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Altered dynamics of brain connectivity in major depressive disorder at-rest and during task performance

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ABSTRACT

Major depressive disorder (MDD) has been associated with alterations in several functional brain networks. Previous studies investigating brain networks in MDD during the performance of a task have yielded inconsistent results with the function of the brain at rest. In this study, we used functional magnetic resonance imaging at rest and during a goal-directed task to investigate dynamics of functional connectivity in 19 unmedicated patients with MDD and 19 healthy controls across both experimental paradigms. Patients had spatial differences in the default mode network (DMN), in the executive network (EN), and in the dorsal attention network (DAN) compared to controls at rest and during task performance. In patients the amplitude of the low frequency (LFO) oscillations was reduced in the motor and in the DAN networks during both paradigms. There was a diagnosis by paradigm interaction on the LFOs amplitude of the salience network, with increased amplitude change between task and rest in patients relative to controls. Our findings suggest that the function of several networks could be intrinsically affected in MDD and this could be viable phenotype for the investigation on the neurobiological mechanisms of this disorder and its treatment.

1. Introduction

Major depressive disorder (MDD) is a severe psychiatric disorder with a lifetime prevalence of 10–20% in the general population and a significant risk for chronicity and disability (DeRubeis et al., 2008). Altered structure and/or function of a large number of brain regions has been associated with MDD, thus suggesting that the pathophysiology of depression entails multiple brain circuits (Pandya et al., 2012).

Resting-state functional magnetic resonance imaging (RS-fMRI) is a valuable method to understand how functional alterations in different brain regions are related to intrinsic networks (INs, Biswal et al., 2010). Previous evidence from RS-fMRI indicates that spatially separated brain regions show temporal correlations in their blood-oxygen-level-dependent (BOLD) signal (Biswal et al., 1995). These synchronous neuronal signal fluctuations are considered to reflect functional connectivity (FC) of segregated neuro-anatomical INs (Fox and Raichle, 2007; Seeley et al., 2007). Based on their spectral profile, low frequency oscillations (LFO) are those spontaneous neuronal signal fluctuations with frequency < 0.08 Hz (Buzsaki and Draguhn, 2004). BOLD LFOs are thought to originate in the gray matter and therefore are associated with the neural processes underlying FC of the brain networks (Zuo et al., 2010).

In MDD alterations of multiple INs have been reported (Hamilton et al., 2011; Marchetti et al., 2012; Northoff et al., 2011; Pizzagalli, 2011), including the default mode network (DMN), which comprises a set of brain regions more engaged during rest relative to goal-oriented tasks (Raichle and Snyder, 2007). Whole brain functional connectivity patterns at rest were able to differentiate with high confidence patients

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with MDD from healthy controls (Zeng et al., 2012). Interestingly, the patterns of FC with highest discriminative power were located in multiple networks, including the DMN. More recently, two meta-analyses and a systematic review of RS-fMRI studies agreed upon a role of functional alterations in multiple networks in MDD including the DMN, and dorsal attention network (DAN), the executive network (EN), and the salience network (SN) (Kaiser et al., 2015; Sundermann et al., 2014; Wang et al., 2012b). Furthermore, we and others have demonstrated altered LFOs during resting state in patients with MDD (Guo et al., 2012; Sambataro et al., 2013; Wang et al., 2016). Notably, temporal network dysfunctions are already present in patients at the first MDD episode and medication naïve (Liu et al., 2013). Widespread alterations of LFOs of resting state networks have been described in multiple brain circuits including the SN , the DAN, the DMN (Guo et al., 2012; Sambataro et al., 2013; Wang et al., 2016), and the motor networks (Wang et al., 2016).

Neuroimaging literature implicates altered network function in MDD also during the performance of a task, including those networks associated with emotional, cognitive (Roiser et al., 2012), and motor processing (Liberg and Rahm, 2015). Nonetheless, the extent to which spatial and temporal characteristics of intrinsic networks are also altered during task performance has not been extensively studied. A recent meta-analysis on the brain activation differences in task-based fMRI concluded that MDD was associated with a pattern of functional activation abnormalities in cortico-limbic/cortico-striatal circuits rather than with regions of the DMN (Graham et al., 2013), thus showing a poor spatial overlap between task-based and RS-fMRI findings in MDD (Sundermann et al., 2014).

