

Review

Mindfulness based intervention in Parkinson's disease leads to structural brain changes on MRI

A randomized controlled longitudinal trial



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ABSTRACT

Objective: The aim of the current study is to investigate structural changes on brain MRI using voxel based morphometry (VBM) related to an eight-week mindfulness based intervention (MBI) in Parkinson's Disease (PD).

Methods: A total of 27 out of 30 PD patients completed a randomized controlled longitudinal trial. Fourteen patients participated in a structured eight-week program of MBI. Thirteen patients received usual care (UC) alone. MRI data sets of the brain were obtained at baseline and after eight weeks follow-up. VBM analysis was performed using DARTEL from the SPM8 software. The resulting difference maps were statistically compared to examine gray matter density (GMD) differences. Results were reported at $p < 0.001$, uncorrected for multiple comparisons.

Results: Increased GMD was found in the MBI compared to the UC group in the region of interest (ROI) analysis in the right amygdala, and bilaterally in the hippocampus. Whole brain analysis showed increased GMD in the left and right caudate nucleus, the left occipital lobe at the lingual gyrus and cuneus, the left thalamus, and bilaterally in the temporo-parietal junction. In contrast, GMD differences were found in the UC group in the left anterior lobe and dentate nucleus of the cerebellum.

Conclusions: To the best of our knowledge this is the first quantitative analysis of neurobiological effects of MBI in PD. Increased GMD was found in the MBI group in the neural networks that have been postulated to play an important role in PD. These areas have also been implicated in the functional networks mediating the benefits of meditation.

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1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder with a world-wide prevalence of approximately 10 million people. Projecting on current demographic changes, the estimated prevalence of PD is expected to double by 2050 [1]. As such, PD remains an important public health problem due to the chronic and progressive nature of this disease [2,3].

In PD large numbers of dopaminergic neurons located within basal ganglia circuitry degenerate. Evidence suggests that symptoms in PD are related to a more extensive pathological process involving a progressive caudal to rostral aggregation of alpha-synuclein in select nerve cells [4]. Clinical parkinsonism can be responsive to pharmacological therapies other than dopaminergic agents such as serotonergic and cholinergic drugs. As such, the neuropathology of PD also involves non-dopaminergic systems or cortical structures of the nervous system not directly involved in motor control [5]. Moreover, structural brain changes in cortical and limbic areas have been reported in PD [6–8]. These complex alterations contribute to clinical motor symptoms (including the hallmark triad: bradykinesia, tremor, rigidity) and non-motor symptoms (NMS). NMS which comprise cognitive changes, emotional dysregulation, anxiety, apathy, depression, and sensory symptoms such as pain may antedate motor symptoms and affect the majority – if not all – of PD patients in time [9]. With PD progression, NMS can be more disabling than the motor symptoms [10]. It has been estimated that up to 25% of individuals present with cognitive dysfunction in the absence of dementia [11,12]. This may be of concern as it relates to both the understanding and the following of instructions, pertinent to non-pharmacological interventions such as mindfulness.

In a small pilot study using a MBI, we had indications which lead us to hypothesize that PD patients may realize benefits based on self-reported measures (PDQ-39) (unpublished data). The experiences of participants in an eight-week mindfulness-based cognitive therapy (MBCT) course and closely related MBI, indicated that patients with PD might benefit by changing patterns of coping, consolidating coping skills and establishing group support after participating in MBCT [13]. These authors also concluded that MBCT is an acceptable form of group intervention benefiting people with PD.

Mindfulness meditation as conceived and described by Kabat-Zinn [14] involves both the understanding and development of awareness of present-moment experience with a compassionate, non-judgmental stance. MBIs have been shown to improve well-being and quality of life in a mixed clinical population of individuals dealing with stress-related problems [15]. A growing body of literature in non-PD populations has established the efficacy of MBI in reducing symptoms commonly described in NMS of PD such as anxiety [16,17], depression [16,18], and chronic pain in fibromyalgia [19]. Trait-like effects, extending beyond the actual time that a subject is meditating, have been shown in quality of life improvements in multiple sclerosis [20].

Anatomical brain MRI studies of long-term meditators have shown GMD increases in experienced subjects in multiple brain regions in comparison with non-meditating individuals [21–26]. In addition, a longitudinal VBM study showed GMD changes in the left hippocampus, posterior cingulate cortex, temporo-parietal

junction and the cerebellum after eight weeks of MBSR in individuals seeking stress reduction [27].

