NEUROIMAGING AND NEUROPSYCHOLOGY OF MEDITATION STATES

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NEUROIMAGING AND NEUROPSYCHOLOGY OF MEDITATION STATES

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The Light above the Sea of Fog. Image taken from Subit, Udine, Italy
Image by Barbara Tomasino

Neurophysiological and psychological modifications induced by meditation practice have been consistently addressed by neuroscience. Training meditation practice induced plasticity (Barinaga, 2003; Knight, 2004), and as a consequence several benefit for mental and physical health (Davidson & McEwen, 2012), and cognitive performance.

One goal of meditation is to achieve the light of consciousness observing with equanimity (the right distance) clouds of the mind wandering. This Frontiers Research Topic brings together studies from groups of authors whose research focus on neuropsychological systems involved in meditation demonstrating how meditation activates and can modify brain areas, cognitive mechanisms and well-being.

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EDITORIAL
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Editorial: Neuroimaging and Neuropsychology of Meditation States

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One way of training cognitive functions and triggering plasticity can be through exercising meditation (Barinaga, 2003; Knight, 2004). Accordingly, it has been shown that this complex cognitive state induces both neurophysiological and psychological modifications, which have been consistently addressed by neuroscience regarding their potential benefit for mental and physical health (Davidson and McEwen, 2012).

In particular, the brain network governing meditation has been studied using a variety of strategies eliciting different cognitive processes (e.g., silence, attention to own body, sense of joy, mantras, etc.). Furthermore, the effect of expertise (i.e., short- vs. long-term) has been shown to influence the areas activated by meditation. Lastly, meditation training has been found to influence cognitive performance, e.g., attention, executive functions.

In order to promote the development of the neuroscientific investigation on how meditation activates and can modify brain areas, this Frontiers Research Topic aimed at bringing together studies from groups of authors whose research focus on neural mechanisms involved in meditation.

We collected fifteen contributions addressing this issue from a neuroimaging and a neuropsychological perspective. We solicited studies addressing meditation-related changes by using functional imaging (*fMRI*), resting state (*default mode network*), structural analyses (e.g., voxel based morphometry, *VBM*) as well as functional connectivity and structural connectivity (diffusion tensor imaging, *DTI*). In addition, we collected studies in which behavioral and neuropsychological studies in which meditation techniques have been used and in which cognitive changes have been found. Lastly, we included studies in social-affective neuroscience, reporting meditation-related modifications of personality, or changes of emotion-related network regulating stress and cognitive resource.

There are three activation likehood estimation (ALE) meta-analyses on studies using PET, SPECT, or fMRI techniques in which subjects performed meditation. In the first study (Sperduti et al., 2011) analyzed 10 studies and reported significant activations in the basal ganglia, the enthorinal cortex, and the medial prefrontal cortex. In a second study (Tomasino et al., 2012) analyzed 24 experiments and 150 activation foci which were divided according to different aspects of meditation (focused attention, mantra and the effects of experience). The meta-analysis evidence that meditation based on focus attention activates a network involving the medial gyrus bilaterally, the left superior parietal lobe, the left insula, and the right supramarginal gyrus (SMG). Mantra based meditation activates the right SMG, the SMA bilaterally and the left postcentral gyrus. The effect of meditation experience influenced the meditation network of activation. Expert meditators as compared to those with a short meditation experience had an increase activation in posterior areas such as the right SMG, whereas short-term experienced meditators has an increased frontal lobe activation.

In an another study (Tomasino et al., 2014) performer an ALE meta-analysis on meditation studies divided according to whether they were inspired to Buddhist (16 experiments, 263

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subjects, and 96 activation foci) or to Hinduism traditions (8 experiments, 54 activation foci, and 66 subjects). The first type of meditation enhanced activations in some frontal lobe structures associated with executive attention, possibly confirming the fundamental role of mindfulness shared by many Buddhist meditations [see for a recent review on mindfulness meditation (Tang et al., 2015a)]. By contrast, the network related to Hinduism-inspired meditation triggered a left lateralized network of areas including the postcentral gyrus, the superior parietal lobe, the hippocampus and the right middle cingulate cortex. The dissociation between anterior and posterior networks support the notion that different meditation styles and traditions are characterized by different patterns of neural activation. These meta-analyses evidenced the importance of specifying the type of meditation under study and the spiritual tradition from which it derives, thus particular care has been taken in the present special topic in defining in each contribution the type of meditation which has been studied.

The forms of meditation inspired to Buddhist tradition, and in particular those involving mindfulness, are related to voluntary attention (*anapanasati*), to body awareness (body scan) and to the observation of the mind (*vipassana*) and are correlated to activation of the executive frontal system, of some part of the insula and of medial frontal structures (Tomasino et al., 2012, 2014). The forms of meditation inspired to Hinduism tradition, as well as subjects performing meditation inspired to Buddhism tradition with a long-term meditation experience, have the aim of reaching *samadhi*, a condition characterized by an emptying state of consciousness [this concept has been discussed in Berensten's opinion article (Baerentsen, 2015)], who has recently been classified as an enhanced non-cognitive/non-affective state (NC/NA) (Nash and Newberg, 2013). These forms of meditation are related to activation/deactivation of posterior areas, in particular of the right supramarginal gyrus (Tomasino et al., 2014), a brain area related to out-of-body-experience phenomena (Blanke et al., 2002, 2004; Blanke and Mohr, 2005) and auto-transcendence (Urgesi et al., 2010; Crescentini et al., 2014).

From a practical point of view is useful classifying the different forms of meditation [see for instance Lippelet et al.'s mini review article (Lippelt et al., 2014)], this working strategy is not so straight. Hasenkamp et al. (2012) and Malinowski (2013) evidenced how mindfulness meditation is a process in which different phases are continuously reached (e.g., focus on breathing, mind wanders, recognize wandering, letting go, return to the task) and each of these phases is correlated with activation or deactivation of different brain networks. This logic is valid also for the other forms of meditation either those inspired to Buddhist and those inspired to Hinduism traditions. In light of this observation, the network analysis techniques proposed in the Special topic by Kemmer et al. (2015) in an original research article looks very promising.

Numerous experimental studies and revisions presented in this issue reaffirmed the beneficial effects on the psychological and clinical level of meditation trainings or meditation practice see Simon and Engström (2015) in a perspective article on the positive effects of meditation in treating psychological disorders; Sun et al. (2015) in a review article, on the effects of meditation on decision making; Mascaro et al. (2015) in an hypothesis and theory article on how meditation can enhance prosocial emotions; McConnell et al. (2014) in an original research article, on the use of binaural beats; Tang et al. (2015b) in an original research article on the effect of 5-h integrative body-mind training on frontal asymmetry; Fan et al. (2015) in an original research article on the effect of 5-h integrative body-mind training on conflict resolution; and Kirk and Montague (2015) in an original research article on self-control in Buddhist meditators. Crescentini and Capurso (2015) in a mini review article summarized the results of studies in which the effects of mindfulness meditation training had an impact on personality profiles and self-concepts. Authors argue that meditation can shape in addition to attention regulation, emotional regulation and body awareness, also subjects' personality toward more healthy functioning by transforming habitual patterns of responding.

In particular, Nakata et al. (2014) in a review article addressed the mechanisms involved in the use of meditation in pain control. They reported that several studies on meditation showed an increase of activation in brain structures related to psychophysiological pain processing, instead of a reduction. The authors referred to this inconsistency of results by using the following expression "the mystery of meditation." In our view, the increase of activation could be related to a general attitude in meditation inspired to Buddhist tradition. According to Buddha's indications the most correct behavior does not correspond to pain reduction or avoidance, but in facing the experience of pain through meditation. Indeed escaping and avoidance of pain-related experience increase suffering, whereas facing with mindfulness the experience of pain although activates the brain circuits related to pain processing, causes a decrease of suffering (Fabbro and Crescentini, 2014).

Other studies discussed the structural brain changes induced by meditation trainings. It has been shown that brief meditation trainings could increment white matter pathways connecting the anterior cingulate cortex to other brain areas. Posner et al. (2014) in an hypothesis and theory article put forward an hypothesis about the molecular mechanisms that could be the basis of white matter changed. Luders et al. (2015) in an original research article evidenced how meditation could trigger an increase of gray matter in the hippocampus with differences in male and female meditators. Furthermore, the same group (Luders et al., 2014) in a second original research article performed a study on a large sample of adult meditators and showed that the decrease of gray matter that occurs with aging could be significantly slowed in meditators as compared to non-meditators. This result indicates that meditation, as well as bilingualism, is a factor that favoring the cognitive reserve, both in neurological diseases and in aging.

Unfortunately the present special topic lacks of neuropsychological studies in which meditation has been used as a training with neurological patients. We believe that this leaves open the debate on meditation potential brain effects and could be subject of a future special issue.

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OPINION
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Patanjali and neuroscientific research on meditation

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Keywords: Patanjali, meditation, brain processes, consciousness, resting state, contrastive method in fMRI, functional brain networks, dynamical systems

The definition of meditation (or yoga) by Patanjali as "restriction (or stilling) of the fluctuations of the mind" (cf, Woods, 1927/2003, p. xxx, 8) may be an appropriate starting point for research on meditation using fMRI. An operational definition of the neural substrate of meditation which is adequate to Patanjalis definition, may be developed on the basis of a non-reductionistic understanding of the neural underpinnings of the mind in terms of dynamical functional brain systems.

Awasthi (2013) argue that Patanjali belongs to a dualistic philosophical tradition (Sankhya), in which meditation is a spiritual phenomenon, inaccessible to objective research. But in the Sankhya philosophy, an intimate relationship is assumed to exist between the spiritual, including meditation, and the material concomitants of states of mind (Rao, 2011). Further, Patanjali suggested that a number of persistently motivated goal-directed sensory-motor activities, and socially oriented moral and mental exercises, must be accomplished in order to reach meditation (Woods, 1927/2003, p. xxx–xxxi, 34ff). Since neuroscience considers objectively measurable phenomena only, it may thus be impossible to investigate meditation as such, but the material concomitants of the mind during meditation and preceding exercises may be as accessible to objective research as during other states of mind. While the social and moral issues calls for other methods, some of the mental and concomitant sensory-motor exercises are accessible for objective neuroscientific investigation.

Awasthi (2013) and Rao (2011) express the need for a clear and commonly accepted definition of meditation to get beyond the present situation of mixed, and to some extent contradictory results. Increased attention to the practical details of the investigated specific forms of meditation, is necessary. They suggest an explicit consideration of what is meant by "meditation," and of the corporeal operational details of the investigated activity, in order not to confuse various kinds and levels of meditation with each other. This is clearly relevant, and merits serious attention, but a thorough discussion of this topic is not possible here.

Another methodological problem also needs careful consideration. Most current research into meditation using PET, SPECT, or fMRI uses the contrastive method. The brain is scanned during various different states (at least two), one of which is the target state (meditation), and the other(s) some different state(s) of mind. The result is reached by subtracting the contrast state from the target state (cf, Raichle, 1998), and usually reported as (networks of) brain areas displaying increased or decreased activity levels during meditation. Although the results are usually described as information about the target state (meditation), they actually inform about relative differences in local brain activities related to changes of mind between various cognitive activities, including "mind wandering," into the target state, attempted meditation (e.g., Bærentsen et al., 2010; Hasenkamp et al., 2012).

Simple arithmetic tells us that the result of this subtraction depends on both the subtrahend and the minuend, and the result is informative about the difference, not about the target state as such. Although some consensus has been reached, results may depart substantially from each other (cf, Cahn and Polich, 2006; Neumann and Frasch, 2006; Ivanovski and Malhi, 2007; Ospina et al., 2007;

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Tang et al., 2012). To some degree reflecting the confusion as to precisely what kind of meditative activity is investigated, and the contrasts that are used (Rao, 2011; Awasthi, 2013).

But maps of local activations and deactivations during "meditation" obtained with contrastive fMRI brain imaging only inform us of about approximately 1–5 % local variations in the level of neural activity (Raichle and Gusnard, 2005; Raichle and Mintun, 2006; Raichle, 2009). These variations are relevant, but contrary to what is often implicitly believed, the contrastive analysis provides us with *no knowledge* about the (equally intense) concurrent activity in the rest of the brain, apart from the fact, that there is no statistically significant difference in the level of neural activity between the contrasted states. But this is *not* information, that activity in the rest of the brain is *irrelevant* to the investigated states of mind, nor about what possible relation this ongoing activity may have to the investigated state of mind. Attempts to go beyond the concepts of activation and deactivation of local areas are represented by investigations of functional connectivity (e.g., Farb et al., 2007; Brewer et al., 2011; Hasenkamp and Barsalou, 2012; Pagnoni, 2012; Taylor et al., 2013; Josipovic, 2014), but although interesting, a thorough consideration of these efforts is impossible here.

Patanjalis definition consider meditation and its obstacles, i.e., flutuations of the mind. According to Patanjali, five types of fluctuations of mind should be overcome in order to attain concentration (meditation): (1) veridical cognition on the basis of perception, logical reasoning, and verbal communication, (2) illusory imagination, (3) linguistic conceptualizations, (4) sleep, and (5) memory (Woods, 1927/2003; Rao, 2011, p. xxx, 17ff). These fluctuations corresponds to, roughly speaking, the full range of mental states which the mind may pass through during normal life activity as they are described in modern psychology.

All of these different "states of mind" in activity are more or less goal-directed (e.g. internally vs. externally defined) and characterized by continuously changing constellations of motivations, goal-related cognition-emotion, and operational regulatory mental and sensory-motor processes (Leont'ev, 1974; Leontev, 1978). They are realized by task-related functional brain systems integrating functionally differentiated and anatomically distributed areas of the whole brain, not by patches of local "activated" areas (Brodmann, 1909/1985; Vygotsky, 1934/1997; Anokhin, 1969, 1974; Luria, 1973; Edelman and Tononi, 2000; Freeman, 2000; Raichle and Gusnard, 2005). The evolution of the functional brain systems is reflected in changing patterns of local activations and deactivations as revealed by fMRI. They correspond to the establishment and dissolution of functional synchronization of neural activity in distributed local populations of synapses (Magri et al., 2012), reflecting changes in intentional focus, emotional coloring, cognitive strategies, and processing routines etc. One example is the change from mind wandering (whatever its specific content) into concentration on a chosen meditative focus (e.g., Guo and Pagnoni, 2008; Bærentsen, 2011; Hasenkamp et al., 2012).

Even if it would be possible to control the exact nature of the momentary meditative focus and the qualitative contents of the contrasting "mind wandering" episode, it is however unlikely, that any two instances would be reflected in identical patterns of local activations and deactivations (cf, McGonigle et al., 2000). Meditation as such is probably not reflected in a specific momentary pattern of "activations" and "deactivations," as these are currently understood. But meditation may correspond to a specific kind of global dynamic of changing systems of coactivated brain areas, and this dynamic may be different from those that corresponds to the five mentioned "fluctuations" during mundane states of consciousness.

Patanjali may view meditation as a spiritual phenomenon, but it is not stated in the sutras that the material concomitants of mind are irrelevant to the mentioned fluctuations, nor that they cease to exist if the spirit eventually attains liberation. Although different schools of meditation use specific techniques and procedures (Focused Attention, Open Monitoring, Nondual Awarenes etc., cf, Josipovic, 2014), the ultimate aim always includes some form of "restriction (or stilling) of the fluctuations of the mind." Assuming that meditation entails brain activity that differ from common resting or various goal-directed mental activities including various techniques of meditation exercise (Guo and Pagnoni, 2008; Bærentsen, 2011; Hasenkamp et al., 2012), neuroscience research may try to unveil the dynamic characteristics of the material concomitants of mind during various kinds and levels of meditation (cf, Rao, 2011), with or without the use of the contrastive method (cf, Beckmann et al., 2005; Guo and Pagnoni, 2008; Smith et al., 2009).

Meditation is a whole-brain (body) activity and needs characterization in terms of whole brain dynamics. The research strategy might follow the non-reductionist proposal of Edelman (2003) and Edelman and Tononi (2000 p. 18f) and concentrate on the brain processes, not just the brain areas, that support consciousness, and examine what kind of neural interactions may explain the fundamental properties of consciousness such as phenomenological unity, differentiation, variability and informativeness, that may reveal characteristics conforming to the phenomenological descriptions of the target states (e.g., rest vs. various forms and states of meditation).

In terms of dynamical systems, states of mind may be considered and understood as temporary stable patterns of activity, i.e., as trajectories in bounded regions of a state space created by the evolution of the global patterns of activity in the brain (cf, Edelman and Tononi, 2000; Freeman, 2000; Haken and Schiepek, 2010). Each state may be of varying temporal duration, and more or less stable according to the characteristics of the attractors and control parameters (e.g., arousal, motivation, concentration, skill). In stable states, it will remain in a bounded area of state space. During state transitions it may reveal characteristic instabilities etc. States like mind wandering and meditation may pertain to various phases and show characteristic patterns of stability, fluctuations, instabilities, transitions between states, etc.

The descriptions given by Patanjali provides references to which types of states could be compared. These conventional states of mind define trajectories in the brain's state space—and may well be described as "fluctuations" therein, more or less intense according to the level of wakefulness, the amount of drive, levels of motivation or intensity of emotional content etc. They may be more or less coherent, integrated, and stable according to the level of concentration on the intended goal or direction, and they may be more or less qualitatively differentiated and encompassing according to the level of operational sensory-motor coordination to the situational conditions, and their emotional color.

In everyday activities, conscious attention may be variously focused on a particular intentional goal to achieve, a problem to solve, the aesthetic or emotional qualities of a situation, etc. During resting when no explicit goal is aimed at, attention is moving from one topic to another and focus on varying qualities and aspects of imagined situations according to drives, previous experiences, distractions and random influences (cf, Smallwood and Schooler, 2006; Schooler et al., 2011) as reflected in the fluctuations in ongoing brain activity (Raichle, 2011).

During the practice of meditation one may suddenly realize that the mind has been caught by thoughts about some issue and that awareness of the present situation and the goal has faded. In such cases the mind may be refocused on the situation and the intended action when awareness of the distraction emerges in consciousness (Hasenkamp et al., 2012). The contents of perception or thoughts, and the focus of conscious attention or mind, may not be identical, and during the transition from one issue to the other, it is not residing in neither of the contents (Schooler et al., 2011). Before and after the transition however, the conscious mind usually resides in (i.e., identifies with) the content, i.e., the fluctuations, and these fluctuations are reflected in the measurable activity of the brain (Hasson et al., 2004).

It may be expected, that the fluctuations are large, when the mind is caught emotionally and engages in cognitive imagination with a rich and varied qualitative content. When meditation is achieved, the mind does—according to Patanjali—not identify with these "fluctuations," and the concomitant fluctuations of brain activity are possibly minimal (controlled, stilled, suppressed), as reflected in the Buddhist expression "The flame will only burn steadily when we can calm the air around it… when we have stilled the turbulence of our thoughts and emotions" (Rinpoche, 1992, p. 64). But if "stillness" is conceived of as "being balanced" in relation to fluctuations and disturbances, it may actually be expressed in compensatory activities to counterbalance these influences. "once we have found a stability in our meditation, noises and disturbances of every kind will have far less impact" (Rinpoche, 1992, ibid.).

