Increased gray matter volume in the right angular and posterior parahippocampal gyri in loving-kindness meditators

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Previous voxel-based morphometry (VBM) studies have revealed that meditation is associated with structural brain changes in regions underlying cognitive processes that are required for attention or mindfulness during meditation. This VBM study examined brain changes related to the practice of an emotion-oriented meditation: loving-kindness meditation (LKM). A 3T magnetic resonance imaging (MRI) scanner captured images of the brain structures of 25 men, 10 of whom had practiced LKM in the Theravada tradition for at least 5 years. Compared with novices, more gray matter volume was detected in the right angular and posterior parahippocampal gyri in LKM experts. The right angular gyrus has not been previously reported to have structural differences associated with meditation, and its specific role in mind and cognitive empathy theory suggests the uniqueness of this finding for LKM practice. These regions are important for affective regulation associated with empathic response, anxiety and mood. At the same time, gray matter volume in the left temporal lobe in the LKM experts appeared to be greater, an observation that has also been reported in previous MRI meditation studies on meditation styles other than LKM. Overall, the findings of our study suggest that experience in LKM may influence brain structures associated with affective regulation.

Keywords: temporo-parietal junction; voxel-based morphometry; metta meditation; empathy; affective regulation

INTRODUCTION

It is well known that the human brain is a malleable organ. This suggests that intense training can induce structural changes in brain regions that are needed to produce the trained behavior (Draganski and May, 2008). Indeed, scientists coined the term 'neuroplasticity' to describe the fact that the human brain changes in response to experiential learning. The classic study of London taxi drivers is one of the best illustrations of experience-induced neuroplastic change. In their study, Maguire *et al.* (2000) demonstrated that experience navigating London streets was associated with significantly larger bilateral posterior hippocampi. The hippocampus is known to be a spatial navigation center (Maguire *et al.*, 1998). Along similar lines, Aydin *et al.* (2007) found that math experts have higher gray matter density in the parietal cortex than did controls. In fact, the parietal cortex is known for its involvement in arithmetic calculations and visuospatial processing (Dehaene *et al.*, 1999).

Meditation is a process of training mental states, and such experiential learning may affect the human brain. Lazar *et al.* (2005) were the first to investigate the relationship between meditation and structural brain changes. They found that expert insight meditators had a thicker prefrontal cortex and right anterior insula than novice meditators. Since then, other studies have reported differences in brain structures

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between experts and novices in a number of meditation practices, including Zen (Pagnoni and Cekic, 2007; Grant et al., 2010), insight (Hölzel et al., 2008), concentrative practices and open awareness (Vestergaard-Poulsen et al., 2009) and a mixed style (Luders et al., 2009). Zen experts have a thicker anterior cingulate cortex (ACC) compared with novices (Grant et al., 2010). The ACC actively helps people focus and refocus attention voluntarily in response to distraction and, thus, may help Zen meditators maintain their state of 'emptiness' (Pagnoni et al., 2008). In insight experts, the right anterior insula is cortically thicker than in novices (Lazar et al., 2005). The insula is important for interoceptive awareness, which connects us with our subjective internal states (Hölzel et al., 2008). Some studies have reported that cortical thickness/gray matter volume is associated with years/hours of meditation practice (Lazar et al., 2005; Hölzel et al., 2008) while other studies have failed to identify any relationship between these two variables (Luders et al., 2009; Vestergaard-Poulsen et al., 2009).

In general, scientific studies have focused on types of meditation that train attention regulation to produce a calm mind. Therefore, it should be no surprise that they have found differences in the brain regions in the attention system. Following this line of thought, meditation that focuses on affective processing should have an effect on the emotion-processing system. If meditation really can change how the brain processes emotions, the finding could influence how clinicians design interventions for clinical affective dysregulation.