The goal of our study was to evaluate the effects of an eight-week MBI on anatomical brain MRI scans in patients with PD using a VBM analysis approach. To this end, a total of 30 PD patients were included in a randomized controlled longitudinal study comparing a MBI consisting of a structured eight-week program (*n* = 14) with usual care (UC) alone (*n* = 13). Based on the literature we expected to observe structural differences in the amygdala and hippocampus between groups. To the best of our knowledge, this is the first study that evaluates mindfulness meditation in PD using anatomical MRI scans.

2. Materials and methods

2.1. Study participants

A total of 30 PD patients were recruited from the outpatient neurology clinic of the University Hospital Antwerp, from referring physicians and through advertisements in the patient support association magazine. The study was conducted from May to the end of June 2012.

Experienced neurologists verified all the patients for the following set of criteria: (1) diagnosis of PD according to the UK Brain Bank Criteria, (2) patients in Hoehn & Yahr stage I–III, (3) lack of features suggestive of atypical parkinsonism, (4) exclusion of usage of neuroleptics or other drugs that induce parkinsonism 60 days prior to inclusion, (5) optimally treated PD with medication and unlikely to be requiring anti-PD medication adjustments in the next 3 months, (6) stable dose of all medications for 30 days prior to inclusion, (7) lack of cognitive dysfunction as evidenced by the Montreal Cognitive Assessment test (MoCA) (score ≥ 26), (8) no known unstable or life threatening concomitant disease, (9) no previous mindfulness training, (10) no contra-indications for MRI scanning (i.e., metallic implants, claustrophobia) and (11) commitment to attend all eight MBI classes and perform the prescribed daily homework.

The demographic characteristics of the study group are reported in Table 1. The groups were comparable at baseline with respect to age, gender and disease severity. Study participants were randomized 1:1 into MBI or UC groups (Fig. 1). Eligible patients completed

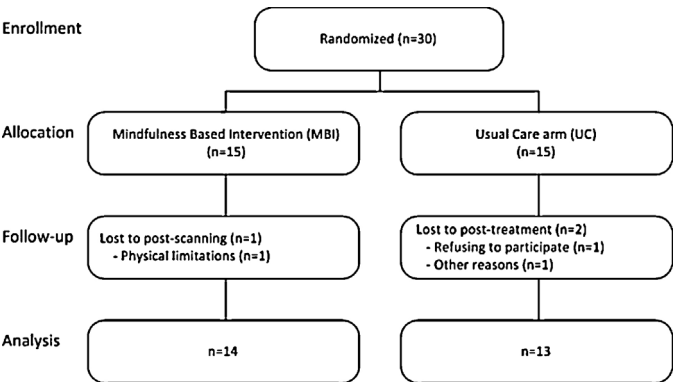


Fig. 1. The process of the participant randomization after inclusion, allocation to the MBI or UC group and final analysis of MRI data is illustrated.

Table 1
Baseline demographic characteristics by intervention status.

Characteristic	Overall (n = 27)	MBI (n = 14)	UC (n = 13)	Comparison between groups
Age, y, (SD)	61.8 (9.1)	61.4 (11.3)	62.2 (6.6)	$t = -.20, p = .84$
Women, n (%)	13 (48)	7 (50)	6 (46)	$\chi^2 = .04, p = .84$
H&Y, (SD)	2.2 (0.4)	2.1 (0.3)	2.2 (0.5)	$U = 74, p = .34$

Legend MBI, Mindfulness Based Intervention Group; UC, Usual Care Group; y, years; H&Y, Hoehn and Yahr; SD, standard deviation.

all pre-intervention (outcome) measures before randomization. Randomization was conducted by a blinded investigator. All patient-reported outcome measures were entered into a database by personnel blinded to group assignment. Standard protocol approvals, registration, and patient consent forms were approved by the Institutional Review Board of the University Hospital Antwerp, Antwerp, Belgium. The study was registered at the ClinicalTrials.gov (A service of the U.S. National Institutes of Health – NIH) NCT01607697. All participants gave written informed consent.

