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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.

**Keywords:**

Self-referential brain network, DMN, subjective sense of self, first-person perspective, EEG, alpha rhythm, operational synchrony, functional connectivity, depression, rumination.

## 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.

## 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 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) occipitoparieto-temporal OMs (Fingelkurts and Fingelkurts, 2011; Fingelkurts et al., 2016a,b). 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., 2012, 2016c), as well as during self-control training (Fingelkurts et al., 2016a,b), we have proposed a *three-dimensional construct model* for the complex experiential selfhood (Fingelkurts et al., 2016a,b).

The "triad" model of selfhood (Fingelkurts et al., 2016a,b) 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., 2016a,b).

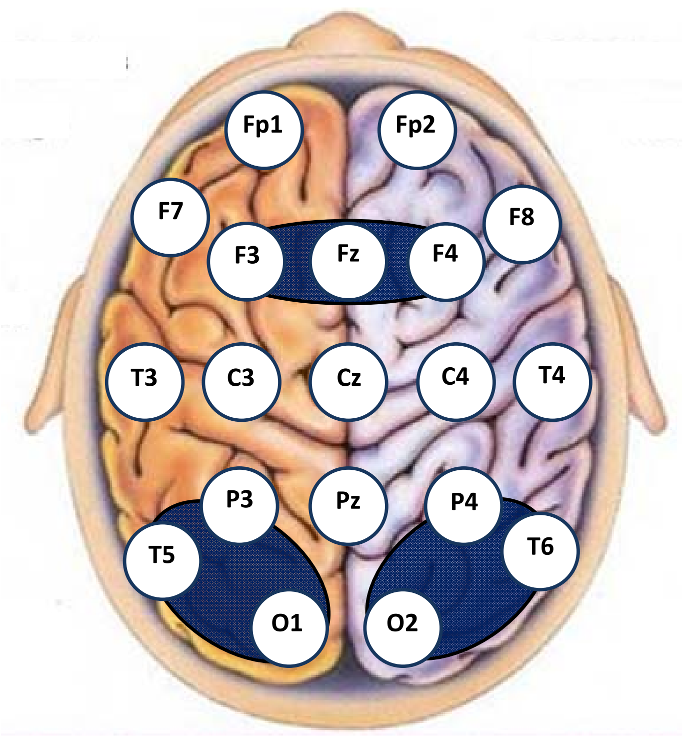


**Figure 1. Operational modules (subnets) of the self-referential brain network.** The statistically significant ($p < 0.05$) values of operational synchrony among EEG locations (marked by white circles with EEG electrode IDs) that are involved in every OM are mapped onto schematic cortex map as dark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

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., 2016a,b) 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.

## 2. Methods

### *2.1. Subjects*

In the current study we re-analysed 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 Committee. The current re-analysis study was approved by the BM-Science Review Board. Data use (including potential future re-analyses) was authorized by means of written informed consent by all subjects prior to EEG scanning.

*2.2. EEG registration and pre-processing*

All EEG recordings were performed in a magnetically and electrically shielded room (Euroshield, Eura, Finland) using a 60-channel EEG data acquisition system (Neuromag Vectorview, Helsinki, Finland) during 20 minutes (eyes closed) with a frequency band of 0.06–86 Hz (sampling rate 300 Hz) at the BioMag Laboratory, Helsinki University Central Hospital. Nose electrode was used as a reference. The impedance of recording electrodes was monitored for each subject with an impedance meter prior to data collection; this was always below 5 kΩ. Vertical and horizontal electro-oculograms were also recorded.

All EEG recordings were done late in the morning. The subject (either control or patient) was asked to relax and engage in no specific mental activity. The presence of an adequate EEG-signal was determined by visual inspection of the raw signal. Epochs containing artifacts due to eye movement, eyes opening, significant muscle activity, and movements on EEG channels, as well as drowsy episodes (indexed by slowing of background frequencies by ≥1 Hz, vertex sharp waves and slow eye movements) were marked and then automatically excluded from further analysis.