Stillness may be understood as controlled variability counterbalancing "fluctuations" of the mind (Hasenkamp et al., 2012), which is reminiscent of the discussion about whether "stilling the fluctuations" or "relaxation" entails lowering arousal, which seems not to be the case (Bærentsen et al., 2010; Amihai and Kozhevnikov, 2014).

How the different states of mind may be reflected in the different measurable fluctuations of global brain processes is a question to be asked.

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Focused attention, open monitoring and loving kindness meditation: effects on attention, conflict monitoring, and creativity – A review

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Meditation is becoming increasingly popular as a topic for scientific research and theories on meditation are becoming ever more specific. We distinguish between what is called *focused Attention meditation*, *open Monitoring meditation*, and *loving kindness* (or compassion) *meditation*. Research suggests that these meditations have differential, dissociable effects on a wide range of cognitive (control) processes, such as attentional selection, conflict monitoring, divergent, and convergent thinking. Although research on exactly how the various meditations operate on these processes is still missing, different kinds of meditations are associated with different neural structures and different patterns of electroencephalographic activity. In this review we discuss recent findings on meditation and suggest how the different meditations may affect cognitive processes, and we give suggestions for directions of future research.

Keywords: open monitoring, focused attention, attention, ACC, conflict monitoring, vipassana

INTRODUCTION

Even though numerous studies have shown meditation to have significant effects on various affective and cognitive processes, many still view meditation as a technique primarily intended for relaxation and stress reduction. While meditation does seem to reduce stress and to induce a relaxing state of mind, it can also have significant effects on how people perceive and process the world around them and alter the way they regulate attention and emotion. Lutz et al. (2008) proposed that the kind of effect meditation has is likely to differ according to the kind of meditation that is practiced. Currently the most researched types of meditation include focused attention meditation (FAM), open monitoring meditation (OMM), and loving-kindness meditation (LKM). Unfortunately, however, the methodological diversity across the available studies with regard to sample characteristics, tasks used, and experimental design (within vs. between group; with vs. without control condition) renders the comparison between them difficult. This review is primarily focused on FAM and OMM studies[1] and on how these two (proto-)types of meditation are associated with different neural underpinnings and differential effects on attentional control, conflict monitoring, and creativity.

MEDITATION TYPES

Usually, FAM is the starting point for any novice meditator (Lutz et al., 2008; Vago and Silbersweig, 2012). During FAM the practitioner is required to focus attention on a chosen object or event, such as breathing or a candle flame. To maintain this focus, the practitioner has to constantly monitor the concentration on the chosen event so to avoid mind wandering (Tops et al., 2014). Once practitioners become familiar with the FAM technique and can easily sustain their attentional focus on an object for a considerable amount of time, they often progress to OMM. During OMM the focus of the meditation becomes the monitoring of awareness itself (Lutz et al., 2008; Vago and Silbersweig, 2012). In contrast to FAM, there is no object or event in the internal or external environment that the meditator has to focus on. The aim is rather to stay in the monitoring state, remaining attentive to any experience that might arise, without selecting, judging, or focusing on any particular object. To start, however, the meditator will focus on a chosen object, as in FAM, but will subsequently gradually reduce this focus, while emphasizing the activity of monitoring of awareness.

Loving-kindness meditation incorporates elements of both FAM and OMM (Vago and Silbersweig, 2012). Meditators focus on developing love and compassion first for themselves and then gradually extend this love to ever more "unlikeable" others (e.g., from self to a friend, to someone one does not know, to all living beings one dislikes). Any negative associations that might arise are supposed to be replaced by positive ones such as pro-social or empathic concern.

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[1] It is important to note that even though this mini review is based on the theoretical framework of distinguishing FAM and OMM, another one includes the distinction between concentrative meditations, practices that regulate or control attention/awareness, and meditation practices which instead do not explicitly target attentional/effortful control (Chiesa and Malinowski, 2011; see also Chiesa, 2012 for a recent review on the difficulty of defining Mindfulness). Moreover, Travis and Shear (2010) have pointed out a third meditation category besides FAM and OMM: the *automatic self-transcending* which trascends FAM and OMM through the absence of both (a) focus and (b) individual control or effort.

MEDITATION TYPES, ATTENTIONAL SCOPE, AND ENDOGENOUS ATTENTION

Whereas some meditation techniques require the practitioners to focus their attention on only a certain object or event, other techniques allow any internal or external experiences or sensations to enter awareness. Different meditation techniques might therefore bias the practitioner to either a narrow or broad spotlight of attention. This distinction is thought to be most evident with regard to FAM and OMM. FAM induces a narrow attentional focus due to the highly concentrative nature of the meditation, whereas OMM induces a broader attentional focus by allowing and acknowledging any experiences that might arise during meditation.

In a seminal study, Slagter et al. (2007) investigated the effects of 3 months of intensive Vipassana meditation (an OMM-like meditation) training on the allocation of attention over time as indexed by the "attentional-blink" (AB) deficit, thought to result from competition between two target stimuli (T1 and T2) for limited attentional resources. After the training, because of the acquisition of a broader attentional scope, participants showed a smaller AB deficit as an indication of being able to distribute their brain-resource allocation to both T1 and T2. The reduced AB size was accompanied by a smaller T1-elicited P3b, a brain-potential thought to index attentional resource allocation.

A more recent study comparing meditators (trained in mindfulness-based stress-reduction) to non-meditators found that meditators show evidence of more accurate and efficient visual attention (Hodgins and Adair, 2010). Meditators monitored events more accurately in a concentration task and showed less interference from invalid cues in a visual selective attention task. Furthermore, meditators showed improved flexible visual attention by identifying a greater number of alternative perspectives in multiple perspectives images. Another study compared OMM and FAM meditators on a sustained attention task (Valentine and Sweet, 1999): OMM meditators outperformed FAM meditators when the target stimulus was unexpected. This might indicate that the OMM meditators had a wider attentional scope, even though the two meditator groups did not differ in performance when the stimulus was expected.

Electrophysiological evidence for meditation-induced improvements in attention comes from a recent study in which Vipassana meditators performed an auditory oddball task before and after meditation (in one session) and random thinking (in another session; Delgado-Pastor et al., 2013). The meditation session was composed by three parts. First, an initial part of self-regulation of attention focused on sensations from air entering and leaving the body at the nostrils. Second, a central part of focusing attention on sensations from all parts of the body while maintaining the non-reactivity and acceptance attitude. Last, a final brief part aimed on generating feelings of compassion and unconditional love to all living beings. Meditators showed greater P3b amplitudes to target tones after meditation than either before meditation or after the no-meditation session, an effect that is thought to reflect enhanced attentional engagement during the task.

Support for the assumption that FAM induces a narrow attentional focus comes from several studies that show that FAM increases sustained attention (Carter et al., 2005; Brefczynski-Lewis et al., 2007). Neuroimaging evidence by Hasenkamp et al. (2012) suggests that FAM is associated with increased activity in the right dorsolateral prefrontal cortex (dlPFC), which has been associated with "the repetitive selection of relevant representations or recurrent direction of attention to those items" (D'Esposito, 2007, p. 765). Thus, in the context of meditation experience, dlPFC might be involved in repeatedly redirecting or sustaining attention to the object of focus. It would be interesting to investigate whether this pattern of activation is unique to FAM or whether other kinds of meditation lead to similar increases in activity in the dlPFC. If the dlPFC is indeed involved in the repetitive redirection of attention to the same object of focus, then it should not be as active during OMM during which attention is more flexible and continuously shifted to different objects. Alternatively, however, if during OMM the meditator achieves a state of awareness where (only) awareness itself is the object of focus, the dlPFC might again play a role in maintaining this focus. Similarly, it would be interesting to examine how LKM modulates attentional processes and the activation of the dlPFC.

In a follow-up study, Hasenkamp and Barsalou (2012) found that, during rest, the right dlPFC connectivity to the right insula was improved in experienced meditators compared to novices. The authors suggest that improved connectivity with the right insula might reflect enhanced interoceptive attention to internal bodily states. In a support of this idea, a recent study reports that mindfulness training predicted greater activity in posterior insula regions during interoceptive attention to respiratory sensation (Farb et al., 2013). Various studies have shown theta activity to be increased during meditation, primarily OMM-like meditations (e.g., Baijal and Srinivasan, 2010; Cahn et al., 2010; Tsai et al., 2013; for review see Travis and Shear, 2010). This increase in theta activity, usually mid-frontal, has been suggested to be involved in sustaining internalized attention. As such, similar increases in theta activity would be expected for LKM during which attention is also internalized, but not during FAM where attention is explicitly focused on an external object, even though typically the object of meditation in FAM, at least for beginners, is the breath, which is internal.

Additionally, active mindfulness meditation (versus rest) was associated with increased functional connectivity between the dorsal attention network, the Default Mode Network and the right prefrontal cortex (Froeliger et al., 2012). Thus, meditation practice seems to enhance connectivity within and between attentional networks and a number of broadly distributed other brain regions subserving attention, self-referential, and emotional processes.

MEDITATION TYPES AND CONFLICT MONITORING

A fundamental skill acquired through meditation is the ability to monitor the attentional focus in order to "redirect it" in the case of conflicting thoughts or external events. Not surprisingly, several studies have already shown improvements in conflict monitoring after meditation. Tang et al. (2007) investigated whether a training technique based on meditational practices called integrative body-mind training (IBMT; most similar to OMM) could improve performance on an attentional network task (ANT; Fan et al., 2002). The ANT was developed to keep track of three different measures, namely orientation, alerting, and conflict resolution. While IBMT had no effect on orienting and alerting scores, it did improve conflict resolution. In a similar study FAM and OMM were compared on an emotional variant of the ANT. Both types of meditation improved conflict resolution compared to a relaxation control group (Ainsworth et al., 2013). Surprisingly, there was no difference between the two meditation types, even though, mindfulness disposition at baseline (i.e., trait mindfulness) was also associated with improved conflict resolution.

Further evidence for improvements in conflict monitoring come from a study investigating the effect of 6-week long FAM trainig (versus relaxation training and a waiting-list group) on a discrimination task intended to investigate the relationship between attentional load and emotional processing (Menezes et al., 2013). Participants had to respond to whether or not the orientation of two lines presented to either side of an emotionally distracting picture was the same. Importantly, those who underwent a meditation or relaxation training commited fewer errors than the waiting list control group. Furthermore, error rates were lowest in the meditation group, higest in the waiting list group, while the relaxation group scored in between. With regard to emotional regulation meditators showed less emotional interference than the other two groups when attentional load was low, and only meditators showed a relationship between the amount of weekly practice and reductions in emotional interference.

In a study of Xue et al. (2011), meditation-naïve participants were randomly assigned to either an 11 h IBMT course or a relaxation training. Compared to the relaxation training, the IBMT group showed higher network efficiency and degree of connectivity of the anterior cingulate cortex (ACC). As the ACC is involved in processes such as self-regulation, detecting interference and errors, and overcoming impasses (e.g., Botvinick et al., 2004), improvements in ACC functioning might well be the neural mechanism by which IBMT improves conflict resolution. In an interesting study of Hasenkamp et al. (2012), experienced meditators engaged in FAM inside an fMRI scanner and pushed a button whenever they started to mind-wander. The moment of awareness of mind-wandering was associated with increased activity in the dorsal ACC. Thus, as the mind starts to wander during meditation, the ACC might detect this “error” and feed it back to executive control networks (Botvinick et al., 1999; Carter and van Veen, 2007), so that attention can be refocused. Various other studies have also shown improvements in ACC functioning after meditation (Lazar et al., 2000; Baerentsen et al., 2001; Tang et al., 2009, 2010). Hölzel et al. (2007) compared experienced and novice meditators during a concentrative meditation (akin to FAM) and found that the experienced meditators showed greater activity in the rostral ACC during meditation than the novices, even though the two groups did not differ on an arithmetic control task. Similar results were obtained in another study comparing novices and experienced meditators (Baron Short et al., 2007) by showing more activity in the ACC during FAM compared to a control task. The activity in the ACC was more consistent and sustained for experienced meditators. Related to that, Buddhist monks exhibited more activity in the ACC during FAM than during OMM (Manna et al., 2010). This suggests that the effects of meditation on the ACC and conflict monitoring do not seem to be limited to temporary state effects but carry over into daily life as a more stable “trait.” Future large scale longitudinal studies should to be conducted to address this issue and to disentangle short-term and long-term effects on conflict monitoring.

Improved conflict monitoring does not necessarily entail increased brain activity. Kozasa et al. (2012) compared meditators and non-meditators on a Stroop task in which semantic associations of words have to be suppressed to retrieve the color of the word. While behavioral performance was not significantly different for the two groups, compared to meditators, the non-meditators showed more activity in brain regions related to attention and motor control during incongruent trials. Given that the aim of many meditation techniques is to monitor the automatic arise of distractible sensations, such skill may become effortless by repeated meditation, therefore leading to less brain activity during the Stroop task. LKM has been shown to improve conflict resolution, as well, when LKM and a control group were compared on a Stroop task. The LKM group was faster in responding to both congruent and incongruent trials, and the difference between congruent and incongruent trials (the congruency effect) was smaller as well (Hunsinger et al., 2013). As LKM incorporates elements of both FAM and OMM, it would be interesting to investigate how the effect size associated with LKM may be positioned in between FAM and OMM.

Recently, meditators and non-meditators were compared with regard to measures of cortical silent period and short intra cortical inhibition over the motor cortex before and after a 60 min long meditation (for the meditators) or cartoon (for the non-meditators), respectively, measuring $GABA_B$ receptor-mediated inhibitory neurotransmission and $GABA_A$ receptor-mediated inhibitory neurotransmission (Guglietti et al., 2013). Given that deficits related to cortical silent periods in the motor cortex had been previously associated with psychiatric illness and emotional deregulation, the activity over the motor cortex was measured. No differences were found between meditators and non-meditators before the meditation/cartoon. However, after meditation there was a significant increase in $GABA_B$ activity in the meditator group. The authors suggest that “improved cortical inhibition of the motor cortex, through meditation, helps reduce perceptions of environmental threat and negative affect through top down modulation of excitatory neural activity” (Guglietti et al., 2013, p. 400). Future research might investigate whether similar GABA related mechanisms underlie the suppression of distracting stimuli during meditation and how different types of meditation might have distinguishable effects on these processes.

MEDITATION TYPES AND CREATIVITY

The scientific evidence regarding the connection between meditation and creativity is inconsistent. While some studies support a strong positive impact of meditation practice on creativity (Orme-Johnson and Granieri, 1977; Orme-Johnson et al., 1977), others found only a weak association or no effect at all (Cowger, 1974; Domino, 1977). Recently, Zabelina et al. (2011) found that a short-term effect of mindfulness manipulation (basically OMM) facilitated creative elaboration at high levels of neuroticism. As pointed out by Colzato et al. (2012), these inconsistencies might reflect a failure to distinguish between different and dissociable processes underlying creativity, such as convergent and divergent thinking (Guilford, 1950). Accordingly, Colzato et al. (2012) compared the impact of FAM and OMM on convergent thinking (a process of identifying one "correct" answer to a well-defined problem) and divergent thinking (a process aiming at generating many new ideas) in meditation practitioners. Indeed, the two types of meditation affected the two types of thinking in opposite ways: while convergent thinking tended to improve after FAM, divergent thinking was significantly enhanced after OMM. Colzato et al. (2012) suggest that FAM and OMM induce two different, to some degree opposite cognitive-control states that support state-compatible thinking styles, such as convergent and divergent thinking, respectively. In contrast to convergent thinking, divergent thinking benefits from a control state that promotes quick "jumps" from one thought to another by reducing the top-down control of cognitive processing—as achieved by OMM.

CONCLUSION

Research on meditation is still in its infancy but our understanding of the underlying functional and neural mechanisms is steadily increasing. However, a serious shortcoming in the current literature is the lack of studies that systematically distinguish between and compare different kinds of meditation on various cognitive, affective or executive control tasks—a criticism that applies to neuroscientific studies in particular. Further progress will require a better understanding of the functional aims of particular meditation techniques and their strategies to achieve them. It will also be important to more systematically assess short- and long-term effects of meditation, as well as the (not yet understood) impact of meditation experience (as present in practitioners but not novices). For instance, several approaches (like Buddhism) favor a particular sequence of acquiring meditation skills (from FAM to OMM) but evidence that this sequence actually matters is lacking. Moreover, the neural mechanisms underlying meditation effects are not well understood. It might be interesting that the three main research topics we have covered in the present review (attentional control, performance monitoring, and creativity or thinking style) imply the operation of extended neural networks, which might suggest that meditation operates on neural communication, perhaps by impacting neurotransmitter systems. Finally, it may be interesting to consider individual differences more systematically. If meditation really affects interactions between functional and neural networks, it makes sense to assume that the net effect of meditation of performance depends on the pre-experimental performance level of the individual—be it in terms of compensation (so that worse performers benefit more) or predisposition (so that some are more sensitive to meditation interventions).

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Network-based characterization of brain functional connectivity in Zen practitioners

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In the last decade, a number of neuroimaging studies have investigated the neurophysiological effects associated with contemplative practices. Meditation-related changes in resting state functional connectivity (rsFC) have been previously reported, particularly in the default mode network, frontoparietal attentional circuits, saliency-related regions, and primary sensory cortices. We collected functional magnetic resonance imaging data from a sample of 12 experienced Zen meditators and 12 meditation-naïve matched controls during a basic attention-to-breathing protocol, together with behavioral performance outside the scanner on a set of computerized neuropsychological tests. We adopted a network system of 209 nodes, classified into nine functional modules, and a multi-stage approach to identify rsFC differences in meditators and controls. Between-group comparisons of modulewise FC, summarized by the first principal component of the relevant set of edges, revealed important connections of frontoparietal circuits with early visual and executive control areas. We also identified several group differences in positive and negative edgewise FC, often involving the visual, or frontoparietal regions. Multivariate pattern analysis of modulewise FC, using support vector machine (SVM), classified meditators, and controls with 79% accuracy and selected 10 modulewise connections that were jointly prominent in distinguishing meditators and controls; a similar SVM procedure based on the subjects' scores on the neuropsychological battery yielded a slightly weaker accuracy (75%). Finally, we observed a good correlation between the across-subject variation in strength of modulewise connections among frontoparietal, executive, and visual circuits, on the one hand, and in the performance on a rapid visual information processing test of sustained attention, on the other. Taken together, these findings highlight the usefulness of employing network analysis techniques in investigating the neural correlates of contemplative practices.