2.2. Intervention

Fifteen PD patients included in the study received a MBI closely following MBSR as described by Kabat-Zinn [14]. The MBI consisted of 2.5 h meetings on eight consecutive weeks without the one-time full-day (6.5 h) session in the sixth week of practice as described in MBSR. In order to facilitate the development of the capacity for mindfulness, the formal mindfulness exercises in body scan, mindful movement (also known as mindful yoga) and sitting meditation were intensively practiced during the eight sessions. To facilitate the integration of mindfulness into daily life, instructions were given on how to practice and integrate mindfulness in everyday activities such as eating, walking, or performing household chores. Participants also received instructions in using mindfulness for coping with stress in daily life. Audio recordings containing 45-min guided mindfulness exercises (meditation, body scan, mindful movement) were given with instructions for daily home practice corresponding to the course sequence. Time spent in mindfulness practices, as reported by the participants, was recorded weekly for each participant. The intervention was conducted by two experienced mindfulness teachers. All patients in both the UC and MBI groups received regular, currently optimal medical care during the duration of the study. UC patients were offered the MBI two months after the study.

2.3. MRI data acquisition

All MRI examinations were performed on a 3 Tesla scanner (Magnetom Trio Tim, Siemens AG, Siemens Medical Solutions, Erlangen, Germany). Acquisition was performed by scanning personnel, blinded to group allocation. A 32-channel head coil was used to obtain images with an isotropic resolution of 1 mm³. For volumetric measurements a high resolution anatomical T1-weighted MR dataset was obtained, using a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence with 176 slices and a field of view of 256 mm × 192 mm. Repetition time TR and echo time TE were 1910 ms and 3.37 ms, respectively; the flip angle was 15°. All patients underwent an MRI scan at baseline (up to one month before) and at eight weeks (after the intervention within one month).

2.4. MRI data analysis

VBM analysis was performed using Statistical Parametric Mapping (SPM)8 software (www.fil.ion.ucl.ac.uk/spm/software/spm8/). All T1-weighted data sets were segmented into gray

matter (GM), white matter (WM) and cerebrospinal fluid (CSF), using a unified tissue segmentation approach [28]. Intensities were modeled by a gaussian mixture model. Resulting images were bias field corrected for the smoothly varying intensity inhomogeneity caused by magnetic field imperfections using discrete cosine transformations and were registered into standard space. Subsequently, diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) was used to account for more detailed shape variability in the population [29]. The DARTEL registration involves alternating between computing a template, based on the average tissue probability maps of all subjects, and warping the tissue maps of all subjects into increasingly good alignment with the template. Images were then transformed to standard Montreal Neurological Institute (MNI) space, followed by a smoothing procedure with a Gaussian Kernel of 12 mm. For each individual patient, the registered baseline T1-weighted image was subtracted from the eight weeks follow-up T1-weighted image to obtain images that represent changes over time for each patient. These subtracted images were then compared between both intervention groups using a *T*-test. For the whole brain analysis, a statistical threshold of $p < 0.001$ (uncorrected for multiple comparisons) with an extent threshold of at least 5 voxels was used to present the results. In addition, ROIs in the amygdala and the hippocampus were defined in MNI space to evaluate GMD changes in the hypothesized regions. For the latter ROI analysis, an FWE corrected statistical threshold of $p < 0.05$ was used.

3. Results

Twenty-seven out of 30 PD patients completed the study (Fig. 1). Two patients, allocated to the UC group, dropped out for personal reasons (not relevant to the study) during follow-up while one patient of the MBI group discontinued study participation due to acute back pain limiting access to the MRI scan. The medication remained stable in 26 out of 27 patients. One patient in the UC group had an increase of 50 mg levodopa and the addition of 50 mg sertraline, as deemed necessary by the general practitioner during the study. Attendance rate at the training sessions of the MBI group was 97.3%. Of the 14 participants in the MBI group, 11 were present for all eight sessions and 3 subjects missed one session. The participants reported spending a total of 32,244 min (537.4 h, mean = 38.4 h, SD = 11.9 h) performing formal homework exercises over the 8-week training (average = 55 min per day). The time spent on practicing was 47.45% on meditation, 21.79% on body scan and 30.76% on mindful movement.

As demonstrated in Table 2 and Fig. 2, MRI findings showed increased GMD in the MBI group compared to the UC group over time in the left and right hippocampus and a small region in the right amygdala. Whole brain analysis revealed a large cluster in the right caudate nucleus and a smaller cluster in the left caudate nucleus. Significant clusters were also found in the left occipital lobe at the lingual gyrus and cuneus, in the left thalamus and bilaterally in the temporo-parietal junction.

