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The mechanism of mindfulness meditation on pain by functional magnetic resonance imaging method

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ABSTRACT

Pain is a subjective feeling having sensory, cognitive and emotional components. Brain regions that cognitively and affectively contribute to pain sensation are the anterior cingulate cortex (ACC), insula, prefontal cortex (PFC) and the default mode network (DMN). Depression and anxiety may accompany pain and they may exaggerate the pain via cognitive and affective disturbance. As a complementary treatment of pain, mindfulness meditation which is a therapeutic technique may be described as "non-judgmental awareness of the present moment". Mindfulness meditation aims to focus on the experiences of bodily sensations and breathing in a non-judgmental and accepting manner. The functional magnetic resonance imaging (fMRI) is one of the tools that can explain the mechanism of action of mindfulness meditation on pain intensity, pain unpleasantness and the cognitive and affective disorders which accompanying pain. This study compiles studies examining the mechanism of action of mindfulness meditation on pain and pain accompanying pain unpleasantness, depression, anxiety with fMRI.

Keywords: Pain, mindfulness meditation, functional magnetic resonance imaging

Pain is a clinical symptom that causes suffering making life sometimes unbearable. The generally accepted definition of pain has been made by the International Association for the Study of Pain as *"an unpleasant sensory and emotional experience associated with or similar to actual or potential tissue damage"* [1]. The sensory and the emotional aspect of the pain sensation is described by the parameters of "pain intensity" and "pain unpleasantness" determined by various scales that are validated and reliable [2, 3]. Due to the pain-related quality of life impairment, psychological comorbidity, reduction of productivity and other negative social and economic consequences pain needs to be treated [4]. Many pharmacological (such as tricyclic antidepressants, anticonvulsants such as gabapentin, opioids) and non-pharmacological (such as Cognitive Behavioral Therapy, Transcutaneous Electrical Nerve Stimulation) methods are used in the treatment of pain [5, 6]. Mindfulness meditation is one of the non-pharmacological treatment methods offered in the treatment of pain. There are many studies in the literature demonstrating the ameliorative effects of mindfulness meditation for the treatment of pain, depression and anxiety [7-12]. In some studies, the mechanisms underlying the ameliorating effect of mindfulness meditation on pain, depression and anxiety were examined with functional Magnetic Resonance Imaging (fMRI). In this review, a

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comprehensive compilation is conducted using a combination of the keywords "pain, mindfulness meditation and fMRI". The purpose of this review is to evaluate the fMRI findings that could explain underlying neural mechanisms of mindfulness meditation for the patients with pain.

TRANSMISSION AND PROCESSING OF PAIN SENSATION

The pain receptors (nociceptor) are specialized sensory receptors that convert noxious stimulus to pain sensation in the form of free nerve endings. The nociceptors transmit the painful stimuli to the Central Nervous System (CNS) via action potential. Sensory neurons that receive the sensation of pain from the nociceptors and transmit it to the CNS, are primary afferent neurons. The processing of pain sensation in the central nervous system is a complex process. Primary afferent neurons that receive pain sensation with nociceptors (C type and A delta type fibers) reach the posterior horn of the spinal cord and synapse here. They innervate the second neuron with the neurotransmitters (glutamate and substance P) secreted into the synaptic gap via the spinothalamic pathways to transmit the pain sensation to the thalamus. The spinothalamic pathway is divided into two as the neospinothalamic pathway which transmits fast and sharp pain and the paleospinothalamic pathway which transmits slow, dull pain. Via these two pathways, the third neurons that receive the sensation of pain from thalamus reach the primary and secondary somatosensory cortex in the parietal cortex. These neurons are represented topographically in the sensory homunculus region that are corresponding to them and pain is perceived in the body region that topographically fits its location [6, 13].

In addition to the pathway that the pain is carried, it is clinically divided into acute and chronic pain according to its duration. "Acute pain" defines pain that lasts less than 30 days, while pain that lasts longer than 6 months is called "chronic pain". Acute pain is self-limiting and is attenuated when nociceptive input is blocked by medications. However, the patients suffer more from chronic pain due to comorbidities such as depression and anxiety [14].

