Brief mindfulness training increased glutamate metabolism in the anterior cingulate cortex

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Mindfulness meditation has become a promising intervention for promoting health and well-being. Neuroimaging studies have shown its beneficial effects on brain functional activity, connectivity, and structures following months to years of practice. A series of randomized controlled trials indicated that one form of mindfulness meditation, the integrative body-mind training (IBMT) induces brain functional and structural changes in brain regions related to self-control networks such as the anterior cingulate cortex (ACC) after 2–10 h of practice. However, whether IBMT could change brain metabolism in the ACC remains unexplored. Utilizing a noninvasive 3T proton magnetic resonance spectroscopy, our results showed a significant increase in glutamate metabolism in the rostral ACC following 10 h of IBMT, suggesting that brief training not only increases ACC activity and structure, but also induces neurochemical changes in regions of the self-control networks. To our knowledge, this is the first study demonstrating the positive effects on brain metabolism in the ACC following brief intervention, suggesting a potential mechanism and implications of mindfulness meditation in ameliorating disorders such as addiction, depression and schizophrenia, which often involve the dysfunction of self-control networks and glutamatergic system (i.e. lower glutamate metabolism). *NeuroReport* 31: 1142–1145 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Mindfulness meditation involves paying attention to the present moment without judgment and has become a promising intervention for promoting health and well-being [1–3]. Our series of randomized controlled trials (RCTs) showed significant changes in behavior, physiology, and brain after 2–10 h of one form of mindfulness meditation, the integrative body-mind training (IBMT), and underlying mechanisms involve in enhanced self-control and its brain networks such as anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) [2–5]. Although most studies have focused on examining functional and structural changes following mindfulness, few studies have investigated neurochemical changes.

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive technique for the detection of brain metabolites, which has been widely used in research and clinical settings [6–10]. One ^{1}H-MRS study in long-term Zen meditators showed that myo-inositol was increased in the PCC, while glutamate, *N*-acetylaspartate (NAA), and NAA/creatine were reduced in the left thalamus [11]. However, these findings are inconsistent with literature that elevated myo-inositol and reduced NAA are associated with mild cognitive impairment (MCI), Alzheimer's disease, and other disorders with cognitive impairments [12–15]. In contrast, another study failed to detect any significant changes in brain metabolites, such as glutamate, NAA/NAAG, choline, and gamma aminobutyric acid in ACC and hippocampus following 12 weeks of combined Yoga and meditation [8]. Therefore, it remains unclear whether and how meditation changes brain metabolism. To our knowledge, there has not been a ^{1}H-MRS study that directly addresses the neurochemical changes following short-term mindfulness training only. Here, we conducted the first pilot study investigating whether brief IBMT could change neurotransmitters in the ACC or PCC.

Methods

Subjects

Twenty-two healthy college students without any previous meditation experience and psychiatric disorders were recruited (mean ± SD = 22.82 ± 4.35 years old; 13 male) and randomly assigned to IBMT and non-IBMT control group (11/group). Participants received ten 60-min IBMT sessions in group (half online sessions) within 2 weeks and nine completed the whole intervention study. In each session, participants concentrated on achieving a balanced state of body and mind guided by an experienced IBMT coach. IBMT stresses no effort to control thoughts but instead, encourages a natural state of restful alertness and accepts whatever arises in one's

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awareness at each moment that facilitates a high degree of awareness of body, mind, and environment.

The cooperation and interaction between mind and body in IBMT involves both the central and autonomic nervous system [5]. Non-IBMT control did not receive any training. All participants provided written informed consent and the experiment was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

Behavioral measurements

To assess self-control and emotion regulation, we chose widely used scales demonstrating excellent reliability and validity and recommended by the NIH RDoC matrix and PhenX Toolkit: (1) Perceived Stress Scale; (2) The Positive and Negative Affect Schedule; (3) Emotion Regulation Questionnaire; (4) Mindful Attention Awareness Scale; and (5) The PROMIS Short Form for assessing emotional distress caused by anxiety.