Loving-kindness meditation (LKM) is a form of meditation that trains emotion regulation. LKM practitioners explicitly cultivate positive feelings, generating an emotional state that is full of unconditional love, compassion and empathy toward the self and others, without any discursive thoughts (Salzberg, 1995). Previous research has shown that a short LKM practice in the laboratory was sufficient to induce

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'feelings of social connection and positivity towards strangers on both explicit and implicit levels' (Hutcherson et al., 2008). Furthermore, after completing a 12 week focused-attention meditation (FAM) and LKM intervention, college students had significantly less anxiety and negative affect (Sears and Kraus, 2009). LKM's unique focus on cultivating positive emotions and heartfelt care for self and others makes it a valuable technique to counteract negative symptoms such as anhedonia and blunted affect from which people with schizophrenia suffer (Johnson et al., 2009; Garland et al., 2010). However, despite the potential value of LKM in reducing negative emotions and improving mental well-being and social connectedness, it has received only sparse scientific attention. In particular, it is important to understand how LKM might affect brain structure, yet this issue has remained unexplored. To date, only a few functional magnetic resonance imaging (fMRI) studies have addressed the neural correlates of LKM. Lutz et al. (2008) had LKM experts and novices listen to neutral and emotional (including positive and negative) human vocalizations during meditation and rest states, respectively. They found significantly higher activation in LKM experts than in novices during meditation than in the rest state (i.e. state-by-group interactions) in the amygdala and temporo-parietal junction (TPJ), which is constituted by the inferior parietal lobule (IPL), superior temporal gyrus (STG) and posterior superior temporal sulcus (pSTS) during all sounds; in limbic regions such as the insula and cingulate cortices during emotional sounds and in the insula during negative sounds. These results are in agreement regarding the networks that are important for social cognition, for instance, mind and empathy theory (Saxe and Kanwisher, 2003; Decety and Lamm, 2007). This has led to speculation that long-term LKM practice may enhance mentation toward human voices and emotion sharing (Lutz et al., 2008). In their follow-up study, Lutz et al. (2009) further investigated the relationship between the brain and the cardiovascular system on the same group of subjects, listening to emotional sounds during the compassion state. The neural activity in the right insula, somatosensory cortices, right IPL and premotor areas was found to be positively associated with heart rate; also, this positive association was especially strong in LKM experts compared with novices during the compassion state. These data suggest that LKM training may change brain representations toward affective stimuli and these functional brain changes may be tied to the visceral system.

To verify the possibility that the devoted cultivation of positive emotion and compassion could bring about changes in brain structures, on top of that provided by mindfulness training, we adopted automated voxel-based morphometry (VBM) to examine differences in gray matter volume between LKM experts and novices on a whole-brain voxel-by-voxel basis. In general, meditation practitioners usually commence their practice in forms that train attention or mindfulness and then move on to the forms of practice they want to pursue. Different forms of meditation are thought to reinforce one another. Therefore, we hypothesized that LKM experts would have more gray matter volume than novices not only in brain regions previously indicated for attention or mindfulness meditation but also in those regions related to social cognition and affective processing as reviewed above, such as the right TPJ (including the IPL, STG and pSTS) and the amygdala. Furthermore, we examined the relationship between hours of meditation practice and gray matter volume in our LKM experts.

MATERIALS AND METHODS

Participants

Twenty-five healthy Chinese men participated in this study, 10 of whom were LKM experts, while the remaining 15 were novices without long-term meditation experience. Both groups were matched on age and education levels. The experts were recruited from a Buddhist meditation network in Hong Kong and had at least 5 years of LKM practice based on the Theravada tradition. To control for any possible confounding variance introduced by different motivations for meditation practice, for the comparison group for the LKM experts, we used novices interested in meditation who had undergone a total of 7 h of training in basic meditation self-practice. The home-based meditation self-practice was carried out based on written instructions for practicing concentration/calming/kindness-cultivation skills prepared by our co-investigator, the Venerable Jing Yin, who is himself an expert in meditation. The instruction was similar to that offered by the Venerable Dr M. Ricard, who has a great deal of experience practicing and teaching meditation. All subjects were right-handed, measured with the Edinburgh Handedness Inventory (Oldfield, 1971). The subjects had no history of traumatic brain injury, medical conditions or psychiatric disorders that could have affected their brain structure at the time of the study. All subjects gave their written informed consent to take part in this study, which was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster.

Image acquisition

High-resolution MRI brain images were acquired via a 3.0 Tesla Philips Medical Systems Achieva scanner with an eight-channel SENSE head coil. A three-dimensional, T1-weighted, magnetization-prepared rapid acquisition gradient-echo sequence was used with 164 contiguous sagittal slices 1 mm in thickness, time to repetition = 7 ms, time to echo = 3.2 ms, flip angle = 8°, field of view = 164 mm, matrix = 256×240 mm and voxel size = $1 \times 1 \times 1$ mm.

