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Reductions in perceived stress following Transcendental Meditation practice are associated with increased brain regional connectivity at rest

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A R T I C L E I N F O

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A B S T R A C T

Transcendental Meditation (TM) is defined as a mental process of transcending using a silent mantra. Previous work showed that relatively brief period of TM practice leads to decreases in stress and anxiety. However, whether these changes are subserved by specific morpho-functional brain modifications (as observed in other meditation techniques) is still unclear. Using a longitudinal design, we combined psychometric questionnaires, structural and resting-state functional magnetic resonance imaging (RS-fMRI) to investigate the potential brain modifications underlying the psychological effects of TM. The final sample included 19 naïve subjects instructed to complete two daily 20-min TM sessions, and 15 volunteers in the control group. Both groups were evaluated at recruitment (T0) and after 3 months (T1). At T1, only meditators showed a decrease in perceived anxiety and stress ($t_{(18)} = 2.53$, $p = 0.02$), which correlated negatively with T1-T0 changes in functional connectivity among posterior cingulate cortex (PCC), precuneus and left superior parietal lobule. Additionally, TM practice was associated with increased connectivity between PCC and right insula, likely reflecting changes in interoceptive awareness. No structural changes were observed in meditators or control subjects. These preliminary findings indicate that beneficial effects of TM may be mediated by functional brain changes that take place after a short practice period of 3 months.

1. Introduction

The term 'meditation' refers to a range of different mental practices that are associated with thought, reflection and contemplation and that determine an enhancement of psychological and cognitive functions, such as emotion regulation, stress management, empathy, interpersonal abilities, attention and working memory (Lutz, Brefczynski-Lewis, Johnstone, & Davidson, 2008; Lutz, Slagter, Dunne, & Davidson, 2008; Sedlmeier et al., 2012; Tang, Hölzel, & Posner, 2015). A classification of meditation practices in three broad categories has been recently proposed: *focused attention*, *open monitoring* and *loving-kindness/compassion* (Lippelt, Hommel, & Colzato, 2014; Vago & Silbersweig, 2012). While for long time Transcendental Meditation (TM) has been considered to represent a particular type of mantra repetition technique within the category of focused attention meditation (Travis & Pearson, 1999), TM may actually constitute a distinct category itself, named 'Automatic Self-Transcending' (Fred Travis & Shear, 2010). Indeed, unlike most meditation techniques (including other mantra-based practices), TM technique does not involve contemplation, concentration, or voluntary attentional control (Travis & Parim, 2017). Rather, TM practice is a process defined of 'effortless transcending' in which the practitioner uses a mantra (a particular sound that has no literal meaning to the practitioner) as a vehicle to reach a state of 'consciousness without content' (Maharishi. , 1969; Tononi, Boly, Gosseries, & Laureys, 2016; Travis & Pearson, 1999). This different mental engagement is consistent with evidence indicating a high Default Mode Network (DMN) activation during TM practice (Mahone, Travis, Gevirtz, & Hubbard, 2018; Fred Travis et al., 2010; Travis & Parim, 2017), which is in contrast to the relative deactivation observed during goal-directed meditation practices in the same cortical network (Brewer et al., 2011; Garrison, Zeffiro, Scheinost, Constable, & Brewer, 2015; Simon & Engström, 2015; Tomasino, Chiesa, & Fabbro, 2014; Tomasino, Fregona, Skrap, & Fabbro, 2013). Moreover, in contrast to most meditation techniques, whose mastering usually requires relatively long training periods,

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ranging from several months to years, research demonstrates that TM can be mastered in a few months (Travis & Arenander, 2006).

TM has been shown to promote psychological well-being, mostly in terms of reduced anxiety and perceived stress (Lane, Seskevich, & Pieper, 2007; Orme-Johnson & Barnes, 2014), reduced depression and improved coping skills (Nidich et al., 2009). This is similar to what has been observed in other meditation techniques (Goyal et al., 2014; Khoury et al., 2013). Interestingly, several studies, including both cross-sectional comparisons between experienced meditators and non-meditators (e.g., Lazar et al., 2005; Hölzel et al., 2008; Farb, Segal, & Anderson, 2013; Fayed et al., 2013), and a few recent longitudinal studies in novice practitioners (e.g., Tang et al., 2010, 2012; Hölzel et al., 2011; Pickut et al., 2013; Wells et al., 2013) related the beneficial effects of goal-directed meditation techniques to changes in brain functional and structural architecture (for reviews see Fox et al., 2014, 2016; Tang et al., 2015; Gotink, Meijboom, Vernooij, Smits, & Hunink, 2016). Of note, several studies conducted on the effects of goal-directed meditation practices, such as mindfulness meditation, reported a strengthened connectivity within areas belonging to the DMN, including the posterior cingulate cortex (PCC), as well as with the frontal central executive network. These changes may result from the switching between externally and internally oriented attentional processes, which occur during those meditation practices (Gentili et al., 2009; Jang et al., 2011; Marchand, 2014; Shaurya Prakash, De leon, Klatt, Malarkey, & Patterson, 2013; Taylor et al., 2013; Wells et al., 2013). However, it is currently unclear whether the beneficial psychological effects of long-term TM practice are supported by morpho-functional brain changes within the same brain networks. Indeed, since TM and other meditation practices are associated with distinct patterns of brain activity, especially within the DMN, it is conceivable that their beneficial effects may be mediated by partially distinct brain modifications (Fox et al., 2016). Moreover, while previous cross-sectional EEG studies in TM practitioners demonstrated that particular changes in brain activity (mainly an increase in frontal alpha coherence) may be related with psychological improvements (S. I. Nidich et al., 2009), several open questions remain. In fact, these studies only evaluated brain activity during TM practice (Fred Travis et al., 2010; Travis & Wallace, 1999), or while performing challenging tasks immediately after a period of TM practice (Travis et al., 2009, 2018), and it is unclear whether task-independent, resting-state functional changes can also be observed. Moreover, EEG does not allow to accurately determine the anatomical localization of potential TM-dependent changes, nor to evaluate possible structural brain modifications.