On the other hand, Table 3 and Fig. 3 shows that increased GMD was found in the UC compared to the MBI group in the anterior lobe and dentate nucleus of the left cerebellum.

Table 2
Increase in GMD from pre- to post MBI. Active versus controls: $p < 0.001$, cluster size greater than 5 voxels.

Region (peak of cluster)	MNI coordinates of the peak voxel x, y, z	Side	Number of voxels	T-value
Amygdala	32, -2, -24	Right	8	3.7
Hippocampus	38, -2, -8	Right	229	4.3
Hippocampus/parahippocampus	-23, -18, -20	Left	54	4.7
Caudate nucleus	18, -3, 9 -18, -2, 17	RightLeft	26012	54
Occipital lobe cuneus	-21, -74, 2	Left	174	4.8
Occipital lobe lingual gyrus	-21, -80, -15	Left	21	4
Temporal lobe middle gyrus	32, -45, 5	Right	30	5
Temporal lobe inferior gyrus	-53, -32, -32 -41, -56, -14	Left Left	710	44
Thalamus	-15, -15, 17	Left	57	4.3

Table 3
Increase in GMD from pre- to post MBI. Controls versus active: $p < 0.001$, cluster size greater than 5 voxels.

Region (peak of cluster)	MNI coordinates of the peak voxel x, y, z	Side	Number of voxels	T-value
Cerebellum anterior lobe	-24, -56, -38 -2, -50, -9	LeftLeft	6128	44.6
Cerebellum dentate nucleus	-17, -60, -35	Left	8	4

4. Discussion

To the best of our knowledge, this is the first morphometric (VBM) study demonstrating structural brain changes in PD after a MBI. Significant changes in brain GMD involving the hippocampus and amygdala were found in a group of 14 PD patients who followed an eight-week program of a MBI as compared to a UC control group of 13 PD patients (Fig. 4). In addition, exploratory whole brain

analyses identified significant increases in GMD with an extensive cluster in the right caudate nucleus and a smaller significant cluster in the left caudate nucleus. Additionally, GMD increases in the MBI group were found in the cuneus and lingual gyrus of the left occipital lobe, the left thalamus, left parahippocampus, and bilaterally in the temporoparietal junction. In the UC group GMD increases were found in the left anterior lobe and left dentate nucleus of the cerebellum. GMD increases in the amygdala, the caudate nucleus