Keywords: meditation, fMRI, functional connectivity, sustained attention, network analysis

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Introduction

In recent years, brain-wise functional connectivity analyses have become an increasingly important tool for understanding normal brain function as well as its alterations across specific subpopulations (Lowe, 2012). In particular, the investigation of intrinsic connectivity networks by resting state functional magnetic resonance imaging (fMRI) has proven capable of revealing fundamental elements of human brain architecture and organization. Resting state functional connectivity (rsFC) analyzes the temporal correlations of the spontaneous BOLD signal fluctuations across the brain in the absence of any experimental task, a reflection of the neural activity intrinsically generated by the brain (Fransson, 2005; Fox and Raichle, 2007). Since Biswal et al. (1995) first noted the preservation of the functional connectivity structure of the sensorimotor cortical network during rest, several other resting state networks (RSNs) have been consistently identified in the human brain (Smith et al., 2009; Zuo et al., 2010; Allen et al., 2011; Laird et al., 2011), with a particular emphasis on the so-called default mode network (DMN; Raichle et al., 2001; Greicius et al., 2004). Furthermore, significant differences in intrinsic connectivity networks across clinical and demographic subpopulations have also been reported (Bassett et al., 2008; Dosenbach et al., 2010; Satterthwaite et al., 2014).

Brain imaging has been employed quite extensively in the last decade to explore the potential neural changes associated with contemplative practices. In particular, functional connectivity alterations in DMN areas, frontoparietal attentional circuits, saliency-related regions, as well as in primary sensory cortices, have been observed in experienced meditators compared to meditation-naïve controls (Farb et al., 2007, 2013; Brewer et al., 2011; Jang et al., 2011; Josipovic et al., 2011; Kilpatrick et al., 2011; Froeliger et al., 2012; Hasenkamp and Barsalou, 2012; Taylor et al., 2013; Garrison et al., 2014). We have also previously investigated the neural correlates of conceptual processing associated with the practice of Zen meditation using fMRI and a lexical decision task (Guo and Pagnoni, 2008; Pagnoni et al., 2008; Guo, 2011; Guo and Tang, 2013); in the same sample of volunteers (12 practitioners of Zen meditation and 12 matched control subjects), we have additionally reported on the functional connectivity and temporal properties of the BOLD signal from the posterior cingulate cortex, the main node of the DMN, during a meditative attention-to-breathing condition (Pagnoni, 2012).

In the present work, we further examined the fMRI data collected during the attention-to-breathing condition in the cohort of subjects described in Pagnoni (2012), aiming to detect differences in rsFC between meditators and controls across the whole brain using a network approach. In order to obtain a fine-grained parcellation of the whole cerebral cortex, we adopted the 264-node system proposed by Power et al. (2011). We also assigned the nodes to a set of nine functional modules that were consistently identified as RSNs in larger populations (Smith et al., 2009). Network connectivity differences between meditators and controls were assessed using modulewise and edgewise comparisons of network connections and multivariate pattern analyses via a support vector machine (SVM) classifier. The multivariate pattern analyses aimed to find a hyperplane based on the high-dimensional pattern of brain connectivity measures able to separate meditators from control subjects. Finally, we examined the association between selected brain connectivity measures and individual scores on a rapid visual information processing (RVIP) test of sustained attention and working memory.

Materials and Methods

Subjects

Twelve Zen meditators with more than 3 years of daily practice (MEDT) were recruited from the local community and meditation centers, along with 12 control subjects (CTRL) who never practiced meditation. All the volunteers in the meditators group had more than 3 years of daily practice of zazen (Zen objectless meditation) under the guidance of a certified teacher (mean = 8.7 years, SD = 6.5 years, minimum = 3 years, maximum = 20 years). Almost all of them (11/12) were practicing within the Zen Soto tradition, but a few of them also had some experience with different contemplative practice styles (Zen Rinzai 3/12, Tibetan 2/12, Vipassana 2/12); three meditators were ordained Soto monks. The meditator and control groups were matched for gender (MEDT: 10 M, CTRL: 9 M), age (mean ± SD: MEDT, 37.3 ± 7.2 years; CTRL, 35.3 ± 5.9 years; 2-tailed, 2-sample *t*-test: $p = 0.45$), and education level (mean ± SD: MEDT, 17.8 ± 2.5 years; CTRL, 17.6 ± 1.6 years; $p = 0.85$). All participants were native speakers of English and right-handed, except one meditator who was ambidextrous. Subjects gave written informed consent for a protocol approved by the Emory University Institutional Review Board.

Neuropsychological Computerized Testing

Approximately 1 week before the MRI scanning session, every volunteer completed a selected subset of the CANTAB computerized neuropsychological battery (Sahakian and Owen, 1992). The CANTAB tests included: (1) a task assessing sustained attention (RVIP) in terms of sensitivity to the target (*A'*, a non-parametric analog of *d'* from signal detection theory) and response time; (2) a test of simple reaction time (RTI simple) to a visual stimulus appearing in a fixed location on the computer screen, in terms of reaction time proper (time to raise the finger from the resting pad) and movement time (time to reach the target on the touch screen with the finger); (3) a complex reaction time task (RTI five choice), similar to the previous one, but where the visual target appeared randomly in one of five screen locations; (4) a test of visuospatial working memory capacity (Spatial Span, SSP), assessed in terms of span length (number of remembered items); (5) a test of rule learning and rule-switching [Intra–Extra Dimensional Set Shift (IED)] with two sets of rules ("intradimensional" and "extradimensional") that assess cognitive flexibility in terms of the number of completed stages of progressive difficulty and number of errors for intradimensional and extradimensional rule learning. The reader can find a demo and a longer description of the tasks at http://www.cambridgecognition.com/academic/cantabsuite.

MRI Acquisition and Preprocessing

A T1-weighted high-resolution anatomical image (MPRAGE, 176 sagittal slices, voxel size: 1 mm isotropic) and a single series of resting state functional images (echo-planar, 200 volumes, 35 axial slices, voxel size: 3 mm isotropic, TR = 2.35 s, TE = 30 ms) were acquired with a 3.0 Tesla Siemens Magnetom Trio scanner. Participants were instructed to keep their eyes open and pay attention to their breathing throughout the full length of the run (∼8 min), and to calmly return their attention to breathing every time they found themselves distracted by thoughts, memories, or physical sensations. A fixation cross was kept on the MRI display screen to help concentration and minimize eye movement. The functional volumes were corrected for slice acquisition timing differences and head motion. The anatomical image was first registered to the mean of the corrected functional images and then spatially warped to the MNI standard brain space by using the segmentation routine of SPM5 (http://fil.ion.ucl.ac.uk/spm/software/spm5). The estimated warping parameters were subsequently applied to the functional images, which were finally smoothed with an 8 mm isotropic Gaussian kernel. Low-frequency signal drifts were removed from the time series by regressing out a Legendre polynomial of order two.

Network Construction and Functional Module Parcellation

We adopted the 264-node cortical parcellation system defined by Power et al. (2011), where each node is a 10 mm diameter sphere in MNI space representing a putative functional area. Such a parcellation was determined using a combination of meta-analysis of task-based fMRI studies and rsFC mapping techniques; it constitutes a finer grid compared to the Automated Anatomical Labeling (AAL) set (Tzourio-Mazoyer et al., 2002), but is not as granular as a collection of single voxels. It thus represents an appealing choice, in that it provides a good balance between spatial localization and dimension reduction (Fornito et al., 2010; Power et al., 2011).

Our network analysis considered 238 of the 264 nodes that were within the boundary of the data gray matter mask. We assigned these nodes to nine functional networks or "modules" that correspond to the major RSNs described by Smith et al. (2009). The RSN maps, determined by ICA decomposition of a large database of activation studies (BrainMap) and resting state fMRI data, are circuits whose BOLD activity is temporally coherent during both task activity and at rest. The functional modules include a medial visual network ("Med Vis," 14 nodes), an occipital pole visual network ("OP Vis," six nodes), a lateral visual network ("Lat Vis," 16 nodes), the "DMN," 21 nodes, the cerebellum (one node), a sensorimotor network ("SM," 29 nodes), an auditory network ("Aud," 29 nodes), an executive control network ("EC," 38 nodes), and a right and left frontoparietal network ("FPR" and "FPL," 30 and 26 nodes, respectively). To determine the module membership at each node, we identified the RSN z-statistic map with the largest value in the location of the node, above a chosen threshold ($z > 3$). Twenty nine of the 238 nodes in gray matter were not strongly associated with any RSN map, and were therefore not included. Also, since only one node was contained in the cerebellum, the latter module and corresponding node were discarded as well. A visualization of the remaining 209 nodes that are used in the subsequent network analysis, classified by functional module, is shown in **Figure 1**. A map of the functional modules is also displayed in **Figure 2**. The parcellation of nodes into functional modules allows examination of within- and between-module connectivity. All brain visualizations were created using BrainNet Viewer (Xia et al., 2013).

Graph Construction

To construct the network connectivity matrix, we extracted the time series from each node with the following steps. First, the time series at each voxel was detrended by regressing out a Legendre polynomial of second order, demeaned, and whitened. We then performed singular value decomposition (SVD) on the time series for all the voxels in each node to extract the representative time series within that node. A 209 × 209 symmetric connectivity matrix was defined for each subject by calculating Pearson correlations between the summary time series extracted from each node. To avoid the issue of arbitrary thresholding, our network analyses were conducted on fully connected graphs with both positive and negative weights. All graphical network visualizations were

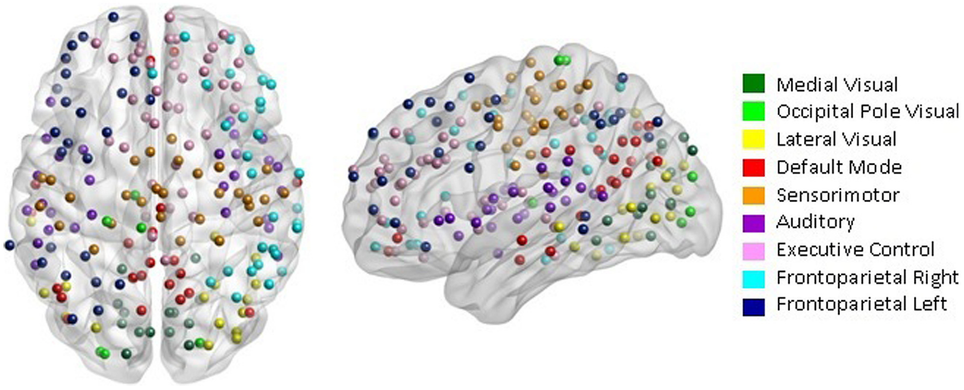


FIGURE 1 | Parcellation scheme and network assignment. The 209 nodes used in our network analysis are adapted from the 264-node parcellation system defined by Power et al. (2011). Each node is a 10 mm diameter sphere in MNI space representing a putative functional area, and is color-coded to indicate its module membership. Functional modules are defined by the 10 primary resting state networks (RSNs) described in Smith et al. (2009).

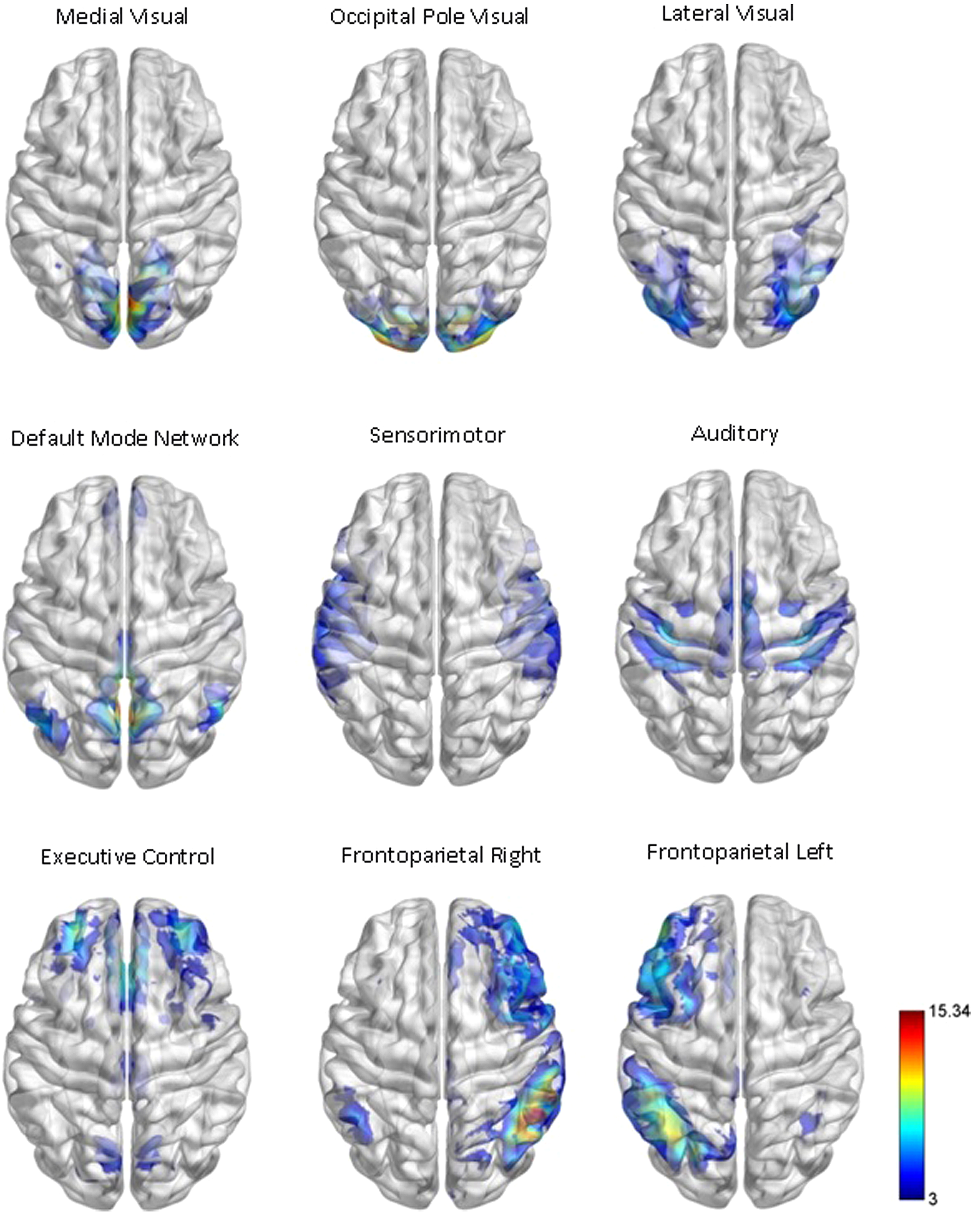


FIGURE 2 | Functional module maps. The functional module *z*-score maps (thresholded at $z > 3$) defined by the 10 primary RSNs described in Smith et al. (2009). To categorize nodes by module membership, we find the RSN map with the largest *z*-score in the location of the node, above a certain threshold ($z > 3$). The module corresponding to the cerebellum is not shown or used in our analysis, as it contained only one node in gray matter.

created using the igraph package in R (Csardi and Nepusz, 2006).

Group Differences in Modulewise Functional Connectivity

In order to summarize the 21,736 unique edges in the 209-node network by the nine functional modules reported in Smith et al. (2009), we first performed a dimension reduction on the original subject-specific connectivity matrices. More in detail, we divided the upper-triangle of the 209 × 209 edgewise connectivity matrix into 45 modulewise blocks representing the nine within- plus the 36 between-module connectivity strengths. For each modulewise block i ($i = 1,\ldots,45$; each containing m_i edges), we concatenated the block's m_i edgewise connection strengths into a vector, then formed a ($m_i \times 24$) block-specific connectivity matrix by stacking these vectors side by side across all 24 subjects. After removing the mean from each row, we performed a SVD on this matrix and extracted the first left singular vector ($m_i \times 1$) and the first right singular vector (1×24). The first left singular vector represents the first principal component direction of block *i*'s connectivity pattern (i.e., one value for each edge in block, representative of all subjects), and the first right singular vector corresponds to the subject-specific coordinates when projecting each subject's connectivity pattern on to the first principal component (i.e., one value per subject for each block *i,* representative of all the edges in the block). The set of right singular vectors, or principal component coordinates, can be seen as a compact representation of subjects' module-to-module connectivity patterns, reducing the original 24 subject-specific edgewise connectivity matrices (209×209) to 24 subject-specific modulewise principal component coordinate matrices (9×9). For each of the 45 unique modulewise blocks, we calculated the standardized mean difference (Cohen's *d*) in the modulewise principal component coordinates, and used an effect size threshold of 0.5 to identify group differences with at least a medium effect size (Cohen, 1988); for completeness, and as an exploratory inferential assessment, we also performed a non-parametric Wilcoxon rank sum test comparing meditators and controls on the principal component coordinates from each module-module block, reporting the associated uncorrected *p*-values. Finally, as we will describe in Section "Group Differences Based on Multivariate Pattern Analysis," the modulewise principal component coordinates were also used as input to a multivariate pattern analysis aimed at identifying an overall pattern of module-to-module connectivity discriminating between meditators and controls.

Of note, one consequence of summarizing the original 209×209 edgewise connectivity matrices into the SVD-based compact 9×9 modulewise connectivity matrices is that these compact matrices no longer directly provide information on the predominant sign of the connectivity strength in each of the module-to-module block. In order to recover such information (i.e., whether the BOLD signals from two modules were on average positively or negatively correlated), we also computed the mean connectivity strength within each module-to-module block by averaging across all the edgewise correlations in the block (see **Figure 4**). This allowed us to interpret and display between-group differences in the SVD-based compact connectivity results.

Inspection of Edgewise Connectivity and Consistency of Group Effects within each Module–Module Block

The group differences in functional connectivity observed in the modulewise (SVD-based) analysis were further inspected at the edgewise level and checked for within module-module block consistency with the following approach. For each of the 21,736 unique edges in the 209×209 symmetric connectivity matrix, we calculated the standardized group difference at each edge using Cohen's *d*, and selected those edges with an effect size magnitude of at least 0.5, representing a medium or larger difference (Cohen, 1988) between meditators and controls. We then grouped the selected edges into the nine within- and 36 between-module connection blocks described above and, for each module block, we assessed the dominant direction of the group difference at the edge-level (i.e., MEDT>CTRL or CTRL>MEDT) by calculating a consistency metric. This metric, based on the well-known McNemar test for consistency between two outcomes, was defined as $(N_{m > c} - N_{c > m})/(N_{m > c} + N_{c > m})$, where $N_{m > c}$ and $N_{c > m}$ are the number of supra-threshold edges in the module-module block for the MEDT>CTRL or CTRL>MEDT effects, respectively. Thus, a value of 0 for the above metric indicates a complete lack of edgewise consistency in the direction of the MEDT–CTRL effect within a module-module block, while a value of 1 (or −1) represents a full edgewise consistency. In order to screen out module-module blocks with low block-consistency for the group effect, we set a threshold for the consistency metric of 0.33, corresponding to an effect where there are at least twice as many edges in a block showing a group effect in one direction compared to the other. This procedure allowed us to identify module-module blocks with consistently stronger connections either in meditators or controls. In order to avoid drawing conclusions based on just a few edges, we only calculated the consistency metric on module-module blocks where at least 5% of the total edges met the $|d| > 0.5$ threshold. We separately examined the thresholded edges with positive and negative average connectivity in both groups.