In light of the above premises, in this preliminary study we combined psychometric assessment, structural and resting-state functional (RS-fMRI) magnetic resonance imaging (MRI) to investigate whether short-term TM practice in naïve subjects could lead to measurable modifications in brain structure and function related to its psychological effects. Specifically, based on previous evidence linking the DMN to subjective anxiety, stress and depression symptoms (Coutinho et al., 2016; Gentili et al., 2015), we hypothesized that TM-dependent psychological changes may be mediated by a functional and/or structural reorganization within this network.

2. Materials and methods

2.1. Participants

Volunteers were recruited by word of mouth and were assigned to the meditation/control group based on their individual preference. Twenty-two participants (16 F; 30 ± 9 years, mean ± SD; age range 24-58 years, 5 non-native Italian speakers) were included in the meditation group, while fifteen volunteers (7 F; 32 ± 11, mean ± SD; age range 23-58 years) participated in the passive control group. Of the 22 subjects in the meditation group, two participants (1 M/1 F) withdrew for personal reasons and one female participant was excluded from subsequent analyses because of excessive movement artifacts in fMRI data, leading to a final sample of 19 meditators (10 F; 29 ± 9 years).

All subjects underwent medical interview and examinations to rule out history or presence of any disorders that could affect brain function and development. Participants of both groups were provided with a detailed description of all the experimental procedures and were required to sign a written informed consent. The study was conducted under a protocol approved by the local ethical committee (protocol n. 1616/2003).

2.2. Experimental design

Subjects in the meditation group were instructed to meditate each day (two 20-minutes restful periods, one in the morning and the other one in the evening) for a three-month period, for an expected grand total of 66 h of meditation. TM is practiced while sitting comfortably with eyes closed, and is based on the inner and silent repetition of a *mantra*, a word without any meaning. A certified trainer (M.F.F.) taught the TM technique to the meditation group in the standard 4-day course preceded by an introductory session; the trainer also offered to participants the possibility to receive assistance and supervision (upon request) for the whole three-month period. However, none of the participants took advantage of this opportunity. Adherence to the protocol was also verified using a 'meditation diary' that volunteers were required to fill each day, reporting the start and end times of each meditation period. Subjects in the meditation group were required to submit the diary at the end of each week (missing reports were considered as no meditation, that is 0-h). Participants in the control group did not receive any meditation training and did not change their daily routines.

Volunteers in both groups completed two experimental sessions: at recruitment (T0) and after a 3 months' period (T1). During each experimental session, validated psychometric questionnaires were administered to assess the effects of TM practice on stress, anxiety, depression, resilience, interpersonal abilities and sleep disturbances. In addition, two anatomical and resting-state functional MRI scans were performed to explore the effects of TM on brain structure and function (Fig. 1).

2.3. Psychometric questionnaires

2.3.1. Stress and anxiety

Perceived stress, anxiety and depression were measured using two validated questionnaires. The Depression-Anxiety Stress Scale-21 (DASS-21; Bottesi et al., 2015) is a 21-item self-report questionnaire assessing core symptoms of anxiety, depression and stress. Each item is scored on a 4-point Likert scale, ranging from 0 ("Did not apply to me at all over the last week") to 3 ("Applied to me very much or most of the time over the past week"). The DASS-21 has been shown to have good psychometric properties (i.e., internal/external consistency and validity, test–retest stability) both in clinical and non-clinical samples, and contains three subscales: Depression, Anxiety, and Stress. The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) is a 10-item self-report questionnaire and represents the most common

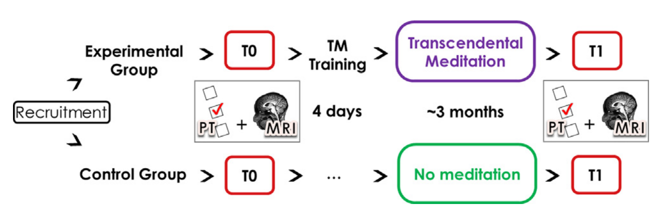

Fig. 1. Experimental design. Participants included in meditation and control groups underwent psychometric assessment and f/MRI at T0 and after 3 months (T1). Only the meditation group was required to practice Transcendental Meditation for 20 min twice a day throughout the 3 months period.

measure of subjective stress for the general population. Participants are asked to rate how often they felt their life had been overwhelming, unpredictable or overloaded during the previous 30 days on a 5-point Likert scale (from 0 = 'Never', to 4 = 'Very Often').

2.3.2. Resilience and interpersonal abilities

The Resilience Scale for Adults (RSA; Bonfiglio, Renati, Hjemdal & Friborg, 2016) measures six resilience protective factors, of which four are intrapersonal factors (personal strength, planned future, social competence, and structured style) and two are interpersonal factors (family cohesion and social resources). This scale comprises 33 items, scored along a 7-point semantic differential scale. The Interpersonal Reactivity Index (IRI; Davis, 1983) measures empathy and interpersonal abilities through a 28-item scale answered on a 5-point Likert scale ranging from "Does not describe me well" to "Describes me very well". The questionnaire has four subscales: Perspective Taking, Fantasy, Empathic Concern and Personal Distress.

2.3.3. Personality assessment

The Zuckerman-Kuhlman Personality Questionnaire (ZKPQ; De Pascalis & Russo, 2003) is based on the alternative Five Factors Model of personality (Zuckerman, Kuhlman, & Camac, 1988) and comprises 99 true/false items. The five dimensions measured are: (1) Impulsive Sensation-Seeking, (2) Neuroticism-Anxiety, (3) Sociability, (4) Aggression-Hostility and (5) Activity.

2.3.4. Sleep related disturbances

The Insomnia Severity Index (ISI; Castronovo et al., 2016) is a 7-item self-report questionnaire designed to assess severity of insomnia symptoms. Questions refer to the last 30 days and participants are asked to report severity of symptoms on a 5-point Likert scale (ranging from 0 = no problem to 4 = very severe problem). This questionnaire was included as sleep quality is affected by anxiety/stress levels and is modulated by meditation practices as well (Caldwell, Harrison, Adams, Quin, & Greeson, 2010; Gross et al., 2011; Ong et al., 2014; Winbush, Gross, & Kreitzer, 2007).

