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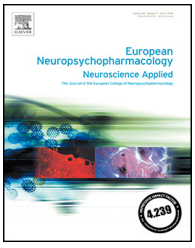

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# Mindfulness-based therapy modulates default-mode network connectivity in patients with opioid dependence

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**Abstract**
Recently, mindfulness-based programs have shown promising clinical effects in the treatment of substance-use disorders (SUD). While several studies linked mindfulness to decreased default mode network (DMN) connectivity in meditators, only a few studies investigated its effects in patients with SUD. This study aimed to detect changes in DMN connectivity in opiate dependent patients receiving mindfulness based therapy (MBT) during their first month of treatment. Data from 32 patients that were assigned to MBT or treatment as usual (TAU) groups was investigated using resting-state functional MRI at 1.5 T before and after four weeks of treatment. Independent Component Analysis was used to investigate distinct (anterior vs. posterior) DMN subsystems. Connectivity changes after treatment were related to measures of impulsivity, distress tolerance and mindfulness. Increased mindfulness scores after treatment were found in patients receiving MBT compared to TAU. Within the anterior DMN, decreased right inferior frontal cortical connectivity was detected in patients who received MBT compared to TAU. In addition, within the MBT-group decreased right superior frontal cortex connectivity was detected after treatment. Inferior frontal cortex function was significantly associated with

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mindfulness measures. The data suggest that MBT can be useful during abstinence from opiates. In opiate-dependent patients distinct functional connectivity changes within the DMN are associated with MBT.


## 1. Introduction

Mindfulness is a state that can be cultivated through explicit practices, such as meditation and yoga, through creative processes or even less explicitly through simple awareness of basic sensory perceptions. It aims primarily at attaining peaceful equanimous state (Kabat-Zinn, 1990), enhancing affect regulation (Jimenez et al., 2010), and reducing stress (Song and Lindquist, 2015). Preliminary findings also confirmed its effects on emotional regulation (Lutz et al., 2014), self-regulation (Tang et al., 2014), memory and cognition (Zeidan et al., 2010). Other effects include not only a decrease in mind wandering and distractibility but also an increase in cognitive flexibility (Mrazek et al., 2012; Moore and Malinowski, 2009) and a change in enduring self-perception (Farb et al., 2007).

Since the introduction of mindfulness to the western world it has been conceived as a healing practice. Its therapeutic potential has been shown in mental disorders such as depression (Teasdale et al., 2000) and schizophrenia (Chien and Thompson, 2014). Evidence suggests that besides its therapeutic potential in several mental disorders, mindfulness-based interventions as the Mindfulness-Based Stress Reduction (MBSR) program (Kabat-Zinn, 1990), initially developed for the treatment of chronic pain, can be also of benefit in patients with substance-use disorders. Specifically tailored interventions as Mindfulness-Based Relapse Prevention (Bowen et al., 2011) and Mindfulness-Oriented Recovery Enhancement (Garland, 2013) later proved effective in various forms of dependence including polysubstance (Bowen et al., 2009) and prescription-opioids (Garland et al., 2014). Although mindfulness practices have been typically secularized for clinical populations, their underlying assumptions remain particularly relevant for the treatment of Substance Use Disorders (SUD) and other addictive behaviors. Notably, mindfulness training shows counter-addictive properties by facilitating habit modification, restoring natural reward responsiveness, regulating emotions and improving cognitive appraisal and stress reactivity (Garland et al., 2013, 2014).

Neuroimaging studies exploring structural changes associated with mindfulness practices showed increased cortical thickness in the prefrontal cortex, the insula, the somatosensory cortex (Lazar et al., 2005). Functional imaging studies comparing meditation state and brain activity at rest suggested neural similarities between resting and meditative states in expert meditators (Brewer et al., 2011). This provided evidence that, similar to other forms of cognitive training, mindfulness can be associated with long lasting stable brain changes that may be linked to the duration of practice (Debarnot et al., 2014). Along with the type of meditation practice, differences in the qualitative pattern of functional connectivity changes across different studies were mostly related to the level of expertise (Brefczynski-Lewis et al., 2007; Hasenkamp and Barsalou, 2012). However, a consistent outcome of mindfulness meditation is modulating activation in regions outlining the so called default mode network (DMN) (Tomasino et al., 2013; Garrison et al., 2015; Simon and Engström, 2015).

The DMN includes a set of brain regions that show greater activity during an experimentally defined "rest" or "baseline" relative to a goal-directed behavior (Raichle et al., 2001). Anatomically, the DMN includes both midline areas as the medial prefrontal cortex (mPFC), the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC) and the precuneus, as well as lateral regions encompassing bilateral inferior temporoparietal cortices and medial temporal regions (Andrews-Hanna et al., 2014). Recent studies, however, have challenged the notion of a unitary DMN system and suggested that its architecture can be further subdivided into distinct anatomical-functional subsystems (Sambataro et al., 2014; Andrews-Hanna et al., 2010); an anterior DMN (aDMN), predominantly comprising the mPFC and ACC and associated with the identification of stimuli as self-salient, and a posterior DMN (pDMN), predominantly comprising the precuneus, PCC, parietal cortices and the parahippocampal complex and linked to mentalizing abilities, autobiographical processes and memory retrieval (Lois and Wessa, 2016).