Group Differences Based on Multivariate Pattern Analysis

In addition to the modulewise and edgewise univariate analyses, we also performed a multivariate analysis aimed at identifying an overall pattern of module-to-module connectivity discriminating between meditators and controls. The information from all 45 module-to-module SVD-derived summary measures was thus used jointly as input to a SVM classifier to predict group membership for each volunteer, using the LIBSVM package (Chang and Lin, 2011).

The SVM model produced three important outcomes. First, we evaluated the accuracy of the SVM classifier using a fourfold cross-validation procedure, in which the multivariate model was trained on 75% of the data, and then tested on the remaining 25% of the data. The results based on the cross-validation procedure reflect how accurately we can identify meditators on the basis of their brain connectivity features. Second, we obtained a vector of weights of the 45 modulewise connectivity features on the multivariate classifier, which represent the relative importance of these features in discriminating meditators and controls. Third, for each subject, the SVM yielded a dimensional classification score, a continuous predictor that reflects the confidence with which a volunteer was classified as a meditator or control.

We also performed an additional SVM analysis to classify meditators and controls, based this time on the outcome measures of the five CANTAB tests described in Section "Neuropsychological Computerized Testing." The accuracy rate of the CANTAB-based multivariate classifier was evaluated using the fourfold cross-validation procedure described previously, and compared to the accuracy rate from the modulewise connectivity-based SVM. From the SVM, we derived the CANTAB-based dimensional classification score, which reflects the degree to which a subject classified as a meditator or control, based on the subject's neuropsychological performance. Finally, we tested whether the brain-connectivity-based dimensional scores and the CANTAB-based dimensional scores were significantly correlated; this analysis tested whether the brain connectivity patterns that differentiated meditators from controls were significantly associated with the neuropsychological profile that best discriminated meditators and controls.

Lastly, we conducted a third SVM analysis using as input the joint set of the SVD-based modulewise connectivity measures *plus* the CANTAB scores, and compared its classification accuracy to that of the SVM analyses based on modulewise connectivity or CANTAB scores alone.

Association between Brain Connectivity Measures and Attentional Performance

As the sustained attention scores from the RVIP test have been previously shown to be sensitive to differential effects in meditators and controls (Pagnoni and Cekic, 2007; Pagnoni, 2012), we examined the correlation between each of the 45 modulewise first principal component coordinate values and the RVIP test scores, across all subjects (CTRL + MEDT). The purpose of this analysis was to identify a subset of the brain functional connectivity structure that was specifically associated with the capacity for sustained attention, a cognitive aspect generally assumed to be affected by meditative practice.

Results

Group Differences in Modulewise Functional Connectivity

Meditators and controls were compared on the subject-specific modulewise principal component coordinates extracted from the SVD analysis, using Cohen's d as a measure of effect size for each of the 45 module-module blocks. Among them, we identified 14 module-module connections with at least a medium-sized mean difference (i.e., Cohen's d magnitude of at least 0.5) between meditators and controls. Module pairs with positive and negative average connectivity (as assessed by the original full edgewise correlation matrices, see Group Differences in Modulewise Functional Connectivity) for both groups are reported separately (**Tables 1A,B**), along with uncorrected p-values from the rank sum test. The modulewise results shown in this table are also displayed visually in **Figure 3**.

Inspection of Edgewise Connectivity and Consistency of Group Effects within each Module–Module Block

The complete average correlation matrices, for meditators and controls, are shown in **Figure 4** as heat-maps, with edges grouped by their module membership. For the sake of interpretability, we separately examined the edges that were positive or negative in both groups average correlation maps, which represented the majority (82%) of the total edges.

TABLE 1A | Group differences in positive modulewise functional connectivity.

Module-module connection	Standardized mean difference, d	Direction of difference	p-value (uncorrected)
Med Vis – OP Vis	0.77	MEDT>CTRL	0.126
Lat Vis – SM	−0.57	CTRL>MEDT	0.312
DMN – EC	−0.67	CTRL>MEDT	0.069
Aud – Aud	−0.53	CTRL>MEDT	0.403
EC – FPR	0.89	MEDT>CTRL	0.026
EC – FPL	0.57	MEDT>CTRL	0.046
FPR – FPR	0.71	MEDT>CTRL	0.157
FPR – FPL	0.56	MEDT>CTRL	0.141

*Meditators had, on average, higher positive connections compared to controls for the Med Vis–OP Vis, EC–FPR, EC–FPL, FPR–FPR, and FPR–FPL module pairs. On the other hand, controls had, on average, higher positive connections for the Lat Vis–SM, DMN–EC, and Aud–Aud module pairs (**Figure 3A**).*

TABLE 1B | Group differences in negative modulewise functional connectivity.

Module-module connection	Standardized mean difference, *d*	Direction of difference	p-value (uncorrected)
Med Vis – DMN	−0.54	MEDT–>CTRL–	0.175
Med Vis – FPR	−0.80	MEDT–>CTRL–	0.046
Med Vis – FPL	−0.78	MEDT–>CTRL–	0.046
OP Vis – DMN	0.79	MEDT–>CTRL–	0.069
OP Vis – FPL	−0.77	MEDT–>CTRL–	0.069
SM – FPL	0.79	CTRL–>MEDT–	0.100

*Meditators had, on average, larger negative connection values for the Med Vis–DMN, Med Vis—FPR, Med Vis–FPL, OP Vis–DMN, and OP Vis–FPL module pairs, compared to controls; controls had higher negative connections compared to meditators for the SM–FPL module only (**Figure 3B**).*

Of the 21,736 unique edgewise connections, 37% were positive in both groups, on average. **Figure 5A** displays positive edges with between-group difference of medium or larger effect size (i.e., $|d| > 0.5$; Cohen, 1988). In the figure, orange or green edges indicate that edgewise positive connectivity was higher in meditators or controls, respectively. For module-module blocks with at least 5% of edges exceeding the chosen effect size threshold, we computed the within-block consistency of the effect with the metric described in Section "Group Differences Based On Multivariate Pattern Analysis." The value of the consistency metric, as well as the percent of the block's edges retained post-thresholding, are displayed for each module-to-module block in **Figure 5B**. In this figure, shaded cells identify blocks with a highly consistent edgewise effect (i.e., consistency metric magnitude of at least 0.33); orange or green cells indicate that positive connections were higher among meditators or controls, respectively. Meditators had consistently higher positive connections than controls within the Med Vis and FPR modules, and for the Med Vis–OP Vis, Med Vis–Aud, EC–FPR, and FPR–FPL module pairs. Controls had higher positive connections than meditators within the Lat Vis, DMN, Aud, and

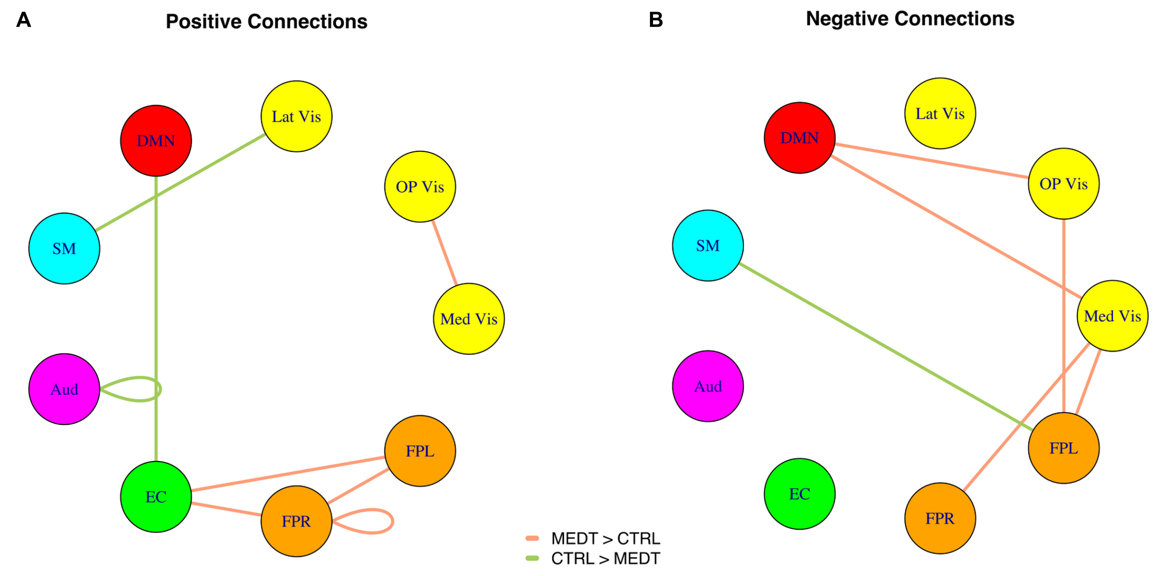


FIGURE 3 | (A) Positive and **(B)** negative connections with at least a medium standardized mean difference (Cohen's | d| > 0.5) between meditators and controls, as per the SVD-based modulewise analysis.

EC modules, and for the following module pairs: Lat Vis–SM, DMN–EC, SM–Aud, and Aud–FPR. Module pairs that were also identified in the modulewise FC analysis (i.e., Med Vis–OP Vis, Lat Vis–SM, DMN–EC, Aud–Aud, EC–FPR, FPR–FPR, and FPR–FPL), are marked with bold font in **Figure 5B**.

Of the 21,736 unique edgewise connections, 45% were negative in both groups, on average. **Figure 6A** displays negative edges with between-group difference of medium or larger effect size (i.e., | d| > 0.5; Cohen, 1988). In the figure, orange or green edges indicate that edgewise negative connectivity was higher in meditators or controls, respectively. With a similar approach to that used for positive connections, we identified module-module blocks with a highly consistent edgewise group difference in the negative connections and selected the blocks with at least 5% suprathreshold edges for further analysis. **Figure 6B** shows the value of the consistency metric and the percent of edges retained post-thresholding for each block. Shaded cells identify blocks with a highly consistent edgewise effect within the block, with orange, and green color corresponding to a modulewise negative connection stronger in meditators or controls, respectively. Meditators had consistently stronger negative connections than controls for the following module pairs: Med Vis–DMN, Med Vis–SM, Med Vis–FPR, Med Vis–FPL, OP Vis–SM, OP Vis–EC, OP Vis–FPR, OP Vis–FPL. Controls had consistently stronger negative connections than meditators for the Lat Vis–DMN, Lat Vis–EC, Lat Vis–FPL, DMN–SM, DMN–Aud, DMN–FPL, SM–FPL, Aud–EC, EC–FPR, and FPR–FPL module pairs. Module pairs that were also identified in the modulewise FC analysis (i.e., Med Vis–DMN, Med Vis–FPR, Med Vis–FPL, OP Vis–FPL, and SM–FPL), are marked with bold font in **Figure 6B**.

Modulewise connections with consistent group effects for positive and negative connections are displayed in circular graphs in **Figure 7**, for easier comparison to the SVD-based results portrayed in **Figure 4**.

Group Differences Based on Multivariate Pattern Analysis

The fourfold cross validation procedure for the connectivity-based SVM classifier using the 45 modulewise principal components yielded an overall accuracy rate of 79.2% (19/24 subjects correctly classified). The most heavily weighted modulewise connections in the SVM model, along with their weights, are displayed in **Figure 8**. They included the within OP Vis and SM module connections, and the following module–module connections: Med Vis–SM, Med Vis–OP Vis, Med Vis–FPL, OP Vis–FPL, OP Vis–FPR, OP Vis–SM, FPR–SM, and OP Vis–DMN. These connections, taken together, were the most critical for distinguishing meditators, and controls.

The fourfold cross-validation procedure for the second SVM analysis, aimed at classifying meditators and controls based on subjects' CANTAB test scores yielded an overall accuracy rate of 75% (18/24 subjects correctly classified). The brain connectivity features demonstrated thus slightly better classification accuracy than the CANTAB scores. As an additional check, we also performed an SVM analysis using as input both the modulewise FC values (measured by first principal component coordinates) and the CANTAB scores: the model attained a classification rate of 79.2%, that is, the same rate achieved using the modulewise FC alone, showing that the amount of information embedded in the brain FC measures, for what concerns subjects' classification, was not significantly augmented by further inclusion of the employed neuropsychological tests' scores.

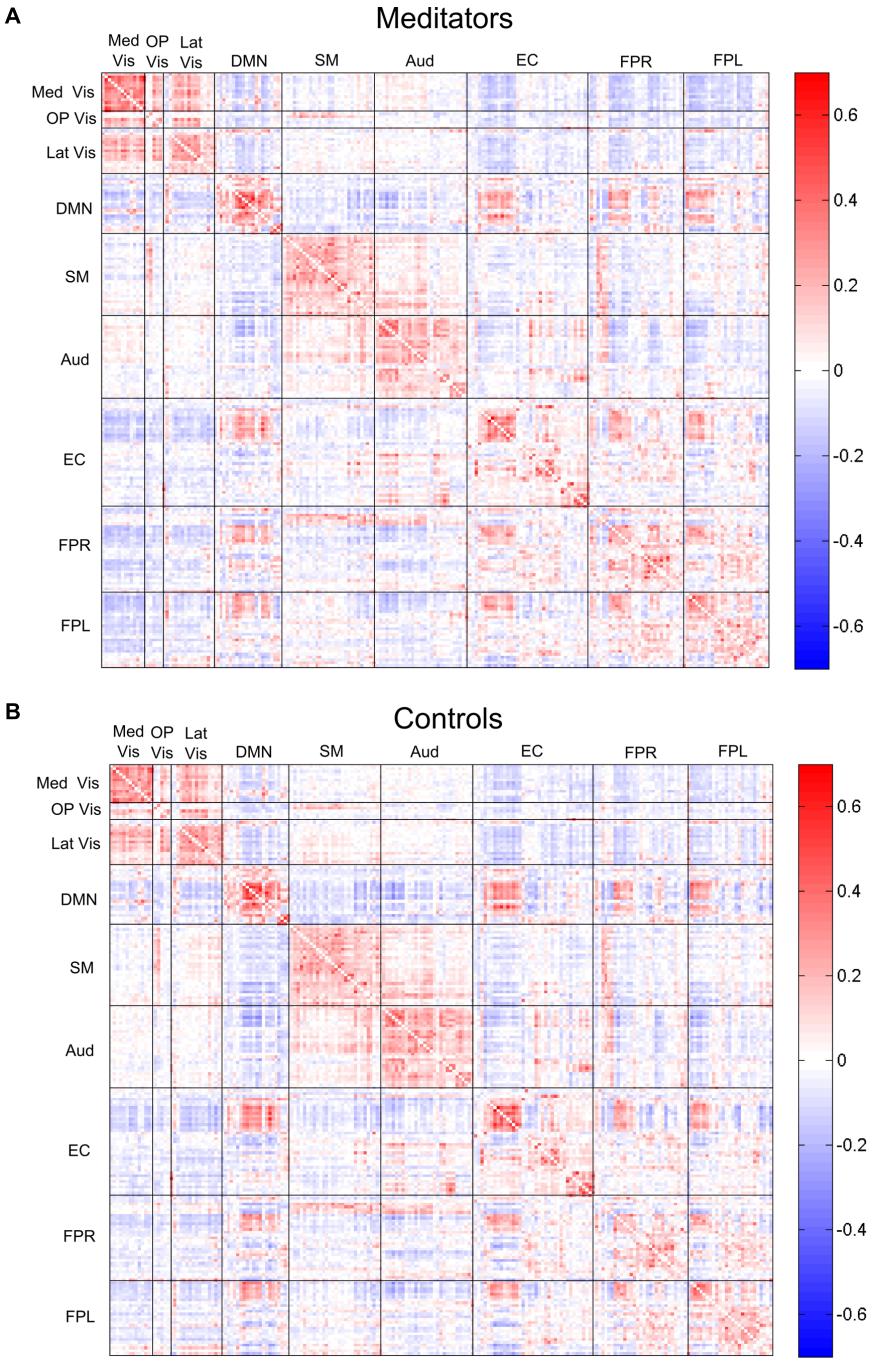


FIGURE 4 | Edgewise connectivity matrices, averaged by subject group. The symmetric 209 × 209 connectivity matrices (as measured by Pearson correlations), averaged over the **(A)** meditators and **(B)** control groups. Edges are shown grouped by their module membership. Red edges indicate positive connectivity, while blue edges indicate negative connectivity.

Finally, the dimensional classification scores from the connectivity- and CANTAB-based SVM were strongly correlated ($r = 0.69$, $p = 0.002$; see **Figure 9**); demonstrating that subjects with more "meditator-like" patterns of connectivity also exhibited more "meditator-like" patterns of CANTAB test performance.