COGNITIVE AND EMOTIONAL ASPECTS OF PAIN

Pain is not a simple somatosensory sensation perceived by nociceptors and transmitted by spinothalamic pathways. There are also cerebral cortex regions that affect the perception of pain by cognitive and affective factors [13]. Among the neuroimaging methods, fMRI is an important tool in determination of the effect of the psychology, cognitive and emotional status of a patient on the changes in the structure and functions of the brain during pain. In fMRI studies it has been reported that regions in the brain such as the insula, anterior cingulate cortex (ACC), prefrontal cortex (PFC), amygdala and hippocampus where the pain is processed cognitively and affectively contribute to pain sensation [15-19]. Animal studies have shown that the ACC and amygdala play an important role in pain avoidance behavior and the affective/motivational aspect of pain [15, 16]. It has been reported that the PFC, primarily responsible for executive functions such as “decision making”, may also be responsible for the cognitive and affective aspects of pain [17, 18].

In addition, Default Mode Network (DMN) activity reveals during pain. DMN is a neural network characterized by oscillatory activity in certain brain regions (medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior and lateral temporal cortex). This network is activated by self-referential processes (mind-wandering and ruminations) and pain [20-22]. Pathways as “top-down control” that reflect on the horn of the Periaquaductal Gray Matter (PAG) and the posterior medulla spinalis are also effective in terms of painful sensory and emotional aspects. In this pathway, the main transmitters are serotonin and noradrenaline that may modify the perception of pain via cognitive and emotional factors by cortical control, indicating the importance of the psychological aspect of pain [23-25].

The depression and anxiety are among the most common diseases in primary care diseases in which cognitive and affective disorders are seen [26]. In the “Netherlands Study of Depression and Anxiety”, a large sample study, a significant relationship was found between depression-anxiety and pain severity in patients with pain and with depression and anxiety [27]. It has been reported that the reason for the strong relationship between pain, depression and anxiety may be that they share the same pathophysiological mechanisms. Pain, depression and anxiety may share the same cognitive and behavioral processes and they can occur with a change in activation in the same brain areas (ACC, PFC, insula) [27, 28]. Since cognitive and emotional factors affect the pain intensity, the offered treatment method should improve depression and anxiety to relieve the patients with pain. At this point, mindfulness meditation emerges as a complementary treatment approach for pain, pain unpleasantness, depression and anxiety that may accompany pain [29].

EFFECT OF MINDFULNESS MEDITATION ON PAIN

Mindfulness meditation has its origins in Ancient Eastern culture. Although it is originated from 2500 years of Buddhism tradition, it is a cognitive and behavioral therapeutic technique used for medical practices in the West medicine. Basically, mindfulness can be defined as *"moment-by-moment awareness"*. However, mindfulness is purely experiential [29, 30]. During the mindfulness meditation process, people intentionally direct their attention and awareness to a certain focus by often breathing or arising physical sensations. People are encouraged to experience their mental stance (thoughts and emotions) and sensations in a non-judgemental, accepting manner and nonelaborative attitude. Meditators who are aware of the transience of thoughts, feelings and sensations reduce their stress and rumination [31, 32].

Although there are different mindfulness practices, mindfulness meditation is basically divided into two as "Focused Attention" and "Open Monitoring" in terms of the quality of the practice. In "Focus Attention", the meditators focus on a certain object such as breathing and bodily sensation, by repeatedly shifting their attention from thought / emotion / external stimuli focuses to the selected object. Via "Open Monitoring", on the other hand, the meditators become aware of their sensory/cognitive/emotional experience observing them with an openness attitude, non-judgement and nondetailed evaluation. It can be defined as "awareness of awareness". Through the continuity of these practices, the meditators reach the ability to become aware of the thoughts, emotions in their mind and somatosensory experiences (trait mindfulness), even when they do not practice meditation [12, 33]. Recently, the effect of mindfulness meditation on pain, depression and anxiety which may accompany pain have been the most common research topic. Kabat-Zinn [29], who has an important role in the widely acceptance of mindfulness, carried out an important study at Massachusetts Medical Center, in which patients experienced pain and stress for various reasons. As a result of this study, it was determined that pain, depression and anxiety decreased, after mindfulness meditation and this improvement – excluding pain – continued for 15-months follow-up [29]. This was MBSR (Mindfulness-Based Stress Reduction) used as a method in many clinical pain studies. MBSR is a structured and standardized program that includes a variety of practices such as breath focusing, yoga, body scanning and silence retreats [34]. After Kabat-Zinn *et al*. [29], scientific studies investigating the therapeutic effect and underlying mechanism of mindfulness meditation and MBSR on pain, depression and anxiety have increased over the years [7, 35-37]. Reiner *et al*. [38], reported that mindfulness-based practices reduced pain severity and this reduction continued for a long time through learned techniques.