A full artifact-free EEG stream for every subject was fragmented into consecutive 1-minute epochs. Further data processing was performed for each separate 1-minute portion of the signal (in total per EEG recording 18-20 min). For the purpose of this study and prior to further processing procedures each 1-minute epoch of EEG-signal was resampled to 128 Hz and bandpass-filtered (Butterworth filter of the sixth order) in the alpha (7–13 Hz) frequency band. Phase shifts were eliminated by forward and backward filtering. Even though different EEG frequency bands may have correlation with the DMN (Berkovich-Ohana et al., 2012; Neuner et al., 2014), the alpha frequency band was chosen in the current study because: (1) it has been repeatedly demonstrated that the DMN has significant positive correlation with alpha rhythm (Laufs et al., 2003; Mantini et al., 2007; Jann et al., 2009) in comparison to other EEG bands (Knyazev et al., 2011); (2) alpha oscillations dominate the EEG of humans in the absence of external stimuli when mind-wandering and spontaneous thoughts are most pronounced (Shaw, 2003; Palva and Palva, 2007; Klimesch et al., 2007; Basar and Guntekin, 2009; Fingelkurts and Fingelkurts, 2010, 2014); (3) it has been shown that operational connectivity within three modules of the self-referential brain network (identified by EEG alpha band) clearly correlate with the presence or absence of self-consciousness: it was smallest or even absent in patients who are in a vegetative state, intermediate in patients who are in a minimally conscious state and highest in healthy fully self-conscious subjects (Fingelkurts et al., 2012); (4) the resting alpha rhythm determines one's risk for certain affective disorders, such as major depression and anxiety (for review, see Coan and Allen, 2004; Davidson, 2004).

*2.3. Estimation of OMs and their strength*

As it has been shown in our earlier EEG studies (Fingelkurts and Fingelkurts, 2011; Fingelkurts et al., 2012; 2016a,b,c) a constellation of nine operationally synchronized cortical areas indexed by three distinct OMs (*anterior* OM: $F_3$-$F_z$-$F_4$; *left posterior* OM: $T_5$-$P_3$-$O_1$; and *right posterior* OM: $T_6$-$P_4$-$O_2$) could, in large, account for the self-referential brain network (Fig. 1). Based on the reference study of Koessler et al. (2009) on the anatomical correlations of EEG electrode positions, where a clear match between EEG electrode position and anatomical area of the cortex was established and verified through an EEG-MRI sensor system and an automated projection algorithm (see also Kaiser, 2000 for the correlations between EEG activity in a given electrode position and its correspondent cortical area), in the current study the following EEG positions (and correspondent cortical areas, Koessler et al., 2009) were used to estimate the operational synchrony within the three OMs. EEG positions $F_3$ and $F_4$ (left and right middle frontal gyri or Brodmann's area 8), EEG position $F_z$ (bilateral medial areas or Brodmann's area 6), EEG positions $T_5$ and $T_6$ (left and right middle temporal gyri or Brodmann's area 21), EEG positions $P_3$ and $P_4$ (left and right precuneus or Brodmann's area 19), and EEG positions $O_1$ and $O_2$ (left and right middle occipital gyri or Brodmann's area 18).