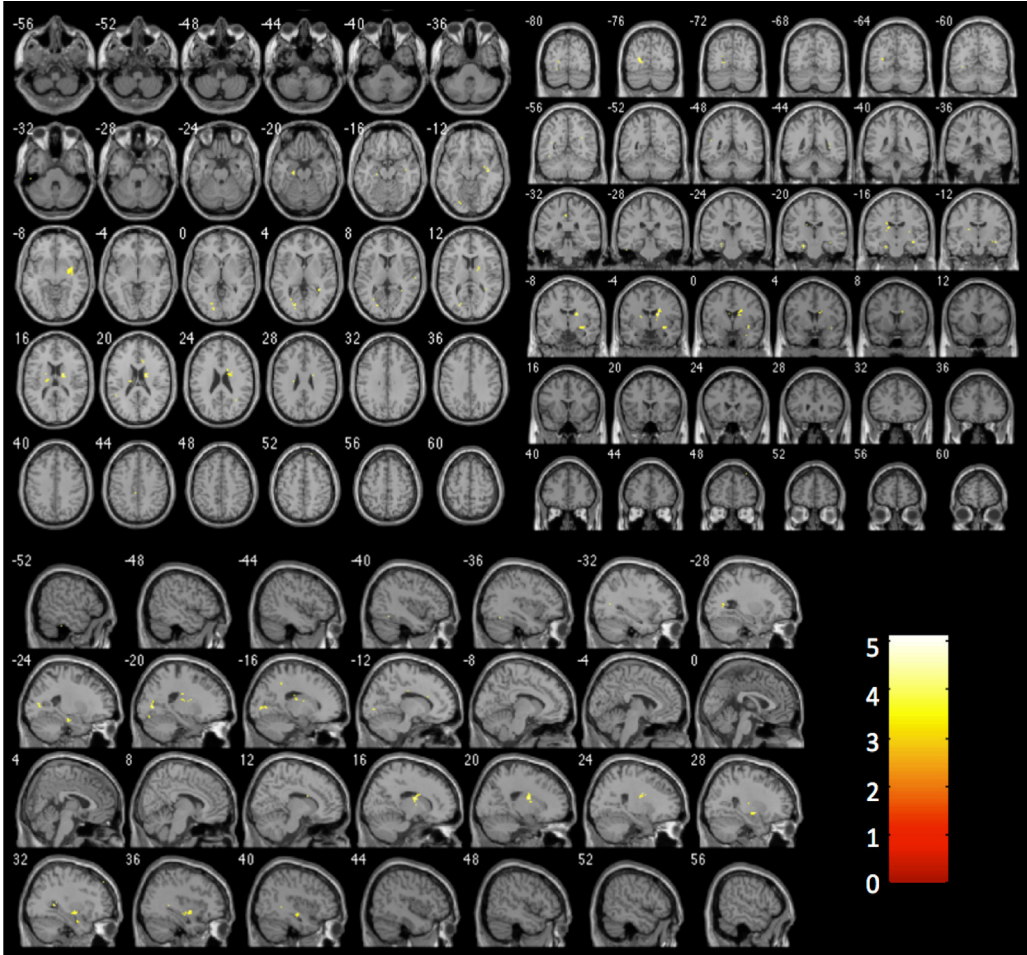


Fig. 2. Increases in GMD after intervention in the MBI group from pre- to post-intervention compared to the UC group are visualized on axial, coronal and sagittal slices in MNI space. An uncorrected $p < 0.001$ was used as a statistical threshold for clusters of more than 5 voxels. The color bar is scaled for a T-value between 0 and 5.

