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Three-dimensional components of selfhood in treatment-naive patients with major depressive disorder: A resting-state qEEG imaging study

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ABSTRACT

Based on previous studies implicating increased functional connectivity within the self-referential brain network in major depressive disorder (MDD), and considering the functional roles of three distinct modules of such brain net (responsible for three-dimensional components of Selfhood) together with the documented abnormalities of self-related processing in MDD, we tested the hypothesis that patients with depression would exhibit increased connectivity within each module of the self-referential brain network and that the strength of these connections would correlate positively with depression severity. Applying the electroencephalogram (EEG) operational synchrony analysis to extract three modules of the self-referential brain network in 12 medication-free depressive outpatients and 10 control subjects we have found an increase in the strength of EEG synchrony within all three modules in depressive patients (though non-significant for the right module). Furthermore, multiple regression analysis that used 3 factors (values of synchrony strength for all three modules) as input indicated that combined increase in the strength of synchrony in all three modules was positively associated with severity of depression. Taken together the findings of this study suggest that depression is primarily associated with hypersynchrony in all three modules of the brain self-referential network (the anterior module been responsible for "witnessing observation and first–person perspective", the left posterior module been responsible for "reflective agency and narration" and the right posterior module been responsible for "bodily representational-emotional agency"), thus contributing to excessive self-focus, rumination, and body tension.

1. Introduction

The phenomenal sense of selfhood, identified with the core conscious experience of being someone or an agent (Blanke and Metzinger, 2009), is a fundamental feature of everyday human experience (Zahavi, 2005). This sense is associated with a broad spectrum of brain processes that relate to self – so called "*self-related processing*" that predominantly refers to emotional/bodily/autobiographical and cognitive/reflective/ruminative processes resulting in awareness of oneself as an active self or "I" (Northoff et al., 2006; Schneider et al., 2008; Christoff et al., 2011).

It seems that patients with major depression disorder (MDD) have abnormal self-related processing, mostly expressed as increased self-focus, excessive self-reflection (rumination) and association of the self with negative emotions (Northoff, 2007; Lemogne et al., 2012; Zhao et al., 2013). Indeed, depressed patients do show an increased preoccupation with their own self (Northoff et al., 2007), and self-focus in patients with a previous history of MDD has been shown to be a reliable predictor of the re-occurrence of depressive episodes (Nolen-Hoeksema et al., 2008). Generally, excessive ruminative self-focus produces such feelings as worry, guilt, shame, jealousy, which may lead to insomnia (Leary, 2004), increased anxiety (Buss, 1980), and eventually result in clinical depression (Mor and Winquist, 2002). An important aspect of self is bodily awareness, which has been defined as self-body schema or image (Berlucchi and Aglioti, 2010) that is formed by the extero- and interoceptive stimuli (Damasio, 1999, 2003). Patients with depression showed a higher degree of interoceptive awareness (Paulus and Stein, 2010). Moreover, a distorted body self-image is associated with depression (Veale et al., 2003). Therefore, taking together these observations, it may be beneficial to re-think or re-frame depression as a *disorder of selfhood*.

Based on recent neuroimaging studies the general consensus has

Abbreviations: EEG, Electroencephalogram; DMN, Default Mode Network; OA, Operational Architectonics; OM, Operational Module; MDD, major depression disorder; HAM, Hamilton Depression Rating Scale; SCID, Structured Diagnostic Interview; SC, synchrocomplexes; RTP, rapid transitional period; CV, coefficient of variability

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been reached that self-related brain processing is associated with the default mode network (DMN) (Christoff et al., 2003; Wicker et al., 2003; Gusnard, 2005; Buckner and Carroll, 2007; Schilbach et al., 2008; Spreng and Grady, 2010; Qin and Northoff, 2011; Fingelkurts and Fingelkurts, 2011; Fingelkurts et al., 2012; Andrews-Hanna et al., 2014). If so, then the increased self-focus in depressed patients should be associated with enhanced activity and connectivity/integrity within the DMN. This hypothesis has found confirmation in a number of neuroimaging resting-state studies (Wang et al., 2012; Whitfield-Gabrieli and Ford, 2012; Zhu et al., 2012; Nejad et al., 2013; Sambataro et al., 2014) and studies involving stimuli-presentation/cognitive tasks (Lemogne et al., 2009; Sheline et al., 2009; Hamilton et al., 2011; Kessler et al., 2011). Furthermore, greater DMN activation was shown to positively correlate with feelings of depression and hopelessness (Grimm et al., 2009).

Current empirical evidence suggests that the DMN is not a homogenous unit that functions as a single whole (see for the review Fingelkurts et al., 2016a) but rather is a *heterogeneous brain system* composed of at least three spatially separable yet functionally interacting components or subnets each consisting of brain regions showing tight "functional connectivity" within each subnet (Fingelkurts and Fingelkurts, 2011; see also Uddin et al., 2009; Andrews-Hanna et al., 2010; Spreng and Grady, 2010; Leech et al., 2011). These subnets or operational modules (OM) are: the anterior OM and two symmetrical (right and left) occipito-parieto-temporal OMs (Fingelkurts and Fingelkurts, 2011; Fingelkurts et al., 2016b). Considering the empirical findings on the functional-topographical specialization of these OMs during normal/healthy states (Fingelkurts and Fingelkurts, 2011) and pathological conditions when self-consciousness is minimal or lost (Fingelkurts et al., 2016c), as well as during self-control training (Fingelkurts et al., 2016b), we have proposed a *three-dimensional construct model* for the complex experiential selfhood (Fingelkurts et al., 2016b).