PAIN, MINDFULNESS and fMRI

fMRI is a non-invasive method that investigates the effects of cognitive processes on neural activity in the brain. It is based on hemodynamic changes due to alterations in local neural activity [39]. In various studies, the pain-relieving effect of mindfulness meditation was demonstrated using fMRI that can determine the underlying neural mechanism. In the study of Gard *et al*. [40], painful stimuli were applied to expert meditators and novices (control group)(Table 1). They determined that the intensity of pain did not change in both groups via mindfulness meditation. However, in expert meditators, the decrease in pain unpleasantness was accompanied by a decrease in bilateral lateral prefrontal cortex activity. During mindfulness meditation, "accepting the pain non-judgementally" is related to decreased lateral PFC activity. In addition, an increase in posterior insula and seconder somatosensory cortex activity was accompanied by the decrease in anxiety about pain expectation. Because "focusing the attention to the sensory aspect of pain" is related to the insula activity through interoceptive attention (awareness of inner bodily sensations). Also, it has been reported that frontal top-down control was decreased in this process [40]. In this study, the increase in right anterior cingulate cortex and ventromedial prefrontal cortex activity may be related to the effect of reducing pain unpleasantness and anxiety expectation about pain in the positive emotional state created by mindfulness meditation. These are areas where the pain is processed cognitively and affectively. Because the pain and anxiety modulation through mindfulness is associated with decreased sensory processing of the pain in the brain [40].

Lutz *et al*. [9] showed that expert meditators had less pain unpleasantness during painful stimuli and stronger activity in left anterior insula and anterior midcingulate cortex by mindfulness meditation. In addition, it was reported that the activation of the amygdala decreased in experienced meditators anxiety during anticipation of pain. Amygdala activity is related with anxiety and decreased activity may be due to decreased anxiety [9].

In a study, a reduction in pain catastrophizing (negative, destructive thoughts about the pain itself) was accompanied by a decrease in connectivity in DMN nuclei and an increase in connectivity between the DMN and the somatosensory cortex [10]. It was attributed to the increased focus on the sensory stimulus (pain) and the lack of detail of emotional processes. This may lead to the fact that the "state of being mindful" in daily life, which can be improved with formal mindfulness meditation, is also effective in reducing pain [10]. Supporting this result, Zeidan *et al*. [11] suggested that mindfulness meditation during painful stimulus caused in increased "awareness", decreased pain intensity, pain unpleasantness, and dorsal posterior cingulate cortex and precuneus deactivation in the brain in participants who had no previous meditation experience (novice). Mindfulness meditation can be a complementary treatment method in pain symptom via decreasing posterior cingulate cortex and precuneus activity by reducing self-referential and ruminative thoughts [119. Because the posterior cingulate cortex and precuneus, which is the nucleus of the DMN, plays significant role in the processing of pain along with self-referential and ruminative thoughts.