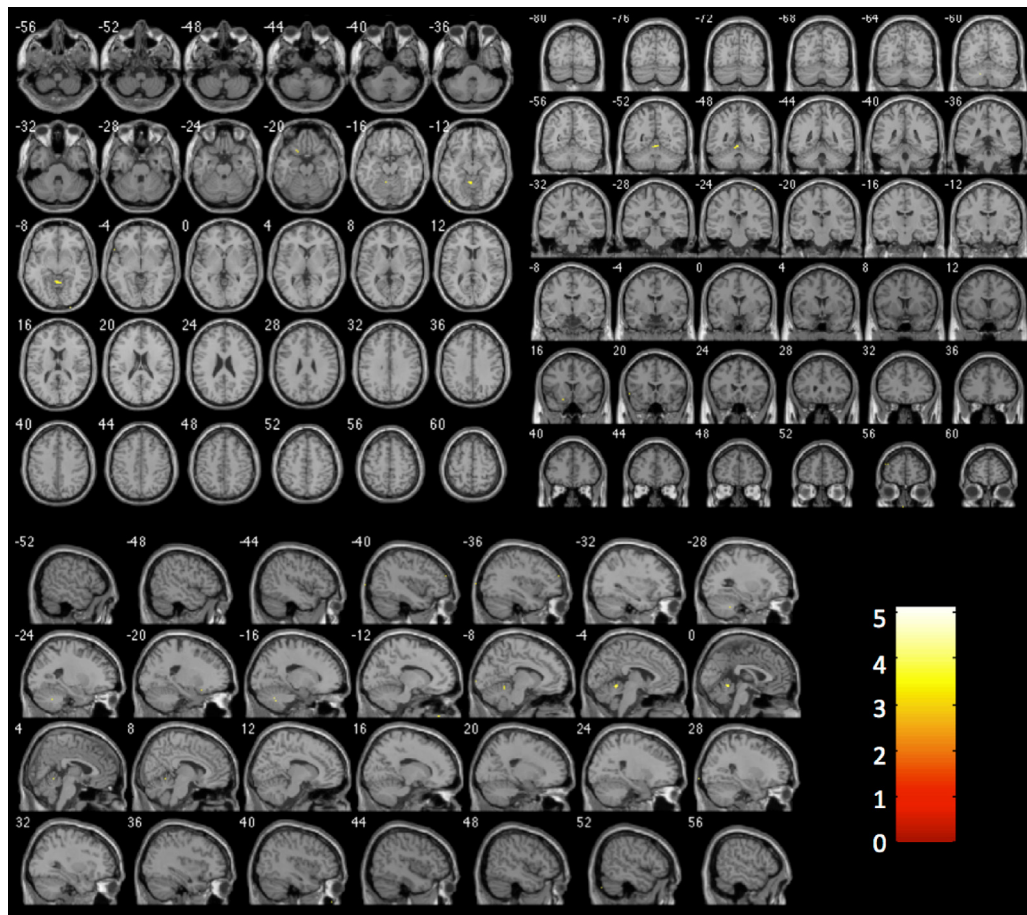


Fig. 3. Increases in GMD after intervention in the UC group from pre- to post-intervention compared to the MBI group are visualized on axial, coronal and sagittal slices in MNI space. An uncorrected $p < 0.001$ was used as a statistical threshold for clusters of more than 5 voxels. The color bar is scaled for a T -value between 0 and 5.

and left occipital lobe in the intervention group, and an increase in cerebellar GMD in the UC group represent findings potentially pertinent to insights in the neurobiology of MBI in PD.

Previous anatomical morphometric MRI brain studies on meditators versus non-meditators have shown structural brain changes in non-PD populations using various types of meditation and measurement techniques. In a pioneer cross-sectional study on cortical thickness, Lazar et al. [21] found an association between regular meditation practice and cortical thickness in frontal regions and the right anterior insula. The authors interpreted this finding as a possible indicator of slowing of age-related cortical thinning.

In another study, an increase in cortical thickness was reported in the right dorsal anterior cingulate cortex and the secondary somatosensory cortex in Zen meditation practitioners as compared to controls [26]. A series of cross-sectional studies have examined GMD increases secondary to meditation using VBM. Changes were reported in the left putamen [22], the left inferior temporal lobe, the right insula, and the right hippocampus [23], the medulla oblongata, the left superior and inferior frontal gyri, the anterior lobe of the cerebellum, the left fusiform gyrus [25], the right orbito-frontal cortex, the right thalamus, the left inferior temporal lobe, and the right hippocampus [24]. A recent randomized longitudinal VBM study in a population of otherwise healthy subjects seeking stress relief showed morphometric changes associated with MBI after eight weeks of training [27]. GMD changes were shown in an *a priori* region of interest in the left hippocampus. A whole brain analysis showed GMD increases in the posterior cingulate cortex, the temporoparietal junction and the cerebellum.

In the current study we anticipated finding hippocampal GMD changes on the basis of prior cross-sectional studies showing morphological differences in the hippocampus between meditators and non-meditators [23,24]. Smaller hippocampal volumes and ventricular changes on MRI have been reported in cognitively normal PD patients [30]. ROI studies have demonstrated hippocampal atrophy in PD patients with and without dementia [7] and during disease progression on VBM [6,31]. Our study conducted in non-demented PD patients shows that MBI induces a significant increase in GMD in both the left and right hippocampus.

In PD a decrease of GMD in the amygdala has been reported as well [7]. In agreement with this finding we expected to find an increase in GMD in the amygdala in our study population after eight weeks of MBI. Consistent with this hypothesis, the results revealed a small and significant increase in the right amygdala GMD in subjects who followed the MBI. In contrast, and on fMRI, Creswell et al. showed for the first time that mindfulness as a dispositional trait was associated with decreased or attenuated amygdala activity [32]. Greater amygdalar volume has been reported to be negatively associated with amygdala activity and blood pressure during a stress task [33]. In a cross-sectional Japanese study on university students, increased GMD in the amygdala positively correlated with higher scoring on the describing facet of the Five Facet Mindfulness Questionnaire [34]. Other specific GMD changes in our study were previously reported after eight weeks of mindfulness training in the temporoparietal junction [27]. GMD increases in the thalamus reported in the current study have been reported in a previous cross-sectional structural imaging study in meditation [24].