The operational synchrony estimation requires several consecutive stages of data processing. The details of these procedures can be found elsewhere (Fingelkurts and Fingelkurts, 2008; 2015). Here we provide only a brief overview of the main steps. At the *first step*, each local EEG signal was reduced to a temporally organized sequence of quasi-stationary (nearly stationary) segments of various duration. To uncover these quasi-stationary segments from the complex nonstationary structure of local EEG signals, an adaptive segmentation procedure was used (Fingelkurts and Fingelkurts, 2008; 2015). The aim of segmentation is to divide each local EEG signal into naturally existing quasi-stationary segments by estimating the intrinsic points of 'gluing' – rapid transitional periods (RTPs). An RTP is defined as an abrupt change in the analytical amplitude of the signal above a particular threshold which is derived experimentally (and verified in modeling studies) using statistical procedures (Fingelkurts and Fingelkurts, 2008; 2015). The RTP duration is very short compared to quasi-stationary segments, and therefore can be treated as a point or near-point (Fingelkurts and Fingelkurts, 2008; 2015). It has been proposed that each homogeneous segment in the local EEG signal corresponds to a temporary stable microstate – an operation executed by a neuronal assembly (Fingelkurts et al., 2010). The temporal coupling (synchronization) of such segments among several local EEG recordings then, reflects the synchronization of operations (i.e. operational synchrony), produced by different neuronal assemblies (located in different cortex regions) into integrated and unified patterns responsible for complex mental operations (Fingelkurts et al., 2010).

Estimation of operational synchrony signifies the *second step* of analysis. Measurement of operational synchrony estimates the statistical level of RTP temporal coupling between two or more local EEG recordings (Fingelkurts and Fingelkurts, 2008; 2015). The measure tends toward zero if there is no synchronization between EEG segments derived from different EEG channels and has positive or negative values where such synchronization exists. Positive values (above upper stochastic threshold) indicate 'active' coupling of EEG segments (synchronization of EEG segments is observed significantly more often than expected by chance as a result of random shuffling during a computer simulation), whereas negative values (below lower stochastic threshold) mark 'active' decoupling of segments (synchronization of EEG segments is observed significantly fewer than expected by chance as a result of random shuffling during a computer simulation) (Fingelkurts and Fingelkurts, 2008; 2015). The strength of EEG operational synchrony is proportional to the actual (absolute) value of the measure: the higher this value, the greater the strength of functional connection.

Using pair-wise analysis, operational synchrony was identified in several (more than two) channels – synchrocomplexes (SC); these define operational modules – OMs. The criterion for defining an OM is a sequence of the same SC during each 1-min epoch, whereas a SC is a set of EEG channels in which each channel forms a paired combination with valid values of synchrony with all other EEG channels in the same SC; meaning that all pairs of channels in an SC have to have statistically significant synchrony linking them together (Fingelkurts and Fingelkurts, 2008; 2015).

It is often argued that volume conduction is the main obstacle in interpreting EEG brain connectivity. Luckily it is not a case for operational synchrony index. It has been shown previously in empirical and modeling studies that the values of the operational synchrony index are sensitive to the morpho-functional organization of the cortex rather than to the volume conduction and/or reference electrode (for relevant results and discussion see Fingelkurts and Fingelkurts, 2008; 2015; Kaplan et al., 2005). Those studies also revealed the existence of fine statistical heterogeneity (anisotropy) of electro-magnetic field in regard to the processes of mutual stabilization of quasi-stable periods among regional EEGs (operational synchrony). Furthermore, contrary to other EEG measures of functional connectivity, the operational synchrony measure, which was used in the current study is based on temporal point-to-point coupling of RTPs determined in local EEG channels and does not require a shared EEG rhythm or activity in different EEG channels (it is exactly this similarity in EEG signals on the scalp that is determined to a large degree by volume conduction or a common activity source). Thus the operational synchrony measure that is based on temporal coincidences of RTPs does not require implicit or explicit source model for the interpretation of its results (Kaplan et al., 2005).