Image processing (VBM-Dartel)

The MRI images were processed using the VBM8 toolbox (Christian Gaser; http://dbm.neuro.uni-jena.de/vbm/download/) within the SPM8 (Wellcome Department of Cognitive Neurology, London, UK; http://fil.ion.ucl.ac.uk/spm) in MATLAB 7.7.0 (Mathworks Inc., Natick, MA, USA). The default settings were used unless otherwise specified. Each MRI image was first displayed in SPM8 to screen for artifacts or gross anatomical abnormalities. For better registration, the orientation of the images was adjusted to match the template and the image origin was manually set to a position as close to the anterior commissure as possible. In the spatial normalization step, the high-dimensional Dartel normalization approach (VBM-Dartel) was chosen (Ashburner, 2007). This deformation technique has much better normalization power across individuals by improving inter-subject alignment, especially for small inner structures (Yassa and Stark, 2009), and it is more sensitive to regional differences, such as those that appear in the hippocampus (Bergouignan et al., 2009). It is thought to be a better alternative to the standard VBM-SPM normalization approach (Ashburner and Friston, 2000). To preserve the actual gray matter values locally and account for individual differences in global brain size, modulated gray matter segments were generated by multiplying them with the non-linear components derived from the normalization matrix instead of the linear components. The covariance between all normalized modulated images was visualized using a boxplot and covariance matrices to check for homogeneity and, thus, inspect for outliers. Finally, the normalized modulated images were smoothed with a standard Gaussian kernel of 8 mm, full width at half maximum. Smoothing rendered the data more normally distributed so that the assumption of parametric statistical comparisons was not violated (Worsley et al., 1996). Normalized and bias-corrected images of all subjects were also obtained and further averaged to create a study-specific template to visualize the results.

Statistical analysis

A series of statistical analyses were performed on the smoothed, normalized and modulated gray matter images in SPM8. Two-sample independent t-tests were run to identify group differences in whole-brain gray matter volume between experts and novices. An absolute threshold masking of 0.1 was used, meaning that only voxels with gray matter values >0.1 were counted. Global normalization was not needed in the statistical model because we applied the correction directly to the data during the modulation step using the non-linear (instead of the linear) component, as recommended in the VBM8 manual. Clusters were considered significant at the combined voxel-extent threshold of an uncorrected voxel level of P < 0.01 and cluster extent >530 voxels, as determined based on Monte Carlo simulations with AlphaSim equivalent to P < 0.05, corrected for multiple comparisons. A more lenient corrected P < 0.1 was then adopted to detect trend-level results, which corresponded to P < 0.01 and a cluster extent of >463 voxels. To further examine the relationship between the duration of meditation training and gray matter volume, correlation analysis was conducted between hours of meditation practice and average gray matter volume extracted from the significant cluster(s) using the REX toolbox for the LKM experts (Susan Whitfield-Gabrieli; http://web.mit.edu/swg/soft ware.htm).

RESULTS

Demographics

Table 1 presents the demographic information for all subjects. The LKM experts were matched with the novices by age [t(23) = 0.651, P > 0.5] and years of education [t(23) = -1.704, P > 0.1]. The experts had 6456.2 h of experience in LKM practice on average.

VBM-Dartel

When LKM meditators were compared with novices, more gray matter volume was detected in the right angular gyrus [Brodmann area (BA) 39; Figure 1A, Table 2] and right posterior parahippocampal gyrus (BA 36; Figure 1B, Table 2) at a significant level (corrected P < 0.05). With a more lenient threshold, more gray matter was also detected in the left inferior temporal gyrus (ITG) and middle temporal gyrus (MTG) (BA 20 and 21; Figure 1C, Table 2) at a trend level (corrected P < 0.1). The same results persisted even after controlling for age and years of education. Novices had no regions with significantly more gray matter than the LKM experts, even after controlling for age or years of education (Table 2). The same results persisted when another group of subjects who did not have any experience in meditation (i.e. zero hours) was used as the control comparison group (for details, please see the Supplementary Data).

