to cognitive and executive function, and emotional processing (Gotlib and Joormann, 2010), with numerous neuroimaging studies reporting structural and functional abnormalities in the brain regions subserving these processes (Hamilton et al., 2013; Peng et al., 2016; Wise et al., 2016). The available neuroimaging data in depressed patients, reveal highly heterogeneous and widespread brain abnormalities, involving prefrontal, as well as temporal and subcortical brain structures. Studies of gray matter (GM) changes in various groups of MDD and BD patients have reported smaller volume in hippocampus, anterior cingulate cortex (ACC), and multiple regions in prefrontal cortex (PFC) such as subgenual and orbitofrontal cortex, and dorsolateral and dorsomedial PFC (Bora et al., 2012; Lai, 2013; Lorenzetti et al., 2009).

Studies in MDD patients investigated immediately after their first episode and in medication-naïve patients often report conflicting findings compared with studies in medicated and chronically ill patients (Peng et al., 2016). For instance, no volumetric differences in patients in the early course of depression relative to non-depressed participants were observed in amygdala, hippocampus or orbitofrontal cortex (OFC) (Arnone et al., 2012; Hastings et al., 2004; McKinnon et al., 2009; Pizzagalli et al., 2004; van Eijndhoven et al., 2009). Other studies reported larger amygdala volume (Frodl et al., 2003, 2002) or larger cortical volume, density and thickness in ACC (Adler et al., 2007; van Eijndhoven et al., 2013; Zhao et al., 2014), or OFC and dorsolateral PFC (Qiu et al., 2014). In conclusion, the described heterogeneity in the neuroimaging findings may well reflect the effects of distinct clinical factors such as chronicity, disorder progression, frequency of depression episodes, and/or medical treatment.

Studies in healthy individuals at increased risk for affective

* Corresponding author at: Psychiatric Centre Copenhagen, Rigshospitalet, Afdeling O, afsnit 6233, Blegdamsvej 9, 2100 Copenhagen, Denmark.
E-mail address: julianm@drcmr.dk (J. Macoveanu).

https://doi.org/10.1016/j.nicl.2017.12.011
Received 27 June 2017; Received in revised form 12 October 2017; Accepted 6 December 2017
Available online 07 December 2017

disorders are instrumental in identifying dysfunctional systems that precede onset of the disorders without being cofounded by clinical factors. Having a first-degree relative with an affective disorder is a strong predictor of increased risk for depression (Gottesman et al., 2010; Oquendo et al., 2013; Sullivan et al., 2000). Our group has previously found reduced hippocampal volumes (Baaré et al., 2010) in healthy co-twins of patients with MDD (n = 59) as compared to healthy twins with no family history of affective disorders (n = 53). In line with this finding, Amico et al. (2011) reported smaller right hippocampal gray matter volumes in individuals with a positive family history for MDD compared to both matched controls with no family history and MDD patients. They further reported gray and white matter volume reductions in dorsolateral PFC in healthy high-risk individuals compared to the low-risk controls. MDD mothers and their healthy daughters showed reduced volume and cortical thickness in temporoparietal regions and the dorsomedial PFC compared to matched healthy mothers and their healthy daughters (Ozalay et al., 2016). In a study investigating a group of high-risk young adults at baseline and following a 2-year period, Papmeyer et al. (2015) found reduced cortical thickness in the right parahippocampal and fusiform gyrus across both time points. However, contrasting previous findings of reduced volume and thickness, Romanczuk-Seiferth et al. (2014) reported grater GM volume in bilateral amygdala and hippocampus, and left dorsolateral PFC in healthy first-degree relatives of MDD patients compared to matched participants with no family history of psychiatric disorders. Peterson et al. (2009) observed both cortical thickening in subgenual, medial OFC, and anterior and posterior cingulate gyrus and cortical thinning across the lateral surface of the right cerebral hemisphere in children and grandchildren of depressed individuals compared to age matched individuals with no family risk of affective disorders.

The present longitudinal high-risk study investigated possible regional brain differences in GM volume in healthy co-twins of patients with MDD or BD as compared to healthy co-twins with no family history of affective disorders over a seven-year follow-up period. MDD and BD show genetic overlap (McGuffin et al., 2003; Smoller et al., 2013) and 10–15% of individuals with an index diagnosis of depression will subsequently develop a bipolar disorder (Kessing et al., 2017). We therefore combined relatives to MDD and BD to reveal gray matter changes related to increased risk in a continuum of affective disorders. Participants were part of a larger longitudinal study (n = 234) on demographic and clinical risk markers for affective disorders, where we initially showed that increased affective symptoms, neuroticism and severe life events (Vinberg et al., 2013a), and impaired executive function and attention (Vinberg et al., 2013b) at baseline were predictive of subsequent onset of an affective disorder. Here we used voxel based morphometry to test the hypothesis that high- and low-risk participants will show a differential temporal development of regional GM volume in brain regions critically implicated in in MDD and BD i.e. PFC, ACC and hippocampus. We further expected that longitudinal changes in GM volume in these regions would be most prominent in those individuals who developed an affective disorder during the 7-years follow-up.