In this study, we investigated clinical and neural effects of MBT in patients with opiate dependence during their first month of abstinence from opiates. We used resting-state functional magnetic resonance imaging (fMRI) to assess changes of intrinsic neural function in patients receiving either treatment-as-usual (TAU) or additional MBT. Given modulatory effects of mindfulness practice on DMN connectivity, we investigated treatment-related changes within two distinct DMN subsystems, i.e., the anterior and the posterior DMN (aDMN, pDMN). We predicted that MBT induces specific modulatory changes that are distinct from TAU, specifically in regions ascribed to both the aDMN and pDMN. Moreover, within these networks we expected MBT effects in regions known to be affected by state mindfulness, such as prefrontal cortices, the anterior cingulate cortex and the insula. On the behavioral level, we expected that MBT can induce changes in distress tolerance and impulsive behavior in patients with substance dependence during recovery. In addition, we sought to examine potential relationships between DMN connectivity changes following treatment and clinical measures, such as impulsivity, distress tolerance and mindfulness.

## 2. Experimental procedures

### 2.1. Participants

The study was carried out in Cairo University Faculty of Medicine Addiction Inpatient Unit (AIU). During the recruitment period, all individuals admitted who met the diagnosis of opiate dependence

**Table 1** Demographics data and clinical scores (mean ±SD) at baseline and at follow-up.

| | TAU ($n=16$) | | MBT ($n=16$) | |
|---|---|---|---|---|
| **Age (years)** | 30.4 ± 5.5 | | 31.8 ± 4.2 | |
| **Gender (m/f)** | 15/1 | | 15/1 | |
| **Duration of illness (years)** | 9.81±5.7 | | 10.25±4.3 | |
| **Clinical score** | **PRE** | **POST** | **PRE** | **POST** |
| **ASI** | 29.6 ± 8.0 | | 25.7 ± 4.9 | |
| **FMI** | 23.7 ± 4.5 | 29.8 ± 4.3 | 26.2 ± 7.9 | 37.5 ± 5.8 |
| **DTS tolerance** | 5.2 ± 2.4 | 7.4 ± 3.1 | 5.9 ± 2.2 | 8.1 ± 2.3 |
| **DTS appraisal** | 13.4 ± 4.0 | 16.1 ± 5.5 | 12.8 ± 3.5 | 16.9 ± 3.4 |
| **DTS absorption** | 5.2 ± 3.7 | 7.3 ± 3.7 | 5.0 ± 2.6 | 8.0 ± 2.9 |
| **DTS regulation** | 6.3 ± 3.4 | 9.0 ± 4.1 | 5.5 ± 2.9 | 9.5 ± 2.6 |
| **UPPS-P positive urgency** | 38.6 ± 8.0 | 34.6 ± 10.6 | 37.0 ± 8.0 | 33.9 ± 8.8 |
| **UPPS-P negative urgency** | 40.3 ± 4.8 | 33.6 ± 10.6 | 37.8 ± 7.0 | 29.5 ± 6.6 |
| **UPPS-P lack of premeditation** | 27.0 ± 9.0 | 24.5 ± 7.7 | 29.2 ± 7.4 | 24.0 ± 5.3 |
| **UPPS-P lack of perseverance** | 23.2 ± 7.2 | 20.6 ± 8.2 | 24.0 ± 6.4 | 18.8 ± 6.1 |
| **UPPS-P sensation seeking** | 36.1 ± 7.3 | 32.0 ± 9.2 | 31.6 ± 9.4 | 31.3 ± 9.6 |

SD: standard deviation; ASI: addiction severity index; FMI: Freiburg Mindfulness Inventory (no. of questions = 14, max. attainable score = 56); DTS: Distress tolerance scales (tolerance: no. of questions = 3, max. attainable score = 15; appraisal: no. of questions = 5, max. attainable score = 30; absorption: no. of questions = 3, max. attainable score = 15; regulation: no. of questions = 3, max. attainable score = 18); Impulsive behavior scale (UPPS-P) (positive Urgency: no. of questions = 14, max. attainable score = 56; negative urgency: no. of questions = 12, max. attainable score = 48; lack of premeditation: no. of questions = 11, max. attainable score = 44; lack of perseverance: no. of questions = 10, max. attainable score = 40; sensation seeking: no. of questions = 12, max. attainable score = 48).

