Selected Summaries

Long-term benefits of mindfulness on white matter tracts in panic disorder

Minji Bang, Borah Kim, Kang Soo Lee, Tai Kiu Choi, Sang-Hyuk Lee. (Department of Psychiatry, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea.) Long-term benefits of mindfulness on white matter tracts underlying the cortical midline structures in panic disorder: A 2-year longitudinal study. *Psychiatry Clin Neurosci* 2023;**77:**355–64.

SUMMARY

Panic disorder is one of the most prevalent psychiatric disorders, with chronic recurrent course. Patients often experience relapse even after the first-line pharmacological intervention. Mindfulness-based cognitive therapy (MBCT) focuses on the present moment and has shown effectiveness in the management of panic disorder. MBCT has been shown to cause neurobiological changes in various cortical midline structures but its impact on the neurobiological changes in patients with panic disorder and their correlation with clinical severity remains unclear.

This study, therefore, aimed (i) to examine the long-term benefits (2 years) of MBCT on white matter plasticity using diffusion tensor imaging (DTI), by assessing fractional anisotropy (FA) in the cortical midline structures, viz. anterior and posterior cingulate cortex (ACC and PCC), precuneus, dorsomedial and ventromedial prefrontal cortex (dmPFC and vmPFC); and (ii) examine its relationship with severity of state and trait symptoms of panic disorder.[1] The primary objective was to compare the differences in the white matter plasticity of the cortical midline structures 2 years after receiving MBCT in patients with panic disorder maintained on pharmacotherapy (MBCT+PT), those treated with pharmacotherapy alone (PT), and healthy controls (HCs).

Treatment-naïve right-handed patients of panic disorder (as per DSM-IV-TR) were included from an outpatient setting of a hospital in Korea, using structured clinical interview. Exclusion criteria were major psychiatric, medical (unstable) and neurological disorders; traumatic brain injury; intellectual disability, and concurrent formally administered psychotherapy. Structured scales were used to assess severity of panic disorder (Anxiety Sensitivity Index-Revised, Panic Disorder Severity Scale), depressive and anxiety symptoms (Beck Depression Inventory-II and Beck Anxiety Inventory), and presence of neurotic traits (NEO personality inventory). HCs were included if they were right-handed with no past or current psychiatric illness and no history of psychiatric illness in a first-degree relative.

The recruited patients were included in the MBCT-PT arm (n=26) or PT (n=20) arm based on their volunteering. Pharmacotherapy was provided as per standard national treatment algorithms and adherence to the medications was monitored. MBCT (eight sessions each lasting about 1.5–2 hours) was delivered weekly in a group of 6–10 participants. The sessions were delivered by trained psychotherapists under the supervision of experts. Twenty-five HCs were recruited. DTI was done at baseline and at 2 years' follow-up. Mixed model regression analysis was done.

The sociodemographic, clinical and neuroimaging parameters were comparable across three groups at baseline. The dose and duration of antidepressants were comparable based on dose equivalence given by Hayasaka and colleagues.[2] A significant main effect of group, time and group-by-time interaction was seen in severity of panic disorder symptoms ($p<0.001$). While FA was comparable across groups at baseline and 2-years, the longitudinal percentage changes in the five cortical midline structures indicated significant group differences in ACC, dmPFC, PCC and precuneus. The percentage FA changes were higher in the PT group, while that of MBCT+PT group and HCs resembled and were lower. On exploratory correlation analysis, the lowering of FA in the white matter tracts underpinning the cortical midline structures was linked to the improvement of state and trait symptoms in the MBCT+PT group. The authors concluded that reduction in excessive white matter connectivity in the cortical midline structures after MBCT leads to improvements in clinical symptoms and trait vulnerability in patients with panic disorder. Certain limitations highlighted in the article include the small sample size, non-randomized design, study focusing on patients with panic disorder who required maintenance pharmacotherapy reducing the generalizability to milder cases.

COMMENT

The present study highlighted the clinical and neurobiological impact of MBCT in patients with panic disorder. This is of particular relevance to India since mindfulness has its roots in India and Zen culture.[3] This should inspire Indian researchers and clinicians in incorporating MBCT in their research activities and daily clinical practice. Further, it has been seen that faith and culture play an important role in acceptance of any form of psychotherapy.[4,5] Hence, it would be worthwhile to use indigenous principles of meditation, yoga, e.g. taking paradigms from *Bhagawad Gita* for better applicability in Indian patients. Despite its roots, MBCT is hardly practised in India. However, applying the concepts of *Bhagwad Gita* may make such interventions more acceptable and understandable in the Indian context. The principles of self-awareness, observing one's thoughts and emotions without judgement, and self-control, explained in the *Gita* align with the goals of MBCT, which also aims to cultivate non-reactive mindsets.