2. Methods

2.1. Participants

73 healthy MZ and DZ twins, with no diagnosis of affective disorder prior to the baseline investigation, were included in the current high-risk structural MRI study. The participants were scanned at baseline and following a period of 7.1 ± 1.2 years (mean ± SD). The baseline scan took place between June 2003 and June 2004 and the follow-up scan between May 2011 and June 2012. All participants were recruited from a larger high-risk study (n = 234) on demographic and clinical risk markers for developing depression (Christensen et al., 2007). At baseline, 174 participants out of the 234 participants took part in the MRI investigation (for details please see Baaré et al., 2010). Of these 125 participants were considered suitable for follow-up and 49 participants were excluded due to: arterial malformations (n = 3), hypertension, diabetes, epilepsy, head trauma or previous chemotherapy (n = 30) or a family history of psychiatric illness other than MDD or BD (n = 16). Of the 125 participants invited for the follow-up MRI scan 7 years later, 85 agreed to participate and 73 of them were scanned. The 73 included participants had a co-twin diagnosed and treated for either MDD or BD in a psychiatric hospital setting (high-risk twins, n = 37, 27 relatives of MDD and 10 of BD patients), or no history of affective disorders or other severe psychiatric illness in first-degree relatives (low-risk twins, n = 36).

The high- and low-risk twins were identified through record linkage between the nation-wide Danish Twin Registry, the Danish Psychiatric Central Research Register and the Danish Civil registration system. Low-risk twins were matched for age, sex and zygosity with the high-risk twins. None of the included twins had a record in the Danish Psychiatric Central Research Register. All participants underwent a clinical interview using Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) (Wing et al., 1990) to ascertain that they did not have a personal history of affective disorders or severe depression episodes, schizoaffective disorders or schizophrenia, or any severe organic brain disease preventing compliance with the study protocol. The participants were further enquired about lifetime family psychiatric history based on the Brief Screening for Family Psychiatric History questionnaire (Weissman et al., 2000). The zygotic status was obtained from the Danish Twin Registry, which records the zygosity of same-sex twins based on mailed questionnaires.

Out of the 73 participants investigated over the follow-up period, 12 had an onset of affective disorder during follow-up (10 from the high-risk group and two from the low-risk group). The time of onset was in average 1141 (± 758) days before the follow-up investigation, with diagnoses categorized according to the International Classification of Diseases (ICD-10) as follows: moderate (n = 3; ICD 32.1) or severe depressive episode (n = 5; ICD 32.2), panic disorder (n = 1; ICD 41), prolonged depressive reaction (n = 1; ICD 43.21), and mixed anxiety and depressive reaction (n = 2; ICD 43.22). When comparing the 73 participants with the 161 participants from the initial cohort that were not included, the included group had a statistically significant lower mean age (40.6 vs. 45.7 years, p = 0.003), higher education level (13.6 vs. 12.4 years, p = 0.005), and a lower percentage of high-risk individuals (50.7% vs. 67%). Groups did not statistically significant differ in sex distribution, zygosity and other clinical measurements.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Danish Ministry of Health and The Danish Regional Scientific Ethical Committee (KF-12-122/99 and KF-01-001/02), and the Data Inspection Agency. Written informed consent was obtained from all participants.

2.2. Demographic, socio-economic and clinical assessment

The participants underwent clinical interviews using Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) (Wing et al., 1990) performed by a trained psychiatrist (MV). At baseline, all participants were rated with the 17-item Hamilton (HamD) rating scale (Hamilton, 1980), self-rating of psychopathology using the 21-item Beck Depression Inventory (BDI-21) (Beck et al., 1961), and personality traits including neuroticism using the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975), the number of severe lifetime life events (prior LEs), (Kendler et al., 1995) and lifetime family psychiatric history based on the Brief Screening for Family Psychiatric History questionnaire (Weissman et al., 2000). Participants were asked to fill in the BDI-21 questionnaire every six-months, sent to them by mail, to monitor if they developed an affective disorder. Moreover, they annually filled in a questionnaire assessing experienced life events in the preceding 12 months, and a cumulative value during the entire follow-