The results of the correlation analysis showed that the number of meditation hours of the LKM experts was negatively related (at a trend level) to the gray matter volume of the right angular gyrus (r = -0.618, P = 0.057) and the left MTG (r = -0.593, P = 0.071), but not with the

	LKM experts		LKM novices		P-value	
	Mean	s.d.	Mean	s.d.		
Age	50.2	10.5	47.7	8.7	0.522	
Years of education	14.0	4.1	16.9	4.3	0.102	
Meditation hours	6456.2	6040.6	-	-	-	
Range in hours	588—	588-14 600		-	-	

P-values represent group differences between LKM experts and novices using independent samples *t*-tests (two-tailed).

right parahippocampal gyrus (r = -0.079, P = 0.828). When the effects of age and education were removed, only the correlation between number of meditation hours and the gray matter volume of the right angular gyrus remained significant (r = -0.761, P = 0.028).

DISCUSSION

This study examined the effect of experience in LKM meditation on brain morphometry in expert Chinese male meditators. We used the VBM-Dartel inter-subject alignment (VBM-Dartel) to minimize the threat of registration errors. The LKM experts appeared to have more gray matter in the left temporal lobe (ITG and MTG) at a trend level. Previous meditation research has reported similar results in the left ITG (Hölzel et al., 2008; Luders et al., 2009). Thus, this finding may be attributable to the general effect of meditation practice. At the same time, we found that the LKM experts had significantly more gray matter than novices in the right angular and right posterior parahippocampal gyri. It is noted that not all hypothesized regions (identified based on previous fMRI studies on normal controls) had more gray matter volume in LKM experts than in novices, no matter how lenient a threshold was used. This observation suggests that the mechanisms involved in structural and functional changes are likely different. An alternative explanation is that the neural correlates of social cognition in LKM experts may differ from those in the participants of these fMRI studies. The structural difference in the right angular gyrus was not observed in previous MRI studies on FAM or mindfulness meditation. Because of the specific role of the right



Table 2 Increased gray matter volumes in LKM experts compared with novices as revealed by VBM-Dartel

Contrast	Brain regions (Brodmann area)	Peak coordinates			Corrected <i>P</i> -value	t-Value	Cluster size
		X	у	Ζ			
Experts > novices	Right angular gyrus (39)	41	-63	46	0.015	4.87	655
	Right posterior parahippocampal gyrus (36)	18	-10	-27	0.049	3.7	531
	Left ITG (20)	-48	-45	-8	0.091 ^a	3.83	478
	Left MTG (21)	-51	-31	—9			
Experts < novices		I	No suprathresh	old voxels			

The corrected P-value was determined by combining the voxel-level and cluster-level thresholds by AlphaSim. For Experts > novices, experts had significantly more gray matter volume than novices in the right angular and right posterior parahippocampal gyri, while more gray matter volume was also detected in the left temporal lobe (the ITG and MTG) at trend-level only^a. For experts < novices, no significant group differences were detected. Controlling for years of education did not affect the results. Coordinates are in MNI space.

angular gyrus in mind and cognitive empathy theory, we consider this finding to be unique to LKM. All these structural differences cannot be explained by individual variations in global brain volume, age or years of education. Previous reports have suggested that LKM is associated with a reduction in anxiety and negative affect (Johnson *et al.*, 2009; Sears and Kraus, 2009; Goldin and Gross, 2010). Taking these findings together, we speculate that the enlarged right angular and right parahippocampal gyri (and the left temporal lobe at a trend level) in LKM experts may play a role in counteracting anxiety and negative affect.