Association between Brain Connectivity and Neuropsychological Tests

The correlation analysis across all subjects (MEDT + CTRL) of the 45 modulewise functional connectivity strengths (summarized by the first principal component coordinates extracted from SVD) and attentional performance, as indexed by RVIP

B

	Med Vis	OP Vis	Lat Vis	DMN	SM	Aud	EC	FPR	FPL
Med Vis	0.36 (31%)	**1.0 (27%)**	-	-	-	0.84 (6%)	-	-	-
OP Vis		-	-	-	-	-	-	-	-
Lat Vis			-0.92 (21%)	-	**-0.77 (9%)**	-	-	-	-
DMN				-0.45 (14%)	-	-	**-0.83 (9%)**	-	-
SM					-	-0.61 (8%)	-	-	-
Aud						**-0.91 (16%)**	-	-0.61 (5%)	-
EC							-0.49 (10%)	**0.33 (7%)**	-
FPR								**0.65 (14%)**	**0.52 (8%)**
FPL									-

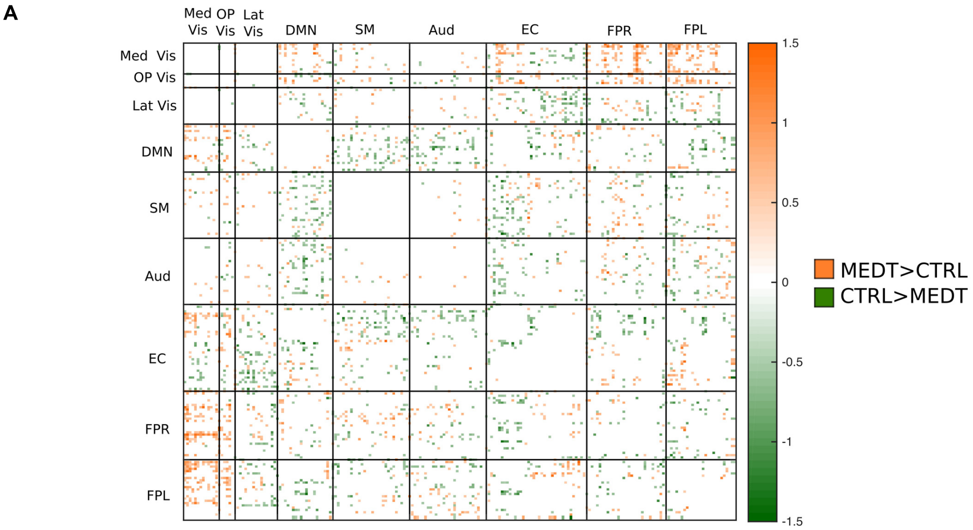
FIGURE 5 | Group differences in positive connectivity. (A) For the edges that were *positive* on average, in both meditators and controls, we calculated the MEDT–CTRL standardized effect size to assess group differences; only edges with at least a moderate effect size (| *d*| > 0.5) are displayed and used in further analyses. **(B)** The results of the within-block consistency analysis are summarized as a table; for each module-to-module block containing at least 5% of edges meeting the required effect size threshold in **(A)**, the value of the consistency metric and the percent of edges retained post-thresholding (in parentheses) are reported. Shaded cells indicate blocks with a highly consistent edgewise effect, and are color-coded according to the direction of the group effect. Bolded values indicate blocks also highlighted in the modulewise analysis.

test scores, identified several associations with a large or greater effect size (i.e., $|r| > 0.5$; Cohen, 1988), reported in **Table 2**. The OP Vis–EC, OP Vis–FPR, DMN–FPR, EC–FPR, and FPR–FPL connections were associated with RVIP target sensitivity, while the OP Vis–EC, OP Vis–FPR, OP Vis–FPL, SM–EC, and Aud–FPR connections were associated with RVIP reaction time.

Discussion

Network analyses of fMRI data are increasingly being used to characterize patterns of brain dynamics associated with a specific mental state, trait, or clinical condition (Filippi et al., 2013; Smith et al., 2013). It has also been recently shown that MRI-based functional connectivity strength is spatially well-matched to the local distribution of regional cerebral blood flow (rCBF), and thus is likely to reflect the degree of neural activation (Liang et al., 2013). While previous studies have employed functional connectivity for the investigation of the neural correlates of contemplative practices (Farb et al., 2007; Josipovic et al., 2011; Kilpatrick et al., 2011; Hasenkamp and Barsalou, 2012; Lehmann et al., 2012; Pagnoni, 2012; Taylor et al., 2013; Garrison et al., 2014; Marzetti et al., 2014), the application of specific techniques from graph theory to this field of research is still scarce (see Gard et al., 2014, for an exception). In the present study, we examined how a group of habitual Zen practitioners and a group of matched control subjects differed on selected MRI-based functional connectivity network measures during a simplified (attention-to-breathing) meditative task without any external experimental stimulation. We also explored the relationship of these measures with the performance of the same subjects on a computerized test of sustained attention (RVIP).

A first, summary outlook on the group differences in functional connectivity is provided by the modulewise (SVD-based) analysis. This analysis revealed a differential group pattern where meditators were characterized by frontoparietal attentional circuits (FPR, FPL) having stronger positive connections to an anterior cingulate-insula-caudate network (EC) involved in executive processing and saliency detection, and stronger negative connections to early visual areas (OP Vis, Med Vis), compared to controls; also, meditators exhibited on average weaker positive connections between DMN and the saliency network (EC), and stronger negative connection between DMN and early visual areas (OP Vis, Med Vis).



B

	Med Vis	OP Vis	Lat Vis	DMN	SM	Aud	EC	FPR	FPL
Med Vis	-	-	-	**0.86 (14%)**	0.62 (5%)	-	-	**0.94 (23%)**	**0.98 (25%)**
OP Vis		-	-	-	0.4 (6%)	-	0.33 (13%)	0.87 (17%)	**1.0 (18%)**
Lat Vis			-	-0.33 (8%)	-	-	-0.45 (16%)	-	-0.39 (12%)
DMN				-	-0.64 (14%)	-0.58 (13%)	-	-	-0.53 (9%)
SM					-	-	-	-	**-0.41 (9%)**
Aud						-	-0.72 (7%)	-	-
EC							-	-0.34 (8%)	-
FPR								-	-0.41 (7%)
FPL									-

FIGURE 6 | Group differences in negative connectivity. (A) For the edges that were negative on average, in both meditators and controls, we calculated the MEDT–CTRL standardized effect size to assess group differences; only edges with at least a moderate effect size (| *d*| > 0.5) are displayed and used in further analyses. **(B)** The results of the within-block consistency analysis are summarized as a table; for each module-to-module block containing at least 5% of edges meeting the required effect size threshold in **(A)**, the value of the consistency metric and the percent of edges retained post-thresholding (in parentheses) are reported. Shaded cells indicate blocks with a highly consistent edgewise effect, and are color-coded according to the direction of the group effect. Bolded values indicate blocks also highlighted in the modulewise analysis.

A complementary analysis, examining the consistency of the edgewise connection strengths within each module-module block, largely confirmed the above findings but also revealed a more nuanced picture, with additional group connectivity differences involving, among others, a weaker negative connectivity, for meditators compared to controls, between the DMN and both the auditory (Aud) and the sensorimotor (SM) networks. Finally, a direct assessment of the subspace of modulewise connectivity that could best separate meditators from control subjects, via an SVM classifier, underscored again the importance of connections between frontoparietal circuits (FPR, FPL) and early visual areas (Med Vis, OP Vis), but also between these occipital regions and both sensorimotor cortex (SM) and DMN.

These results are meaningful, as frontoparietal circuits and the DMN have long been assumed to be affected by contemplative practice. Meditation generally involves a regulation of attentional processes and spontaneous mentation or mind-wandering, along with an increase in meta-awareness (awareness of one's own mental processes). Attentional deployment and regulation are known to impinge crucially on frontoparietal circuits (Corbetta and Shulman, 2002), while DMN has been consistently implicated in mind-wandering, both in and outside the context of meditation (Binder et al., 1999; Mason et al., 2007; Christoff et al., 2009; Brewer et al., 2011). The stronger positive connection between frontoparietal circuits and the saliency network exhibited by meditators in the present study, may be linked the vigilant attitude that meditators aim to keep in order to detect and become aware of the fluctuations in one's own mental state, so that salient events in the mental landscape are accompanied by an activation of regulatory attentional mechanisms. Interestingly, the saliency network has been shown to activate during awareness of episodes of mind-wandering in meditation, an effect putatively ascribed to the fact that mind-wandering episodes represent a violation of the target of remaining concentrated on breathing and thus may trigger neural activity in conflict-processing and arousal-related areas such as anterior cingulate and insular cortices (Hasenkamp et al., 2012). In this perspective, the observed weaker positive connection between the EC and the DMN modules, for meditators compared to controls, could reflect the less-judgmental and more accepting attitude of meditators vis-à-vis the spontaneous occurrence of mind-wandering episodes, compared to control subjects who, because of their lack of experience, may in fact react more emotionally to such violations of the concentrative goal of the task.

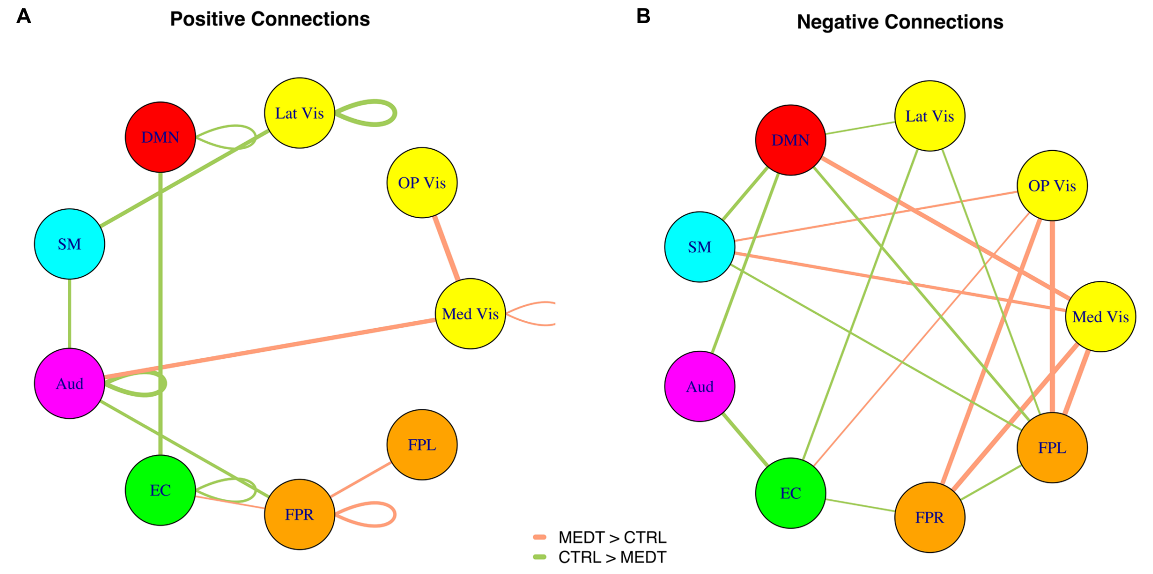


FIGURE 7 | Within-block consistency analysis results. (A) Positive and **(B)** negative connections with a highly consistent group effect across the edges of a module-to-module block. Edge color indicates whether connections are stronger in meditators (orange) or controls (green), while the edge width reflects the value of the consistency metric.

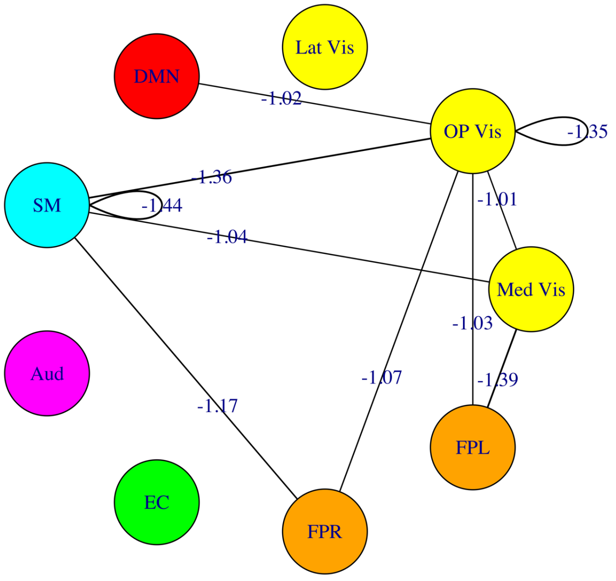


FIGURE 8 | Multivariate pattern analysis results. The most heavily weighted modulewise-connectivities identified by the support vector machine (SVM) model, along with their connection weights. Considered jointly, these modulewise connections are the most critical for distinguishing the meditator and control groups.

Meditators also exhibited weaker *negative* connections between the DMN and a number of modules that process sensory and motor information (Aud, Lat Vis, SM; see **Figure 7B**), one possible interpretation is that, in controls, the spontaneous activation of DMN during episodes of mind-wandering corresponds to a more active dampening, compared to meditators, of the information from channels linked to the external environment, leading to sensorimotor decoupling (Kam and Handy, 2013), and thus to increased mental absorption in internally generated, distracting thoughts. (The stronger negative connection in meditators between the DMN and medial visual cortex would represent, however, an exception to this general pattern).

Of particular interest is the DMN within-module positive connectivity, which was weaker in meditators compared to

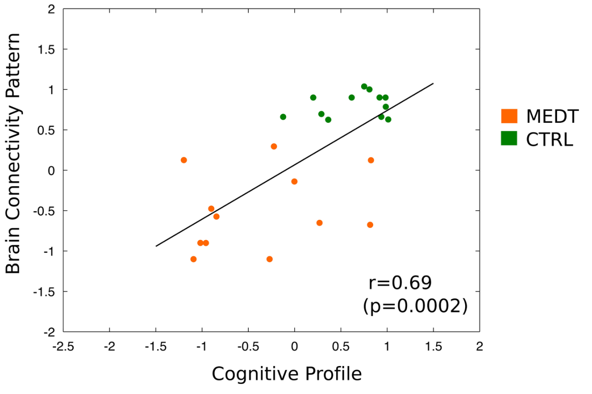


FIGURE 9 | Correlation of brain-based and neuropsychology-based SVM classification scores across all subjects. Scatterplot and linear fitting of dimensional classification scores from the SVM using the CANTAB test scores and from the SVM using the first PC of modulewise brain connectivity. The two sets of scores were strongly correlated across subjects ($r = 0.69$, $p = 0.0002$), indicating that subjects classified as meditators based on their pattern of brain connectivity, also tended to be classified as meditators based on their performance on the neuropsychological tests.

TABLE 2 | The correlation of rapid visual information processing (RVIP) test performance with the 45 modulewise first principal component coordinates revealed these large associations.

	Modulewise connections	Correlation with RVIP task	p-value (uncorrected)
RVIP sensitivity to target	OP Vis – EC	0.54	0.006
	OP Vis – FPR	−0.53	0.008
	DMN – FPR	0.51	0.010
	EC – FPR	0.56	0.004
	FPR – FPL	0.60	0.002
RVIP response time	OP Vis – EC	−0.61	0.002
	OP Vis – FPR	0.51	0.011
	OP Vis – FPL	0.51	0.010
	SM – EC	0.51	0.010
	Aud – FPR	−0.59	0.003

controls (**Figure 7A**). If this can be taken to reflect a less active DMN in meditators during attention-to-breathing, it would be in good agreement with the finding of a similar effect based on an independent measure of the frequency of activation (the skewness of the BOLD distribution) of the main node of the DMN, the retrosplenial cortex, that we had previously observed in the same data (Pagnoni, 2012). The possibility that meditation could provide intervals of momentary respite for an overactive DMN and perhaps, through regular practice, even induce a lasting regularization of the activity in the same circuit outside of formal practice, is especially intriguing. Recent evidence has linked the process of deposition of beta-amyloid peptide and brain atrophy in Alzheimer's disease (AD) – a process whose spatial pattern strikingly resembles the DMN's layout (Buckner et al., 2005) – to the sustained metabolic activity of the DMN (Walker and Jucker, 2011). Although more research is obviously needed, the prospect that the regular practice of certain kind of contemplative techniques could prove even mildly protective against the onset of AD, should not be neglected.

Meditators also exhibited stronger within-module positive connectivity in the FPR (**Figures 3** and **7A**) – a network known for its relevance in sustained attention (Coull et al., 1996; Sarter et al., 2001; Lim et al., 2010) – suggesting an increased engagement of the latter during attention-to-breathing in meditators by virtue of their practice. Enhanced activation of the FPR network has been previously associated with better performance in the RVIP task (Lawrence et al., 2003); such a finding, together with the better performance of this sample of meditators in the RVIP task when controlling for age (Pagnoni and Cekic, 2007) and the prominent featuring of the FPR module in the pool of important correlations of brain connectivity strengths with RVIP performance (**Table 2**), lends further support to the notion of an increased engagement of attentional processes in meditators, compared to controls, during the attention-to-breathing meditative task. Of note, frontoparietal circuits (FPR, FPL) were also more negatively connected to early visual areas (Med Vis, OP Vis) in meditators compared to controls (**Figures 3** and **7B**), a possible correlate of a more effective redeployment of attention toward internally generated stimuli in meditators (e.g., respiratory sensations, monitoring of the appearance of spontaneous thoughts) during the attention-to-breathing task (Cooper et al., 2003). The hypothesis that the strength of the negative connections between frontoparietal and early visual areas during a task that prescribes *inward* attention is related to the individual ability to voluntarily regulate attention may be supported by the finding that subjects who exhibited a stronger negative correlation between FPR/FPL and OP Vis also displayed a better performance in the RVIP sustained attention task (**Table 2**).

An important result is that the module-module connection strengths were able to predict the subjects' group membership via the SVM classifier with quite a high accuracy (79%). A similar SVM analysis based on CANTAB cognitive test scores also produced a reasonable (but inferior) classification rate (75%). The SVM also provided a further characterization of the distinction between meditators and control subjects, via the dimensional classification scores. Correlation analyses showed that the dimensional classification scores from the connectivity-based SVM were significantly associated with the dimensional classification scores from the CANTAB-based SVM, indicating that subjects with more "meditator-like" patterns of connectivity also demonstrated more "meditator-like" patterns of performance in the employed set of neuropsychological tests.

Limitations and Future Directions

We examined the effects of meditation on rsFC across the whole brain using a multi-stage network approach. Our study included a well-controlled matched sample of habitual meditators and meditation-naïve controls during a basic attention-to-breathing fMRI protocol. The limited sample size ($n_{\mathrm{MEDT}} = 12$, $n_{\mathrm{CTRL}} = 12$), along with the large number of examined nodes, and connections, made straightforward multiple comparisons correction of the p-values impractical (and overly conservative, given the non-independence of the nodes). Since the effect size, on the other hand, is not confounded by the sample size (Lang et al., 1998), we chose to report only the findings with a medium or larger effect size (along with uncorrected p-values), acknowledging the fact that such findings should be regarded as having principally an exploratory, hypothesis-generating role.

Also, in our analysis, we calculated the Pearson's correlation coefficients between the time series of two nodes to represent their functional connectivity strength. Correlation is one of the simplest and most commonly used association measures, but it does not imply direct connections between two nodes (i.e., a third node may be mediating their relationship). Partial correlation, which regresses out confounding nodes to distinguish direct from indirect connections, can better estimate the true connectivity network. In fact, some differences between the univariate and multivariate results portrayed in **Figures 3** and **8,** respectively, could probably be reduced, were partial correlations to be employed. Partial correlations can be estimated via the inverse of the covariance matrix, but the algorithm presents computational difficulties when the number of columns of the correlation matrix exceeds the number of rows that we were not able to resolve at the time of writing. Smith et al. (2011) showed that partial correlation performs better than regular correlation in a variety of simulations of fMRI data, and we plan to adopt this approach in future analyses.

Finally, the reported findings indicate that the long-term practice of meditation may be associated with FC changes in several RSNs. However, as this is not a randomized study, the causal direction of the observed association cannot be determined. A longitudinal study, despite a number of issues that make it practically very problematic when aimed at studying the effects of long term training (e.g., subjects' compliance, study dropout, intervening confounding variables), would be necessary to establish causality in a decisive way.