Recently, there are studies by novice and expert mediators on the effect of mindfulness meditation on pain. Wang *et al*. [41] presented that mindfulness meditation reduced pain unpleasantness in expert mediators and that the reason was the separation of the sensory and cognitive/affective aspects of pain. Painful stimuli were accompanied by increased activity in the secondary somatosensory cortex and posterior insula in experts, and decreased activity in the primary somatosensory cortex in novices. The reason may be the difference in the applied meditation directives. Thus; somatosensory activity is modulated by cognitive factors. Shifting attention from the painful stimulus to another thing decreases the activity in the somatosensory region while focusing on the painful stimulus increases the activity. In this respect, it is similar to the results of the study of Harrison *et al*. [10]. Expert mediators could improve pain through decreased activity in the ACC, PFC, and Orbitofrontal Cortex (OFC) (one of the areas responsible for sensory discrimination and emotional reaction), modulation of cognitive functions and decreased emotional reactivity. This once again points to the cognitive and affective aspects of analgesia developed by mindfulness meditation. Attenuation of the pain signal by mindfulness meditation before it reaches the thalamus, may decrease the activity in the thalamus and prevent the pain from reaching the somatosensory cortex as a strong signal. Reduction of self-referential thoughts in expert mediators may alleviate the pain by reducing DMN activity [41]. Considering the role of DMN in pain sensation, this is an expected feature.

Zeidan *et al*. [20] reported that the decrease in pain intensity by mindfulness meditation (Focus Attention) was accompanied by a decreased in ACC and right anterior insula activity which is responsible for the cognitive modulation of pain and interoceptive awareness. In this respect, "Focus Attention" has a different mechanism from "Open Monitoring" mindfulness meditation [20]. In a comprehensive study of Zeidan *et al*. [42] individuals who applied during a painful stimulus were divided into mindfulness meditation, sham and placebo. These groups were compared with fMRI imaging methods in terms of the effect of mindfulness meditation during the painful stimulus. Consequently, it was determined that "the level of awareness" (assessed by a scale) increased only in the group that applied mindfulness meditation and it was reported that although pain intensity and pain unpleasantness de-

Table 1. The effect of mindfulness meditation on pain and the results of the fMRI method

Authors	Areas	Effect	Comments
Gard *et al.* [40]	PFC, Insula, SII	Decreased pain unpleasantness, anxiety expectation	Interoseptive attention, accepting the pain non-judgementally
Lutz e*t al.* [9]	Insula, Amygdala, MCC	Decreased anxiety of pain expectation	Decreased of amygdala activity may due to decreased anxiety
Harrison *et al.* [10]	DMN, Somatosensory Cortex	Reduction in pain catastrophizing	‘’State of being mindful’’ is effective in reducing pain
Zeidan *et al.* [11]	PCC, Precuneus	Decreased pain intensity and pain unpleasantness	Reduced ruminative and self-referential thoughts
Wang *et al.* [41]	ACC, Insula, OFC, Amygdala, PFC, DMN	Decreased pain unpleasantness	Reduced mind-wandering and emotional reaction
Zeidan *et al.* [42]	ACC, Insula, OFC, PAG	Decreased pain intensity and pain unpleasantness	Mindfulness meditation group’s mechanism is different from sham and control groups
Zeidan *et al.* [20]	ACC, Insula	Decreased pain intensity	‘’Focus Attention’’ and ‘’Open Monitoring’’ has different mechanism on pain
Riegner *et al.* [43]	Precuneus, PFC, Amygdala	Decreased pain intensity and pain unpleasantness	‘’Focus Attention’’ result in precuneus deactivation, reduced emotional reaction
Seminowicz *et al.* [45]	Insula, Parietal Cortex	Headache frequency was reduced	MBSR; practice should continue
Braden *et al.* [46]	ACC, PFC	Back pain intensity and depression was reduced	Short-term MBSR is presented
Smith *et al.* [47]	ACC, PCC, PFC	Decreased pain intensity	MBSR is effective by shifting ruminative thoughts from pain
Mioduszewski *et al.* [48]	Brain White matter	Decreased chronic neuropathic pain	MBSR; white matter could new target for investigations
Hatchard *et al.* [49]	Primer Somatosensory Cortex, Precuneus	Decreased pain perception	MBSR; decreased emotional reactivity and pain expectation
Medina *et al.* [51]	Amygdala, ACC, Insula	Nondecreased pain intensity in groups	MBSR; VAS doesn’t reflect general pain intensity

