# Trait Lasting Alteration of the Brain Default Mode Network in Experienced Meditators and the Experiential Selfhood

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# Abstract:

Based on the finding in novices that four months of meditation training significantly increases frontal DMN (default mode network) module/subnet synchrony while decreasing left and right posterior DMN modules synchrony (Fingelkurts et al., 2015a), the current study tested the prediction whether experienced meditators (those who are practicing meditation intensively for several years) had a change in the DMN 'trinity' of modules as a baseline trait characteristic and whether this change is in a similar direction as in the novice trainees who practiced meditation for only four months (Fingelkurts et al., 2015a). Comparison of functional connectivity within DMN subnets (measured by electroencephalogram operational synchrony in the three separate DMN modules) between 5 experienced meditators and 10 naïve participants (who were about to start the meditation training) fully support the prediction. Interpretation that links such DMN subnets changes to the three-dimensional components of the experiential selfhood was proposed.

## **Keywords:**

Default mode network, DMN, subjective sense of self, first-person perspective, electroencephalogram, EEG, alpha rhythm, operational synchrony, functional connectivity, meditation, yoga, mindfulness.

## **INTRODUCTION**

Our previous study showed that four months of meditation training (irrespective of a concrete technique) alters the synchrony within the brain default mode network (DMN) of novices in a peculiar way (Fingelkurts et al., 2015a). Specifically, synchrony within the frontal DMN module/subnet increased significantly, while the synchrony within the left and right posterior DMN modules/subnets decreased as a function of meditation training. Based on the recent conceptualization of the DMN's role in self-consciousness (Kircher et al., 2000; Gusnard et al., 2001; Christoff et al., 2003; Wicker et al., 2003; Gusnard, 2005; Northoff et al., 2006; Buckner & Carroll, 2007; Schilbach et al., 2008; Spreng & Grady, 2010; Fingelkurts & Fingelkurts, 2011; Qin & Northoff, 2011) and empirical findings on the functional-topographical specialization of frontal and parietal DMN modules during normal states (Fingelkurts & Fingelkurts, 2011; see also Uddin et al., 2009; Andrews-Hanna et al., 2010, 2014; Doucet et al., 2011; Yeo et al., 2011) as well as pathological vegetative state when self-consciousness is lost (Fingelkurts et al., 2012, 2015b), we have proposed a three dimensional<sup>1</sup> construct model for the complex experiential selfhood (Fingelkurts et al., 2015a).

According to this proposal and in line with the multi-faceted nature of self-awareness (Musholt, 2013; Limanowski & Blankenburg, 2013; Blackmore, 2015), the frontal DMN module is responsible for the firstperson perspective and the sense of agency (the *witnessing observer*), the posterior right DMN module is responsible for the experience of self as an localized embodied entity, emotion-related thoughts, and autobiographical memories (*representational-emotional agency*) and the posterior left DMN module is responsible for the experience of thinking about oneself, including momentary narrative thoughts (*reflective agency*). Together, such trinity of the DMN subnets provides a coherent representation of complex selfhood (Fingelkurts & Fingelkurts, 2011; Fingelkurts et al., 2012, 2015a).

Conceptualizing the DMN as a functional integration of three subnet modules, each contributing specific functions or qualities characterizing self-referential processing, allows us to give a plausible interpretation of findings that relatively long-term meditation alters the functional synchrony of DMN subnets in opposing directions: increased integrity of the frontal and decreased integrity of two posterior DMN modules (Fingelkurts et al., 2015a). Such changes in the DMN subnet trinity may explain the diverse well-known subjective experiences of meditation training as 'the unbroken experience of existence attained by the still mind' (Nash & Newberg, 2013), avoidance of intruding unintended thoughts with simultaneous unconditional feeling of loving-kindness and compassion (Ricard et al., 2014) and decreased disturbing interoceptive and exteroceptive bodily sensations (Newberg et al., 2001; Newberg & Iversen, 2003).