All participants were fluent in Italian or English language; thus the Italian or English validated version of each questionnaire was selected according to the language participants were most confident with.

2.4. MRI data acquisition and analyses

MRI data were acquired using a 1.5 T Siemens Symphony scanner (12 channels MATRIX head coil). During each session, a high-resolution MP-RAGE T1 weighted anatomical image (TR: 2200 ms, TE: 3.3 ms, TI: 900 ms, FOV: 256, flip angle: 8°, voxel size: $1 \times 1 \times 1$ mm, plane: 256×256, number of slices: 160) and a 7′28″ EPI resting-state (RS) scan (TR: 1800 ms, TE: 55 ms, FOV: 192, flip angle: 70°, 28 interleaved ascending axial slices, voxel size: 3x3x4mm, plane: 64x64, total number of volumes: 249) were acquired. During RS-fMRI, subjects were instructed to keep their eyes closed and to relax, refrain from moving and falling asleep.

2.4.1. Functional data analysis

The AFNI software package (Cox, 1996; Cox, 2012) and the FMRIB Software Library (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) were used to preprocess, analyze and view functional imaging data.

All brain volumes obtained during the RS condition were preprocessed using a standard pipeline. Specifically, all volumes were first de-spiked and temporally aligned. Subsequently, to minimize the contribution of noise caused by movements and physiological artifacts, voxel time-series were further adjusted by regressing out time-series of 6 motion parameters (i.e., x, y, z translations and rotations; *3dvolreg*), movement spike regressors (frame wise displacement above 0.3 as described in (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012); *fsl_motion_outliers*) and were corrected for temporal autocorrelation (ARMA 1,1; *3dREMLfit*). A spatial smoothing based on a 6 mm FWHM Gaussian kernel (*3dBlurToFWHM*) was applied. Individual preprocessed RS data were then normalized, aligned with anatomical images and linearly transformed (*3dAllineate*) into the Montreal Neurological Institute (MNI152) coordinate system using affine registration for group analyses. Finally, a 0.01–0.1 Hz bandpass filter was applied.

Given our hypothesis of expected meditation-dependent changes involving the Default Mode Network (DMN; Fox et al., 2016), a seed-based functional connectivity (correlation) approach was used to derive DMN connectivity maps in each subject. The seed region was selected using the NeuroSynth database (http://neurosynth.org; (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). A database query was conducted in October 2017 for the search term 'DMN', resulting in 229 studies and 6118 activations. Within the reverse inference map, we then identified the association peak which corresponded to the posterior cingulate cortex (PCC; coordinates [x = 0, y = -50, z = 24]). A spherical seed region-of-interest (ROI) with a 6 mm radius was created at this location using the AFNI program *3dUndump*. Functional connectivity maps were obtained by computing the Pearson's correlation coefficient (*3dfim+*) between the mean time-course from the seed region (*3dmaskave*) and the time-course of each gray matter brain voxel (Harvard-Oxford cortical probabilistic atlas thresholded at > 25%). Obtained correlation values were transformed into z-scores using Fisher's transformation.

2.4.2. Structural data analysis

Cortical reconstruction and volumetric segmentation was performed from structural MRI data using the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu). Specifically, non-brain tissues were first removed using the ANTs skull-stripping tool (Avants, Tustison, & Song, 2009). Then, the skull-stripped images were processed using the standard FreeSurfer longitudinal stream pipeline (Reuter, Schmansky, Rosas, & Fischl, 2012). In this approach, an unbiased within-subject template is created using robust, inverse consistent registration, and anatomical parcellations are performed using common information from this individual template, with a consequent increase in reliability and statistical power of structural analyses.

For each time-point (T0 and T1) the automatic processing of structural images included the following steps: segmentation of subcortical white matter and deep gray matter, intensity normalization, tessellation of the gray matter/white matter boundary, automated topology correction and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. All segmented images were visually inspected and manually corrected if necessary. Cortical thickness was calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface. Modifications in cortical thickness were evaluated only for those regions showing meditation-dependent functional changes or significant correlations between functional connectivity and psychometric variations. Mean cortical thickness was estimated in native space after transforming the functional ROIs using the subject-specific inverse transformation matrix (*3dAllineate* and *cat_matvec* programs).

2.5. Statistics

2.5.1. Psychometric data

Descriptive statistics and group comparisons for psychometric data were calculated using SPSS Statistics 23.0 (IBM Corporation) and MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States). A dimensionality reduction approach (Principal Component Analysis) was applied to psychometric scores, scaled between 0 and 1, of the 15 scales and sub-scales of questionnaires completed at T0. In order to compare T0 and T1 psychometric data, the transformation coefficients computed on T0 were applied to T1 scores, thus projecting T1 scores into the T0 PCA space. This approach was chosen to increase the statistical power of our study and limit the testing of multiple related hypotheses. In fact, selected psychometric questionnaires were expected to be substantially related to each other, as in the case of scales measuring anxiety and insomnia. Potential T1-T0 changes in psychometric scores were assessed using paired t-tests. The Fisher's exact test was applied to compare the number of subjects showing relative changes in psychometric scores across the two groups.

2.5.2. Functional connectivity data

To test whether functional connectivity changed following the 3-month TM period paired t-tests were performed in each group. Moreover, the potential relationship between psychometric and functional changes was calculated in each voxel as the Pearsons' correlation between T1-T0 variations (T1 minus T0) of functional connectivity and psychometric data. A non-parametric cluster-based correction for multiple comparisons was applied to reduce the false positive rate, with a cluster-forming threshold of $p < 0.001$ (Eklund, Nichols, & Knutsson, 2016). Activated clusters that survived the cluster-based correction at $p < 0.05$ were considered statistically significant (*3dttest++*, *-Clustsim* option) and used as ROIs in subsequent analyses.

2.5.3. Structural data

Analyses of cortical thickness were performed using mean values extracted from the statistically significant ROIs identified in functional analyses. For each group, potential T1-T0 variations were investigated using a paired *t*-test in SPSS Statistics 23.0 controlling for total (whole-brain) mean cortical thickness. Finally, to investigate the potential association between variations in psychometric scores and modifications in brain structure, a partial correlation was performed between T1-T0 changes in regional cortical thickness and variations in psychometric scores of each group, controlling for mean cortical thickness.