Right angular gyrus

The finding of an enlarged right angular gyrus is novel. Previous studies on insight, Zen and Tibetan Buddhism and a mixed style of meditation practice have demonstrated increased gray matter in the insula, hippocampus, inferior temporal lobe, cingulate cortex, prefrontal regions, brain stem and some other regions (Lazar et al., 2005; Pagnoni and Cekic, 2007; Hölzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Grant et al., 2010), but none has reported gray matter changes in the parietal structures. Although a recent longitudinal study reported an increase in gray matter concentration in the left TPJ after 8 weeks of mindfulness-based stress reduction training, this cluster, in fact, peaked in the left MTG [Montreal Neurological Institute (MNI) coordinates: -50, -48 and 20] (Holzel et al., 2011), whereas the peak coordinates of our angular gyrus cluster were on the right side and more posterior and superior (41, -63 and 46). On the other hand, diffusion tensor imaging offers in vivo examination of whitematter connectivity. A recent study revealed greater connectivity in the left superior longitudinal fasciculus (SLF) and its temporal component (tSLF) in meditators who practiced different forms of meditation compared with control subjects (Luders et al., 2011). Since the SLF connects the frontal and the temporo-parietal regions, the finding of Luders et al.'s (2011) study lays the groundwork for speculation regarding some changes in the parietal lobe associated with meditation. However, the nature and mechanisms of the coupling of the parietal and the fronto-temporal activity for affective regulation in people practicing LKM meditation await verification in future research.

The right angular gyrus may be related to meditation practices that involve LKM in multiple ways. It is one of the main regions that form the TPJ, which has been repeatedly implicated in social cognition, such as mind and empathy theory (Decety and Lamm, 2007). In particular, the right TPJ is believed to be selectively recruited to understand others' thoughts, desires and feelings (Saxe and Wexler, 2005). Together with the medial temporal lobe and ventromedial prefrontal cortex, it forms a cognitive system that is important for cognitive empathy. In particular, the role of the right TPJ in the self–other distinction is fundamental to the mentalizing ability that is central to cognitive empathy (Saxe and Kanwisher, 2003); this may be important for understanding the affective states of others and for sharing compassionate loving kindness to truly recognize the wisdom that all human beings are equal and to appreciate oneness with others (Salzberg, 1995).

Lutz *et al.* (2008) observed that LKM experts had more activity than novices in the right angular gyrus of the TPJ and a number of other brain regions when listening to emotional human vocalizations during compassion meditation. The authors reasoned that long-term LKM may enhance emotion sharing and perspective taking, especially since the increase was strongly modulated by meditation expertise. Their follow-up study further highlighted the importance of the right angular gyrus/IPL in LKM because of the stronger coupling between its activity and heart rate during the compassion state in LKM experts than in novices (Lutz *et al.*, 2009). These findings are in line with our observation of increased gray matter in the right angular gyrus with LKM practice.

The increased gray matter volume of the right angular gyrus in LKM experts corroborates previous findings regarding the benefits of LKM for affective processing (Johnson et al., 2009; Sears and Kraus, 2009; Garland et al., 2010), leaving room for speculation regarding the potential therapeutic effect of LKM on counteracting affective disturbances. On the other hand, we found a negative correlation between hours of meditation practice and the gray matter volume of the angular gyrus in the LKM experts. Previous VBM studies on meditation experts have shown inconsistent results regarding the relationship between brain structure and the duration of meditation practice (Lazar et al., 2005; Hölzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009). Previous fMRI studies have revealed an inverted U-shaped relationship between meditation expertise and neural activity. For example, Brefczynski-Lewis et al. (2007) observed that experts with an average of 19000 h of practice, relative to meditation novices, showed stronger blood-oxygen-level-dependent (BOLD) signals in the attentional default network. However, BOLD signals in the same regions were weaker for those experts who had an average of 44 000 h of practice. This inverted U-shaped function may be explained by the process of skill acquisition-a pattern that has been observed in other domains of expertise (Doyon et al., 2002). It is also consistent with the description in meditation texts that the practice of concentration meditation will become less effortful as one becomes more skillful at the practice. We speculate that, based on the prediction set forth by the inverted U-shaped pattern, it is entirely possible that a positive relationship is revealed during the early stage of meditation practice (e.g. <2000-5000 h). Further research to verify the direction of the relationship between the duration of meditation practice and gray matter volume may consider a longitudinal design or employing cohorts at various levels of meditation expertise.