fMRI = functional Magnetic Resonance Imaging, PFC = Prefontal Cortex, SII = Secondary Somatosensory Cortex, MCC = Midcingulate Cortex, DMN = Default Mode Network, PCC = Posterior Cingulate Cortex, ACC = Anterior Cingulate Cortex, OFC = Orbitofrontal Cortex, PAG = Periaquaductal Gray Matter, MBSR = Mindfulness-Based Stress Reduction creased in all three groups. However, it was determined that the neural analgesic mechanisms accompanying the decreased of pain intensity and pain unpleasantness in the group that practice mindfulness meditation were different from those in the sham and placebo groups. It was reported that the increase in the activity of the subgenual ACC, anterior insula and OFC responsible for the cognitive modulation of pain, was due to the non-judgmental awareness that takes place in mindfulness meditation. Also, significantly reduced neural activity was observed in the thalamus and PAG, where nociceptive information is facilitated and modulated by mindfulness meditation [42].

In a study, people who were applied painful stimuli and practiced mindfulness meditation (Focus Attention) had significantly decreased pain intensity and pain unpleasantness compared to the control group (reading an audiobook). The improvement in pain parameters was accompanied by decreased connectivity between the contralateral thalamus and precuneus and decreased activation of the ventromedial PFC, amygdala, and hippocampus [43]. The areas in which activity changes were observed in the study are similar to the study of Lutz *et al*. [9], Harrison *et al*. [10], Zeidan *et al*. [11] and Wang *et al*. [41]. Precuneus refers to the ‘’awareness of one's self and the surrounding sensory environment’’; pain increases with its activation [43, 44]. ‘’Awareness of breath’’ through ‘’Focus Attention’’ may explain the decreased activation of precuneus and improvement of pain parameters. In addition, mediators did not abandon oneself to the self-referential thoughts related to the painful stimulus, thanks to their “non-judgmental refocusing on their breath when their attention is disengaged from their breath without reacting emotionally”. In the study, changes in ventromedial PFC can have a positive effect on pain by controlling affective processes [19]. The decrease in the emotional reaction to pain may explain the positive effect of these regions on the sensation of pain.

In addition to experimental painful stimuli, the underlying mechanism of mindfulness meditation on the patients with clinical pain was investigated by fMRI imaging method.

In these studies, MBSR, a structured program based on mindfulness meditation, was offered as a method to observe the activity changes in the insula, ACC, PFC and DMN playing an important role in the effect of mindfulness meditation on pain [45-48].

Headache frequency was significantly reduced at 20th weeks compared to the active control group who applied MBSR in migraine patients who were administered two consecutive Stress Management for Headache programs, each lasting 8 weeks. In fMRI analyzes, it was found that connectivity decreased in the left dorsal anterior insula and the right posterior parietal cortex, which are responsible for the cognitive functions of the brain. These effects did not persist in the study at 52nd week. This points to the importance of continuity as well as the effectiveness of mindfulness meditation-based practices [45]. MBSR is a grueling and expensive program. For this reason, it was hypothesized that shorter-term MBSR (4-week) studies could also be done in the clinic. In a study [46], emotional awareness of patients who were given sadness-inducing visual stimuli and music to patients with back pain was determined and graded instantly. After the practices, pain intensity, depression and somatic-emotional symptoms of depression decreased compared to before (compared to the control group) and there was no change in the level of anxiety. In fMRI, right and left subgenual ACC, left ventrolateral PFC activity increased (compared to before) in the MBSR group. In addition, a positive correlation was found between the severity of sadness and left subgenual ACC activity. According to this study, although short-term MBSR programs are presented as a therapeutic method for pain intensity and depression in back pain patients, further research can be conducted with a larger sample and different meditation procedures, since their effects on anxiety are contradictory [46]. One of the painful syndromes is chronic neuropathic pain that does not respond to pharmacological treatments. So as to, the effectiveness of mindfulness-based practices and the underlying neural mechanisms in patients have been investigated via fMRI in many studies.