Proton magnetic resonance spectroscopy data acquisition and processing

Localized ^{1}H-MRS was performed on a Siemens Prisma 3T MR scanner. T1-weighted structural imaging was acquired with $1\times1\times1\,mm^3$ resolution for MRS voxel positioning. Point-resolved spectroscopy (PRESS) was conducted for estimating the metabolite concentrations in three regions of interest (ROIs) – rostral ACC (oACC), dorsal ACC (dACC), and dorsal-ventral PCC (dvPCC) based on literature [3,7,16], see Fig. 1a. We divided ACC into oACC and dACC because of different functions in ACC subregions [16]. Water-suppressed PRESS data were obtained with TR 2s, TE 90 ms, and 256 signal averages. Water suppression and B0 shimming up to second-order were performed with the vendor-supplied tools. Reference water signal was acquired for eddy current compensation and multi-channel combination. Spectral fitting was performed with LCModel software [17], using in-house basis spectra of 15 metabolites, including glutamate and glutamine. The basis spectra were numerically calculated incorporating the PRESS radio-frequency and gradient pulses. The spectral fitting was performed between 0.5 and 4.0 ppm. The Cramer-Rao lower bound was returned as a percentage SD by LCModel. The metabolite signal estimates were corrected for T2 relaxation effects using published T2 values [18]. The millimolar concentrations of metabolites were calculated with reference to water at 42 M and compared between the pre-treatment and post-intervention groups.