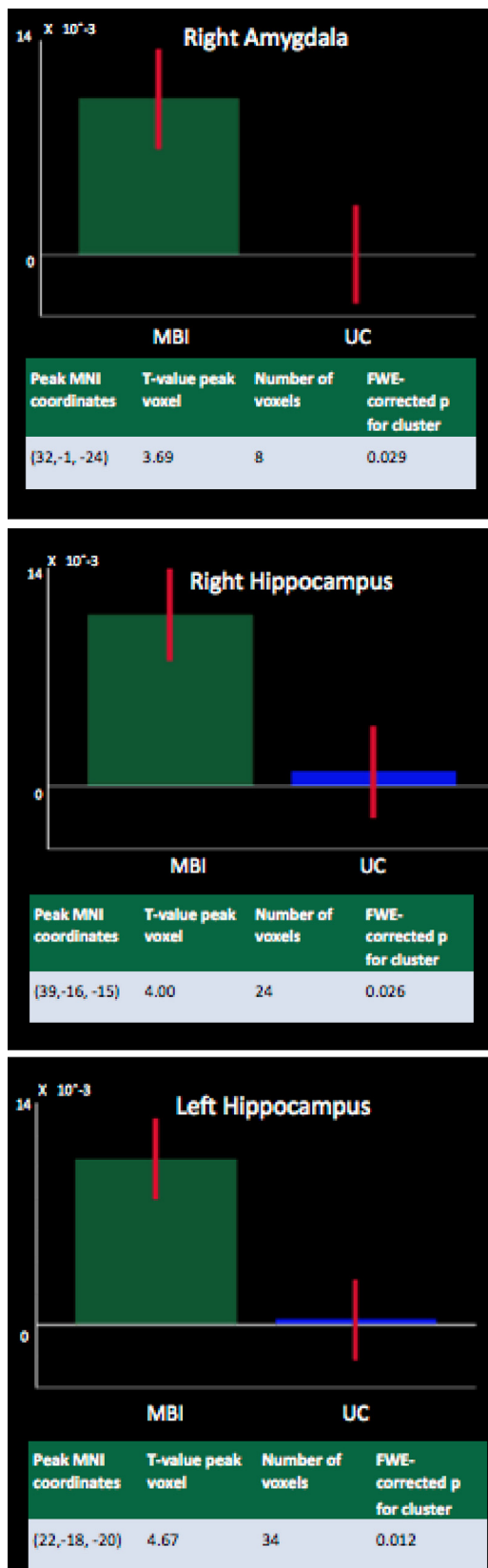


Fig. 4. Region of interest analysis was performed in the right amygdala and right and left hippocampus. The peak MNI coordinates, T-value of the peak voxel, number of voxels in the most significant cluster and the FWE corrected *p*-value for that cluster are shown. In addition a boxplot visualizes the gray matter density changes in the most significant voxel for both subject groups. Note that no cluster survived FWE correction in the left amygdala.

Three regions of increased GMD secondary to MBI in our study may be of interest as they pertain to the pathophysiology in PD – namely the caudate nucleus, the occipital lobe and the cerebellum. A GMD increase was found in the MBI compared to the UC group over time in the right caudate. The caudate nucleus is part of the striatum and is the site for dopaminergic pharmacological interventions in PD. Lou [35] found increased striatal dopamine binding to D2 receptors during meditation on positron emission tomography (PET). In a cerebral blood flow (CBF) study utilizing single photon emission tomography (SPECT), long-term meditators were shown to have increased CBF in the caudate nucleus [36]. In a case report of a long-term meditator, Engström [37] observed a right caudate nucleus activation on fMRI.

To our knowledge, an increase in GMD in the occipital cortex after an MBI has not yet been reported in the VBM literature. A GMD loss, however, has been observed in occipital areas in PD using VBM [31,38]. We found a GMD increase in the cuneus and lingual gyrus of the left occipital cortex. Of interest, Luders [39], found increased cortical gyrification in the cuneus in long-term meditators.

An increase in GMD in the cerebellum secondary to MBI has been reported [25]. We found increased GMD in the control population as opposed to the active MBI group. In PD, the cerebellum may have an altered function [40]. The cerebellum in PD may exert compensatory effects related to motor and non-motor impairments. The relative increase of GMD in the UC group might reflect this compensatory mechanism at the level of the left anterior lobe and left dentate nucleus. That is, PD patients who followed mindfulness training had a decreased GMD in the cerebellum, possibly indicating a diminution of compensatory function.

We acknowledge some limitations of this study. First, the longevity of trait-like effects needs to be established and correlated to motor and non-motor symptoms of PD, and thus future studies are warranted to verify our results and investigate possible behavioral correlations. Secondly, this study lacks an active validated control group to identify MBI specific effects from general effects of a group intervention such as social support or positive expectancies. At the time of the inception of this study there was no validated control for MBI. An active control intervention has recently been published [41] and its applicability in a PD population with MBI should be investigated.

Conflicts of interest

The authors declare no conflicts of interest.

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