If several months of meditation training lead to above-reported changes in DMN integrity of naïve trainees (Fingelkurts et al., 2015a), then an important prediction can be made: the experienced meditators (those who practice meditation intensively for several years) will have an altered DMN trinity as a baseline

<sup>&</sup>lt;sup>1</sup> Dimension means that some construct can be measured or identified (hence 'dimension') and that it should inform hypotheses and conclusions.

trait<sup>2</sup> characteristic (even before any acute meditation exercise). Further, these meditation-induced trait changes should proceed in the same direction as in the novice trainees who practiced meditation for only four months. **The current study aimed to test these predictions**.

#### MATERIALS AND METHODS

## **Participants**

Fifteen (6 males, 9 women; M age = 52.1 years, SD = 10.9) healthy, right-handed subjects participated in the study. Ten (*novices*; 4 males, 6 women; M age = 51.7 years, SD = 10.9) were recruited from the participants who are going to take part in a four-month training course in meditation (but had not yet started the training). The remaining five subjects (*experienced* meditators; 2 males, 3 women; M age = 53.0 years, SD = 12.0) have had long-term meditation practice (on average of 3.9 years, SD = 1.2). Meditation techniques practiced by these experienced meditators were: Kriya yoga (1 subject), High-Vibration meditation (1 subject), Zen meditation (1 subject), Mindfulness (1 subject), and Qigong (1 subject). Even though various meditative states that are reached through practicing of a particular meditation technique are associated with different EEG spatio-temporal and oscillatory signatures (Lobusov et al., 2001; Cahn & Polich, 2006; Saggar et al., 2012), if there is any common long-lasting (trait) effect of meditation (independent of any particular technique) on the DMN integrity (the target of present study), then despite the multitude of possible neurophysiological effects of each concrete meditation, that common effect should emerge (Fingelkurts et al., 2015a).

None of the subjects had history of head trauma, current/past psychiatric disorders, or psychoactive medication/drug use. The inclusion criteria for this study were (a) to be in good general, neurological and psychological/psychiatric health, (b) for novices to have never practiced any meditation technique before entry to the study; for experienced meditators to have had long-term (several years) experience of meditation. Exclusion criteria comprised (a) stressful events during last 3 years, (b) change of job, place of residence, or preoccupation during last 3 years, (c) change of life-style or a diet during last 3 years, (d) any serious disorder during last 3 years.

Participants signed an informed consent form after the experimental procedures were explained, prior to electroencephalogram (EEG) scanning. The study complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and standards established by the BM-Science – Brain and Mind Technologies Research Centre Review Board. The use of the data for scientific studies was authorized by means of written informed consent of the subjects approved by the Review Board of BM-Science – Brain and Mind Technologies Research Centre.

 $<sup>^2</sup>$  Trait effect refers to lasting changes in altered sensory, cognitive, and neurophysiological effects that persist in the meditator irrespective of being actively engaged in meditation at the moment (Cahn & Polich, 2006).

## **EEG** registration

EEGs were recorded with a 21-channel EEG data acquisition system (Mitsar, St. Petersburg, Russian Federation) from 19 electrodes positioned according to the International 10–20 system (i.e.  $O_1$ ,  $O_2$ ,  $P_3$ ,  $P_4$ ,  $P_z$ ,  $C_3$ ,  $C_4$ ,  $C_z$ ,  $T_3$ ,  $T_4$ ,  $T_5$ ,  $T_6$ ,  $F_z$ ,  $F_3$ ,  $F_4$ ,  $F_7$ ,  $F_8$ ,  $F_{p1}$ ,  $F_{p2}$ ) during waking resting state with closed eyes. The recording parameters were: linked earlobes as a reference electrode; 0.5–30 Hz bandpass; 50 Hz notch filter ON; 250 Hz sampling rate; 6-min closed eyes. The impedance was below 5–10 k $\Omega$ . Additionally, an electrooculogram (0.5–70 Hz bandpass) was collected.