### *2.4. Statistical analysis*

The strength of functional connectivity within individual self-referential brain network OMs was assessed using EEG operational synchrony (see the previous subsection). The differences in strength of operational synchrony between depressed patients ("*D*" *group*) and healthy controls ("*C*" *group*) were assessed using a two-sample *t*-test. At first, all strength values of EEG operational synchrony were averaged within each OM for all 1-min EEGs per subject and then averaged across all subjects per group (D and C). In order to measure the OM pattern stability, for every OM we calculated the coefficient of variability (CV =

standard deviation / Mean) for the averaged strength of operational synchrony across all 1-min EEGs ($N$ = 233 for D-group, $N$ = 189 for C-group), with CV~1 indicating nearly random process and CV << 1 reflecting very high stability. Demographic and clinical characteristics were analyzed using Chi-Square tests and Wilcoxon's $t$-test. Correlations between HAM scale and functional connectivity strength within every OM of the self-referential brain network were analyzed using Pearson correlation analysis and multiple regression in the D-group only (12 patients with depression are sufficient to guarantee unbiased estimation of coefficients and $R^2$ values according to a recent modelling study, Austin and Steyerberg, 2015).

## 3. Results

### *3.1. Demographic characteristics*

There were no significant differences in gender ratio (Chi-Square, $p = 0.69$) and age (Wilcoxon's $t$-test, $p = 0.54$) between D- and C- groups. However, the mean HAM score was significantly higher in D-group compared to C-group (Wilcoxon's $t$-test, $p = 0.0001$) in which it was within normal range.

### *3.2. Neurophysiological findings*

We observed a noticeable increase in the strength of EEG operational synchrony within all three OMs of the self-referential brain network in D-group compared to C-group (Fig. 2), though statistical significance was reached only for the anterior OM ($p < 0.000001$) and left posterior OM ($p < 0.05$) OMs. Furthermore, analysis of CV revealed that the strength of EEG operational synchrony within all three OMs was very stable (CV ranged from 0.21 to 0.29 for different OMs) in both groups (Table 1).

The HAM score of depressed patients was positively correlated with the strength of EEG operational synchrony only in the anterior OM of the self-referential brain network ($r = 0.89$, $p < 0.001$). Such correlation reached statistical borderline for the left posterior OM ($r = 0.61$, $p = 0.05$). At the same time, the multiple regression analysis that used 1 dependent factor (HAM) and 3 independent factors (values of strength of all three OMs) as input parameters indicated that a *combined increase in the strength of operational synchrony in all three OMs* was positively associated with an increase in HAM scores ($F = 6.92$, $r = 0.85$, $p < 0.01$). In order to estimate the percentage of variance that is explained by the regression function (coefficient of determination), the $r$ was squared and multiplied by 100. The full model coefficient of determination demonstrated that 72% of the combined operational synchrony strength variance was coupled/associated with HAM score variance in depressed patients. Generally, already 50% (or above) is considered indicative of good dependency of one variable with another(s).