3. Results

A final sample of 34 volunteers was included in the analyses: 19 volunteers from the meditation group and 15 subjects (all the originally recruited volunteers) from the control group. No statistically significant differences between groups were found according to demographic variables such as age, education level, gender and handedness (Table 1). Volunteers provided incomplete reports of the exact time spent meditating. This advocates for caution when interpreting the parametric modulation of psychometric and brain changes. Based on available reports, the average time spent meditating corresponded to 30.6 ± 12.8 h (mean ± SD; range 13.3–55.3 h).

3.1. Psychometric assessment

The Principal Component Analysis applied to the psychometric scores revealed that the first component accounted for 25% of the total variance. This component (C1) was selected for subsequent analyses. Based on PCA loadings, C1 appeared to mainly describe depression, anxiety and stress dimensions as opposed to those of resilience and empathy (Fig. 2A), where positive (negative) values denote subjects reporting higher (lower) depression, anxiety and stress symptoms. No differences in C1 score between the two groups were found at baseline ($t_{(32)} = 0.28$, $p = 0.78$). The performed paired t-tests revealed that three months of TM practice were associated with a significant reduction in C1 score, whereas in the control group no such effect was observed (Fig. 2B; $t_{(18)} = 2.53$, $p = 0.02$, BCa CI = [−0.342, −0.011] and $t_{(14)} = -0.19$, $p = 0.85$, BCa CI = [−0.160, 0.164] respectively). Moreover, at T1 the number of volunteers showing a decrease in C1 score was significantly greater in the meditation group than in the control group [15/19 (79%) vs 6/15 (40%), $p = 0.03$, Fisher's Exact test; Fig. 2C]. Hours spent meditating did not correlate with psychometric changes ($p = 0.7$). We report in Supplementary Table S1 the results of analyses exploring relative changes in each of the collected scales/subscales.

3.2. Correlation between psychometric and functional/anatomical changes

3.2.1. Resting-state connectivity

Unthresholded DMN connectivity maps at T0 and T1 are reported in Fig. 3. A correlation analysis was used to investigate whether the changes in subjective well-being (T1-T0 variation in C1 score) were associated with DMN connectivity modifications (T1-T0). In meditators we found a negative correlation between the change in C1 score and relative changes in connectivity (cluster-size threshold > 456 mm^3; Fig. 4(A and B) between the seed-ROI (PCC) and two parietal clusters corresponding to bilateral precuneus ($r = -0.892$, $p < 0.001$, BCa CI = [−0.961, −0.594]) and left superior parietal lobule ($r = -0.878$, $p < 0.001$, BCa CI = [−0.957, −0.560]; Table 2). No significant correlations were found in the control group ($r = -0.182$, $p = 0.515$, BCa CI = [−0.527, 0.555], $r = -0.3$, $p = 0.277$, BCa CI = [−0.045, 0.656] respectively). To investigate whether the correlations between psychometric scores and functional connectivity found in meditators were different across the two groups, we compared directly the z-score transformed mean correlation coefficients extracted from each of the two ROIs. We found that correlation coefficients differed significantly across meditators and control subjects in both the precuneus (Fig. 4D; $p = 0.001$) and the left superior parietal lobule (Fig. 4C; $p = 10^{-5}$). Hours spent meditating did not correlate with functional connectivity changes between the PCC, the precuneus ($p = 0.4$) and the left parietal lobule ($p = 1$).

3.2.2. Brain structural changes

Structural analyses were performed based on connectivity results. Specifically, we evaluated whether functional connectivity changes matched structural modifications within the same regions. Thus, we performed a correlation analysis between the variation in regional cortical thickness and the variation in C1 score. This analysis revealed no significant correlations either in the precuneus or in the left superior parietal lobule, both in meditators and in control subjects.

3.3. Functional and structural brain changes following meditation practice

3.3.1. Resting-state connectivity

We investigated relative functional changes from T0 to T1 (independently from changes in C1 score) using paired t-tests in each

Table 1
Demographic variables of meditation and control group. Age and years of education are reported as mean ± standard deviation (SD). The third column shows the statistical results of comparisons between the two groups for each variable. Contrasts for mean age and years of education were performed using unpaired t-tests; tests on the distribution of gender and handedness were performed using the Fisher's exact test.

	Meditators ($n = 19$)	Controls ($n = 15$)	Between-group contrasts
Mean age (*y*)	29 ± 9	32 ± 11	$t_{(32)} = -0.95$, $p = 0.35$
Education (*y*)	18 ± 2	20 ± 2	$t_{(32)} = -1.85$, $p = 0.07$
Female (*n*)	11	7	57.9% vs 46.7%, $p = 0.73$
Handedness (*right*)	18	14	94.7% vs 93.3%, $p = 1$