Acknowledgments

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The default mode network as a biomarker for monitoring the therapeutic effects of meditation

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The default mode network (DMN) is a group of anatomically separate regions in the brain found to have synchronized patterns of activation in functional magnetic resonance imaging (fMRI). Mentation associated with the DMN includes processes such as mind wandering, autobiographical memory, self-reflective thought, envisioning the future, and considering the perspective of others. Abnormalities in the DMN have been linked to symptom severity in a variety of mental disorders indicating that the DMN could be used as a biomarker for diagnosis. These correlations have also led to the use of DMN modulation as a biomarker for assessing pharmacological treatments. Concurrent research investigating the neural correlates of meditation, have associated DMN modulation with practice. Furthermore, meditative practice is increasingly understood to have a beneficial role in the treatment of mental disorders. Therefore we propose the use of DMN measures as a biomarker for monitoring the therapeutic effects of meditation practices in mental disorders. Recent findings support this perspective, and indicate the utility of DMN monitoring in understanding and developing meditative treatments for these debilitating conditions.

Keywords: meditation, neuroimaging, default mode network, therapy, mindfulness, functional magnetic resonance imaging (fMRI), biomarker, DMN modulation

Brain activation, measured by regional blood flow, can be visualized in functional magnetic resonance imaging (fMRI) as the blood-oxygen-level-dependent (BOLD) signal. Since the early years of fMRI research, awake, restful brain activity has been used as a baseline for the measurement of specific tasks. During this baseline brain activation, the synchronous behavior of a number of anatomic regions was observed and initially identified as a network of task-specific deactivations, dubbed the default mode network (DMN; Gusnard and Raichle, 2001; Raichle et al., 2001). Later it was determined that these task specific deactivations of the DMN also showed patterns of coherent activation during periods of rest. These ongoing low-frequency fluctuations in the resting state consume 60–80% of the brain's energy (Shulman et al., 2004; Raichle and Mintun, 2006) and though observed by many, their significance was not initially understood (Biswal et al., 1995). The DMN became the first, and now the most extensively studied of the many known resting state functional networks. The main nodes of the DMN have been identified as the medial prefrontal cortex (mPFC), anterior and posterior cingulate cortices (ACC, PCC), precuneus (PCU), inferior parietal cortex (IPC), and lateral temporal cortex (Raichle et al., 2001; Raichle and Snyder, 2007). These primary nodes of the DMN are functionally connected, meaning they exhibit concerted fluctuations during functional tasks. The DMN's robustness has been established both functionally (Shulman et al., 1997; Gusnard and Raichle, 2001; Mazoyer et al., 2001; Raichle et al., 2001;

Lazar et al., 2003; Harrison et al., 2008) and structurally (Shulman et al., 2004; Raichle and Mintun, 2006; Greicius et al., 2009). Network activation has been associated with specific mentation including autobiographical memory, self-reflective thought (Gusnard et al., 2001; Sheline et al., 2009), envisioning future events, mind wandering (Mason et al., 2007), and considering the thoughts and perspectives of others (Raichle et al., 2001; Raichle and Snyder, 2007; Buckner et al., 2008).

The DMN as a Diagnostic Tool

In healthy individuals, DMN activity has been anti-correlated with goal-oriented task-positive networks (TPNs; Fox et al., 2005; Kelly et al., 2008). On the other hand, abnormal DMN activity – such as competitive, antagonistic DMN activation during TPN activity or changes in connectivity between subregions of the DMN – has been associated with a number of psychological disorders such as schizophrenia (Garrity, 2007; Pomarol-Clotet et al., 2008; Camchong et al., 2011; Bastos-Leite et al., 2014), epilepsy (Liao et al., 2010), anxiety (Zhao et al., 2007), depression (Sheline et al., 2009), autism (Assaf et al., 2010), attention deficit hyperactivity disorder (ADHD; Uddin et al., 2008), and Alzheimer's disease (AD; Greicius et al., 2004; Sheline and Raichle, 2013). These associations have popularized the use of DMN analysis as a method by which to study mental disorders, resulting in a growing body of literature concerning disorder-specific variations within the DMN [see reviews (Greicius, 2008; Broyd et al., 2009; Fox, 2010; Whitfield-Gabrieli and Ford, 2012)]. Some examples of network variation include failure to deactivate the DMN during tasks in both autism (Spencer et al., 2012) and depression (Grimm et al., 2008; Sheline et al., 2009); decreased DMN activity and connectivity in AD (Sorg et al., 2007; Sheline and Raichle, 2013); antagonistic activity during attention-demanding tasks in schizophrenia (Whitfield-Gabrieli et al., 2009); differences in functional connectivity in both anorexia (Cowdrey et al., 2014) and autism (Assaf et al., 2010) and network inhomogeneity in ADHD (Uddin et al., 2008) and bipolar disorders (Liu et al., 2013). In some disorders such as AD (Sperling, 2011; Koch et al., 2012; Balthazar et al., 2014), depression (Li et al., 2013; Wise et al., 2014), and schizophrenia (Shen et al., 2014), these abnormalities of the DMN are consistent enough to be evaluated for use as diagnostic biomarkers.

Amongst these disorders, the relationship between the DMN and AD pathology has been the most thoroughly investigated. Anatomical regions of neuron loss and plaque deposition in AD overlap with regions of the DMN (Buckner et al., 2005). Greicius et al. (2004) observed a decrease in DMN activity and connectivity in patients with AD, likely due to decreased metabolism and physiological disruptions from plaque deposition. According to these analyses, patterns of DMN disruption provide a metric by which to distinguish individual AD subjects from healthy elderly controls with a sensitivity of 85% and a specificity of 77% (Greicius et al., 2004). Work by Sorg et al. (2007) also found patterns of DMN disruption and attenuated activation in patients with mild cognitive impairment (MCI), supporting the use of DMN alterations for the early detection of individuals at risk for AD. Most recently, work by Balthazar et al. (2014) found that by using the PCC as a seed region for DMN functional connectivity analysis, early AD patients could be distinguished from healthy controls with a sensitivity of 77.3 and 70% specificity, indicating that DMN analysis of PCC connectivity could represent a promising biomarker for early AD diagnosis (Sheline et al., 2010b; Sheline and Raichle, 2013).

In contrast to AD which has regions of decreased DMN activity and connectivity, investigations in schizophrenia reveal *increases* in DMN activity during task performance as well as increased connectivity relative to controls (Garrity, 2007; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009; Camchong et al., 2011; Bastos-Leite et al., 2014). In a number of studies, the degree of DMN disorder significantly correlated with the severity of psychological symptoms (Garrity, 2007; Whitfield-Gabrieli et al., 2009; Camchong et al., 2011). The same is true in the case of depression, where abnormal DMN activity and functional connectivity correlate with depressive rumination and symptom severity (Greicius et al., 2007; Berman et al., 2010; Sheline et al., 2010a). Many studies have now established this relationship between DMN-related abnormalities and psychological symptoms such as depressive rumination (Greicius, 2008; Broyd et al., 2009; Sheline et al., 2009; Fox, 2010; Whitfield-Gabrieli and Ford, 2012), feelings of hopelessness (Grimm et al., 2008), mind wandering (Mason et al., 2007), and poor cognitive performance (Weissman et al., 2006; Sorg et al., 2007; Sheline and Raichle, 2013) further intimating the role of the DMN in mental illness.

The DMN as a Biomarker for Treatment Response

If abnormalities of the DMN can be employed as diagnostic biomarkers or a metric of symptom severity, can the post-treatment normalization of DMN activity and connectivity also be used to evaluate treatment effectivity? Pharmacological fMRI (phfMRI) studies may be the first to provide an answer to this question (Anand et al., 2005; Sambataro et al., 2009; Di Simplicio et al., 2011; Kozel et al., 2011; Tregellas et al., 2011; Li et al., 2012; Andreescu et al., 2013; Posner et al., 2013; Smucny et al., 2014; Wang et al., 2014). For example, Tregellas et al. (2011) used the DMN as a metric in evaluating patient response to medication in schizophrenics with high posterior DMN connectivity and activity. Post-treatment, they found DMN activity resembling healthy network functioning (Tregellas et al., 2011). For the treatment of depression, Wang et al. (2014) reported changes in resting state functional connectivity resulting from the use of antidepressants. Their work also showed that reductions in functional connectivity of the dorsomedial prefrontal cortex, a subregion of the DMN (Sheline et al., 2009), significantly correlated with symptomatic improvement. For the treatment of AD, Li et al. (2012) showed that after administration of Donepezil, patients exhibited increased blood flow and functional connectivity to the PCC region of the DMN, restoring connectivity to levels resembling healthy controls. As a locus for measuring recovery, these changes in the DMN significantly correlated with improved cognitive performance (Li et al., 2012).

The combined use of clinical evaluations with an objective measure such as DMN analysis, could provide a powerful new metric for assessing the success of differing treatments. The essential precursor to this approach is the establishment of reliable, disorder-specific differences between the DMNs of patient populations and healthy controls. In addition, there is evidence supporting the potential to further subgroup broadly diagnosed disorders based on additional DMN variations within patient populations (Lui et al., 2011; Li et al., 2013; Liu et al., 2013). Although these methods are currently being employed to evaluate pharmacological treatments for mental disorders, few have utilized DMN measures to evaluate non-pharmacological cognitive interventions such as meditation. There is a growing body of evidence indicating that meditative mindfulness practices may provide a promising avenue for the treatment of many of the mental disorders discussed above (see reviews Baer, 2006; Chiesa and Serretti, 2009, 2011; Chiesa, 2010; Keng et al., 2011). In this perspective, we propose the use of DMN analysis as an additional objective metric or biomarker for monitoring the therapeutic effects of meditation in mental disorders.

Meditation and Modulation of the DMN

As research strengthens the link between anatomical regions of the DMN and psychological processes such as self-reflection, rumination, and mind wandering, much interest has been directed toward non-pharmacological means of altering patterns of behavior within this network. Meta-analyses examining the specific neurocorrelates of meditation have shown reductions in DMN activity as a primary outcome of mindfulness meditation practices (Tomasino et al., 2012, 2014). Results from a recent study by Garrison et al. (2015) indicate that meditation is associated with reduced activations in the DMN relative to an active association task for meditators as compared to controls.

For depression, reduced DMN activity in regions associated with subjective evaluation of emotional experience and self-referencing are thought to allow the individual to experience the present moment with greater objectivity, reducing bias or valuation (Ives-Deliperi et al., 2011). A reduction in self-referential evaluation trains the individual to abandon emotionally charged assessments of their internal and external world, thus altering patterns of self-judgment and value assignment (Farb et al., 2007, 2010). Shapiro's model of mindfulness calls this "re-perceiving" and notes its likeness to psychological models of decentering (Safran, 1990) and detachment (Bohart, 1983). In psychotherapy, dis-identification refers to a process where the individual becomes capable of reappraisal by distinguishing thoughts from feelings. Likewise, through meditation, the patient's self-perception changes from an enduring entity to a transient entity. In this way the patient becomes less fixated and less likely to ruminate on faults and mistakes (Jackson et al., 2000; Gross, 2002).

Additional psychological benefits of reduced DMN interferences include improvements in attentional control (Lutz et al., 2008; Hasenkamp and Barsalou, 2012; Hasenkamp et al., 2012) by reducing DMN/TPN competition, commonly associated with mental disorders such as schizophrenia (Whitfield-Gabrieli et al., 2009) and ADHD (Sonuga-Barke and Castellanos, 2007; Uddin et al., 2008). These studies associating psychological changes with DMN modulation as an outcome of meditative practice represent only a few of the results motivating recent trends in fMRI research (see **Table 1**).

Mindfulness Meditation as a Clinical Therapy

Westernized forms of meditation stemming from Buddhist traditions have popularized the concept of "mindfulness" as a therapeutic. These Mindfulness methods have been beneficial in the treatment of psychological disorders such as schizophrenia (Chien and Thompson, 2014), depression (Teasdale et al., 2000; Ma and Teasdale, 2004; Eisendrath et al., 2008; Kuyken et al., 2008), addiction (Bowen et al., 2014), alcoholism (Witkiewitz et al., 2005; Garland et al., 2010), anxiety (Grossman et al., 2004; Baer, 2006; Ludwig and Kabat-Zinn, 2008; Shen et al., 2014), MCI (Wells et al., 2013a), and ADHD (Zylowska et al., 2007; Smalley et al., 2009). Preliminary findings suggest the effects of meditation include increases in emotion regulation (Lutz et al., 2014), memory and cognition (Zeidan et al., 2010), self-regulation (Tang et al., 2014), awareness and self-perception (Hölzel et al., 2011b), as well as gray and white matter differences in experienced meditators (Luders et al., 2009; Hölzel et al., 2011a; Tang et al., 2012, 2015; Fox et al., 2014). Mindfulness-based stress reduction (MBSR) programs incorporate meditation techniques with group meetings, simple yoga, and home assignments (Teasdale et al., 2000; Kabat-Zinn, 2003). This approach allows for broad applications as these programs are standardized and have no religious associations, making them suitable for researchers and clinicians. Though the religious associations of traditional forms of meditative practice have been reduced through such westernized approaches, the number of variables in Mindfulness programs still confound evaluation of clinical efficacy (Chiesa and Serretti, 2009, 2011; Chiesa, 2010). Understanding the specific mechanisms of mindfulness that lead to multi-dimensional mental health outcomes is no trivial task. The reduction of mindfulness into measurable components has been suggested by many resulting in a number of different psychometric assessments (Brown, 2004; Grossman et al., 2004; Feldman et al., 2006; Lau et al., 2006; Baer et al., 2008). In addition to the identification of specific outcomes, meditation efficacy studies have also proven challenging due to variations in meditative practice, length of time practiced, lack of controls, and the inability to conduct double-blind studies – a fault inherent to all therapy efficacy studies. Recent studies using active controls for MBSR programs (MacCoon et al., 2012, 2014; Rosenkranz et al., 2013) have improved upon previous investigations which only used wait list control groups. These types of experimental improvements are necessary to distinguish the specific effects

TABLE 1 | Summary of functional magnetic resonance imaging (fMRI) findings on default mode network (DMN) modulation associated with meditation practices.

Meditation	References	DMN findings associated with meditation
Mindfulness	Farb et al. (2007)	Decreased fc between dmPFC and Insula, Decreased mPFC activity during task
FA	Brefczynski-Lewis et al. (2007)	Decreased DMN activations during distraction
LK	Lutz et al. (2008)	Increased activation in mPFC and PCC/precuneus during LK
LK	Engström and Söderfeldt (2010)	Increased activation in mPFC during LK
FA, OM	Manna et al. (2010)	DMN deactivation during FA Precuneus activation during OM
Brain wave Vibration	Jang et al. (2011)	Increased DMN rsfc to mPFC during rest Increased fc between PCC and dACC/dlPFC during rest, FA, OM, and LK
FA, OM, LK	Brewer et al. (2011)	Overall decrease in mPFC and PCC for FA, OM, and LK
FA	Hasenkamp et al. (2012)	Increase in mPFC and PCC during mind wandering
FA	Hasenkamp et al. (2012)	Increased fc between DMN hubs and orbitofrontalcortex/ventromedial PFC during FA
FA	Pagnoni (2012)	Decreased vPMC activity during FA Increased fc vPMC-right temporoparietal junction
FA, OM	Froeliger et al. (2012)	Increased fc DMN-DAN during meditation Increased fc across all networks during rest
Mindfulness	Taylor et al. (2013)	Decreased fc of mPFC to other DMN nodes during rest Increased fc between rIPL and PCC/PCU/dmPFC during rest
FA	Garrison et al. (2013)	PCC deactivations during FA
LK	Garrison et al. (2014)	Decreased PCC/PCU activation during LK Greater fc between PCC/PCU and left inferior frontal gyrus during LK
Acem Non-directive Concentrative	Xu et al. (2014)	Increased DMN activation during Acem non-directive meditation
FA, OM, LK vs. Task	Garrison et al. (2015)	Decreased DMN activity during meditation relative to task

rs, resting state; fc, functional connectivity; d, dorsal; dm, dorsal medial; dl, dorsal lateral; vPMC, ventral posteromedial cortex; DAN, dorsal attention network; rIPL, right inferior parietal lobe.

resulting from meditation training versus group therapy or other forms of general behavioral modification. These studies highlight the need for more controlled experimental design and specific biomarkers such as the DMN by which to follow the underlying neurological changes associated with meditation training.

As with all emerging fields, consensus building to bridge areas of specialization requires time and a sufficient amount of preliminary data. These issues are widely recognized, leading to the development of a more defined theoretical framework (Hölzel et al., 2011b) and improved operational definitions (Bishop et al., 2004; Shapiro et al., 2006). These improvements help to guide fMRI experiment design in order to provide objective, empirical evaluation of this previously elusive, highly internalized process.

Despite these improvements, variations in meditative methods persist as a barrier in the advancement of this line of research. A majority of the techniques used in experimental approaches are based in Buddhist traditions. Three of the fundamental practices central to nearly all Buddhist meditation have been generalized to include other traditions, and redefined by some researchers as focused attention (FA), open monitoring (OM), and loving kindness (LK), respectively (Lutz et al., 2004, 2008). These are well-developed techniques commonly encountered in research literature which will only briefly be described here, but whose histories, grounding philosophies, and complete descriptions are reviewed extensively by Lutz, Dunne, and Davidson (Lutz et al., 2007). While it is essential for general research purposes that FA, OM, and LK be investigated separately in terms of their DNM-associated neurocorrelates, we hypothesize that the synergy of all three practices is key to cultivating "equanimity" and is essential when considering meditation as a form of general therapy for mental disorders (Desbordes et al., 2014).