Results

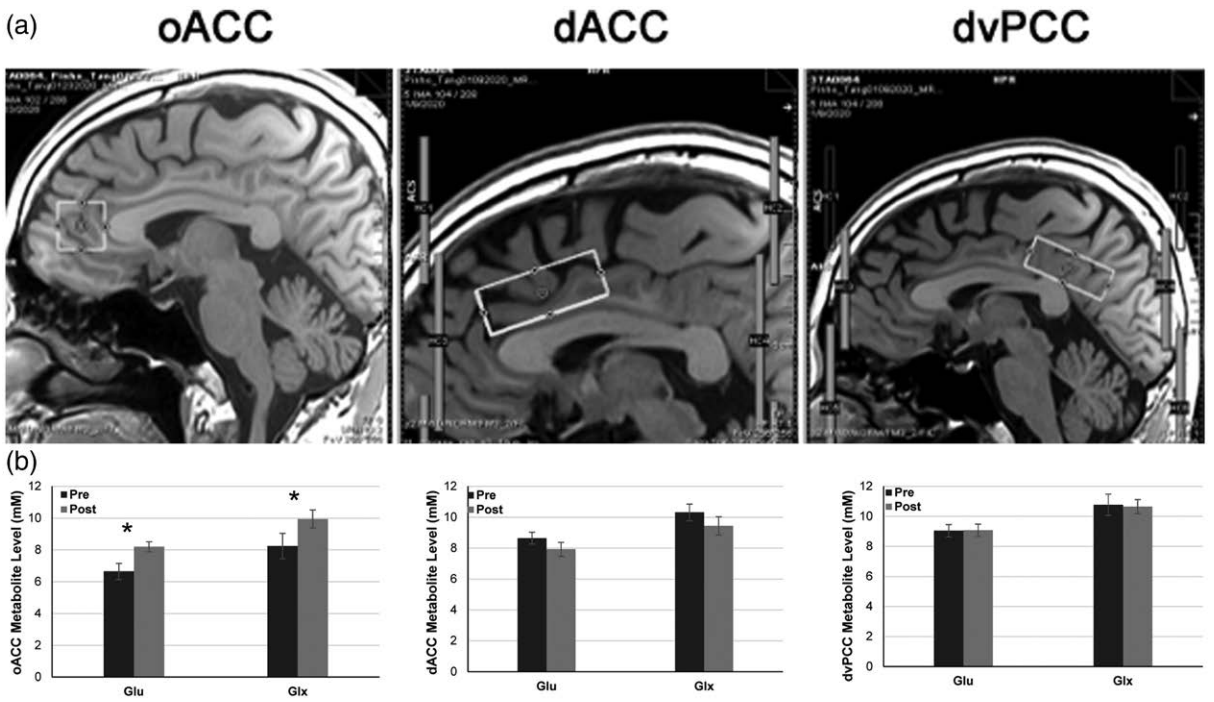
Before training, the two groups (IBMT vs. non-IBMT control) did not differ significantly (independent-samples *t*-tests, all $P>0.05$). Paired *t*-tests were performed for comparison of behavioral or neurochemical changes before and after IBMT and showed that after 10 h training, perceived stress and anxiety were significantly decreased ($t=-3.35$, $P=0.010$, Cohen's $d_z=1.12$ and $t=-3.51$, $P=0.008$, Cohen's $d_z=1.17$), respectively. Meanwhile, positive affect and cognitive reappraisal – an emotion regulation style showed significant improvements ($t=2.84$, $P=0.022$, Cohen's $d_z=0.95$ and $t=3.65$, $P=0.006$, Cohen's $d_z=1.22$) but a marginally significant reduction was detected for negative affect ($t=-2.25$, $P=0.055$, Cohen's $d_z=0.75$), respectively. As expected, non-IBMT conditions did not show any significance after 10 h (all $P>0.05$). However, 10-h IBMT induced a significant increase in glutamate concentrations ($t=3.24$, $P=0.012$), as well as in Glx (glutamate + glutamine) ($t=2.44$, $P=0.041$) in the oACC (Fig. 1b). Meanwhile, total choline (tCho), NAA, and total NAA (tNAA) showed marginally significant increases ($P=0.066$, $P=0.068$, and $P=0.057$) in the oACC, respectively. We also detected a marginally significant decrease in tCr ($P=0.07$) in the dACC, and in taurine and scyllo-inositol in the dvPCC ($P=0.058$ and $P=0.055$), respectively. Pearson correlations between behavior and metabolites in oACC, dvPCC, and dACC were conducted but did not detect significance in both IBMT and control condition (all $P>0.05$). Notably, the major signals of glutamate and glutamine between 2.2 and 2.5 ppm were well separated without considerable overlaps, thereby permitting estimation of the metabolites with precision. The linewidth was overall larger in oACC data compared with dvPCC and dACC data. The linewidth of total creatine (tCr) singlet at 3.03 ppm was 10.8 ± 2.1, 8.7 ± 2.3, and 6.9 ± 1.7 Hz for oACC, dvPCC, and dACC, respectively ($n=18$ for each ROI). The ratio of the tCr peak amplitude to the SD of residuals was 43 ± 8, 50 ± 10, and 71 ± 16 for oACC, dvPCC, and dACC, respectively.

Discussion

Our MRS results indicated a significant increase in glutamate and Glx (glutamate + glutamine) metabolism in the oACC after 10 h of IBMT, consistent with our RCTs that brief IBMT increases functional and structural changes in the ACC within self-control networks. Our behavioral results are consistent with our previous findings that brief IBMT improves self-control ability which leads to better stress management, mood states, and emotion regulation [2,4,5]. However, we did not detect any significant brain-behavior correlation, plausibly because of small sample size in this pilot study.