Right posterior parahippocampal gyrus

The finding of an enlarged posterior parahippocampal gyrus is unique to LKM in our study. No gray matter change was found in this region in previous structural studies on FAM or mindfulness meditation. The parahippocampal gyrus together with the temporopolar area, cingulate cortex, orbitofrontal cortex and insula forms the paralimbic system (Brodmann, 1909, 1994). Having dense connections with the limbic system, especially the amygdala, the paralimbic system is an important transition area that supports communication between the limbic system and the neocortex (Mesulam, 2000), which is important for a range of higher order cognitive affective functions, such as emotion/ mood regulation, self-control and motivational behavior (Kiehl, 2006). As proven by effective connectivity analysis, the parahippocampal gyrus has strong interactions with the amygdala (Stein et al., 2007). Abnormalities such as decreased gray matter volume or altered activity in these two regions are linked with various conditions of emotional dysfunction, such as depression (Gilbert et al., 2010), bipolar disorder (Chen et al., 2011) and schizophrenia (Gradin et al., 2011). A recent study that revealed gender-related differences in neural activity toward the compassion experience is in line with our findings. Pictures of human suffering selectively activated the parahippocampal gyrus and the occipital regions in male participants (Mercadillo et al., 2011). Another VBM study on insight meditators with a relatively high male composition (80%) also reported higher gray matter volume in the right medial temporal (hippocampus) and left temporal (ITG) lobes (Hölzel et al., 2008).

Left temporal lobe

The left temporal lobe has repeatedly been reported to have structural and functional changes associated with meditation. Insight experts had significantly more gray matter in the left ITG than novices, and their ITG size positively correlated with hours of meditation practice (Hölzel et al., 2008). Another study on the common effects of different meditation styles on brain structure also found more gray matter in the left ITG when the statistical threshold was lowered (Luders et al., 2009). The temporal lobe was further found to be activated during the mindfulness meditation state (Holzel et al., 2007). It appears that the temporal lobe is involved in the experience of the mindful state and 'insight into the unity of all reality' (Hölzel et al., 2008). Luders et al. (2011) also observed that meditators (who practiced various forms of meditation) showed higher connectivity in the left tSLF, which traverses through the left middle/superior temporal lobe. This finding corroborates our observation that experts have increased gray matter volume in the left temporal lobe. Future studies should be conducted to examine whether there is enhanced connectivity in the tSLF/SLF in LKM meditators and, if so, how this enhanced connectivity relates to the enlargement of the left temporal lobe. These data suggest that the left temporal lobe is not exclusively implicated in a specific style of meditation but, instead, is involved in various styles ranging from attention to mindfulness to LKM. Caution must be taken, however, in interpreting this structural difference since it appeared as a trend-level result in both the current and previous studies (Luders et al., 2009).

LIMITATIONS

This study has several limitations. First, the sample size of LKM experts was rather small because of the difficulty of subject recruitment. Insufficient power may have led to the negative findings in some emotion-related brain regions, for example, the medial orbitofrontal cortex and the insula. The level of expertise of our LKM experts may also explain these negative findings because specific neural changes may take place at different stages of LKM practice and levels of LKM

competence. These speculations may be verified in future longitudinal studies of large sample sizes. Second, like other cross-sectional studies comparing brain structure between experts and novices, we cannot definitively say that long-term LKM caused the gray matter differences observed in this study or that people with these brain differences are more inclined to practice LKM. Longitudinal studies are needed to explore the causal relationship between LKM practice and brain structure. Third, the current findings have yet to be generalized to female LKM experts since this study recruited only male LKM experts. The purpose of recruiting men was to avoid potential gender confounds, especially since this is the first exploratory study of LKM and brain structure. Future studies may recruit female participants or people of both genders to address this limitation.

CONCLUSIONS

This study found that LKM experts had significantly more gray matter volume in the right angular gyrus, which may be unique to the effect of LKM training. Neuroscience studies have linked the right angular gyrus (a part of the right TPJ) with empathy for others during meditation. Our LKM experts also had more gray matter volume in the right posterior parahippocampal gyrus. It is part of the paralimbic system, which works with the limbic and neocortical regions to regulate emotional or empathic responses, and this may be specific to men. Although more gray matter was also detected in the left temporal lobe in LKM experts at a trend level, this difference may not be specific to LKM since it has also been observed for other meditation styles. Despite some limitations, our findings provide an important initial clue that LKM may be associated with increased gray matter volume in regions that are important for emotion regulation. Future research should investigate the neural processes and mechanisms underlying LKM training to examine its therapeutic potential as an intervention for affective dysregulation.

SUPPLEMENTARY DATA

Supplementary data are available at SCAN online.

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