Progress in Neuropsychopharmacology & Biological Psychiatry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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

Cerebral blood flow velocity positively correlates with brain volumes in long-term remitted depression

Thomas Desmidt[a,b,*], Frédéric Andersson[b], Bruno Brizard[b], Jean-Philippe Cottier[a,b], Frédéric Patat[b,c], Valérie Gissot[c], Catherine Belzung[b], Wissam El-Hage[a,b,c], Vincent Camus[a,b]

[a] CHRU de Tours, Tours, France
[b] INSERM U930 Imagerie et Cerveau, Université François-Rabelais de Tours, Tours, France
[c] INSERM CIC 1415, Université François-Rabelais de Tours, Tours, France

ARTICLE INFO

Keywords:
Depression
Brain volume
Cerebral blood flow
Transcranial Doppler

ABSTRACT

Background: Mechanisms involved in brain changes observed in major depression have been poorly investigated in clinical populations. Changes in cerebral blood flow (CBF) have been found in depressed patients and constitute a potential mechanism by which brain volume varies in depression. We have tested the association of cerebral blood flow velocity (CBFV) as assessed with Transcranial Doppler (TCD) and cerebral blood flow (CBF) as assessed with Arterial Spin Labeling Magnetic Resonance Imaging (ASL-MRI) with Total Brain Volume (TBV) and the volume of seven subcortical regions, in currently depressed and long-term remitted patients. In addition, we have evaluated other potential confounders for the association depression/brain volume, including dimensional symptoms of depression, cardiovascular risk factors (CVRF) and antidepressants.

Methods: Seventy-five individuals were recruited, divided in 3 equal groups (currently depressed, remitted individuals and healthy controls) and were submitted to clinical assessment, MRI and Transcranial Doppler.

Results: CBFV was positively correlated with TBV, Hippocampus and Thalamus volume, but only in remitted patients, who tend to have larger brains compared to both currently depressed and controls. CVRF were negatively associated with brain volumes in the 3 groups and antidepressant use was associated with larger Thalamus. We found no association between brain volumes and CBF as assessed with ASL-MRI, anhedonia, anxiety or psychomotor retardation.

Discussion: Greater CBFV may be a physiological mechanism by which brain is enlarged in remitted patients. Future studies should consider CBFV, CVRF and antidepressants as possible confounders for the association depression/brain volumes, especially in remitted patients.

1. Introduction

Several studies have found that brain volume was changed in major depression. Meta-analyses of cross-sectional studies (Arnone et al., 2012; Schmaal et al., 2016) have concluded that various subcortical regions were smaller or larger in currently depressed subjects, especially in recurrent and severe depression, while longitudinal studies (Dohm et al., 2016; Phillips et al., 2012, 2015) tend to show that remission is associated with brain enlargement.

Some evidence suggests that antidepressant use is involved in the brain enlargement associated with remission. Preclinical studies have robustly found that antidepressants promote neuroplasticity (Malykhin and Coupland, 2015), neurogenesis (Eisch and Petrik, 2012) and myelination (Kroeze et al., 2015), which are mechanisms believed to participate to brain volume change. In contrast, clinical studies have been less consistent with systematic reviews (Dohm et al., 2016) finding insufficient data to resolve the causality between the course of depression, antidepressant use and brain volume change over time. One issue of particular interest relates to the brain volume changes in long-term remission and in long-term antidepressants use, for several months or years, specifically because extended use of antidepressant may be required in some patients to insure clinical stability and to prevent relapse. Interestingly, preclinical studies have found that change in brain physiology related to volume change continues to occur in long-term antidepressant exposure (Kroeze et al., 2015), whereas pathophysiological studies involving long-term remitted patients are lacking. In addition and because brain enlargement is usually not observed in non-remitted patients with antidepressants, the role of antidepressants alone has been questioned, while other mechanisms could be involved in the brain volume changes observed across the course of depression.

* Corresponding author at: Clinique Psychiatrique Universitaire, CHRU de Tours, 2 Boulevard Tonnellé, 37044 Tours, Cedex 9, France.
E-mail address: t.desmidt@chu-tours.fr (T. Desmidt).

http://dx.doi.org/10.1016/j.pnpbp.2017.09.018
Received 31 March 2017; Received in revised form 10 September 2017; Accepted 18 September 2017

Indeed, cerebral blood flow (CBF), as well as cardiovascular risk factors (CVRF), may constitute potential determinants for the depression/brain volume association. Lower CBF and greater CVRF have been associated with brain atrophy in healthy controls (Muller et al., 2010). Besides, CBF was shown to be changed in depression, typically with a decrease in depressive episode, which is restored with remission (Kohn et al., 2007; Vlassenko et al., 2004). Depressed patients also consistently exhibit greater CVRF compared to controls (Taylor et al., 2013). However, to our knowledge, no study has investigated a potential association of CBF and CVRF with brain volume in depression.

Some symptoms of depression may also constitute potential confounding factors for the association depression/brain volume, especially because various categorical diagnoses such as schizophrenia, post-traumatic stress disorder or Alzheimer's disease, which share common symptoms, have been associated with common changes in brain volume (Geuze et al., 2005). Potential candidates for clinical confounders therefore include symptoms common to all these disorders such as anhedonia, psychomotor retardation and anxiety.