were interviewed to verify their willingness to complete a four weeks admission period. Decision of admission was made independent of the research team. Enrolled patients signed an informed consent prior to onset of therapy. Study protocols and consent was approved by Cairo University Ethical Committee. Patients who fulfilled diagnostic criteria were opiate dependent (heroin, tramadol), as indicated by history, SCID-I interview and positive urine analysis results, with no history of neurological disorder, significant head trauma or current co-morbid psychiatric diagnosis. Males and females between 18 and 55 years were included. In all patients opiate dependence was the leading substance (as per patients' account). Fourty-two participants were enrolled in the study and underwent the initial scanning and assessment. Ten subjects dropped out leaving 32 subjects who fulfilled pre and post assessment and MRI scans (16 participants for each group). Drop outs were patients who did not receive their post treatment assessment or who did not complete a minimum duration of treatment (see Section 3.1). Immediately after enrollment, participants were randomly assigned to any of the two groups. One group included 16 participants (1 female) who received MBT in addition to TAU as offered by the Unit. The other group included 16 subjects (1 female) who received TAU only. TAU interventions (see below) did not differ between the patient groups, neither with respect to frequency nor intensity. Since we were specifically interested in effects of an intervention within a patient group, we did not include a sample of healthy controls. Participants' assignment to the groups was done in clusters with the help of their admission number in 2 phases as follows; between January and July 2015, the first three subjects enrolled were included in MBT group while the second three subjects were included in TAU group and so forth. For feasibility reasons, including MRI scanner availability, between January and April 2016, subjects were included in alternating groups of six. See Table 1 for participants' characteristics.

## 2.2. Treatment procedures

### 2.2.1. Treatment as usual

TAU refers to all prescribed medications and various non-MBT therapies offered by the AIU. Due to the naturalistic design, no particular treatment adherence monitoring was set specified for either treatment arm. During treatment, subjects were prescribed mood stabilizers, antipsychotics and sedatives in addition to NSAID and H2 blockers for symptomatic treatment during withdrawal. These prescriptions were made according to the therapists' decision and to the patients' needs. Opiate replacement or benzodiazepines during withdrawal were not prescribed. Based on international guidelines, several group therapies were provided for patients including supportive, motivational groups and Cognitive Behavioral Therapy (CBT) applied in the unit, which is a translated culturally adapted version of the Matrix program for substance abuse (Obert et al., 2006). Individual CBT sessions were also provided by the admitting physician.

### 2.2.2. Mindfulness-based therapy

The MBT program used during this work was a translated, culturally adapted version of MBSR workbook (Stahl and Goldstein, 2010) that was translated from English to Arabic (RF, AW, MW). The program included formal and informal exercises which were either coupled with theoretical sessions or given separately. Theoretical topics included: (1) introduction about mindfulness, (2) mental attitudes during mindfulness and mindful breathing, (3) stop stress technique (4) mental traps (5) how stress and anxiety affect your life (6) mindful self-awareness and dealing with difficult emotions (7) internal rules and mindful self-inquiry (8) transforming stress and anxiety into love and kindness (9) working with resistance (10) mind and body awareness. Informal sessions included mindful eating, stop stress technique and RAIN (Recognize/Acknowledge/Investigate/Non-identify) reappraisal technique. Formal sessions included five basic guided meditation techniques which were audio recorded in lengths of 5, 15, 30 and 40 min. These included check-in, mindful breathing, mindful sitting, body scanning, mindful self-inquiry, and loving kindness. Tapes were heard during group formal exercises and the duration of the sessions was gradually increased in length over the 3 weeks period. Thus, the techniques used included the three cardinal therapeutic exercises of mindfulness, i.e., focused attention, open monitoring (OM) and loving kindness (LK) and participants level of training was a three weeks of concise MBSR which was more than brief meditation (one week) and less than a full 8 week MBSR

program (Zeidan, 2015). Patients were given an average 4 sessions a week over their admission period of one month after improvement of their withdrawal symptoms. Particular emphasis was made on incorporating mindfulness in patients' everyday life perceptions rather than pushing for extra minutes with lack of interest and motivation.

## 2.3. Clinical assessment and psychometric data analysis

Participants of both groups were evaluated once during their admission using the Addiction Severity Index (ASI) (McLellan et al., 1980, Arabic version by Qassem et al., 2003). Participants of both groups also completed the following questionnaires before and after treatment: the *Distress Tolerance scale (DTS)* which measures tolerability of aversiveness, appraisal of emotional situations, absorption of negative emotions and regulation of emotions (Simons and Gaher, 2005), the *Impulsive Behavior Scale (UPPS-P)* which measures positive and negative urgency, (lack of) premeditation, (lack of) perseverance, and sensation seeking (Whiteside and Lynam, 2001), and the *Freiburg Mindfulness Inventory (FMI)* (Walach et al., 2006); see also Table 1 for detailed psychometric scores before and after treatment.

Data were analyzed using SPSS version (Version 23; International Business Machines Corp.; Armonk, NY, USA). Data was summarized using mean and standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. For comparisons of categorical data, Chi square test was performed. As nominal level of significance $p < 0.05$ was considered as statistically significant. Comparisons between groups were done using two sample *t*-tests. For comparison of serial measurements within each group, paired *t*-tests were used. Correlations between psychometric and imaging data were calculated using Pearson's correlation coefficient. Correction for multiple comparisons was performed using a false discovery rate (FDR) correction (http://www.sdmproject.com/utilities/?show=FDR).