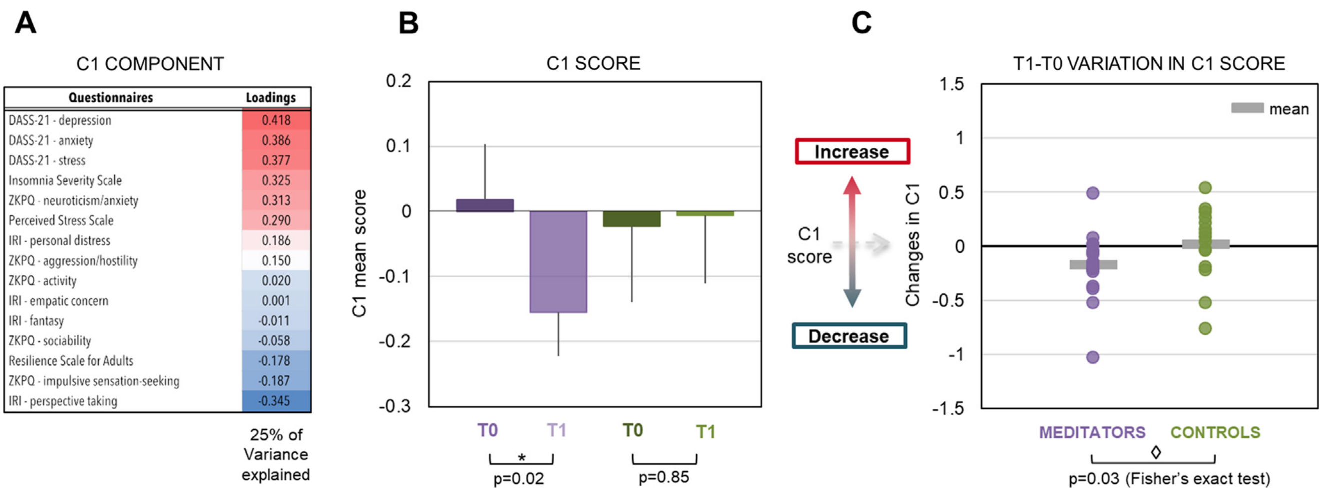

Fig. 2. Psychometric results. (A) Loadings of single questionnaires/subscales on the first principal component (C1). (B) The C1 score at T0 and T1 for the meditation group (N = 19, purple) and the control group (N = 15, green). At T1 the level of C1 score was significantly decreased in meditators ($t_{(18)} = 2.53$, p = 0.02), but not in controls ($t_{(14)} = -0.19$,p = 0.85). (C) At T1 the proportion of volunteers showing a decrease in C1 was significantly different across the two groups (15/19 (79%) vs 6/15 (40%), p = 0.03, Fisher's Exact test). Error bars reflect standard error of the mean (SE). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

group (Figs. 3 and 5). In the meditation group, the fMRI seed-based connectivity analysis showed at T1 an increase in mean connectivity strength between the PCC (seed-ROI) and the right insula (Fig. 5A; cluster-size threshold > 536 mm^3; $t_{(18)} = -7.17$, p = 0.001, BCa CI = [−0.178, −0.099]). In the control group no significant changes were observed neither in whole-brain analysis nor in the right insula cluster found in the meditation group ($t_{(14)} = -0.66$, p = 0.515, BCa CI = [−0.104, 0.043]). A correlation analysis between connectivity changes of this region with PCC and C1 score variations revealed no significant results. Moreover, hours spent meditating did not correlate with functional connectivity changes between the PCC and the right insula (p = 0.1).

3.3.2. Brain structural changes

Cortical thickness in the right insula was extracted based on the ROI defined from the functional results and compared between sessions and across groups. No significant effects were observed.

4. Discussion

Transcendental Meditation (TM) practice is associated with improvements in psychological well-being, especially in terms of perceived depression, anxiety and stress (Goldstein et al., 2018; S. I. Nidich et al., 2009; Orme-Johnson & Barnes, 2014; Tomljenović et al., 2016; Travis & Arenander, 2006). However, the brain correlates of TM effects remain unknown. Here we showed that changes in the first PC scores – reflecting depression, anxiety and stress – that occur just after a 3-month practice of TM are directly related with measurable changes in brain activity. Specifically, our results indicate that psychological benefits of TM are correlated with an increase in DMN functional connectivity, involving the precuneus and the left parietal lobule, consistent with our hypothesis based on previous findings by our and other laboratories indicating a role of DMN in anxiety and stress modulation (Coutinho et al., 2016; Gentili et al., 2009, 2015). In addition, we found that TM practice is associated with an increased functional connectivity between the PCC and the right insula, in line with potential meditation-induced changes in the balance between interoceptive and external awareness (Bornemann, Herbert, Mehling, & Singer, 2015). Finally, we did not find any significant change in cortical thickness after the three-month period of meditation.

4.1. Effects of meditation practice on depression/anxiety/stress

Three months of TM practice led to an improvement in subjective well-being, while the same effects were not observed in the control condition. Specifically, following TM practice, the group of meditators reported a reduction in psychometric scores reflecting perceived depression, anxiety and stress in opposition to resilience and social skills (as determined based on the loadings of a PCA performed on multiple questionnaires/scales; Fig. 2). This finding is in line with previous results reporting positive effects of a 3-month TM practice on negative mood, anxiety and perceived stress in the general healthy population (Tomljenović et al., 2016). Similarly, TM has been shown to be effective in reducing psychological distress and enhancing quality of life in various clinical populations, including patients suffering from HIV (Chhatre et al., 2013), cardiovascular diseases (Schneider et al., 2012; Younge, Gotink, Baena, Roos-Hesselink, & Hunink, 2015), breast cancer (Nidich et al., 2009) as well as PTSD (Herron & Rees, 2018; Rees, Travis, Shapiro, & Chant, 2014). Finally, TM protocols have been adopted to reduce personal distress while enhancing self-efficacy (i.e., resilience, assertiveness, self-determination, self-esteem, dispositional optimism) in high-risk social contexts, for example in ethnic minorities (Elder et al., 2011; Goldstein et al., 2018; Nidich, Seng, Compton, & O'connor, Salerno, & Nidich, 2017).

4.2. Anatomo-functional correlates of psychometric changes associated with TM practice

In the meditation group, but not in the control group, we observed a negative correlation between changes in psychometric scores and post-training variations in the functional connectivity of the PCC (selected as key-region of the DMN). Specifically, a reduction in perceived depression, anxiety and stress was associated with an increased connectivity of the PCC with the precuneus and the left parietal lobule. Of note, these functional adaptations were not accompanied by detectable structural brain modifications, as no significant changes in cortical thickness were observed within the same regions. The reduction in stress and anxiety may be mediated, at least in part, by a relative functional reorganization within the DMN network. This view is supported by previous evidence indicating the existence of a negative relationship between activity in the posterior portion of the DMN and psychometric scores of anxiety and depression. For instance, decreased DMN strength in the parietal cortex (as determined using ICA) has been