The main objective of this study was to investigate the association of potential determinants of brain volume changes, namely antidepressant use, CBF (assessed with arterial spin labeling magnetic resonance imaging – ASL-MRI – and with transcranial Doppler - TCD), CVRF and dimensional symptoms of depression (namely anhedonia, anxiety and psychomotor retardation) with Total Brain Volume (TBV) and the volume of seven subcortical regions, in a population of currently depressed, long-term remitted patients and healthy controls. We used both ASL-MRI and TCD because the two techniques have complementary pros and cons including some of the following: ASL-MRI allows localization of brain structures and provides with region-specific CBF derived from magnetically labeled arterial blood water protons but has a relatively low spatial resolution and low signal-noise ratio, whereas TCD is a portable, costless and easily accessible technique for clinical routine to assess the velocity of blood cells with a high spatio-temporal resolution but only in large vessels. The seven subcortical regions were selected based on previous evidence of depression-related volume changes in these areas, as well as involvement of these regions in the pathophysiology of depression (Belzung et al., 2015) and because subcortical nuclei are particularly sensitive to change in CBF (Moody et al., 1990). In addition, we have evaluated other potential confounders for the association depression/brain volume, including CVRF, dimensional symptoms of depression (namely anhedonia, anxiety and psychomotor retardation) and antidepressants use.

2. Methods

2.1. Participants

Seventy-five females aged 18 to 55 years were recruited and divided into 3 equal groups (currently depressed, remitted individuals and healthy controls) as part of the EMPHILINE project (NCT02026622 on clinicaltrials.gov). Informed consent was obtained from all subjects, and the study protocol was approved by the local human ethical committee. The principal objective of the project was to investigate the cardiovascular and cerebrovascular reactivity in depression during emotional tasks; the baseline data are reported in the present article. To reduce variability, only females were recruited because previous findings have found significant differences in cerebrovascular properties between age-matched males and females (Parkes et al., 2004). Subjects in the depressive group (group D; n = 25) were inpatients or outpatients from the psychiatric ward of the University Hospital of Tours, France. Psychiatrists (TD, WEH) diagnosed the patients as depressed according to the DSM-IV criteria for major depressive disorder (MDD), with a MADRS score higher than 21. The medical records of the psychiatric ward were used to screen subjects for the remission group (group R; n = 25). Subjects in the R group had to have at least one documented history of MDD in the past ten years but no criteria for current MDD in the last 6 months, and they needed a current MADRS score lower than 9. Subjects in the control group (group C; n = 25) were recruited from the local community and from the records of the Clinical Investigation Center of the Hospital of Tours, France. They had to have no history of MDD or any psychiatric disorder and have a current MADRS score lower than 9. The three groups were matched for age. Non-inclusion criteria for all subjects were: 1) any history of psychotic, bipolar, or addictive disorders or suspicion of severe cognitive impairment (MMSE < 25), 2) any history of severe cardiovascular diseases (myocardial infarction, arrhythmia, etc.) or neurological disorders (stroke, brain tumor, severe concussion, migraine, etc.), 3) any current instable medical condition, 4) current use of beta-blockers or antipsychotics, 5) smoking over 10 pack-year, 6) auditory or visual impairments, 7) pregnancy or no reliable contraception, 8) contraindication for MRI and 9) legal guardianship. The exclusion criterion was having no temporal window because ultrasound is attenuated by the thickness of the skull.

2.2. Clinical assessments

Either a psychiatrist (TD) or a trained medical doctor (VG) from the Clinical Investigation Center performed the clinical and psychometric assessments in the research center of the University Hospital of Tours, France. Medical history and medication intake were recorded. The clinical assessment included blood pressure, height and weight measurements. Psychometric assessments included: 1) the Structured Clinical Interview for DSM-IV (SCID) for current and lifetime MDD; 2) the MADRS for severity of depression; 3) the Mini Mental Status Examination (MMSE) to assess global cognitive functioning and screening for dementia; 4) the Pleasure-displeasure Scale, a 82-item self-report questionnaire used to measure the intensity of affective responses to pleasant and unpleasant situations (Hardy et al., 1986). It assesses anhedonia as a low reactivity to pleasant stimuli, as well as the tendency to react to neutral and unpleasant stimuli; 5) the State-Trait Anxiety Inventory (STAI) State Anxiety (S-Anxiety), a 20-item self-report questionnaire used to measure the intensity of current anxiety affects (Spielberger, 1983); and 6) The Retardation Rating Scale (RRS), a 14-item questionnaire used to measure the severity of psychomotor retardation in depression (Dantchev and Widlöcher, 1998).

2.3. Magnetic resonance imaging protocol

MRI scanning sessions were performed immediately after the psychometric assessment (except for 5 subjects for whom an MRI session was performed one week later due to MRI scanner unavailability) on a 3-Tesla Siemens Verio scanner (Siemens AG, Erlangen, Germany).

An high-resolution T1-weighted MRI 3D volumes sequence (192 contiguous sagittal slices; 1 mm slice thickness; TR = 1.9 s; TE = 2.42 ms; TI = 0.9 ms; FA = 9°; in-plane resolution: 1 × 1 mm) was acquired for each subject. Additional sequences (T2-weighted and fluid-attenuated inversion recuperation) were acquired and analyzed to rule out concomitant diseases such as ischemic stroke and susceptibility artifacts from prior hemorrhage or space-occupying lesions. Severe white matter lesion load was used as an exclusion criterion.

2.3.1. Structural image processing

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Fischl et al., 2002, 2004a, 2004b; Ségonne et al., 2004; Reuter et al., 2010). Briefly, this processing includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002, 2004a,b). Intracranial volume