## 2.4. FMRI data acquisition and analysis

### 2.4.1. Data acquisition

MRI scanning was performed using 1.5 T MRI scanners (Achieva and Intera, Philips medical systems). Due to scanner availability, six participants (MBT: $n = 3$, TAU: $n = 3$), were scanned using the Intera magnet, whereas the remaining participants were scanned using the Achieva scanner. All participants were recruited exclusively for resting-state fMRI (rs-fMRI) and structural MRI, i.e., no experimental tasks were included in the study protocol. All participants completed a functional resting-state scan before and after treatment, where T2*-weighted images were obtained using echo-planar imaging (EPI) in an axial orientation for a duration of 7 min (repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view = 210, voxel size = 3 × 3 × 3 mm, whole-brain volumes including 35 slices, gap = 1 mm). Participants were explicitly instructed to relax without falling asleep, to keep their eyes closed, not to think about anything special and move as little as possible. Adherence to these instructions was verified by verbally contacting participants immediately after the resting-state scan, prior to structural data acquisition. None of the patients reported that they had fallen asleep during the rs-fMRI scan. For each participant, a 3-dimensional high resolution magnetization prepared rapid gradient echo pulse sequence was used with isotropic spatial resolution of 1.6 mm was acquired using the following parameters: TR = 25 ms, TE = 5.36 ms, flip angle = 30°, gap = 0.8 mm, number of slices: 160 for the Philips Achieva scanner and TR = 25 ms, TE = 3.84 ms, flip angle = 30°, gap = 0.8 mm, number of slices= 187 using the Philips Intera scanner.

### 2.4.2. Data analysis

The first 4 EPI volumes were discarded from data preprocessing to correct for equilibration effects. Using SPM8 software (Welcome Department of Cognitive Neurology, London, UK), data were slice-time and motion corrected, spatially normalized to the MNI template using structural images, and spatially smoothed with a 9 mm full width at half maximum (FWHM) Gaussian kernel. To allow testing for potential confounds of head motion, mean framewise displacement (FD) values were computed, as suggested by Power et al. (2012). Derivatives of the six rigid-body realignment parameters estimated during standard volume realignment were used for FD calculation. A radius of 50 mm was employed to convert angle rotations to displacements.

### 2.4.3. Independent component analysis

A spatial ICA was performed on preprocessed data using the Group ICA of fMRI Toolbox (GIFT, http://icatb.sourceforge.net) (Calhoun et al., 2001, 2009) entering the data of all subjects for both time points. The dimensionality of functional data for each subject was reduced using two consecutive steps of Principal Component Analysis alternated with data concatenation across the subjects, resulting in one aggregate mixing matrix for all subjects. Components were estimated using the Infomax algorithm (Bell and Sejnowski, 1995). To increase the stability of the components, the Icasso algorithm (Himberg et al., 2004) was used after repeating the ICA estimation 20 times with bootstrapping and permutation. To avoid component underestimation we employed a model order of $n = 23$ components, where robustness of ICA estimation was quantified using a quality index (Iq) ranging from 0 to 1. (Himberg et al., 2004), each consisting of group spatial maps and the related time courses (TC) of the estimated signal. All components were associated with an Iq >0.9 indicating stable decomposition (Allen et al., 2011). Since after visual inspection, several components appeared to spatially overlap with DMN regions, we performed spatial sorting to extract components showing a significant spatial correlation with the DMN prior to 2nd level analyses. For this purpose, spatial masks were defined using the Automatic Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). A first mask included anterior regions of the DMN, i.e., the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC), whereas a second mask included pDMN regions such as posterior cingulate cortex (PCC) and the precuneus. Note that these masks were only used to objectively identify networks of interest. Masks were not used to constrain 2nd level within- and between-group analyses on a certain set of brain regions.

For component visualization the source matrix was reshaped back to a 3D-image, scaled to unit standard deviations (Z) and thresholded at $Z > 2.5$. Maps from the two components described in Section 3.4.2 (see below) were overlaid onto a Montreal Neurological Institute (MNI) normalized anatomical template. Anatomical denominations and stereotaxic coordinates were derived from clusters above a threshold of $Z = 2.5$ by linking the ICA output images (i.e., the chosen components of interest) to the Talairach Daemon data base (http://www.talairach.org/daemon.html).

### 2.4.4. Within- and between-group comparisons

Components of interest (i.e., aDMN and pDMN) were analyzed using SPM8. Random effects 2nd level between-groups and within-group analyses were performed. Between-group comparisons were calculated to investigate differential neural effects of MBT vs. TAU. Within-group analyses were performed to test for treatment-related effects within each group. Differential images between time point one (before treatment) and time point two (after treatment) were calculated for each subject, using the SPM8 "imcalc" function by subtracting pre- from post-treatment components (aDMN and pDMN) per individual. For the aDMN and pDMN, each subject's differential image was entered into a two-sample *t*-test

for between group comparisons and a one sample *t*-test for within-group analysis. Each analysis included age, gender, and head movement (FD values) as nuisance variables. A significance level of $p < 0.005$, uncorrected for height, $p < 0.05$ corrected for spatial extent using FDR correction was used. Anatomical localizations were determined using probabilistic cytoarchitectonic maps, as provided by the Anatomy toolbox (Eickhoff et al., 2005).

#### 2.4.5. Brain-behavior relationships

Correlation analyses ($p<0.05$, uncorrected for multiple comparisons) within the groups (MBT and TAU, respectively) were calculated to investigate the relationship between neural connectivity and clinical measures (FMI, UPPS-P and DTS scores). For this purpose, beta parameters were extracted using SPM8. These parameters were subsequently processed off-line using SPSS (Version 23; International Business Machines Corp.; Armonk, NY, USA). Correlations were calculated between clusters emerging from within- and between group analyses and psychometric scores that showed a significant treatment-related change over time.