This discrepancy could be explained by the paucity of studies investigating connectivity patterns both at rest and during task performance in the same individuals with MDD. Furthermore, results' inconsistency could arise from different analytical methods used to analyze RS- and task-fMRI data. In particular, the use of seed-based analysis which estimates connectivity between *a priori* selected regions-of-interest (seeds) and the rest of the brain (Wang et al., 2012b) could explain the over-representation of DMN alterations in RS-fMRI studies. Spatial and statistical features in the selection of an *a priori* seed per se could also cause an observational bias (Cole et al., 2010). Also, as a single seed can be analyzed at the time, only a limited number of networks are investigated in each analysis. Alternative to this approach, independent component analysis (ICA), a model-independent multivariate statistical analysis, can extract spatially independent and temporally synchronous activity patterns in brain regions, which represent FC (Calhoun et al., 2001). First, this approach allows the estimation of spatial patterns of FC that fluctuate over time; second, FC patterns are estimated across multiple brain networks at once thus avoiding an observational bias in network selection (Veer et al., 2010). To date, few fMRI studies have employed ICA to investigate functional abnormalities in MDD during task (Vasic et al., 2009) or at-rest (Greicius et al., 2007; Sambataro et al., 2013; Shi et al., 2015; Veer et al., 2010; Zhu et al., 2012). Of these studies, only one conducted a comprehensive network analysis. Veer and colleagues (2010) identified 13 INs at-rest, 3 of which showed reduced FC in unmedicated patients with MDD compared to healthy controls. These networks included a DAN, a visual network, and an affective network involved in emotional regulation, but no significant differences were found in the DMN (Veer et al., 2010). However, whether the functional abnormalities of the INs in MDD are similar at-rest and during task remains unclear.

In this study, we set out to investigate the dynamics of network function across different experimental paradigms (at rest and during a cognitive task) in unmedicated patients with MDD and healthy volunteers. Based on this literature, we hypothesized that: 1) patients with MDD would show consistent alterations in patterns of FC of the DMN, the EN, the DAN, and the SN both at rest and during a goal-directed processing; 2) the temporal oscillations of these networks would be altered in the low frequency range. To this aim, we studied FC and spectral properties of multiple brain networks, and their between network connectivity in the same subjects with MDD while at rest and during the performance of a low demanding cognitive task. To reduce the risks of observational biases and false positive results, we used a hierarchical multivariate approach (Allen et al., 2011). With the multi-paradigm approach we aimed at identifying not only those diagnosis-related changes that are associated with paradigm performance, but also those differences that are independent from the experimental conditions and therefore more robust. Also, we wanted to assess whether diagnosis modulated network function depending on the experimental condition.

2. Methods

2.1. Participants

Nineteen unmedicated patients with MDD and nineteen healthy controls without any psychiatric, neurologic, or medical illness (all Caucasians) completed the study (see also Supplemental Information). Groups did not differ for gender distribution, age, years of education and performance in a motion prediction task. Thirteen patients with MDD were medication naïve. All the other patients had been off-medication for at least six weeks before the study (four of them were under antidepressant treatment, and for other two past treatment information was not available). Exclusion criteria for both groups included age <18 or >65 years, current presence of psychosis as assessed by SCID-I interview or self-reported past history of psychosis or bipolar disorder, major medical or neurological illness; current drug or alcohol abuse, MRI contraindications. Inclusion in the MDD group was contingent on a diagnosis of current MDD based on a SCID-I semi-structured interview (DSM-IV-TR). Six subjects with MDD had co-morbid anxiety disorders (Supplemental Information). The study was approved by the University of Zurich's Institutional Review Board, and all subjects gave written informed consent. They were paid 25 CHF/hour and the gains related to the experimental task.

2.2. MRI imaging

2.2.1. Image acquisition

Images were acquired on a Philips Achieva 3-Tesla whole-body MRI unit equipped with an eight-channel head coil using a sensitivity encoded single shot echo-planar sequence (acceleration factor R=2). A T1-weighted gradient echo sequence (turbo field echo) with a spatial resolution of $0.94\times0.94\times1.00$ mm^3 (matrix: 240×240pixels; 160slices), field of view=240×240 mm^2, TE=3.7 ms, TR=8.06 ms, and flip angle=8° was applied. For the acquisition of the functional images, the subjects were told to lie still in the scanner with their eyes closed and let their mind wander (Logothetis et al., 2009; Northoff et al., 2010); 300 functional images were collected in a single 10-min run. The following parameters were used: TR=2000 ms, TE=30 ms, flip angle=75°, ascending acquisition order, 80×80voxel matrix and voxel size=3×3×4 mm^3.

Thirty-six contiguous axial slices were placed along the anterior-posterior commissure plane covering the entire brain. The first four acquisitions were discarded due to T1 saturation effects. Six hundred images of functional imaging data during the performance of a motion prediction task were acquired in the same session with similar scanning parameters. The task is described in details elsewhere (Späti et al., 2014) and the Supplemental Information. The acquisition of resting-state and task data was always separated by about 10-min during which we acquired structural data. Structural MRI scans were screened by an experienced neuroradiologist for structural brain abnormalities and other incidental lesions. Nonetheless, we did not exclude subjects for this reason.