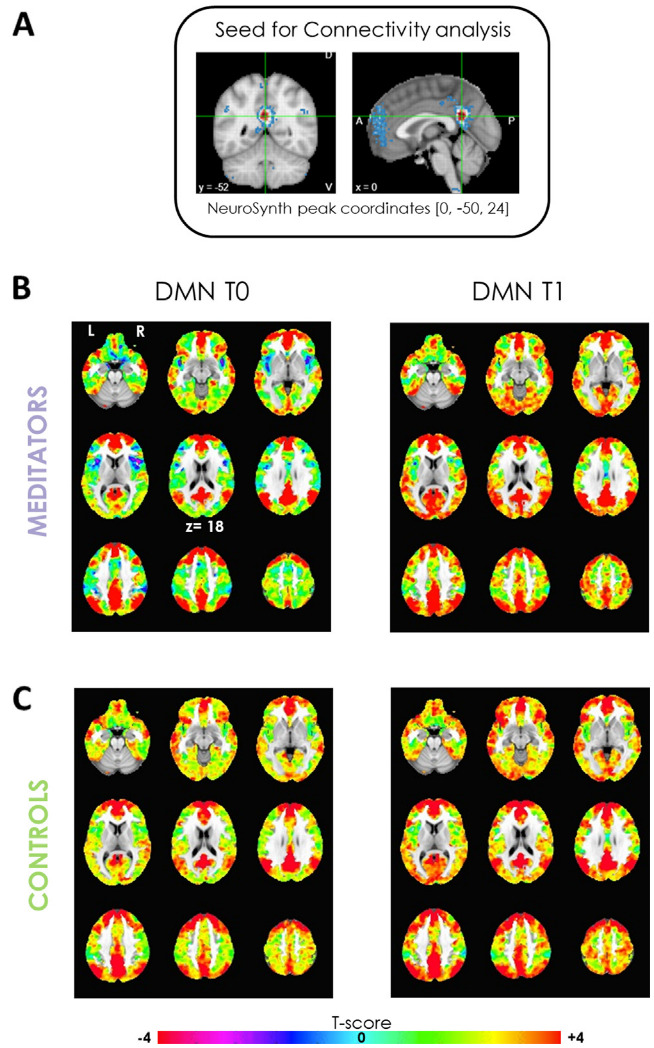

Fig. 3. (A) Seed region used for Default Mode Network (DMN) connectivity analysis (NeuroSynth peak coordinates [0, −50, 24]). Panel (B) shows DMN connectivity maps at T0 and T1 in meditators, while panel (C) shows the equivalent DMN maps obtained in the control group. All results are unthresholded. In each panel, axial brain images are presented with an interslice spacing of 5 mm.

associated with an increased neuroticisms score, implying a higher vulnerability to psychological stress (Sampaio, Soares, Coutinho, Sousa, & Gonçalves, 2013). Similarly, an increased connectivity among the posterior regions of the DMN, including PCC, precuneus, angular gyrus and parietal cortex, correlated negatively with scores of anxiety and depression in healthy individuals (Coutinho et al., 2016). Moreover, significant modifications within the DMN have been demonstrated in clinical populations suffering from depression and/or anxiety disorders, suggesting a pivotal role of this network in mood regulation and emotional processing (Carlson, Rubin, & Mujica-Parodi, 2017; Gentili et al., 2015; Greicius et al., 2007; Hamilton et al., 2011; Zhao et al., 2007; Zhu et al., 2012). This view is also consistent with studies indicating an involvement of the precuneus in higher cognitive functions, such as self-related processing, self-referential judgment and theory of mind (Atique, Erb, Gharabaghi, Grodd, & Anders, 2011; Beyer, Münte, Erdmann, & Krämer, 2014; Cavanna & Trimble, 2006). Importantly, a growing body of evidence indicates that a modulation of the brain activity within the DMN, and between the DMN and other structures as the prefrontal cortex, may be involved in the training-related positive effects previously described for other types of meditative approach (Berkovich-Ohana, Harel, Hahamy, Arieli, & Malach, 2016; Creswell et al., 2016; Fujino, Ueda, Mizuhara, Saiki, & Nomura, 2018; King et al., 2016). Altogether, these results not only provide a strong support to our hypothesis of the involvement of the DMN as the substrate for the positive psychological effects of TM but, combined with findings from independent studies, also suggest that the DMN may be the brain network that sustain the long-term beneficial effects of distinct meditation techniques, in spite of the differential modulation of the attentional processes operated by each of them (Bærentsen et al., 2010; Garrison et al., 2013; Ives-Deliperi, Solms, & Meintjes, 2011; Travis & Parim, 2017). Of note, some studies reported an increased connectivity within the DMN network to be associated with ruminative and negative self-reflection processes (Zhou et al., 2019). In this light, the increase in DMN connectivity may represent a non-specific marker of a variation in introspection and/or self-reflection, whilst it remains unclear which specific functional aspects determine whether these changes will be beneficial or dysfunctional for the individual.

4.3. *Anatomo-functional correlates of TM practice*

In the meditation group, three months of TM practice were associated with an increased functional connectivity between the PCC and the right insula, though these changes showed no significant correlation with changes in subjective levels of depression, stress and anxiety. According to a recent meta-analysis on the functional substrates of different meditation practices (Fox et al., 2016), the insular cortex is the only brain region that is recruited during each of the four categories of meditation, that is focused attention, open monitoring, loving-kindness/compassion and mantra repetition. Given the involvement of the right insular cortex in interoceptive awareness of body states (Aziz, Schnitzler, & Enck, 2000; Craig, 2009), this region may play a role in the shift between external and internal awareness during meditation practices (Fox et al., 2016; Lin, Callahan, & Moser, 2018; Lutz, Jha, Dunne, & Saron, 2015; Tang et al., 2015; Vago & Silbersweig, 2012). In line with this view, recent work demonstrated that mindfulness practice leads to a strengthening of the structural connectome of the right insula (Sharp et al., 2018), which may mediate the increase in interoceptive awareness observed in expert meditators (Bornemann et al., 2015; Farb et al., 2013; Haase et al., 2016; Kok & Singer, 2017). Studies in clinical samples also support a potential relationship between changes in the functional connectivity in the insula and a reduction in anxiety and depression symptoms, following mindfulness-based interventions (Farb et al., 2007; Goldin & Gross, 2010; Goldin, Ramel, & Gross, 2009; Hölzel et al., 2013). However, in the present work we did not find any correlation between changes in PCC-insular functional connectivity and subjective psychological well-being in terms of stress and anxiety. We hypothesize that observed TM-dependent changes involving the insula may actually reflect relative variations in interoceptive awareness rather than in other psychological factors. However, in our experiment interoceptive awareness skills were not directly assessed and future studies are needed to specifically test this hypothesis.