Glutamate is a major excitatory neurotransmitter and key substrate for synaptic plasticity and cognitive functions such as learning and memory [19,20]; therefore, IBMT-induced glutamate increase in the ACC may also facilitate learning and cognitive functions, which may explain why brief IBMT improves attention, creativity, problem solving, and academic performance [2,5]. Glutamate also plays an important role in emotion regulation, health, psychopathology, and disorders [20]. For example, both

Fig. 1



(a) Regions of interest (ROIs) in ^{1}H-MRS. Voxel positioning is shown on structural MR images for three regions of interest (ROIs). The voxel size was $20 \times 20 \times 20\,mm^3$ for rostral ACC (oACC), and $40 \times 15 \times 15\,mm^3$ for dorsal-ventral PCC (dvPCC) and dorsal ACC (dACC). (b) Glutamate and Glx concentrations in three ROIs before and after IBMT. Glutamate (Glu) and Glx (glutamate and glutamine) concentrations (mM) in three brain regions (oACC, dvPCC, and dACC) following 10 h IBMT.

animal and clinical studies have suggested that glutamatergic dysfunction (i.e. lower glutamate metabolism) is implicated in the pathophysiology of depression, addiction, schizophrenia, and other disorders [7,9,10]. Given that brief IBMT could regulate glutamate metabolism, our observations may suggest IBMTs potential intervention effects on diverse disorders involved the dysfunction of glutamatergic system. We also detected a marginally significant decrease in tCr in the dACC following IBMT. This result may suggest the potential of IBMT in improving symptoms of depression through changing tCr, as the tCr level has been shown to be higher in the ACC in patients with major depressive disorder [21].

ACC is also involved in cognitive decline and aging. For example, studies showed that the ACC gray matter volume decreases with age [8,22]. Age is also negatively correlated with blood flow in the ACC [23]. In contrast, more daily exercise in cognitive games is associated with greater ACC gray matter volume in older adults [8]. Similarly, 2–10 h of IBMT induces greater brain activity, blood flow, and white matter in the ACC [5]. These evidences raise the possibility that engaging in mindfulness or cognitive training could prevent and ameliorate age-related cognitive decline through functional and structural changes in the ACC.

In the present study, after 10 h of IBMT, tCho, NAA, and tNAA showed a marginally significant increase in the oACC, whereas taurine and scyllo-inositol in the dvPCC showed a marginally significant decrease. Extensive studies showed that ^{1}H-MRS metabolites such as reduced Cho (or tCho), NAA and NAA/NAAG and elevated scyllo-inositol or myo-inositol are related to aging or memory complaints, MCI, Alzheimer's disease, and depression [12,13,24]. For example, a longitudinal study indicated that decreased ^{1}H-MRS NAA/myo-inositol ratio in the PCC may be one of the risk markers of preclinical Alzheimer's disease. Another ^{1}H-MRS study also showed that reduced NAA and elevated scyllo-inositol in patients with mild Alzheimer's disease and with amnestic MCI [12]. These results suggest that cognitively normal elderly subjects with low NAA or tCho, and elevated scyllo-inositol or myo-inositol in the PCC might be at risk of progression to clinical Alzheimer's disease. Therefore, tCho, NAA, scyllo-inositol, and myo-inositol in the ACC or PCC may be biomarkers of preclinical Alzheimer's disease, which can be targeted by mindfulness training or other treatments [5,14,15,25]. Taken together, IBMT may also be a promising intervention for cognitive decline and preclinical Alzheimer's disease through increasing brain metabolites such as tCho, NAA,

scyllo-inositol, or myo-inositol, although a future full-scale RCT replication is warranted.

Limitations and future directions

Given the exploratory nature of the study, we did not include an active control condition. Future research will include an active control to replicate the pilot results in large sample size. Moreover, the 10 IBMT only shows acute intervention effects on brain metabolism such as glutamate, future longitudinal study is warranted to reveal the long-term intervention effects. Nevertheless, the first study may provide preliminary evidence that brief mindfulness training changes neurotransmitters in the ACC and may help develop interventions that can prevent and ameliorate addiction, depression, schizophrenia, cognitive decline, and age-related disorders involving the dysfunction of neurochemical systems such as glutamate, choline, and *N*-acetylaspartate.

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Conflicts of interest

There are declare no conflicts of interest.

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