## 3. Results

### 3.1. Drop outs

Four participants that were assigned to the MBT group and six participants that were assigned to the TAU group dropped out. Drop outs were participants who did not receive their post-treatment assessment (e.g., did not show up for follow-up scanning) or who did not complete a minimum number of ten MBT sessions or those who have attended less than two weeks of group therapy (e.g., CBT). Failure to attend the complete number of sessions was either due to prolonged or difficult withdrawal symptoms (e.g., severe pain) or medical complications associated with withdrawal or developing side effects to medications (e.g., confusion), which rendered the patient unfit for group treatment. During the pre-processing stage of fMRI data analysis, three individuals from the MBT and one individual from the TAU group were excluded due to poor fMRI data quality (head movement more than 3 mm or visually identifiable artifacts) leaving out full pre/post and quality-checked data sets from 13 individuals that received MBT and from 15 participants that received TAU.

### 3.2. Demographic and clinical data at baseline

No significant differences were found between the groups with respect to age, gender, educational and professional levels, duration of drug intake, average number of admissions or ASI total or sub-scores. Also no significant difference in DTS, UPPS-P or FMI scores were detected at baseline; Table 1.

### 3.3. Psychometric data: within- and between-group changes over time

While no significant between-groups difference was found in FMI scores pre-treatment; post-treatment scores were significantly higher in MBT- than TAU-group ($p < 0.001$). No significant difference between the groups emerged regarding DTS or UPPS-P scores; Table SI 1.

Within the MBT-group, there was a significant increase in FMI scores ($p < 0.001$), together with significant increases in all DTS scores, i.e., tolerance ($p = 0.005$),

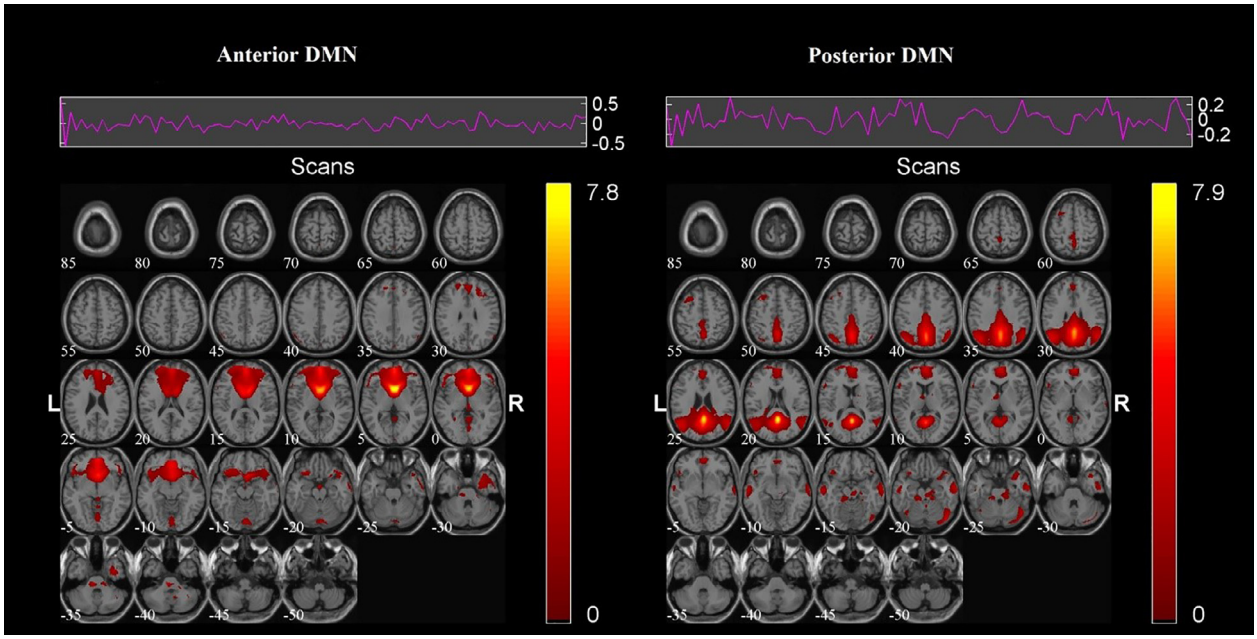


**Fig. 1** Patterns of functional connectivity within the anterior and posterior DMN.
The figure displays independent components (IC) maps and their corresponding time courses using the GIFT software (http://mialab.mrn.org/software/gift/index.html). The color bars indicate *Z*-values. IC's were thresholded at $Z = 2.5$.
Scans = total number of scans, translating into a scanning time of approximately 7 min (see also Section 2.4.1). *L* = left. *R* = Right.
(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