During FA, the participant sits calmly with all attention focused on some object of interest, commonly the breath. Each time the mind begins to wander, the meditator is trained to guide the focus of attention back with non-judgmental awareness. This practice is meant to develop the individual's meta-awareness, focus, and attention – skills required for all subsequent meditative practices. FA practice can be viewed as mental training to reduce the competitive distraction and daydreaming activities of the DMN. Hasenkamp et al. (2012) investigated the neurocorrelates of fluctuating FA phases in experienced meditators. Participants were asked to maintain FA on breath and instructed to press a button when they realized their attention had wandered. Activity could be detected in brain regions associated with FA, mind wandering, and awareness of mind wandering. DMN activations were correlated with periods of mind wandering, contrasting with attentional activations during awareness, shifting, and maintaining FA. A follow-up resting state study revealed that connectivity in attentional networks correlated with hours of meditative experience, indicating that the repeated process of refocusing the attention leads to increases in attentional control and reduced distractibility of the practitioner in everyday life (Hasenkamp and Barsalou, 2012). This study thus supports the

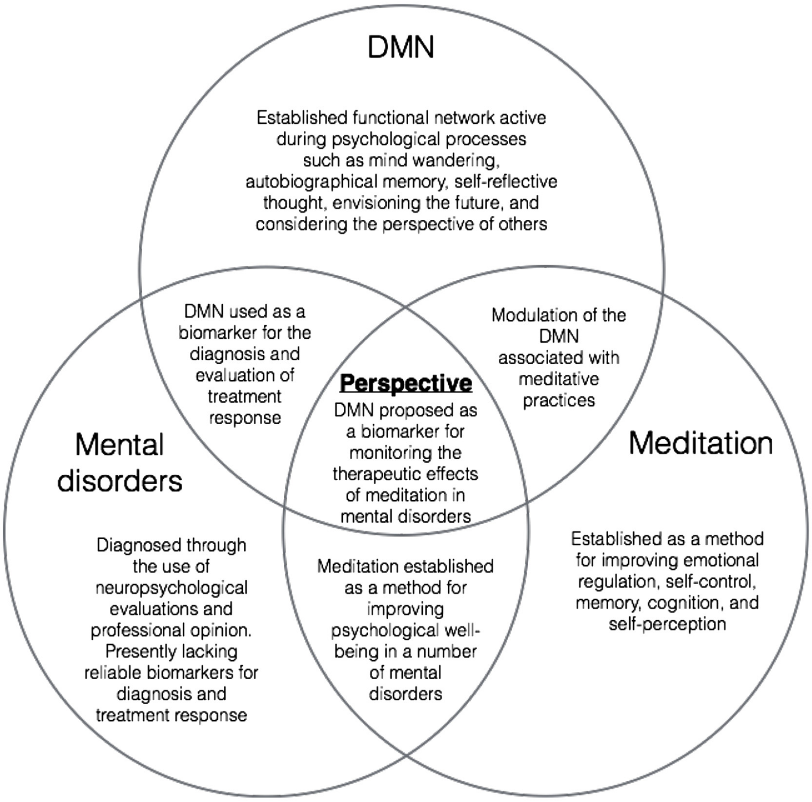

FIGURE 1 | A visual representation of overlapping areas of research converging on the present perspective.

use of FA as a form of training to reduce DMN/TPN competition. Work by Brefczynski-Lewis et al. (2007) supports this hypothesis of decreased distractibility with increased meditative practice. They found that while listening to distractive sounds, relative to novices, expert meditators had less activation in regions within the DMN and more activation in regions related to response inhibition and attention. These results support the hypothesis that the mental health benefits of FA meditation are a result of the cultivation of attentional control through trained disengagement of the DMN, reducing related mentation associated with rumination (Berman et al., 2010; Sheline et al., 2010a), mind wandering (Mason et al., 2007), and unhappiness (Killingsworth and Gilbert, 2010). The practice of FA lays a foundation for all subsequent techniques, as distractibility is detrimental to meditative practice.

The second common technique of mindfulness practice is OM, where the meditator directs their attention toward the non-judgmental awareness of internal and external physical sensations. The meditator's attention is expected to wander, yet the individual neither cultivates nor forcefully suppresses distracting thoughts. In OM, the meditator is instructed to non-judgmentally observe thoughts and sensations while remaining unreactive. This trains the individual to reduce emotional reactivity and volatility. The objective in OM is to develop insight into the subjective and constantly changing nature of reality while maintaining present awareness. For beginners, establishing oneself in OM meditation often begins with some form of FA. However, this requirement is thought to depend on hours of experience (Brewer et al., 2011). Manna et al. (2010) observed an increase in activation of the PCU, a hub of the DMN, during OM when compared to FA. This study, which investigated differences between OM and FA meditation, found that when compared to novices, expert practitioners' patterns of brain activity during OM resembled their normal resting state activity. They postulated that with extended practice, this state of non-judgmental awareness or "mindfulness" becomes the intrinsic or default mode of brain activity (Manna et al., 2010).

Although some amount of mind wandering during OM is accepted, identifying with, attaching to, or engaging in these thoughts is discouraged. We suggest that in this way, one develops an ability to be simultaneously present and aware of physical stimuli while engaging in DMN-associated creative processes such as reflection and mind wandering without emotional attachment or reactivity. Put another way, training to suppress the DMN through FA allows for the gradual and controlled reintroduction of DMN-related activities in OM with an enhanced metacognition, abrogating uncontrolled emotional reactivity and self-identification.

The third common element of most Buddhist meditation practices is LK, or LK, where the meditator focuses on feelings of LK and compassion toward others. During LK meditation, all forms of stimuli can be called upon, such as visualization, memory, self-reflection, and auditory mantras, in an effort to dissolve feelings of separation, isolation, and conflict between the meditator and others. This process utilizes skills developed in both FA and OM meditation. This element of Buddhist practice was not included in the proposed operational definition of mindfulness by Bishop et al. (2004). For treatment of psychological disorders however, there is a strong argument for the inclusion of this practice as the objective is to develop empathy and compassion for oneself and others (Hofmann et al., 2011; Farb et al., 2012; Shonin et al., 2014). A study by Garrison et al. (2014) showed that DMN connectivity was reduced during LK meditation, possibly as a result of reduced self-referential processing. Related findings investigating the neurocorrelates of empathy and forgiveness have observed DMN activations in the PCC/PCU (Farrow et al., 2001; Völlm et al., 2006). Engström and Söderfeldt (2010) found activations in the mPFC during LK meditation which others propose reflects processing which is important for experiencing empathy (Seitz et al., 2006). The basic link between the practice of empathy and the mental processes associated with the DMN – considering the perspective of others, autobiographical memory, and self-referential thought – seems self-evident. However, much work remains to define the specific changes in the DMN resulting from this form of meditative training.

Across all three types of meditation, Brewer et al. (2011) observed that two primary nodes of the DMN, the PCC and mPFC, were less active in experienced meditators compared to novices. Thus, for experienced meditators relative to novices, DMN processes such as mind wandering are reduced even before task engagement. In addition, they found increased functional connectivity in experienced meditators between the PCC and task-positive regions during all conditions including rest, indicating trait-based neural differences in long-term meditators. Like Manna et al. (2010) they suggest that long-term meditative practice may transform the individual's intrinsic resting state into a more "present-centered" meditative state (Brewer et al., 2011).

First Steps: Clinical Trials

Taken together, these studies provide evidence to support further investigation into the use of DMN metrics for the evaluation of meditative therapies (see **Figure 1**). Indeed, controlled studies correlating resting state DMN modulation with neuropsychological measures for the evaluation of Mindfulness therapies are emerging with promising results. Wells et al. (2013b) conducted a pilot study to investigate the effects of MBSR training on a group of mild cognitively impaired (MCI) patients at risk for AD. The results indicated that after MBSR training, MCI patients had increased DMN connectivity in the PCC, mPFC, and hippocampus, relative to controls. They also investigated changes in the volume of the hippocampus, a region known to atrophy in MCI/AD, and found trends toward less hippocampal atrophy in MBSR-trained patients relative to controls. As a result of these findings they suggest that DMN connectivity could be used as a non-invasive biomarker for assessing the impact of mindfulness interventions in MCI patients, though larger studies need to be conducted (Wells et al., 2013b).

Ives-Deliperi et al. (2013) conducted a controlled study investigating the effects of Mindfulness-based Cognitive Therapy (MBCT) in bipolar disorder. Previous to treatment, bipolar patients had significantly higher levels of stress and anxiety, lower scores on working memory tasks, and decreases in mPFC signals during task relative to healthy controls. After treatment, they observed BOLD increases in the mPFC and posterior parietal lobe during task, significant increases in mindfulness measures and working memory, as well as decreases in anxiety and emotional dysregulation. Region of interest analysis verified a correlation between mindfulness measures and mPFC increases in BOLD signals. This study provides additional support that the DMN represents a suitable network by which to assess the effects of meditative therapies in the treatment of mental disorders (Ives-Deliperi et al., 2013).

Future Perspectives

These recent findings demonstrate use of the DMN as a potentially useful clinical tool for evaluating the therapeutic effects of meditation. Research to establish disorder-specific DMN irregularities is a necessary first step. Determining DMN differences relative to healthy controls allows for an objective measure of patient recovery or return to control-like activity and connectivity within the DMN. Correlation with neuropsychological tools for measuring symptomatic changes and cognitive improvement will help to guide the development of this emerging tool and to define its significance. However, many experimental design issues still confound the evaluation of clinical efficacy (Tang et al., 2015). First, reducing the number of coinciding therapies in Mindfulness programs and having proper control groups is essential. Documenting explicit instructions for the meditation practice will also be important for comparative studies and meta-analysis. Future studies could also include analysis of the dynamic functional connectivity associated with mental disorders and treatment response. This may allow for further subgrouping under broad diagnoses and predictions concerning treatment outcomes. Although the DMN is the best studied of the resting state networks, the analysis of other networks should also be investigated (Froeliger et al., 2012). In addition, the development and incorporation of new neuropsychological metrics – such as "equanimity" outcomes – with resting state correlates will provide new tools for assessment (Desbordes et al., 2014). Finally, finding ways to integrate objective data and subjective patient reporting will be useful in understanding patient experiences associated with meditative practices (Garrison et al., 2013; Brewer and Garrison, 2014; Hasenkamp, 2014). It seems fitting that a method as internalized as meditation would be useful in treating conditions associated with neural processes so deeply intrinsic as to be called the "default mode" of brain function.

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REVIEW
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Calm and smart? A selective review of meditation effects on decision making

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Over the past two decades, there has been a growing interest in the use of meditation to improve cognitive performance, emotional balance, and well-being. As a consequence, research into the psychological effects and neural mechanisms of meditation has been accumulating. Whether and how meditation affects decision making is not yet clear. Here, we review evidence from behavioral and neuroimaging studies and summarize the effects of meditation on social and non-social economic decision making. Research suggests that meditation modulates brain activities associated with cognitive control, emotion regulation and empathy, and leads to improved non-social and social decision making. Accordingly, we propose an integrative model in which cognitive control, emotional regulation, and empathic concern mediate the effects of meditation on decision making. This model provides insights into the mechanisms by which meditation affects the decision making process. More evidence is needed to test our explanatory model and to explore the function of specific brain areas and their interactive effects on decision making during meditation training.

Keywords: meditation, decision making, empathy, prosocial behavior, neuroimaging

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> If we are to make peace in the world, we must first make peace in ourselves.
> —The Dalai Lama

There is a growing body of evidence suggesting that interventions including regular physical exercise (Scully et al., 1998; Hassmén et al., 2000), cognitive behavior therapy (Beck, 1993), and ancient contemplative practices (Rice, 2001; Astin et al., 2003; Hill et al., 2006) leads to a range of positive psychological outcomes such as improved cognitive performance, enhanced emotional regulation, and even plasticity-related alterations in the brain. In particular, one type of contemplative practice, meditation, has attracted wide attention from both psychologists and neuroscientists over the past two decades due to a growing appreciation for its ability to affect cognition, emotion, and decision making.

There are various definitions of meditation depending on what main interventions are emphasized. In general, meditation is defined as a broad variety of practices designed to cultivate emotional balance and psychological well-being, including relaxation, the observation of one's own inner or outer experiences, and the intentional self-regulation of attention (Lutz et al., 2008b; Slagter et al., 2011; Awasthi, 2012). There are many forms of meditation practice such as mindfulness meditation, concentrative meditation, transcendental meditation, Buddhist meditation, and others (Cahn and Polich, 2006; Travis and Shear, 2010). In the current review, for the most part we focus on the literature regarding mindfulness meditation, and sometimes also compassion meditation and loving-kindness meditation. Mindfulness meditation refers to a broad range of practices based on promoting a non-judgmental and non-reactive state of awareness that may improve one's ability to modify automatic behaviors in the long run (Kabat-Zinn, 2003). Compassion meditation focuses one's awareness mainly on alleviating the suffering of all other sentient beings, and the central point of loving-kindness meditation is a loving and kind concern for the well-being of oneself and others (Hofmann et al., 2011). Among all types of meditation, these three types are most common and most studied in research on meditation and human decision making (Chambers et al., 2008; Hofmann et al., 2011; Chiesa et al., 2013).

Evidence from behavioral studies has provided support for potential applications of meditation. In particular, a 3-month meditation retreat has been found to be associated with decreased variability in attentional processing of target tones, suggesting improved sustained attention (Lutz et al., 2009b). Also, in a 10-day program in mindfulness meditation, individuals showed decreased reaction time on an internal switching task and better performance in the Digit Span Backward subscale, suggesting a greater capacity for sustained attention, working memory, and executive function (Chambers et al., 2008). From other perspectives, researchers also found that compassion-focused meditation may increase happiness as well as decrease worry and emotional suppression (Jazaieri et al., 2014), and general meditation training may reduce emotional interference from unpleasant pictures (Ortner et al., 2007).

Notably, previous research mainly illustrates the impacts of meditation on basic emotions and cognitive functions such as attention, memory, and executive function. Beyond emotion and cognition, individuals also need to make decisions in situations involving complex social interactions (Sanfey, 2007). Decision making can be regarded as the thought processes during which a judgment or course of action is identified and selected from several alternative possibilities based on one's values and preferences (Rilling and Sanfey, 2011). The process of decision-making is often characterized by a competition between reflection and intuition. Based on existing literature (Fehr and Camerer, 2007; Sanfey, 2007; Rilling and Sanfey, 2011), we divide decision making into non-social and social categories. Non-social decision-making research focuses on individual decisions that are made purely based on one's own beliefs, values, and preferences, whereas research on social decision making focuses on interactive decisions that are made based on the concomitant choices and preferences of others (Fehr and Camerer, 2007; Sanfey, 2007; Rilling and Sanfey, 2011). It is not known, however, whether meditation-related experience can facilitate non-social and social decision making.

We postulate that the effects of meditation may not be limited to those aspects of cognition and emotion that are prerequisites of high-level decision making, but can also extend to decision-making processes. In particular, recent evidence has suggested that meditation may play a role in reducing economic decision biases, and enhancing the empathy, compassion, and altruism involved in social decisions (Birnie et al., 2010; Leiberg et al., 2011; Klimecki et al., 2012). Also, clinical evidence has demonstrated that meditation can be a useful tool to reduce substance abuse, alcohol addiction, and the craving to smoke (Breslin et al., 2002; Zgierska et al., 2009; Fernandez et al., 2010; Westbrook et al., 2013). These disorders are associated with impulsive behaviors (e.g., taking risks) and suboptimal decision making (Keng et al., 2011; Sedlmeier et al., 2012; Carim-Todd et al., 2013). The aforementioned behavioral findings have indicated a potential role of meditation on improving decision making in both social and non-social conditions.

As neuroimaging techniques advance, it becomes possible to study changes in the brain that occur long-term meditation. Several recent studies have provided evidence of meditation-dependent cortical plasticity, demonstrating that, compared to non-mediators, long-term meditators show long-lasting changes in the brain, such as increased cortical thickness in the prefrontal cortex and right anterior insula, greater gray matter concentration in the right insula, and increased gray matter density in the brain stem (Lazar et al., 2005; Hölzel et al., 2008; Vestergaard-Poulsen et al., 2009). Beyond brain variations, researchers also have observed increased neural activity during meditation in the dorsolateral prefrontal cortex (DLPFC), parietal cortex, hippocampus and para-hippocampus, temporal lobe, striatum, and anterior cingulate cortex (ACC) during meditation, suggesting a crucial role of meditation in cognitive control, memory processing, conflict monitoring, and reward processing (Lazar et al., 2000). Taken together, these findings have provided further neural evidence for meditation which may influence decision making via changes in the brain regions involved in reward processing, cognitive control, and emotion management.

Both behavioral and neuroimaging studies have provided new insights into the psychological function of meditation on decision making. However, no systematic review has yet integrated the evidence of these psychological effects and underlying mechanisms of meditation on decision making. In business, decision making is one of the central activities of management and is critically important for the implementation of ideas (Simon, 1987). For individuals, families and organizations making good decisions can lead to happiness (Hsee et al., 2008) and greater achievement (Shen et al., 2015). Ineffective decisions may lead to regret (Coricelli et al., 2007; Van Dijk and Zeelenberg, 2007), pain (Frantsve and Kerns, 2007) and even mental disorders (Goudriaan et al., 2005). Thus, it is of great significance to systematically review the potential effects of meditation on decision making and the neural mechanisms of these effects.

Here, we limit our review to published, peer-reviewed and empirical studies that assessed psychological outcomes of meditation on decision making. In particular, we focus on mindfulness, loving-kindness, and compassion meditation techniques, and review their influences on non-social economic and social decision making. The literature search was performed using the main keywords "mindfulness meditation," "loving-kindness meditation," "compassion meditation" from the electronic databases Google scholar, PubMed, Springer, ProQuest, PsycINFO, and Elsevier. We chose these databases because they include almost the whole literature related to mental health, medicine, psychology, and neuroscience. Next, we further restricted our keywords to "decision making," "decisions," or specific topics such as "decision bias," "gambling," "prosocial," or "altruism." Beyond articles from the main database, we also carefully identified citations from the chosen articles. Our review was restricted to English-language journal articles over the past two decades (1995–2015). There were 55 studies that met our criteria when searching with these keywords. Of these, we included only original research with a control group and a specific technique of meditation. Case studies, correlation studies, original research without control group, and any reviews or abstracts were excluded. In total, 13 studies were included in this review. We aim to (1) summarize the psychological effects of meditation on social and non-social decision making based on selected literature, (2) discuss the psychological and neural mechanisms of meditation with regard to how they impact the decision process, and (3) address major challenges encountered and directions for future studies. We hope that our review will provide some novel ideas for future research on the application of meditation to improve personal judgments, decision making, organizational behavior, and management.

The Effects of Meditation on Non-Social Economic Decision Making

In the domain of non-social decision making, most researchers have utilized paradigms developed in game theory and behavioral economics to investigate economic preferences and decision biases in both personal and interactive situations (e.g., reward anticipation, risk taking, compulsive gambling, decision biases; Lakey et al., 2007a; Kiken and Shook, 2011; Kirk et al., 2011; Leiberg et al., 2011; Hafenbrack et al., 2014). One prominent dual-process theory has been proposed by Kahneman and Frederick (2002) to explain personal judgments and decision bias. They argued that mental processes are divided into two distinct categories based on whether they operate automatically or in a controlled, intentional fashion. Generally, decision biases are induced by instantiating controlling difficulties or emotional interference. Here, we review studies investigating the influence of mindfulness meditation on non-social decision-making processes including risk taking, impulsive gambling, negativity bias, and sunk cost bias (see **Table 1**).

In general, risk-taking refers to a tendency to engage in behaviors that can be harmful or dangerous, but which meanwhile create an opportunity for positive outcomes. In particular of the economic domain, risk-taking is defined as a disposition to gamble after loss, increased preoccupation with gambling, enhanced necessity to take risks, and more restlessness when losing money (Winters et al., 2002). Such decision-making deficits are generally reflected in gambling tasks like the Georgia Gambling Task (GGT), which measures overconfidence and willingness to take risks (Goodie, 2003), and the Iowa Gambling Task (IGT) which assesses risk preference in relation to uncertainty, reward, and penalties (Bechara et al., 1994; Lakey et al., 2007b). Using both the GGT and the IGT with a large sample of college students ($N = 309$), Lakey et al. (2007a) explored the influence of trait mindfulness on risk-taking behavior. They found that increased dispositional mindfulness predicted a reduced severity of gambling outcomes and increased adaptability of decision making. Alfonso et al. (2011) first investigated the effects of meditation on risk taking among 18 abstinent polysubstance abusers (who were considered to have clinically significant deficit in executive function and decision making). These authors also found a significant beneficial effect of mindfulness meditation on response inhibition and risky decision making, suggesting a potential role of meditation for improving impulsive gambling inhibition, decision-making dysfunction, and addiction treatment.