The findings must also be interpreted in the light of scarce healthcare resources in India. MBCT sessions in the study were delivered by a trained therapist whose competence and adherence to the therapy was monitored by experts. In India, since there is a dearth of mental health resources including psychiatrists and phycologists,[6] a validated manual for uniform application, without the need for supervision, would be more feasible.

Some observations as a reader included not excluding severe agoraphobia, which might affect severity of panic disorder. Moreover, while efforts were made to control for duration and dose of antidepressants, a major limitation of the method used for calculating dose equivalence is the 'not well-established' assumption of the dose-dependent effect of antidepressants.[2] Since it has been established that patients prefer to use psychological therapy over pharmacological treatment,[7] it may be designed to include patients with mild to moderate disorders (excluding the severe forms) who can be treated solely with non-pharmacological measures considering the differential effects

of antidepressants on the brain. This would control for an important confounder.

Other points of concern pertain to not specifying the age of onset and duration of illness, which may have an impact on the neurobiological changes at baseline or with treatment. Also, assessment of intelligence quotient is important in cognitive behavioural therapy. The authors mentioned excluding individuals with intellectual disability but it is difficult to know from the article which tests were applied to ascertain the intelligence quotient.

Considering the various strengths and limitations, it is apparent that the study has opened gates to the possibility of sustained neurobiological effects of MBCT in patients with panic disorder, which may be adapted to subsequent research and incorporated into clinical practice in India as the acceptance for non-pharmacological measures for psychiatric illnesses is high.

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Peritumoural infiltration of lidocaine during breast cancer surgery

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SUMMARY

Events during surgery are seldom taken into account in the natural history of breast cancer. There is evidence of dissemination of tumour cells leading to metastases during surgical removal of the tumour. It might also stimulate growth of pre-existing micrometastases, leading to an early increase in metastatic disease. Surgery-induced hypoxia may activate pro-metastatic pathways through voltage-gated sodium (Na) channels.

Local anaesthetics inhibit voltage-gated Na channels and thus inhibit cellular proliferation and facilitate cell-to-cell adhesion, thus reducing metastatic capability of the primary tumour. They are also known to modulate non-receptor tyrosine-protein (Src) kinases.

A Cochrane review concluded inadequate evidence to support the use of regional anaesthesia agents[1] and therefore an open-labelled, randomized controlled trial to assess the effect of infiltration of local anaesthetic (LA) around a primary breast cancer before extirpative surgery (BCS [breast conservation surgery]/modified radical mastectomy [MRM]) in women with early breast cancer (EBC) was conducted.

Patients with operable breast cancer with clinical N0/N1 nodal status with no evidence of distant metastasis and ECOG (Eastern Cooperative Oncology Group) performance status score of 0 were included. Those who had had a prior incisional or excisional biopsy, had received neoadjuvant chemotherapy (NACT) or hormone therapy, or had benign disease were excluded. The patients were stratified by treatment centre, tumour size and menopausal status.

Patients allocated to the LA arm were administered 0.5% lidocaine around all six surfaces (superior, inferior, anterior, posterior, medial, lateral) of the primary tumour after induction. The planned surgical procedure (MRM/BCS) was initiated 7–10 minutes after administration of lidocaine. Postoperatively, all patients received standard adjuvant therapy. Systemic chemotherapy was given using six cycles of anthracycline in node-negative and four cycles of anthracycline followed by 12 weeks of taxane therapy in node-positive disease. Her-2-neu-positive patients received adjuvant trastuzumab. Patients who underwent BCS and those who had MRM with tumour size ≥5 cm and/or node-positive disease were administered standard postoperative radiotherapy. Patients with hormone receptor-positive status were planned for tamoxifen if premenopausal or aromatase inhibitor if postmenopausal, for at least 5 years. All patients were followed up at 6-month intervals with history and clinical examination. Mammography of the contralateral and/or remnant breast was done every 18–24 months. Evaluation for distant metastatic disease was done in symptomatic patients or in those with loco-regional recurrence.

The primary end-point of the study was disease-free survival (DFS). It was defined as the time interval between randomization and local/regional/distant metastases or contralateral breast cancer or death due to any cause whichever occurred first. The secondary end-point was overall survival (OS) defined as the time interval between randomization and death due to any cause.