**Table 2** Neuroanatomical patterns identified in the anterior and posterior DMN components.

| Brain region | Brodmann area | *L* *Z*-score/coordinates (*x*,*y*,*z*) | *R* *Z*-score/coordinates (*x*,*y*,*z*) | Volume (cc) *L*/*R* |
|---|---|---|---|---|
| **Anterior DMN** | | | | |
| Caudate | | 6.6 (−6, 14, 3) | 7.1 (6, 16, 3) | 3.6/3.4 |
| Anterior Cingulate | 10, 24, 25, 32 | 5.5 (−2, 17, −3) | 5.1 (2, 15, −4) | 6.0/6.2 |
| Medial Frontal Gyrus | 9, 10, 11, 25 | 4.6 (−2, 50, −3) | 4.7 (2, 54, −3) | 4.1/4.9 |
| Subcallosal Gyrus | 25, 47 | 2.7 (−4, 17, −13) | 3.6 (4, 17, −14) | 0.3/1.0 |
| Inferior Frontal Gyrus | 47 | 2.8 (−53, 23, −5) | 2.4 (50, 25, −8) | 0.8/0.3 |
| Middle Frontal Gyrus | 10, 11 | 2.7 (−26, 59, 6) | 2.1 (34, 53, 8) | 0.6/0.1 |
| Superior Frontal gyrus | 10 | 2.5 (−16, 61, 10) | 2.3 (20, 59,6) | 0.7/0.1 |
| Thalamus | | 2.1 (−8, −3, 13) | 2 (6, -3, 11) | 0.1/0.1 |
| **Posterior DMN** | | | | |
| Posterior Cingulate | 23, 29, 30, 31 | 8.1 (0, −51, 21) | 7.1 (4, −49, 23) | 3.7/3.6 |
| Cingulate Gyrus | 23, 24, 31 | 6.8 (0, −51, 28) | 6.5 (4, −51, 27) | 4.4/4.2 |
| Precuneus | 7, 19, 23, 31, 39 | 6.4 (0, −55, 32) | 6.0 (4, −53, 30) | 11.0/9.0 |
| Cuneus | 7, 19, 30 | 5.4 (0, −66, 31) | 5.1 (4, −64, 31) | 0.6/0.5 |
| Angular Gyrus | 39 | 3.4 (−46, −64, 31) | 3.2 (53, −61, 31) | 1.7/1.2 |
| Middle Temporal Gyrus | 21, 39 | 3.3 (−48, −61, 29) | 3.0 (53, −61, 27) | 1.8/0.8 |
| Superior Temporal Gyrus | 39 | 3.2 (−50, −57, 29) | 2.9 (51, −57, 29) | 0.8/0.6 |
| Inferior Parietal Lobule | 39, 40 | 3.1 (−44, −68, 38) | 2.5 (50, −62, 38) | 0.5/0.3 |
| Supramarginal Gyrus | 40 | 3.0 (−50, −59, 32) | 2.8 (48, −57, 32) | 0.7/0.9 |

For the networks shown in Fig. 1, voxels $>Z=2.5$ were converted from MNI to Talairach coordinates and coupled with the Talairach Daemon database to provide anatomical labels. Maximum Z-values and stereotaxic coordinates (x, y, z) are provided for each hemisphere (left = *L*, right = *R*). The volume of voxels in each area is provided in cubic centimetres (cc).

appraisal ($p=0.001$), absorption ($p=0.002$) & regulation ($p<0.001$). The UPPS-P negative urgency score showed a significant decrease ($p=0.001$); Table SI 2.

Within the TAU-group, results showed a significant increase in FMI ($p=0.001$), significant increase in Tolerance ($p=0.004$) and Regulation ($p=0.009$) scales of DTS, significant decrease in UPPS-P sensation seeking scale scores ($p=0.008$); Table SI 3.

## 3.4. Rs-fMRI data

### 3.4.1. Component estimation and selection

Twenty three independent components were extracted by ICA decomposition. Using spatial sorting, two components were identified for further analyses: one component predominantly included aDMN, whereas the second component included predominantly pDMN areas ($r=0.287$ and $r=0.470$, respectively, $p<0.0001$); Fig. 1 and Table 2.

### 3.4.2. Neural connectivity changes over time: between-group comparisons

Within the aDMN, patients receiving MBT showed regionally decreased connectivity in the right inferior frontal gyrus ($x=44$, $y=14$, $z=12$, $Z=4.72$, $k=89$ voxels, $p<0.05$ FDR-corrected) compared to individuals receiving TAU (Fig. 2).

### 3.4.3. Neural connectivity changes over time within the groups

In the MBT group, decreased connectivity after treatment was found within the aDMN (right superior frontal gyrus, $x=22$, $y=-12$, $z=56$, $Z=4$, $k=99$ voxels), Figure SI 1.

In the TAU group, changes over time after treatment were found in the pDMN component, particularly in the right hippocampus ($x=32$, $y=-10$, $z=-22$, $Z=3.6$, $k=108$ voxels) and the left precentral gyrus ($x=-38$, $y=0$, $z=26$, $Z=3.54$, $k=161$ voxels), where connectivity decreased after treatment. In the aDMN, increased connectivity after treatment was detected in a cluster comprising the right superior and right middle temporal gyrus ($x=58$, $y=-22$, $z=10$, $Z=4.74$ and $x=50$, $y=$-20, $z=-10$, $Z=3.96$, $k=154$ voxels). Decreased connectivity was detected in a cluster comprising the left thalamus and the left pallidum ($x=-16$, $y=-20$, $z=2$, $Z=3.78$ and $x=-18$, $y=-6$, $z=0$, $Z=3.45$, $k=121$ voxels).