All EEG recordings were done in late morning for all subjects. The subjects were asked to relax and engage in no specific mental activity, and to not apply any specific relaxation or meditation techniques during the EEG recording. The EEG (used for this study) for all subjects were recorded during closed eyes resting condition within one week *before* meditation training course commenced (the results of meditation training are published elsewhere, Fingelkurts et al., 2015a), because for the purpose of the current study we were not interested in the specific and immediate effects of meditation training ('state' effect<sup>3</sup>). The aim was to estimate how long-lasting routine meditation practice ('trait' effect) would influence the DMN modules in baseline resting condition (experienced meditators) in comparison to subjects who had never practiced meditation or relaxation techniques before (naïve participants).

We focused on the resting-state condition, because we were interested in trait effects and because it permits assessment of "pure" self-relevant brain activity (Koenig et al., 2002; Smallwood & Schooler, 2015) such as spontaneous processing of an internal mental context (Von Stein & Sarnthein 2000), internal "narrative," and "autobiographical" self (Gusnard et al., 2001; Johnson et al., 2002; Buckner & Carroll, 2007).

# EEG-signal data pre-processing

The presence of an adequate EEG signal was determined through visual inspection of the raw signal. Epochs containing artefacts due to eye movement/opening, significant muscle activity and movements on EEG channels, as well as drowsy and sleep episodes were marked and then automatically removed from further analysis.

A full artefact-free EEG stream was fragmented into consecutive 1-min epochs for each subject. The division of the EEG stream into a 1-min intervals permitted us to obtain a relatively large number of the analysis epochs (within which we searched for the naturally accruing quasi-stationary segments, see 'Estimation of DMN OMs and their strength' section below) – this was important for the unbiased estimate of the operational synchronicity index (more details and justifications could be found in Fingelkurts & Fingelkurts, 2008). Further data processing was done separately for each 1-minute epoch of the signal. Due

<sup>&</sup>lt;sup>3</sup> State effect refers to altered sensory, cognitive, and neurophysiological effects that can arise during meditation practice (Cahn & Polich, 2006).

to the technical requirements of the tools used to process the data, EEGs were re-sampled to 128 Hz. This procedure should not affect the results since 128-Hz sampling rate meets the Nyquist Criterion (Faulkner, 1969) of a sample rate greater than twice the maximum input frequency for the alpha activity, thus avoiding aliasing and preserving alpha activity information of the input signal.

After re-sampling and prior to further processing procedures, each EEG signal was bandpass-filtered (Butterworth filter of the sixth order) in the alpha (7–13 Hz) frequency band. Phase shifts were eliminated through forward and backward filtering. The alpha frequency band was chosen for several reasons. First, it allows us to compare current and prior study (Fingelkurts et al., 2015a) results. Second, 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; Sadaghiani et al., 2010; Brookes et al., 2011) and that the alpha band independent component of EEG-signal showed the highest spatial correlation to the DMN template when compared to other EEG bands (Knyazev et al., 2011). Third, alpha oscillations dominate the EEG of humans in the absence of external stimuli (rest-condition) when internal life (mind-wandering and spontaneous thoughts) is most pronounced (Palva & Palva, 2007; Klimesch et al., 2007; Basar & Guntekin, 2009; Fingelkurts & Fingelkurts, 2010, 2014). Moreover, the existence of an association between selfreferential thoughts and EEG alpha band spectral power within the DMN has been repeatedly established (Knyazev et al., 2011, 2012). Fourth, it has been shown that operational connectivity within the DMN (identified by EEG alpha band) clearly correlated with the presence/absence of self-consciousness: it was smallest or even absent in patients in vegetative state, intermediate in patients in minimally conscious state and highest in healthy fully self-conscious subjects (Fingelkurts et al., 2012, 2015b).

#### Estimation of DMN operational modules and their strength

As it has been shown in a series of earlier EEG studies (Fingelkurts & Fingelkurts, 2011; Fingelkurts et al., 2012, 2015a,) a constellation of nine operationally synchronized cortical areas indexed by three distinct operational modules – OMs (*frontal 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 DMN (Figure 1). Similarly, in the current study the following EEG positions (and correspondent cortical areas, Koessler et al., 2009) were used to estimate the operational synchrony within 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 anatomical correlations of EEG electrode positions used were taken from the reference study of Koessler et al., (2009), where a clear match between the EEG electrode positions and anatomical areas 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).