The "triad" model of selfhood (Fingelkurts et al., 2016b) states that the *anterior module* of the self-referential brain network (Fig. 1) is responsible for the first-person perspective and sense of agency (therefore it may be called the "witnessing observer" or simply "Self"). The *right posterior module* of the self-referential brain network (Fig. 1) is responsible for the experience of self as a localized embodied entity (through the interoceptive and exteroceptive bodily sensory processing), emotion-related thoughts, and autobiographical memories (in short the "representational-emotional agency" or simply "Me"). The *left posterior module* of the self-referential brain network (Fig. 1) is responsible for the experience of thinking about and reflecting upon oneself, momentary narrative thoughts and inner speech, as well as reinterpretation of short-term memory events related to self (it may be called the "reflective agency" or simply "I"). Together this OM triad is simultaneously engaged in the construction of phenomenal selfhood (Fingelkurts and Fingelkurts, 2011; Fingelkurts et al., 2016b).

Based on previous studies implicating increased functional connectivity within the self-referential brain network in MDD (Wang et al., 2012; Whitfield-Gabrieli and Ford, 2012; Zhu et al., 2012; Nejad et al., 2013; Sambataro et al., 2014), and considering the functional roles of the three OMs within DMN (Fingelkurts and Fingelkurts, 2011; Fingelkurts et al., 2016b) along with the abnormalities of self-related processing in MDD (Mor and Winquist, 2002; Northoff, 2007; Nolen-Hoeksema et al., 2008; Lemogne et al., 2012; Zhao et al., 2013), we predicted that patients with depression (i) should exhibit increased connectivity (though to a different extent) within each OM, and that (ii) the strength of this connectivity should positively correlate with depression severity. To test these predictions was the *aim of the present study*. To the best of our knowledge, no existing studies have tracked changes in the three modules of the self-referential brain network in relation to a three components of selfhood in depressed patients.

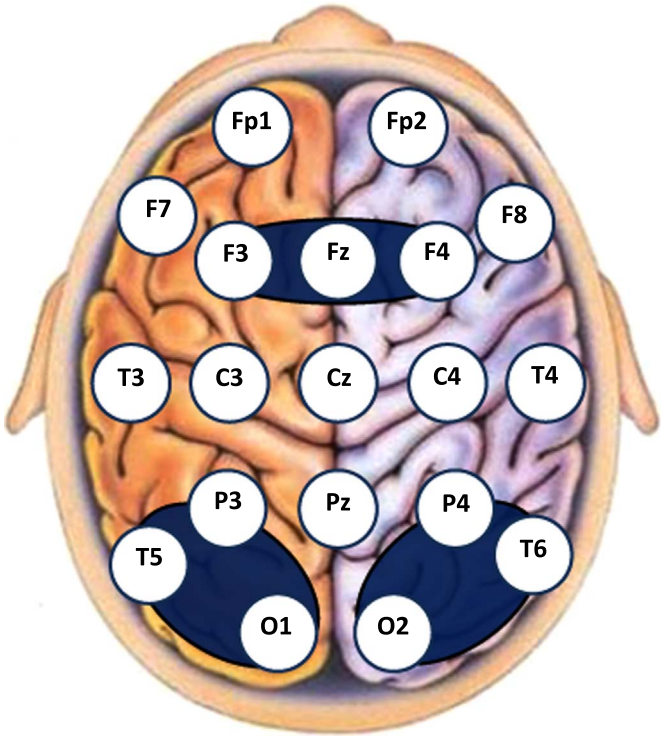

Fig. 1. Operational modules (subnets) of the self-referential brain network. The statistically significant ($p < 0.05$) values of operational synchrony among EEG locations (marked by white circles with EEG electrode IDs) that are involved in every OM are mapped onto schematic cortex map as dark blue coloured areas indicating OMs. Abbreviations: EEG: electroencephalogram; OM: operational module.

2. Methods

2.1. Subjects

In the current study we re-analyzed data from a previously conducted study (Fingelkurts et al., 2007) to explore the new aspect – the functional connectivity within the three OMs of the DMN – that is distinct from and has not been addressed in the original research. For the purpose of this study EEG and medical data were extracted from the database of 12 medication-free clinically depressed outpatients (7 males, 5 females, mean age 43 ± 14 years, all right handed). Based on the Structured Diagnostic Interview (SCID) First et al., 1994) all patients met the criteria for a major depressive episode. The mean HAM score was 24 ± 4 based on the 17-item Hamilton Depression Rating Scale (HAM) (Hamilton, 1960). Physical examination and blood tests, as well as renal and thyroid analyses revealed that beside been depressed the patients were in otherwise good physical health. The exclusion criteria were a DSM axis I diagnosis other than major depression, a history of mania, a history of schizophrenia, alcohol or drug dependence within 5 years preceding the EEG registration, or active signs of suicidal ideation.

As a healthy control the data from 10 sex- and age-matched nonsmoking healthy volunteers (5 males, 5 females, mean age 42 ± 12 years, all right handed) were used. The control subjects were included in the study after medical examination and screening for a depression. None of the control subjects had DSM axis I diagnosis of depression in the SCID evaluation (First et al., 1994). Furthermore, all control subjects had no history of neurological or psychiatric pathology and were free from psychotropic medication. The mean HAM score for healthy controls was 0.5.

All participants gave written informed consent before enrolling in the original study in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the study protocol was approved by the Helsinki University Central Hospital Ethics