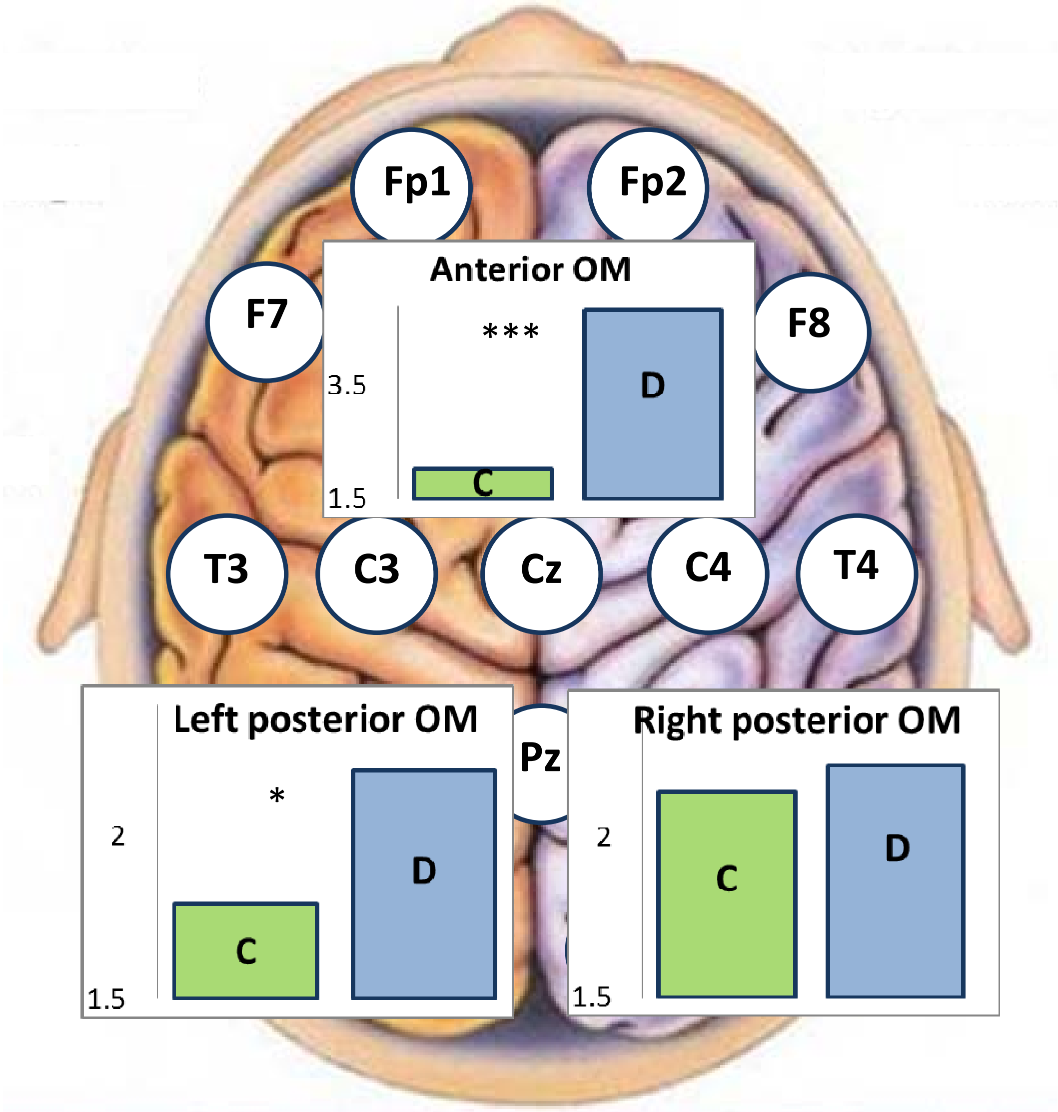


**Figure 2. Operational synchrony strength within three OMs of the self-referential brain network in depressed patients and healthy controls**. Data in graphs are averaged across corresponding EEG channels that constitute each of the OMs and across all 1-minute EEGs for each group (C and D). The *Y*-axis presents values of strength of operational synchrony. Circles indicate the EEG electrode locations (some locations are hidden behind the graphs representing the OMs, refer to Fig. 1) mapped onto the schematic cortex map. Abbreviations: EEG: electroencephalogram; OM: operational module; C: control group; D: depression group. *** – $p < 0.000001$; * – $p < 0.05$.

**Table 1. Stability of the averaged strength of operational synchrony across all 1-min EEGs for every OM separately for D and C group.**

| Group | Anterior OM | Right postrior OM | Left postrior OM |
|---|---|---|---|
| D | 0.22 | 0.29 | 0.25 |
| C | 0.29 | 0.21 | 0.22 |