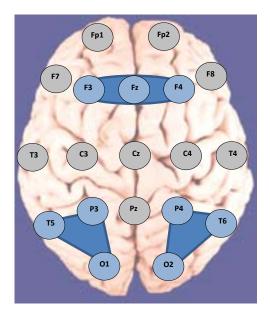


Figure 1. Operational modules of the DMN. The statistically significant (p < .05) values of operational synchrony among EEG locations (marked by grey circles with EEG electrode IDs) are mapped onto schematic cortex map as dark blue shapes that indicate OMs. Abbreviations: OM: operational module; DMN: default mode network.

To estimate DMN OM synchrony and strength, several stages of data processing were required. The details of these procedures can be found elsewhere (Fingelkurts & Fingelkurts, 2008, 2015). Therefore, here we provide only a brief overview of the main steps. The **first step** involved reducing each local EEG signal to a temporally organized sequence of nearly stationary (quasi-stationary) segments of varied duration (~300 ms in average for alpha rhythm). To uncover these quasi-stationary segments from the complex nonstationary structure of local EEG signals, an *adaptive segmentation procedure* was used (Fingelkurts & Fingelkurts, 2008, 2015). The aim of the 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, derived experimentally (and verified through modelling studies) based on the Student criteria (with different coefficients for different levels of analysis) (Fingelkurts & Fingelkurts, 2008, 2015). The RTP duration is very short compared to quasi-stationary segments, and therefore can be treated as a near-point (Fingelkurts & Fingelkurts, 2008, 2015). It has been proposed that each homogeneous segment in the local EEG signal corresponds to a temporary stable microstate<sup>4</sup> – a *simple operation* executed by a neuronal assembly (Fingelkurts et al., 2010). The temporal coupling (synchronization) of such segments among

<sup>&</sup>lt;sup>4</sup> Such microstate should not be confused with Lehmann's microstate which stands for the result of the momentary whole-brain electric field segmentation (Lehmann, 1971). Lehmann's methodology is based on the calculation of the spatial localization of the vector of the maximal potential difference; therefore it searches (in contrast to the technique mentioned here) the sequences of stable whole-brain microstates (Lehmann et al., 1987), but it does, however, lack time-dimensional information of each separate local EEG signal registered from separate cortex locations. The segmentation procedure used in the present study searches for the naturally occurring quasi-stationary segments (microstates) within each separate EEG signal (Fingelkurts & Fingelkurts, 2008, 2015).

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 the analysis. Measurement of operational synchrony estimates the statistical level of RTP temporal coupling between two or more local EEG recordings (Fingelkurts & Fingelkurts, 2008, 2015). The measure tends towards 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 frequently than expected by chance as a result of random shuffling during a computer simulation), whereas negative values is observed significantly less frequently than expected by chance as a result of random shuffling during of segments (synchronization of EEG segments is observed significantly less frequently than expected by chance as a result of random shuffling during a computer simulation) (Fingelkurts & 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 detected 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 synchrocomplexes (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<sup>5</sup> linking them together (Fingelkurts & Fingelkurts, 2008, 2015).

The measure of operational synchrony is sensitive to the morpho-functional organization of the cortex rather than to volume conduction and is independent of the signal power (Fingelkurts & Fingelkurts, 2008, 2015).

