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Persistent decrease in alpha current density in fully remitted subjects with major depressive disorder treated with fluoxetine: A prospective electric tomography study

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ABSTRACT

Major depressive disorder (MDD) is recurrent, and its pathophysiology is not fully understood. Studies using electric tomography (ET) have identified abnormalities in the current density (CD) of MDD subjects in regions associated with the neurobiology of MDD, such as the anterior cingulate cortex (ACC) and medial orbitofrontal cortex (mOFC). However, little is known regarding the long-term CD changes in MDD subjects who respond to antidepressants. *The aim* of this study was to compare CD between healthy and MDD subjects who received 1-year open-label treatment with fluoxetine.

Thirty-two-channel electroencephalograms (EEGs) were collected from 70 healthy controls and 74 MDD subjects at baseline (pre-treatment), 1 and 2 weeks and 1, 2, 6, 9 and 12 months. Variable-resolution ET (VARETA) was used to assess the CD between subject groups at each time point. The MDD group exhibited decreased alpha CD (αCD) in the occipital and parietal cortices, ACC, mOFC, thalamus and caudate nucleus at each time point. The αCD abnormalities persisted in the MDD subjects despite their achieving full remission. The low sub-alpha band was different between the healthy and MDD subjects. Differences in the amount of αCD between sexes and treatment outcomes were observed. Lack of a placebo arm and the loss of depressed patients to follow-up were significant limitations. The persistence of the decrease in αCD might suggest that the underlying pathophysiologic mechanisms of MDD are not corrected despite the asymptomatic state of MDD subjects, which could be significant in understanding the highly recurrent nature of MDD.

1. Introduction

Major depressive disorder (MDD) is considered a recurrent and relapsing illness; only approximately 30-60% of patients remain without a relapse during 1-2 years of maintenance with antidepressants or cognitive therapy (CT) (Bulloch et al., 2014; Jarrett et al., 2013; McGrath et al., 2006; Mulder et al., 2009; Prudic et al., 2013; Rush et al., 2006; Steinert et al., 2014). Additionally, there are no effective methods to diagnose MDD objectively, to assess its severity or the patient's response to treatment or to predict relapses (Schmidt et al., 2011). Conversely, little is known regarding the long-term brain pathophysiological changes once MDD patients have recovered from a major depressive episode (MDE).

The studies of the effects of the pharmacologic antidepressant treatment (ADT) on the brain structure have found contradictory results. Some authors have reported a hippocampus volume reduction in remitted MDD patients (Ashtari et al., 1999; Axelson et al., 1993; Kronmuller et al., 2008; Pantel et al., 1997; Rusch et al., 2001; Rydmark et al., 2006). Several studies performed in stable, remitted MDD patients have identified grey matter density decreases in the left hippocampus, left anterior cingulate cortex (ACC), left dorsomedial prefrontal cortex (DMPFC), and dorsolateral prefrontal cortex (DLPFC) volumes after 3 years of ADT, compared with healthy controls (Frodl et al., 2008; Janssen et al., 2007; Sheline et al., 1996, 1999). Phillips et al. (2012) reported a significant mean increase in whole-brain volume and grey-matter volume in the right orbitofrontal cortex and in the right inferior temporal gyrus in MDD remission of subjects with treatment-resistant unipolar depression. In contrast, some studies that evaluated the subgenual anterior cingulated cortex (sgACC) identified a 14-39% decrease in the volume over a broad range of ages of MDD patients related to the number of previous MDEs and male sex but not to pharmacologic ADT (Boes et al., 2008; Botteron et al., 2002; Chen et al., 2007; Drevets et al., 2007; Hastings et al., 2004; Tang et al., 2007; Yucel et al., 2008).

Several functional studies undertaken using diverse techniques, such as positron emission tomography (PET) and functional magnetic

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resonance imaging (fMRI), have found abnormalities in MDD subjects in diverse brain regions, such as the prefrontal cortex (PFC), sgACC, amygdala, dorso lateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), hippocampus, and thalamus and in the connectivity between the amygdala and the dorsal anterior cingulate cortex (dACC) (Abler et al., 2007; Anand et al., 2005; Bhagwagar et al., 2004; Chen et al., 2008; Dannlowski et al., 2009; Drevets et al., 1997, 1999, 2002, 2007, 2008; Fales et al., 2008; Gotlib et al., 2005; Greicius et al., 2007; Hamilton and Gotlib, 2008; Hirvonen et al., 2008; Keedwell et al., 2008; Kegeles et al., 2003; Kumano et al., 2007; Mayberg et al., 2000; Meltzer et al., 2004; Moses-Kolko et al., 2008; Nahas et al., 2007; Pizzagalli et al., 2004; Sargent et al., 2000; Sheline et al., 2001; Siegle et al., 2002; Yang et al., 2009). However, the majority of these studies have not addressed the changes induced by the ADT. There have been few published fMRI studies that have addressed the functionality in remitted MDD patients. These studies have demonstrated abnormalities in brain activation despite the achievement of remission (Foland-Ross et al., 2013; Hooley et al., 2009; Jing et al., 2013; Nixon et al., 2013; Schiller et al., 2013; Smoski et al., 2013).

