Addictive Behaviors 82 (2018) 50–56

Contents lists available at ScienceDirect

Addictive Behaviors

journal homepage: www.elsevier.com/locate/addictbeh

Mindfulness-based interventions modulate structural network strength in patients with opioid dependence

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HIGHLIGHTS

- We investigated effects of MBI on brain volume in patients with opioid dependence.
- Patients receiving MBI showed distinct structural network changes after treatment.
- An increase in striatal and prefrontal network strength was observed.
- Prefrontal network strength was associated with impulsivity levels.

ARTICLE INFO

Keywords:
MRI
Opiates
Source-based morphometry
Frontal cortex
Striatum
Impulsivity

ABSTRACT

Mindfulness-based interventions (MBI) are increasingly used in the treatment of patients with mental disorders, in particular in individuals presenting with affective disorders or in patients exhibiting abnormal levels of impulsive behavior. MBI have been also offered to patients with substance use disorders, where such treatment options may yield considerable clinical effects. Neural effects associated with MBI have been increasingly acknowledged, but is unknown whether MBI exert specific effects on brain structure in patients with substance use disorders. In this study, we investigated 19 inpatients with opioid dependence receiving treatment-as-usual (TAU, n = 9) or additional MBI (n = 10). Structural magnetic resonance imaging data were acquired before and after four weeks of treatment. Source-based morphometry was used to investigate modulation of structural networks after treatment. Both treatment modalities led to significant clinical improvement. Patients receiving MBI showed a significant change in distress tolerance levels. An increase in bilateral striatal/insular and prefrontal/cingulate network strength was found in patients receiving MBI compared to individuals receiving TAU. Prefrontal/cingulate cortical network strength was associated with impulsivity levels. These findings suggest that MBI can have a recognizable role in treatment of substance use disorders and that neural effects of MBI may be captured in terms of frontostriatal structural network change.

1. Introduction

In the past years, mindfulness-based interventions (MBI) have attracted substantial clinical and scientific interest (Kurdyak, Newman, & Segal, 2014). Defined as bringing one's complete attention to the experiences occurring in the present moment in a non-judgmental and accepting manner, mindfulness-based practices enhance discriminative awareness, while responding to uncomfortable or challenging situations with complete acceptance, thus discouraging the brain's automatic responses and giving way to a novel form of thought and behavior (Witkiewitz, Lustyk, & Bowen, 2013). Distinct effects of mindfulness-based practices on brain activity, both during state mindfulness and as a

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https://doi.org/10.1016/j.addbeh.2018.02.013
Received 3 November 2017; Received in revised form 7 February 2018; Accepted 7 February 2018
Available online 08 February 2018

result of long-term practice, have been revealed by functional neuroimaging studies. Brain areas that have been consistently reported responsive to mindfulness include medial and lateral prefrontal cortices, anterior cingulate cortex (ACC), insula, parietal and medial temporal lobe regions such as hippocampus and parahippocampus (Baerentsen et al., 2010; Brefczynski-Lewis, Lutz, Schaefer, Levinson, & Davidson, 2007; Sperduti, Martinelli, & Piolino, 2012; Tomasino, Fregona, Skrap, & Fabbro, 2012). Such functional changes have been found to be associated with various higher-order cognitive processes, such as emotional regulation (Luders, Toga, Lepore, & Gaser, 2009), attentional monitoring (Lazar et al., 2005), and increased executive control (Teper & Inzlicht, 2013). Effects of mindfulness-based practice on brain volume have been shown by structural magnetic resonance imaging (sMRI) studies. In Vipassana meditators gray matter volume increases were detected in regions that are typically activated during meditation, such as insula, inferior temporal gyrus and hippocampus (Holzel et al., 2008). Other sMRI studies provided evidence for higher GMV in lower brainstem regions (Vestergaard-Poulsen et al., 2009), increased cortical thickness in dorsal anterior cingulate and secondary somatosensory cortex (Grant, Courtemanche, Duerden, Duncan, & Rainville, 2010) and absent age-elated decline in putamen in meditators compared to non-meditators (Pagnoni & Cekic, 2007).