#### **Subjective reports**

Participants were asked to describe their subjective experience during EEG recording (with eyes closed) without analysis or judgment (Jack & Roepstorff, 2002; Lutz & Thompson, 2003) by ranking the complexity of the experience (on a 1-5 scale, with 1 – very simple and 5 – very complex); the speed of thoughts (on a 1-5 scale, with 1 – very slow/still and 5 – very fast/racing); as well as the presence or absence of self-agent, happiness, and calmness. The reports were collected immediately after the EEG recording was completed

<sup>&</sup>lt;sup>5</sup> Statistical significance of synchrony was measured by a direct estimation of a 5% level of statistical significance (p < .05) using the numerical modeling (500 independent trials). As a result of these tests the stochastic level of RTPs coupling and the upper and lower thresholds of its significance were calculated. These values represent an estimation of the maximum (by module) possible stochastic rate of RTPs coupling (Fingelkurts & Fingelkurts, 2008). Thus, only those values of operational synchrony which exceeded the upper (active synchronization) and lower (active unsynchronization) thresholds of stochastic levels have been assumed to be statistically valid (p < .05).

(Retrospective method, Smallwood & Schooler, 2015) in order to minimize reliance on episodic recall (Jack & Roepstorff, 2002) and avoid cognitive influences during scanning which can confound neural activity (Schneider et al., 2008).

#### **Statistics**

The strength of functional connectivity within the individual DMN OMs was assessed using EEG operational synchrony (see the previous subsection). The differences in strength of operational synchrony between experienced meditators (EXP group) and novices (NOV group) were assessed using Wilcoxon's *t*-test, which is used in the majority of functional connectivity studies (for the overview, see Weiss & Rappelsberger, 2000). At first, all strength values of EEG operational synchrony were averaged within each OM for all 1-min EEGs per subject and then averaged for all subjects per group (EXP and NOV). Differences between the items in the subjective reports were assessed either by Wilcoxon's *t*-test or by Chi-square test.

## RESULTS

#### **Subjective report results**

Analysis of the first-person reports revealed that the participants from the EXP group had significantly simpler subjective experiences (score 1.8 vs 2.9; Z = 2.33, p < .05) and slower speed of thoughts (score 2.2 vs 3.2; Z = 2.32, p < .05) than participants in the NOV group. Further, 100 % of participants from the EXP group had experience of self-agent, while only 40 % of participants from the NOV group had such experience (Chi-square, p < .0000001). The emotional content reported by the participants also differed between the groups: more participants experienced calmness (20 % vs 0 %) and happiness (60 % vs 40 %) from the EXP group when compared with NOV group (Chi-square, p < .0000001 for calmness and p < .0001 for happiness).

#### Neurophysiological results

We observed a mild but statistically significant increase (Z = -2.02, p < .05) in the strength of EEG operational synchrony within the frontal DMN OM of the EXP group compared to the NOV group, and a significant decrease (Z = 2.02, p < .05 for the right OM; Z = 2.02, p < .05 for the left OM) in the strength of EEG operational synchrony within the right and left posterior DMN OMs in the EXP group compared to the NOV group (Figure 2).

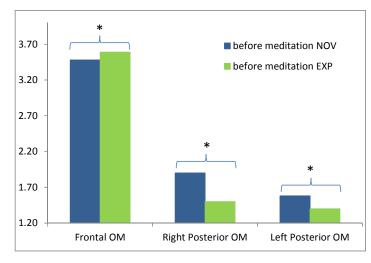


Figure 2. EEG operational synchrony strength within the DMN subnets (OMs). DMN – default mode network; OM – operational module; NOV – novices; EXP – experienced meditators. *Y*-axis indicates the strength of EEG operational synchrony. \* - p < .05. Due to very small values of standard error for all means, their values presented in the legend and not on the graph. Standard error of the means: Frontal OM in NOV: 0.01 / in EXP: 0.01; Right posterior OM in NOV: 0.02 / in EXP: 0.04; Left posterior OM in NOV: 0.02 / in EXP: 0.05.

## DISCUSSION

The results of this study fully confirm our prediction: the experienced meditators have the DMN structure significantly altered already at the baseline condition (closed eyes resting state) when compared to the baseline condition of subjects who did not practice any meditation or relaxation technique (and had not yet started the training) (Figure 2). Specifically, the frontal DMN OM had increased strength of EEG operational synchrony, whereas right and left posterior OMs had decreased strength of EEG operational synchrony. These findings are comparable to a previous study where subjects who did not practice any meditation or relaxation technique had similar changes in the DMN subnets/modules after only 4-month of meditation training (Fingelkurts et al., 2015a), and thus reflect trait (lasting) changes in the DMN structure that persist in long-term meditators irrespective of current meditation engagement<sup>6</sup> (Cahn & Polich, 2006).