Here we found that three months of TM practice are associated with functional but not structural adaptations in the right insula. This may appear in contrast with the results of a recent meta-analysis showing that meditation practices are typically associated with structural changes involving the insular cortex as well as the rostrolateral prefrontal cortex, anterior/mid cingulate cortex, hippocampus, inferior temporal cortex and fusiform gyrus, in terms of greater cortical thickness, density of gray matter and fractional anisotropy, larger volumetric measure or higher gyrification index (Fox et al., 2014). Of note, however, such structural adaptations have been reported mostly in cross-sectional studies in long-term meditation practitioners (Hölzel et al., 2008; Kang et al., 2013; Lazar et al., 2005; Luders et al., 2012). Thus, the relatively short training used in the present research may have not been sufficient to determine consistent, detectable structural changes in the TM sample.

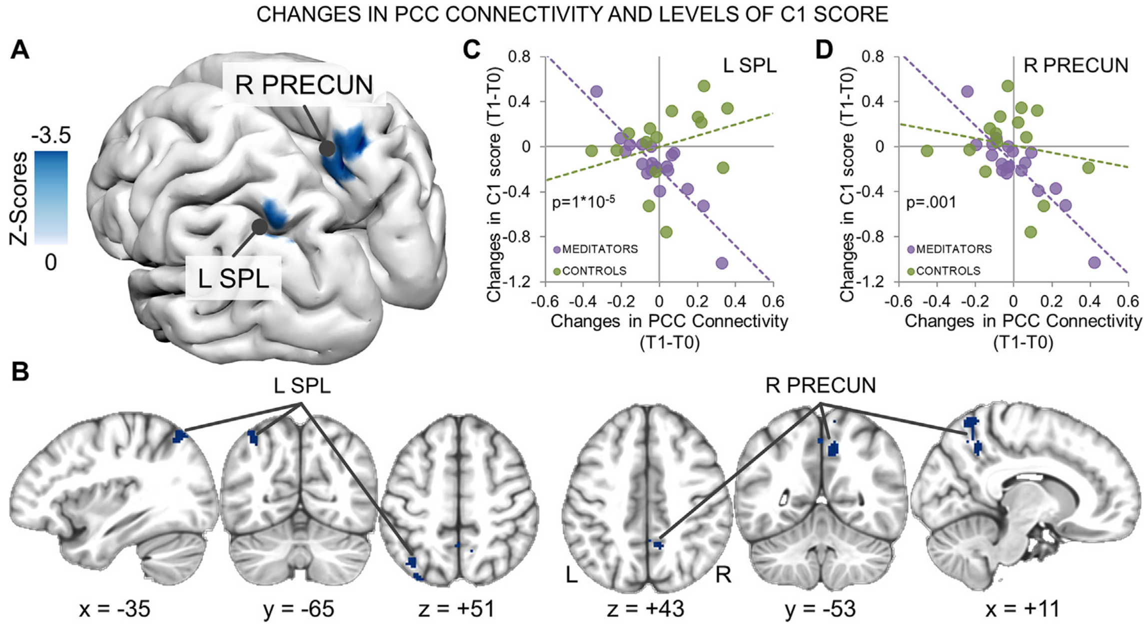

Fig. 4. Correlation between T1-T0 variations in connectivity strength and C1 score in meditators. (A, B) The significant negative correlation between variations in C1 score and changes in DMN connectivity observed in meditators ($p < 0.05$ cluster-corrected; voxel level $p < 0.001$, cluster-size threshold > 456 mm^3). Scatterplots describe the correlations between T1-T0 variations in C1 score and connectivity strength within the left superior parietal lobule (C) and the precuneus (D) respectively, in meditators (N = 19, purple) and control subjects (N = 15, green). Observed correlations are significantly more robust in the meditation group for both the precuneus ($Z = -3.27$, $p = 0.001$) and the left superior parietal lobule ($Z = -4.39$, $p < 0.001$). R = right, L = left, SPL = superior parietal lobule. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Coordinates of significant voxel clusters (effect peak) as obtained from analyses described in Fig. 3 (correlation between changes in C1 score and connectivity) and in Fig. 4 (contrast T1 and T0 in meditators).

Contrast T1 vs T0 in meditators						
Region	MNI coordinates			Cluster size	Voxel p	Z-score
	x	y	z			
Right Insula	42	16	0	74	< 0.0001	4.28
Correlation between changes in anxiety/stress score and connectivity						
Region	MNI coordinates			Cluster size	Voxel p	Z-score
	x	y	z			
Precuneus	11	−53	43	118	< 0.0001	−4.50
Left Superior parietal cortex	−35	−65	51	78	< 0.0001	−4.46

4.4. Limitations

This study represents a preliminary investigation of the relationship between the psychological and brain changes following TM practice. The relative small sample size as compared to similar studies in the field may have limited the statistical power of our analyses, thus restricting the ability to detect differences between groups and sessions. Of note, most of the investigations are cross-sectional studies, while the present work is based on a longitudinal evaluation which required multiple assessments per subject. Moreover, participants were allowed to voluntarily choose between the meditation and the control group, and this may have led to potential biases related to personal beliefs on the meditation benefits. In this light, future studies in larger samples selected using unbiased randomization procedures will be required to verify our findings. However, no statistically significant differences in demographic parameters and psychometric measures were found between the two groups. In addition, the consistency of our results with those of other studies investigating training-dependent effects of TM and other meditation practices (Goyal et al., 2014; Orme-Johnson & Barnes, 2014; Sedlmeier et al., 2012; Tomljenović et al., 2016), as well as of those investigating the neural bases of anxiety and stress (Coutinho et al., 2016; Sampaio et al., 2013), provide support to our preliminary observations.