### 3.4.4. Correction for scanner type

Since two different scanners were used for functional and structural MRI data acquisition, additional fMRI within- and between-group comparisons were computed. These analyses included "scanner type" as an additional nuisance variable, besides age, gender and head movement parameters (i.e., FD values). These complementary analyses essentially confirmed the main findings, i.e., scanner type did not alter any of the main findings presented above.

### 3.4.5. Brain-behavior relationships

Across the groups, negative relationships between FMI scores and connectivity of the right inferior frontal cortex ($p=0.013$, $r=-0.464$). Within the MBT group there was also a negative relationship between FMI scores and superior frontal gyrus ($p=0.032$, $r=-0.594$).

Detailed statistical information on non-significant findings as well as scatter plots can be provided upon request.

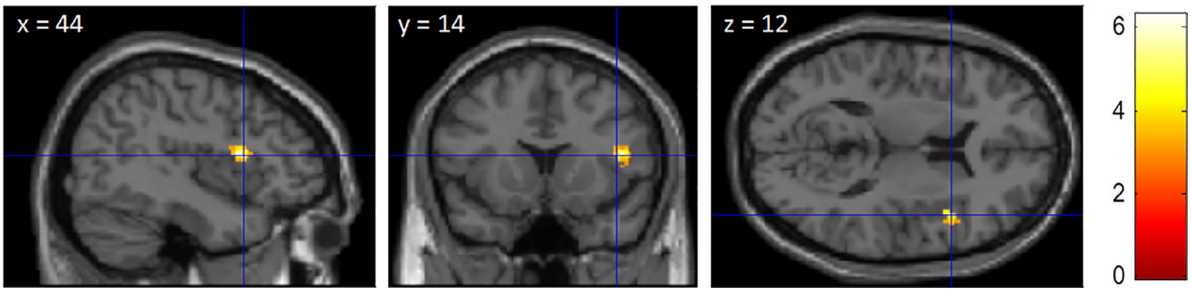


**Fig. 2** Decreased right inferior frontal cortex connectivity in MBT compared to TAU.
A significant group *x* time interaction was found within the aDMN, where patients receiving MBT showed decreased right inferior frontal gyrus (IFG) connectivity compared to individuals receiving TAU only.
Results are derived from 2nd level analysis between-group two sample *t*-tests, $p<0.005$ (uncorrected at the voxel level), $p<0.05$ FDR-corrected for spatial extent. The IFG cluster was rendered onto the anatomical template implemented in SPM8. The color bar indicates *T*-values. *X, y, z* indicate stereotaxic coordinates. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

## 4. Discussion

We used resting-state fMRI to investigate DMN connectivity changes in patients with opioid dependence receiving MBT vs. TAU. Mindfulness measures (i.e., FMI scores) differed between the groups over time and this was accompanied by regionally confined aDMN connectivity change in the MBT group compared to TAU. Several clinical scores also improved in MBT individuals, such as the UPPS-P negative urgency subscore, which showed a decrease over time, as well as measures of distress tolerance, that showed a significant increase after treatment. In contrast, significant clinical improvement in the TAU group was limited to sensation seeking, tolerance and regulation.

Impulsivity is a well-documented marker of treatment outcome in SUD (Moeller et al., 2002; Patkar et al., 2004). Higher levels of impulsivity have been linked to a wide range of maladaptive and addictive behaviors (Lejuez et al., 2005; Odum et al., 2000). In this study, both patient groups showed decreased impulsivity levels over time, indicating beneficial treatment effects. In particular, MBT individuals showed significantly decreased negative urgency scores, indicating a lower tendency to act rashly in negative emotional states, whereas TAU individuals showed a significant decrease in sensation seeking measures, reflecting a lower tendency to favor stimulating and exciting activities. In addition, TAU patients showed improved distress tolerance and regulation only, yet significant increases in all subscales of the DTS were found longitudinally post-MBT. According to the negative reinforcement model of drug motivation (Baker et al., 2004), one of the primary motivations of substance dependence is to escape or avoid emotional suffering or negative affect. Thus, distress tolerance which reflects the perceived or actual ability to withstand this negative affect and persist despite discomfort (Leyro et al., 2010) was associated to abstinence from smoking (Brown et al., 2002). It was suggested that treatment strategies that specifically target improving tolerance of discomfort during withdrawal lead to prevention of early relapse (Carmody et al., 2007). In that regard MBT did not only improve all measures of distress tolerance longitudinally but also decreased the tendency to act on such negative affect.