In patients with substance-use disorders (SUD), clinical evidence suggests that practicing mindfulness during recovery is significantly associated with lower rates of substance use and greater craving decrease (Witkiewitz & Bowen, 2010; Witkiewitz, Bowen, Douglas, & Hsu, 2013). Only a few such studies were performed on patients with opioid dependence (Garland, Froeliger, & Howard, 2014; Imani et al., 2015). Complementing clinical data, neurobiological evidence also showed that distinct areas of the brain that have been associated with craving, negative affect, and relapse, i.e. prefrontal cortex, ACC and amygdala, are also affected by mindfulness training (Fox et al., 2014; Holzel et al., 2008). For instance, mindfulness reduced regional ACC activity and connectivity to the striatum during exposure to substance related cues suggesting a modulation of bottom-up reactivity to drug-related stimuli in nicotine dependent patients. Following a course of “mindfulness-based relapse prevention” patients with SUD were less likely to experience craving in response in to a depressed mood and this was associated with diminished substance intake (Witkiewitz & Bowen, 2010).

Although beneficial effects of MBI in patients with opioid misuse and dependence (Garland et al., 2014; Imani et al., 2015) have been shown, there's a striking paucity of data considering neural effects associated with such interventions. Mindfulness has been shown to enhance electrocortical and autonomic responsiveness to natural rewards in opioid misusers (Garland et al., 2014; Garland, Froeliger, & Howard, 2015), yet studies investigating effects on neural structure are lacking. Here, we investigated effects of MBI on brain structure in inpatients with opioid dependence using sMRI and a multivariate statistical technique for sMRI data analysis, i.e. “source-based morphometry” (SBM, Xu, Groth, Pearlson, Schretlen, & Calhoun, 2009). SBM uses Independent Component Analysis (ICA) to extract spatially independent patterns that occur in structural images. SBM capitalizes on the inter-relationship across voxels to identify patterns of structural variation, i.e. “structural networks”. The application of SBM to patients with mental disorders has been shown to be successful in identifying distinct patterns of structural change, which may not be fully revealed by mass-univariate techniques (Depping et al., 2016; Xu et al., 2009). SBM has been also successfully used to identify treatment-related changes of structural network strength in patients with affective disorders (Wolf et al., 2016). We predicted that in patients receiving MBI in addition to standard inpatient treatment, cingulate, prefrontal and insular network strength would be sensitive to treatment response. In addition, we sought to examine potential relationships between structural network change following treatment and clinically relevant measures, such as impulsivity, distress tolerance and mindfulness.

2. Material and methods

2.1. Participants

The study was carried out in the Cairo University Faculty of Medicine addiction inpatient unit over a period of six months. This research was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written informed consent was obtained from all participants.

Twenty-eight patients were enrolled in the study. All participants were opiate dependent patients (as indicated by history, SCID-I interview, urine analysis) with no history of neurological disorder, significant head trauma or other co-morbid psychiatric diagnosis. We were primarily interested in treatment-related effects on brain volume in patients presenting with opioid dependence, either treatment as usual (TAU) or MBI in addition to TAU. Thus, a healthy control group was not included.

Patients were enrolled in two groups receiving TAU only or TAU and additional MBI. Group assignment was done immediately after patients' inclusion in the study. Assignment was performed using the admission number automatically issued by the hospital administration, where the first 3 participants enrolled were assigned to MBI, the second 3 participants were assigned to TAU and so forth. The total duration of the inpatient treatment program was four weeks. Of the initial sample 19 patients resumed the accounted treatment duration to receive the second assessment. Nine participants (TAU/MBI: n = 5/4 patients) dropped out for various reasons: 1. lack of willingness to complete the treatment program followed by hospital discharge, 2. severe medical complications during the first week of hospitalization, 3. withdrawal of consent, or 4. failure to meet post-treatment MRI (for further details see also Fig. 1, supplementary data).

TAU included various therapeutic groups offered by the hospital including group cognitive behavioral therapy (CBT), motivational and social support groups according to the Matrix program (Rawson et al., 2005). CBT sessions were also provided by the admitting physician.

The MBI program used during this work was a translated, concise and culturally adapted version of Mindfulness-Based Stress Reduction (MBSR) workbook (Stahl & Goldstein, 2010; Tang, Posner, & Rothbart, 2014). Translation from English to Arabic was performed by RF and MW. The translation was revised by the Egyptian research team. 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) impact of stress and anxiety (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 and reappraisal techniques. 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 and, 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 treatment period. Patients were given an average of 4 sessions per week over a total admission period of one month, starting after marked clinical improvement of withdrawal symptoms was observed.

Patients were offered medical treatment for withdrawal as needed, including antipsychotic, mood stabilizers, sedatives, non-steroidal anti-inflammatory drugs and proton pump inhibitors. Participants of both groups were required to complete the following questionnaires at the beginning as well as at the end of the treatment program: (1) the short-form Freiburg Mindfulness Inventory (FMI), a 14 items questionnaire designed to measure the concept of mindfulness, measured as either an