In a study, MBSR was applied for the management of chronic neuropathy in patients with breast cancer. The decrease in pain intensity in the MBSR group (compared to the wait-list group) was accompanied by an increase in PCC, medial PFC activity and ACC connectivity of the DMN. This finding was attributed to shifting the focus of attention from ruminative thoughts about pain and emotional evaluation of pain [47]. In this study, fMRI findings accompanying the decrease in pain intensity contradict with the studies of Zeidan *et al*. [11] and Harrison *et al*. [10]. The reason for this result may be the difference in the mindfulness meditation procedure practiced. In addition to the ACC, insula, PFC and DMN imaged with fMRI in mindfulness meditation, there is another study in which brain white matter is also imaged as a new approach. In that study, it was reported that in patients with breast cancer after the MBSR program, the intensity of chronic neuropathic pain was decreased. The development was observed in the left lateralized uncinate fascicle, hippocampus, amygdala and outer capsule. These regions are responsible for executive functions, attention, emotional state and pain perception targeted by MBSR. As a result, it was presented as a non-pharmacological method for chronic neuropathic pain, which is a treatment-limiting factor in breast cancer [48]. Also in the patient group with chronic neuropathic pain, visual stimulus (compared to the control group) after MBSR was accompanied by a decrease in pain perception, accompanied by decreased activity in the primary somatosensory cortex (activated in chronic pain). A decrease in activity was observed in the precuneus. This finding points to the "mindful trait (ability of being aware of one's self and the surrounding sensory stimuli)". The decrease in activity seen in the dorsolateral PFC has been attributed to a decrease in pain expectation and reduced effort to control emotions. This study is one of the studies reporting the role of decreased emotional reactivity developed via mindfulness meditation in its improved effect on pain [49].

Fibromyalgia Syndrome is a pain disorder characterized by widespread skeletal-muscular pain and tenderness by palpation. Itis accompanied by cognitive and affective disorders [50]. For this reason, mindfulness meditation, one of the treatments offered, has took part an approach that also targets these psychological comorbidities. In the study of Medina *et al*. [51], pain intensity and accompanying fMRI findings were compared in patients who continued their routine treatment (TAU), healthy lifestyle recommendations added to their routine treatment (TAU+FibroQol) and in addition to MBSR (TAU+MBSR). In the TAU+FibroQoL group, amygdala activation was decreased in fMRI and it was reported that the patients were not engaged in negative emotions. Amygdala has the role in the top-down processes and the contribution of top-down control to the affective aspect of pain can explain this result. However, no significant reduction in pain perception was reported in any of the three groups. This may indicate that mindfulness-based practices have no effect on chronic pain. However, measurement of pain intensity by VAS (Visual Analog Scale), which is an instant assessment, may not provide information about the pain in general of patients with chronic pain [51].

CONCLUSIONS

The fMRI findings about the effects of mindfulness meditation on pain intensity, pain unpleasantness and depression and anxiety may accompanying pain are similar. During pain, activity changes in the ACC, insula, amygdala, PFC and DMN are observed with mindfulness meditation. This may indicate that the effect of mindfulness meditation on pain intensity occurs by affecting the areas where pain is processed cognitively and affectively. So that, mindfulness meditation can be offered as a complementary treatment method for pain intensity and accompanying psychological comorbidities such as pain unpleasantness, depression and anxiety.

In future studies, it may be aimed to determine the underlying neurophysiological abnormalities in patients with pain with different clinical diagnoses by fMRI and to determine the optimum meditation protocol and duration. In addition, the mechanism of action of mindfulness meditation in pain treatment can be investigated by using neurophysiological methods such as PET (Positron Emission Tomography), EEG (Electroencephalography) and Heart Rate Variability, as well as fMRI.

Authors' Contribution

Study Conception: YY; Study Design: N/A; Supervision: SK, MÖ, AEÇ; Funding: N/A; Materials: N/A; Data Collection and/or Processing: N/A; Statistical Analysis and/or Data Interpretation: N/A; Literature Review: YY; Manuscript Preparation: YY and Critical Review: YY, SK.

Conflict of interest

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