Several studies mentioned general benefits and efficacy of MBT in SUD (see e.g., Zgierska et al., 2009); however imaging studies are yet very scarce. In this study, the MBT group showed lower connectivity in distinct regions of the aDMN regions, i.e.,inferior and superior frontal cortex. Connectivity strength in these regions was also inversely related to mindfulness measures. These findings are consistent with several studies reporting that changes in connectivity associated with mindfulness practice in healthy populations include the involvement of the DMN (Jang et al., 2011; Hasenkamp and Barsalou, 2012; Taylor et al., 2013). Previous evidence of DMN-involvement during meditative practices showed some conflicting reports. While activations were detected during meditation in the rostral ACC and the dorsal medial prefrontal bilaterally, compared to controls in task-based design (Hölzel et al., 2007), others showed decreased DMN connectivity in meditators relative to controls (Tomasino et al., 2013). Specifically decreased activity was noted in the ACC and the PCU/PCC, mPFC, and anterior insula during meditation compared to implicit baseline, or compared to an active task (Ives-Deliperi et al., 2011; Garrison et al., 2015). Nevertheless, these studies suggested that suppression of the DMN may represent a central process during state mindfulness compared to other active cognitive tasks. Potential shortcomings of previous studies, however, included cross-sectional designs, comparing state meditation to cognitive tasks or using healthy experts, thus missing the "after" effect of mindfulness when practiced by non-expert practitioners or patients where its healing powers are particularly proclaimed/needed.

Previous findings in healthy meditation practitioners showed increased connectivity within the DMN during non-meditative states, specifically in the mPFC, supporting the notion of increased internalized attention even when meditation is not being practiced (Jang et al., 2011). The contradictory findings between the data provided by Jang and colleagues (Jang et al., 2011) and the results of this study could be attributable to the difference in study design as well as the population. While the Jang study compared healthy practitioners to controls and opted for seed-based analysis, this study deals with opioid dependent patients and whole brain analysis. Our findings support the comprehensive

view proposed by Zeidan (2015) which perceived mindfulness meditation as multi-staged mental training. At early stages, practitioners engage in an effortful top-down regulation of lower-level afferent processing, aimed at forcefully refraining from further processing of judgmental and ruminatory emotional stimuli. Then gradually as mindfulness harnesses more skill at attending to sensory and emotional experiences without interpretation or elaboration, a decoupling between appraisal and sensory processing occurs. This yields a decrease in higher-order brain activity in the PFC. Hence, a decrease in its resting state connectivity is essentially related to the function expected to be played by mindfulness.

Our results showed decreased connectivity in the IFG, which was inversely correlated with mindfulness. The IFG is not known to be a central part of the DMN; however, several studies have reported changes in its connection with the DMN during LK meditation practices (Lee et al., 2012) particularly intrinsic connectivity between the IFG and the reduced PCC/PCU regions of the DMN (Garrison et al., 2014). Decreased connectivity in the IFG might suggest a decoupling in the circuit relating this emotional processing to self-thoughts and self-dialogue during rest.

Changes within the MBT-group revealed that the higher the mindfulness after treatment, the greater the decrease in right superior frontal connectivity. The superior frontal gyrus is known to be involved in higher cognitive and executive functions (Boisgueheneuc et al., 2006) as well as introspective self-awareness (Goldberg et al., 2006). Previous evidence of signal decreases in the mPFC and other cortical midline structures during mindfulness meditation compared to an active task were attributed to decreased subjective emotional experiencing (Ives-Deliperi et al., 2011). It was shown that meditation state or mindfulness-based tasks compared to resting-state activation reveal stronger activation in the dorsolateral prefrontal cortex (Ives-Deliperi et al., 2011; Gotink et al., 2016). Thus the role of the prefrontal cortex is consistently replicable and its deactivation during meditation or at resting state in expert practitioners may be an indication of the attenuation of the critical observer component of subconscious processing (Goldberg et al., 2006).

One of the major limitations of this study is the modest sample size, which we consider as inherent difficulty to recruit and motivate patients with opioid-dependence to spend 30 days hospitalized with regular urine analyses and full abstinence. Also, cultural introduction of mindfulness to Egyptian patients suffering from substance dependence and seeking therapy in a public hospital was a major barrier. Another limitation of this study is the absence of a healthy control group. Therefore, conclusions on the effects of MBT on behavior and brain activation are limited and replication using a large sample including a healthy control group is highly desirable.

Keeping such potential shortcomings in mind, we have shown that MBT induces resting state functional changes in the brains of opiate dependent patients during abstinence involve regions similar to those reported to be involved during state mindfulness. MBT induces decrease in the DMN compared to treatment as usual and decreased frontal connectivity after only 4 weeks of practice. This finding is also associated with significant improvement in distinct components of impulsivity in the same period of time. It has been previously reported that integration of MBT and CBT strategies can improve overall treatment efficacy (Hoppes, 2006). Our findings confirm that while CBT promotes adaptive proactive coping strategies, meditation targets maladaptive responses by improving appraisal, acceptance and delayed discounting of negative affective states. Thus, MBT-related skills can complement skills acquired through CBT in treatment of SUD.

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## Conflict of interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

## Authors' contribution

RF, MW and RCW were responsible for the study concept and design.

RF, AW, RM and MW were responsible for mindfulness program translation and application.

KM was responsible for imaging data collection and revision.

RF drafted the manuscript.

RF, FS and RCW were responsible for imaging data interpretation.

MMS, KMK and NDW provided critical revision of the manuscript for important intellectual content.

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The DAAD and STDF had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.03.002.

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