Of note, relative inter-subject differences in adherence to the meditation practice (as expressed by the high variability in the numbers of hours spent meditating) may have affected our results, and may contribute to explain the lack of a correlation between total hours of practice and changes in levels of psychological and functional brain correlates. A more objective assessment of the number of hours of meditation practice (e.g., through direct monitoring of meditators or actigraphic recordings) should be considered for future studies. On the other hand, the detection of significant changes in the meditation group suggests that the occurrence of positive psychological effects and of brain functional changes may not require a strict meditation routine. While the use of a resting-state fMRI protocol may have the advantage of not requiring specific cognitive and behavioral skills, confounds may arise from inter-subject differences in the ability remain awake and relax in the MRI scanner. Indeed, some of the functional differences observed in meditators after the 3-months practice could also reflect a change in their ability to relax in a potentially stressful context such as that represented by the experimental setting. Finally, the present work only included a passive control condition (i.e., no controlled activity), thus limiting the possibility to evaluate the specificity of practice-dependent changes. Future studies should investigate how the observed effects relate to other types of intervention, such as educational interventions, relaxation programs, hypnosis, physical trainings or other forms of meditation (Halsband & Wolf, 2019; Krisanaprakornkit, Sriraj, Piyavhatkul, & Laopaiboon, 2006).

5. Conclusions

Results of the present work provide a first indication of the potential relationship between the beneficial effects of Transcendental

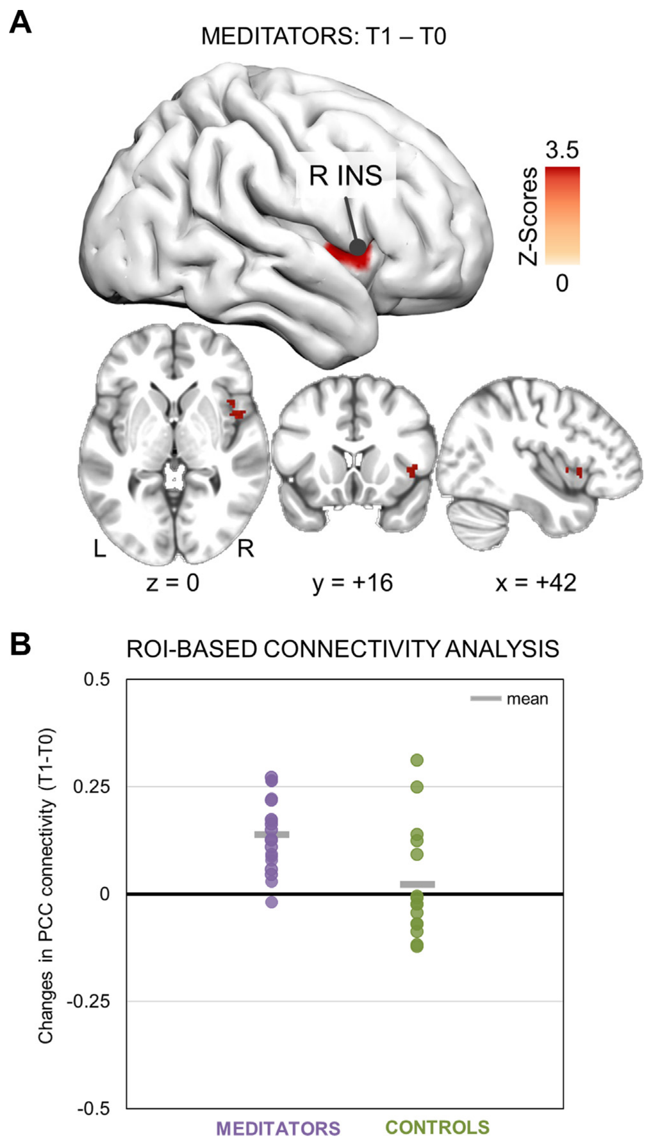

Fig. 5. Connectivity changes in the meditation group. (A) T1 increased mean connectivity strength between the PCC and the right insula in meditators ($p < 0.05$ cluster-corrected; voxel level $p < 0.001$, cluster-size threshold $>$ 536 mm^3). Panel (B) shows the T1 vs. T0 variation in connectivity strength in the two groups. Meditation group ($N = 19$) is represented in purple, while control group ($N = 15$) in green. L = left, R = right. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Meditation on perceived depression, anxiety and stress and a reorganization of functional connectivity involving the posterior component of the DMN. In addition, we showed that TM practice may lead to an increased coupling between PCC, a key-region within the DMN, and the right insula, potentially reflecting an experience-dependent adaptation in the regulation of the balance between internal and external awareness. Interestingly, these changes were observed after a relatively brief practice period (3 months), in healthy adult subjects who practiced TM at home, with no need for specific day-by-day assistance or supervision. While a longer follow-up would be required to determine whether psychological and functional changes remain stable or recede after interruption of the 3-months practice period, our results suggest that TM may effectively counteract dysfunctional brain changes associated with increased anxiety and stress.

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CRediT authorship contribution statement

Giulia Avvenuti: Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing - original draft. **Andrea Leo:** Methodology, Investigation, Formal analysis, Supervision, Writing - review & editing. **Luca Cecchetti:** Methodology, Investigation, Formal analysis, Visualization, Supervision, Writing - review & editing. **Maria Fatima Franco:** Funding acquisition, Writing - review & editing. **Frederick Travis:** Conceptualization, Writing - review & editing. **Davide Caramella:** Resources, Project administration, Writing - review & editing. **Giulio Bernardi:** Methodology, Investigation, Formal analysis, Visualization, Supervision, Writing - original draft, Writing - review & editing. **Emiliano Ricciardi:** Conceptualization, Resources, Project administration, Funding acquisition, Supervision, Writing - review & editing. **Pietro Pietrini:** Conceptualization, Resources, Project administration, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

M M.F.F. is a member of the David Lynch Foundation and has received a teacher honorarium for the initial training of subjects in the meditation group. M.F.F. was not involved in data collection and analysis. The other authors declare that they have no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2020.105517.

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