In contrast, perhaps due to their low cost and non-invasive nature, neurophysiological studies (e.g., electric brain tomography and event-related potentials) have been widely used to examine the differences between healthy subjects and MDD patients and to predict antidepressant response in the acute phase of treatment. MDD patients exhibited significantly elevated current density (CD) in the delta, theta, alpha, beta1, and beta2 frequency bands in the ACC and PFC, compared with the controls (Korb et al., 2008). Additionally, some studies have identified a high pre-treatment theta CD in the rostral anterior cingulate cortex (rACC) and the medial orbitofrontal cortex (mOFC). This activity has been associated with greater symptom improvement at weeks 2 and 8. Furthermore, this activity is a "state" marker that varies over the course of a depressive episode (Hunter et al., 2013; Korb et al., 2009, 2011; Pizzagalli et al., 2001, 2003). The majority of these studies were performed over a short time period and were designed to measure early response to antidepressants.

Given the evidence that alpha activity is involved in sensory processing, cognition, memory, mood and anxiety (Başar, 2012; Başar and Güntekin, 2012), the smaller number of published studies that have addressed this particular topic and the scarce amount of information, we decided to focus our attention on this topic in the present paper, and the remainder of these topics will be analysed in future publications.

Based on the results of previous functional studies and the highly recurrent nature of MDD, we hypothesised that the abnormalities identified in short-term studies of alpha current density (αCD) would be persistent despite clinical recovery.

1.1. Objectives

The aim of the present study was to compare the resting state electrical activity between healthy controls and MDD patients before and at several time points during the acute, continuation and maintenance phases of ADT for 1 year using variable resolution electric tomography (VARETA).

2. Materials and methods

2.1. Subjects

This study included 70 healthy controls without a personal or family history of MDE/MDD and 74 MDD subjects who never received antidepressants and had no comorbid mental or medical disorders. The MDD patients were in the acute phase, with a minimum of 17 points scored on the Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1960), 17 points scored on the Beck Depression Inventory II (BDI-II) (Beck et al., 1961, 1996) and 20 points scored on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

The following individuals were excluded from the study: patients currently diagnosed with (or with a history of) substance abuse disorders, hypomanic or manic episodes, encephalic trauma, and medical or psychiatric conditions; patients who were under treatment for any medical condition, were pregnant, or who were in postpartum status; patients under previous or current psychiatric treatment (including psychopharmacological, psychotherapeutic, electroconvulsive or transcranial stimulation therapies); and patients with any abnormalities on their laboratory tests.

The diagnosis of an acute episode of MDD was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) criteria, using a checklist of symptoms. The Mini International Neuropsychiatric Structured Interview (M.I.N.I.), Spanish version 5 (Sheehan et al., 1998), was administered to all of the participants by two experienced and independent clinicians, to confirm the diagnosis of MDE and to exclude any other mental disorders. The kappa index for MDE/MDD was 95.

The healthy controls and MDD individuals were selected from the general community in an urban area of Querétaro, México. Recruitment was achieved by open invitation posters in public places and by referrals from public and private medical and psychiatric facilities. The entire duration of the study spanned from November 2010 to March 2014. After the study procedure was fully explained to all of the participants, written informed consent was obtained (in accordance with general health regulations in México). Certified clinicians obtained a full medical history from and performed a physical examination on each participant.

The Spanish version of the Edinburgh Handedness Inventory (EHI) was used to assess handedness (Oldfield, 1971). A subject was considered right-handed if his/her total score on the EHI was $>+40$ points. The subjects who scored <-40 points were considered left-handed, and the subjects who scored between -40 and $+40$ points were considered ambidextrous.

The Institutional Review Board (IRB) of the General Hospital of Querétaro, México, approved the study protocol and the informed consent forms. There was no financial sponsorship from any medical equipment or pharmaceutical companies, and there are no conflicts of interest to report.

The MDE subjects were treated with fluoxetine at doses of 20 mg/day during week 1 and at doses of 40 mg/day from week 2 to 1 year, using an open-label study design. The HDRS-17, BDI-II and MADRS were administered by an experienced clinician at baseline, at weeks 1 and 2, and at months 1, 2, 6, 9 and 12.

2.2. Electroencephalogram (EEG) acquisition

Thirty-two-channel Neuronic™ MEDICID 5.36 equipment and its corresponding software, designed to obtain a digital EEG, were used (I.C. Neuronic S.L., La Muela, Zaragoza, Spain). Grass™ gold electrodes (Grass Technologies, West Warwick, RI, USA) were placed individually on the scalp as shown in Fig. 1 and were cleansed with ethyl alcohol; Nuprep™ abrasive skin prepping gel was applied (Weaver and Company, Aurora, CO, USA). The electrodes were fixed with Ten 20™ conductive electrode paste (Weaver and Company, Aurora, CO, USA). The EEG study was conducted at 8:00 AM, after breakfast and without sleep deprivation. The impedance for each electrode was set at ≤ 5 KΩ, and the amplifier bandwidth was set between 0.5 and 30 Hz. The sampling rate of digitisation was of 200 samples/s. According to Lieberson (2010), we considered the broadband frequencies as follows: delta, 0–4 Hz; theta, 4–8 Hz; alpha, 8–12.8 Hz (low 8–10.5 Hz/high 10.5–12.88 Hz); and beta, >12.89–19.14 Hz. Fourier analysis was used to obtain the narrow and broadband frequencies (Kropotov, 2009).

The participants were placed on a comfortable couch in a temperature-controlled, soundproof, dark room with dim light. The EEG acquisition consisted of a first phase of 20 min in a waking state