## 4. Discussion

Consistent with prior reports of greater DMN functional connectivity during depression (Wang et al., 2012; Whitfield-Gabrieli and Ford, 2012; Zhu et al., 2012; Nejad et al., 2013; Sambataro et al., 2014), the results of this study fully confirm our prediction that (i) patients with depression indeed exhibit increased connectivity (to a different extent) within all three OMs of the self-referential brain network (Fig. 2) and (ii) that the strength of such connectivity positively correlated with depression severity. In light of our discussion in the Introduction section, a dramatic increase in synchrony strength within the anterior OM (Fig. 2) of the self-referential brain network may explain increased self-focus in depressed patients (Wang et al., 2012; Nejad et al., 2013; Sambataro et al., 2014). The brain structures comprising the anterior OM have been shown to be involved in the sense of being a self, being a subject/agent of self-conscious experience (Andrews-Hanna, 2012; Moran et al, 2013; Musholt, 2013) and support the point of view from which person experiences the world (Baars et al., 2003; Feinberg, 2009). Thus the increased integrity of this OMs may accompany increased self-focus, which considered to be a core factor in the psychopathology of depression (Northoff, 2007). This conclusion is consistent with recent observation that the transcranial magnetic stimulation delivered to this brain subnet with parameters of stimulation leading to a disruption of interconnectivity, causes significant reduction of self-perception (Kwan et al., 2007) and 'private' self-awareness (Gruberger et al., 2015). Together these findings suggest that the anterior OM of the self-referential brain network acts as a hub for integrating many abstract aspects of experience, such as social, emotional and self-evaluation into self-relevant context (Baars et al., 2003), thus constructing the experience of the witnessing observer (Fingelkurts et al., 2016a,b). At the same time, such a phenomenal observing self seems to require a 'narrative interpreter' in order to establish complete self-awareness (Baars et al., 2003).

The left posterior OM of the self-referential brain network is responsible for such narration (Fingelkurts et al., 2016a,b). Increased synchrony within this OM in patients with depression (Fig. 2) may explain increased self-rumination in such patients who experience increased attention paid to the self, where the person keeps repetitively wonder about his or her self-worth (Joireman, 2004), about symptoms of distress and the possible causes or consequences of these symptoms (Nolen-Hoeksema et al., 2008). Complementary findings come from neuroimaging studies that show a correlation between increased connectivity in the DMN parietal areas with high maladaptive depressive rumination scores, and reduced adaptive rumination scores (Hamilton et al., 2011). Additionally, it has been documented that trait rumination predicts activation and synchrony of the left posterior areas of the DMN not only when observing negative images but also when reappraising neutral images in a negative way (Ray et al., 2005). Together, these findings may explain why patients with depression tend to focus more on negative self-referential thoughts. Indeed, negative self-referential thoughts seem to persevere in depressed patients (Nejad, 2013). For example, it has been documented that compared to healthy subjects, depressed patients attend more to negative stimuli, and also recall more negative stimuli than positive ones (Williams et al., 1996). Furthermore there is a large body of empirical evidence suggesting a reciprocally reinforcing connection between rumination and negative affect

(Mor and Winquist, 2002), whereas rumination tends to increase when negative emotions are up-regulated and vice versa (Ray et al., 2005). Excessive rumination decreases the attentional efficiency and general information processing capacity (Rimes and Watkins, 2005), further supporting the claim of insufficient brain functioning during depression (Fingelkurts et al., 2007).

Since the multiple regression analysis indicated that a combined increase in the strength of operational synchrony in all three OMs (including the right posterior OM) was positively associated with an increase in HAM scores, we would like to discuss the increased operational synchrony, albeit statistically non-significant, in the right posterior OM of the self-referential brain network in depressed patients (Fig. 2). It could contribute to understanding of a well-documented increase in interoceptive awareness in such patients (Paulus and Stein, 2010), leading to distorted body self-image (Veale et al., 2003) and negative emotional tone (Craig, 2004). Indeed, most of the models of emotional processing assume that subjective emotional feelings are related to changes in the skeletomuscular, neuroendocrine, and autonomic nervous systems (James, 1884; Levenson, 2003; Barrett et al., 2007; Damasio and Carvalho, 2013; Nummenmaa et al., 2014). The right posterior OM of the self-referential brain network is typically associated with bodily self-consciousness (Fingelkurts et al., 2016b). Additional support comes from neuroimaging studies that show that the right inferior parietal sulcus, posterior insula, and precuneus (anatomically approximating the right posterior OM) are involved in integrating multisensory bodily signals and reflecting the conscious experience of self as a localized embodied entity having emotion-related thoughts from the first-person perspective (Ionta et al., 2011; Blanke, 2012; Terasawa et al., 2013).