As previously mentioned in the Introduction section, the conceptualisation of DMN trinity as a functional integration of three subnet modules, each contributing specific functions or qualities characterizing self-referential processing that form complex selfhood, helps us to interpret findings of the current study in a plausible way, compatible with the subjective experiences of meditators. The brain structures comprising the frontal DMN OM have been shown to be involved in the sense of being a self (i.e., being a subject/agent of self-conscious experience, Andrews-Hanna, 2012; Musholt, 2013; Moran et al., 2013), where one feels directly present as the center of an externalized multimodal perceptual reality, thus having the first-person perspective (Metzinger, 2004; Revonsuo, 2006; Trehub, 2007; Blanke & Metzinger,

<sup>&</sup>lt;sup>6</sup> It could also be related to an introverted self-related cognition (Knyazev, 2013) which might be a characteristic of meditators and which might differ between beginners and advanced practitioners (Tang, Holzel & Posner, 2015).

2009). Instead of being lost, the sense of such a 'center' gets sharper in professional meditators (Lutz et al., 2008; Kerr et al., 2011), who describe it as 'the unbroken experience of existence attained by the still mind' or a 'samadhi' state, accompanied by joy and happiness (Nash & Newberg, 2013; Raffone et al., 2014; Ricard et al., 2014). These first-person experiences are compatible with the subjective reports of the experienced long-term meditators of the current study who have reported persistent experience of self-agency, calmness and happiness (see Results section) accompanied by increased integrity of the frontal DMN OM (Figure 2).

The subjective experiences of meditators mentioned above usually include 'self-boundarylessness', or loss of bodily perceptions (Newberg et al., 2001; Newberg & Iversen, 2003). In Fingelkurts et al. (2015a) it has been argued that such subjective experiences when practiced systematically in the course of long-term meditation training result in long-lasting (trait) diminished integrity (measured by functional connectivity) of the right and left occipito-temporal-posterior DMN subnets (indexed as bilateral posterior OMs). Specifically, the proposition suggests that decreased functional connectivity within these posterior DMN OMs is responsible for (a) the right OM: diminished experience of embodiment and localization of self within bodily space (diminished interoceptive and exteroceptive bodily sensory processing), as well as limiting autobiographical thoughts (all these aspects of experiences have been related to the activity of areas comprising the right OM, Damasio, 1999; Critchley et al., 2004; Ionta et al., 2011; Blanke 2012; Múnera et al., 2014) and (b) the left OM: diminished thinking about oneself, diminished narrative thoughts and the pervasive role of inner speech, as well as reinterpretation of events related to self (all these aspects of experiences have been related to the activity of areas involved in the left OM, Mar, 2004; D'Argembeau et al., 2005; Moriguchi et al., 2006; Brownsett & Wise, 2010; Longe et al., 2010; Friston, 2011). Consistent with these interpretations the experienced meditators participated in the current study reported a diminished sense of thought speed, which is compatible with the diminished narrative of thoughts and decreased disturbing interoceptive and exteroceptive bodily sensations. Also, consistent with such subjective feelings was the reported by the experienced meditators participated in the current study sense of time slowing which is compatible with previous reports (Wittmann, 2015).

Summarising, long-term routine meditation brought about trait (long-lasting) alterations in the integrity of three modules/subnets of the brain DMN which are compatible with a three-dimensional account of the complex experiential selfhood as it has been presented here (see also Musholt, 2013; Limanowski & Blankenburg, 2013; Blackmore, 2015). At the same time, due to a small sample size, to confirm the results presented in this article, future studies with a larger sample of subjects for each group are warranted.

# **DISCLOSURE STATEMENT**

No potential conflict of interest was reported by the authors.

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