Our analysis (using multiple regression) suggests that combined increase in the strength of operational synchrony in *all three OMs is important* in maintaining the depressive state, and that the higher the synchrony, the more severe the depression. It seems that such relations between three OMs of the self-referential brain network reflect the plausible pathophysiological mechanism of depression and account for the failure of depressed patients to disengage from negative thoughts and increased negative self-evaluation in such patients. Based on multiple studies about the functional specialization of brain areas involved in the three studied OMs and considering the three-dimensional construct model for the complex experiential selfhood (Fingelkurts et al., 2016a,b), it could be speculated that in such constellation of the operational modules of the self-referential brain network the anterior OM organises, represents and appraises the salience interoceptive/emotional information presented in the right posterior OM and the narrative and semantic-conceptual information presented by the left posterior OM.

Taken together the findings of this study suggest that depression is primarily associated with hypersynchrony in all three OMs of the self-referential brain network (the anterior OM having the strongest synchrony increase and the right posterior OM – the weakest increase), thus contributing to excessive self-focus, rumination, and body tension. One may speculate that these three components of complex selfhood (indexed by distinct OMs of the self-referential brain network) synergize one another in a maladaptive loop and overtime become habitual, leading to a vicious circle that maintains a disordered affective state clinically manifested as depression. Such interpretation is highly compatible with a model proposed by Beck (1987) who suggested that when maladaptive scripts and schemas are constantly re-activated throughout life, "they skew the information processing system which then directs attentional resources to negative stimuli and translates a specific experience into a distorted negative interpretation. The hypersalience of these negative schemas leads not only to a global negative perception of reality but also to the other symptoms of depression, such as sadness, hopelessness, loss of motivation and regressive behaviors such as social withdrawal and inactivity" (Beck, 2008; p. 138). Thus, the pathophysiological mechanism of depression may consist of a continuous positive feedback loop among three highly self-synchronized subnets of the self-referential brain network leading to a pathological self-focus, negative interpretations and attentional biases with the subjective and behavioral symptoms reinforcing each other.

## 5. Conclusion

Here we report the first qEEG study of changes in three modules of the self-referential brain network in relation to the three components of complex selfhood in depressed patients. The findings point that parallel hypersynchrony within each of the three OMs of the self-referential brain network could lead to dysfunctional self-referential and affective processing in the form of excessive negative self-focus, excessive self-reflection (rumination) and association of the self with negative emotions. Importantly, the synchrony increase in any single OM may not necessarily indicate association with depression, as for example, the anterior OM synchrony increase been a proportional/"normal" response to self-regulatory (meditation) training (Fingelkurts et al., 2016a,b) or positive self-evaluation (Beer et al., 2010; Pauly et al., 2013). However, simultaneous increase in synchrony within all three OMs seems to be a necessary pre-requisite for abnormal self-referential processes in patients with major depression. Here it is important to keep in mind that the three aspects of selfhood (indexed by the three OMs) are not entities that simply modify something that has its own independent existence, but rather together form a dynamic pattern, that as a whole constitutes a complex selfhood (for a similar view see Gallagher, 2013).

While been speculative such conceptual model is useful as an explanatory construct of depression, but more studies are needed before a more comprehensive theory of depression is formulated. Furthermore, due to a fact that no standardized scales specifically targeting the studied three aspects of selfhood were used in the current study, future studies should adopt a design that along with neurophysiological assessment of OMs would also utilize both standardized scales for self-focus, rumination and interoceptive awareness/body image as well as the first-person reports of patients. Also, small sample size of this study warranted future studies with a larger group of patients/subjects.

**Conflict of interest**

The authors confirm that this article content has no conflict of interest.

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