People are highly susceptible to judgment and decision biases (Weng et al., 2013). Negativity bias is the tendency to weigh negative information, events, or emotions more heavily than the positive (Rozin and Royzman, 2001). This bias may be related to threating signals or habitual responses (Rozin and Royzman, 2001; Kiken and Shook, 2011). Using a 15-min instructional mindfulness breathing exercise, one study among 175 college students demonstrated that meditation can decrease negativity bias ($\eta_p^2 = 0.023$) and increase positive judgments in an attitude formation task (Kiken and Shook, 2011). Another study of 102 undergraduate students revealed that a standardized 10-min instruction in a mindful breathing meditation can weaken thoughts that emphasize negativity ($\eta_p^2 = 0.86$) (Kiken and Shook, 2014). The findings suggest that meditation interventions can significantly reduce negativity by precluding habitual reactions toward negative ratings or stimuli.

Sunk cost bias, also known as the sunk cost fallacy, is a tendency to continue to pursue a failing endeavor once an investment in money, effort, or time has been made (Maréchal, 2010). People often report falling victim to the sunk cost bias, even though they know that continuing is not the best choice. This bias may be related to the escalation of commitment, entrapment, anticipated regret, and loss aversion (Brockner et al., 1986; Brockner, 1992; Tversky and Kahneman, 1992; Wong and Kwong, 2007). Recently, Hafenbrack et al. (2014) investigated the short-term effects of mindfulness meditation on sunk cost biases and found that mindfulness meditation can modulate one's temporal focus away from the future and past, and reduce negative affect, thereby decreasing the strength of the sunk cost bias ($\varphi = 0.35$).

From the above findings, we conclude that meditation-related experience can reduce impulsivity, pathological gambling, and decision biases in non-social decision making. These effects indicate a modulating role of meditation during decision making by controlling risky responses, precluding habitual actions, regulating temporal focus, and reducing negative emotions.

The Effects of Meditation on Social Decision Making

The behavioral studies mentioned above mainly addressed irrational decisions or decision biases in non-social situations.

TABLE 1 | Summary of studies of meditation on decision making.

Psychological effects	Reference	Interventions	Samples	Psychological tasks and main scales	Design	Main findings (compared to matched controls) and effect sizes
Studies of meditation on non-social economic decision making						
Risk taking decisions	Lakey et al. (2007a)	Meditation & control (study 2): distinguished by dispositional state test (MAAS); without specific meditation manipulations	Mindfulness & Control (study2): n = 309 (age: 19.23 ± 1.31 years)	(1) Georgia gambling task; (2) Iowa gambling task; (3) DIGS, DSM-IV, MAAS,SCS	CT	(1) Reduced severity of gambling problems; (2) Increased adaptability of decision making
Impulsive gambling	Alfonso et al. (2011)	Mindfulness: 7-week mindfulness training (14 sessions, 60 min long, twice weekly, on two different days); Control: standard community treatment	Mindfulness: $n = 18$ Control: $n = 16$	Iowa gambling task	Pre-post design; CT	(1) Improved performance on decision-making; (2) Reduced decision-making deficits in polysubstance abusers
Negativity bias	Kiken and Shook (2011)	Mindfulness: 15-min instructional mindful breathing; Control: instructional unfocused attention or mind wandering	Mindfulness and Control: $n = 175$ (age: 19.6 ± 2.4 years)	(1) Bean Fest paradigm; (2) PANAS, FES, MAAS	RCT	(1) Reduced negativity bias; (2) Increased positive affect Effect size: $\eta_p^2 = 0.023$
Sunk-cost bias	Hafenbrack et al. (2014)	Mindfulness (study 2a): 15-min focused-breathing meditation exercise; Control: mind-wandering induction to think of whatever came to mind	Mindfulness and Control (study2a): $n = 57$ (age: 19.40 ± 1.10 years)	(1) Sunk-cost decision task; (2) PANAS, MAAS, DMCI, SES	RCT	(1) Decreased negative affect; (2) Decreased sunk-cost bias Effect size: $\varphi = 0.35$
Negativity bias	Kiken and Shook (2014)	All participants listened to a standardized 10-min audio recording (study 2). Mindfulness: received instruction in a mindful breathing meditation; Control: received instruction to let their minds wander freely	Mindfulness and Control (study 2): $n = 102$ (age: 21.00 ± 3.73 years)	(1) Thought valence: a common thought listing procedure; (2) MAAS	RCT	(1) Mindfulness is associated with less negatively weighted thoughts, but is not directly related to positively weighted thoughts. (2) Attenuate thoughts that emphasize negativity but not those that emphasize positivity. Effect size: $\eta_p^2 = 0.86$
Studies of meditation on social decision making						
Fairness	Kirk et al. (2011)	Meditators: meditation experience (9.5 ± 7.8 years); Control: non-meditators	Meditators: $n = 26$ (age: 40.4 ± 10.4 years) Control: $n = 40$ (age: 36.8 ± 10.1 years)	(1) Ultimate game (2) MAAS, KIMS	CT fMRI scan	(1) Meditators accept more unfair offers than controls; (2) Different network of brain when assessing unfairness in anterior/posterior insula, DLPFC, ACC, and thalamus
Fairness	McCall et al. (2014)	Meditation: full-time meditation retreat for at least 3 years; Control: no relative practice	Meditation: $n = 18$ (age: 54.3 ± 5.8 years) Control: $n = 15$ (age: 54.3 ± 5.8 years)	(1) A dictator game with second party punishment (2PP), third-party punishment (3PP), and third party punishment and recompense (3PR). (2) Emotional questionnaire (3) Fairness questionnaire	CT	(1) Less anger and punishment in response to unfairness; (2) More compensation of victims in response to fairness violations

(Continued)

TABLE 1 | Continued

Psychological effects	Reference	Interventions	Samples	Psychological tasks and main scales	Design	Main findings (compared to matched controls) and effect sizes
Altruism	Weng et al. (2013)	Compassion: 30 min compassion training per day for 2 weeks; Control: matched reappraisal training	Compassion: $n = 20$ (age: 21.9 years) Control: $n = 21$ (age: 22.5 years)	Redistribution game	CT fMRI Behavior	(1) Increased altruistic redistribution of funds to a victim; Effect size: $d = 0.65$ (2) Altered activation in brain regions including the IPC and DLPFC
Prosocial behavior	Reb et al. (2010)	Loving-kindness: review a loving-kindness meditation audio clip lasts 8 min; Control: review a neutral audio clip lasts 8 min	Loving-kindness and Control: $n = 49$	(1) Dictator game; (2) Positive feelings on a 5-point likert scale	RCT Behavior	(1) More distribution of money to the counterpart; Effect size: $\eta_p^2 = 0.08$ (2) Positive feelings toward the counterpart Effect size: $\eta_p^2 = 0.17$
Prosocial behavior	Leiberg et al. (2011)	Compassion: a 1-day training lasts 6-h; Memory control: a 1-day training last 1-hour	Compassion: $n = 27$ (age: 24.74 ± 4.22 years) Control: $n = 32$ (age: 22.66 ± 3.8 years)	(1) Zurich prosocial game; (2) Sociodemographic questions online; (3) TAS,BDI, CLS	RCT	(1) Enhanced prosocial behavior; Effect size: $\eta_p^2 = 0.21$ (2) Increased positive mood and compassionate feelings and decreased negative mood Effect size: $\eta_p^2 = 0.30$
Prosocial behavior	Condon et al. (2013)	Meditation: 8-week study on meditation; Control: no intervention	Meditation and control: $n = 39$ (age: 25.23 ± 4.66 years)	Cognitive ability test on suffering	RCT	Increased altruistic behavior Effect size: $\varphi = 0.36$
Intergroup bias	Kang et al. (2014)	Loving-kindness: an hour practice per week for 6 weeks; 40 min discussion per week for 6 weeks; Waitlist control: have no any contact with the instructor or course materials until the posttest	Lovingkindness and control: $n = 101$ (age: 25.20 ± 5.20 years)	(1) Implicit association test (IAT) (2) MSTI, PSS	RCT	Decreased implicit bias toward blacks and homeless people with loving-kindness practice
Intergroup bias	Lueke and Gibson (2014)	Mindfulness: a 10-min mindfulness recording; Control: a control recording	Mindfulness and control: $n = 72$ (age:18∼23 years)	(1) IAT; (2) MRWP, MAAS	RCT	(1) Less implicit racial bias; Effect size: $\eta_p^2 = 0.06$ (2) Less implicit age bias; Effect size: $\eta_p^2 = 0.06$

ACC, Anterior Cingulate Cortex; BDI, Beck Depression Inventory; CLS, Compassionate Love Scale; CT, Controlled trial; DLPFC: Dorsolateral Prefrontal Cortex; DMCI: Decision-Making Competence Inventory; DIGS: Diagnostic Interview for Gambling Severity; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FES: Future Events Scale; IPC: Inferior Parietal Cortex; KIMS: Kentucky Inventory of Mindfulness Skills; MAAS: Mindful Attention Awareness Scale; MRWP: Motivation to Respond without Prejudice Scale; MSTI: multi-source interference task; PANAS: Positive Affect and Negative Affect Scales; PSS: perceived stress scale; RCT: Randomized controlled trial; SCS: Self Control Scale; SES: Self-esteem Scale; TAS: Toronto Alexithymia Scale.

Whether or not meditation can influence social decision making remains unclear. Here, we describe several of the most relevant studies on this topic, in which mindfulness meditation, loving-kindness meditation, and compassion meditation have been examined in terms of their effects on social decisions, such as assessments of fairness, altruism, prosocial responses, and prosocial behavior.

Assessing the fairness of a social interaction is an important aspect of prosocial behavior. Sensitivity to fairness is generally studied using the ultimatum game. In this game, two people, a proposer and a responder, are involved. The responder decides whether or not to accept or reject offers from the proposer to split a pot of money (either evenly or unevenly). If the responder accepts, both players gain accordingly. If the responder rejects the offer, neither person is paid (Crockett et al., 2010). Using an ultimatum game, it has been found that individuals who meditate are more willing to accept unfair offers compared to non-meditators. At the neural level, control participants exhibit greater activation in the anterior insula during unfair offers. Meditators display attenuated activity of the anterior insula for high-level emotional representations and increased activity of the posterior insula for low-level internal representations. This suggests that a different network of brain regions is involved among meditators to untangle negative emotional reactions (Kirk et al., 2011). Researchers also found that loving kindness meditation practitioners show less anger, less punishment, and more compensation of victims in response to fairness violations compared to controls, and this may result from the enhanced kindness to victims and cultivation of altruism with compassion meditation (McCall et al., 2014). Based on these studies, we suggest that meditation experience can help to regulate negative emotions or cultivate compassion during social decision making, leading to the acceptance of more unfair offers.

Altruism represents a motivational state to benefit others (Schwartz, 1977). Using 8-min loving-kindness meditation training, researchers have explored the effect of meditation on altruistic behavior in a dictator game. In these games, one person (the "dictator") can unilaterally allocate any part of a given resource to others without worrying about reprisal. In one study, participants typically show empathic concern and prosocial orientation toward their counterparts ($\eta_p^2 = 0.08$), and these feelings were fully mediated by positive feelings toward others ($\eta_p^2 = 0.17$; Reb et al., 2010). Meditation experience was shown to promote more altruistic behavior (giving more of the resource to the counterpart), which is mainly modulated by the positive emotions generated during the training.

Using a redistribution task combined with neuroimaging techniques, Weng et al. (2013) investigated the neural mechanisms underlying the effects of short-term compassion meditation on altruistic behavior. During this task, participants observed a virtual circumstance in which a victim received unfair treatment. Participants could then choose to spend any amount of their own money to redistribute funds to the victim. Compared to the control group, compassion meditators were found to give more of their funds to victims ($\eta_p^2 = 0.65$), and this behavior was associated with altered activation in brain regions associated with social cognition and emotion regulation, including the inferior parietal cortex, DLPFC, and its connectivity with the nucleus accumbens. Such studies suggest that greater altruistic behavior may be elicited by increasing engagement of the neural systems associated with understanding the suffering of others, executive control, and reward processing.

In line with this, recent research has also investigated the effects of meditation on more general prosocial behavior, which covers a wide range of actions that benefit others, such as cooperation, helping, and sharing (Batson and Powell, 2003). In one study, Leiberg et al. (2011) instructed participants to navigate a virtual character through a maze to reach a treasure in a limited amount of time. This task limited the influence of reciprocity, cost, and distress, but allowed for the repeated assessment of prosocial behavior. Results demonstrated that subjects with compassion meditation training compared to those who received memory skills training showed more prosocial behavior ($\eta_p^2 = 0.21$). Additionally, the effectiveness of compassion training was further promoted by increasing positive mood and compassionate feelings and by decreasing negative mood ($\eta_p^2 = 0.30$). From such studies, we can conclude that even short-term compassion training can have a positive impact on prosocial behavior toward strangers, which relies on emotion regulation. These findings suggest one pathway by which meditation may promote prosocial behavior.

Beyond these laboratory studies, a recent study used more ecologically valid methods to investigate the effect of meditation on empathy with real-time interpersonal interactions (Condon et al., 2013). Prosocial responses were measured by whether a participant offered his or her seat to an individual with a physical disability. Results revealed that participants who had taken an 8-week course on meditation were more likely to offer up their seats than those on a waiting-list control group ($\varphi = 0.36$), indicating increased altruistic behavior in a real-life situation following a meditation intervention.

Furthermore, researchers have also explored the impact of mediation on implicit and explicit biases. Using an Implicit Association Test (IAT), Kang et al. (2014) found a significant decrease of implicit biases toward Blacks and homeless people with a 6-week loving-kindness practice. They suggested that loving-kindness meditation can automatically activate implicit attitudes toward different stigmatized social groups via the increase of cognitive control and decrease of psychological stress. Another study demonstrated a significant decrease of age and racial biases (both effect size: $\eta_p^2 = 0.06$) among participants who listened to a 10-min mindfulness recording relative to those who listened to a natural history. They suggested that the significant reduction of implicit biases was induced by automatic associations between mindfulness and biases (Lueke and Gibson, 2014).

In summary, the studies presented above suggest a consistent positive effect of both short- and long-term meditation on altruism, prosocial behavior, moral decision making, and intergroup bias. Meditation may facilitate such decision making by modulating executive control, reward processing, emotion regulation, and/or empathic concern involved in the decision process.

The Mechanisms of Meditation and Their Effects on Decision Making

Overall, the research presented above suggests that meditation interventions can promote good decision making, reduce decision bias, and improve altruistic and prosocial behaviors. Next, we introduce one unifying theoretical framework for the effects of meditation on decision making (see **Figure 1**). Our proposed model is based on dual-process theory, in which automatic (or intuitive) and deliberate (or reflective) processes are considered to be two separate components of decision making. This theory is widely accepted by researchers to explain decision-making processes and the relationship between cognition, emotion, and decision making. Here, we extend the dual-process model to explain the effects of meditation on non-social economic and social behaviors and the mechanisms of those effects. We additionally consider the mediating role of empathy in social decision making based on the two studies discussed above (Leiberg et al., 2011; Weng et al., 2013).

Cognitive Control Promotes Reflective Judgments

Conceptually, meditation places an emphasis on observing particular aspects of inner or outer experience, intentional self-regulation of attention, and the promotion of non-judgmental and non-reactive awareness. This collection of processes is similar to cognitive control, which has been defined as the selection of goal-relevant information, performance monitoring, and the storage and manipulation of information in working memory, from which individuals can flexibly adapt their behavior to pursue an internal goal (Slagter et al., 2011). Behavioral evidence suggests that meditation-related interventions can increase sensitivity to sensations, thoughts, and feelings, and lead to more sustained attention (MacLean et al., 2010), cognitive flexibility (Moore and Malinowski, 2009), and working memory (van Vugt and Jha, 2011). Meditation can also decrease rumination (Ramel et al., 2004), negative automatic thinking (Frewen et al., 2008), and habitual responding (Wenk-Sormaz, 2005). Thus, with short- or long-term meditation interventions, individuals can improve their cognitive control capabilities (Chambers et al., 2008). Thus, we propose that meditation can help decision-makers to reach conclusions with a more reflective consideration of their values and objectives, allowing them to better differentiate between relevant and irrelevant information, maintain goal awareness, and reduce irrational behaviors. In addition, with enhanced cognitive control and reflective thinking, people who meditate may be able to reduce some habitual tendencies such as engaging in risky decisions, obsessing about past or future considerations, and reacting automatically in a negative or undue manner. Thus, we propose that meditation can improve decision-making abilities with enhanced self-monitoring and cognitive control.

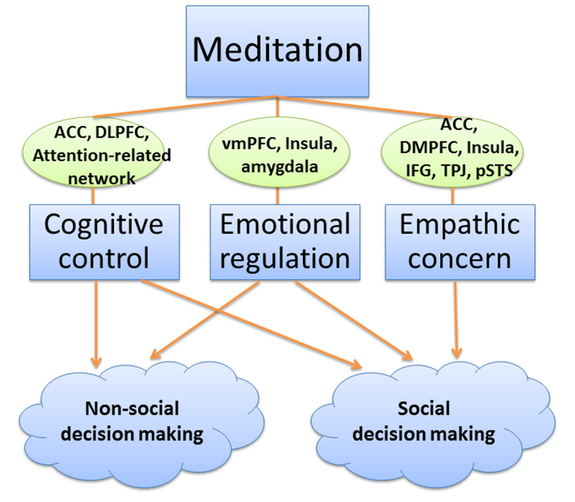

FIGURE 1 | A model for the effects of meditation on decision making. Meditation modulates brain activities associated with cognitive control, emotion regulation and empathy, and lead to improved non-social and social decision making. Our proposed model is a combination of existed behavioral and neuroimaging findings, theoretical guidance of dual-process theory, as well as proper speculations on the underlying mechanisms. Both the specific neural findings and the modulation effects of cognitive control, emotional regulation, and empathic concern between meditation and decision making are supported by extant research literature. However, more evidence is needed to explore the function of specific brain areas and their interaction effects on decision making during meditation training. ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; dmPFC: dorsomedial prefrontal cortex; IFG: inferior frontal gyrus; pSTS: posterior superior temporal sulcus; TPJ: temporo-parietal junction; vmPFC: ventromedial prefrontal cortex.

Recent neuroimaging studies have provided new insights into the potential neural mechanisms by which meditation affects decision making. Specifically, these studies have suggested positive effects of meditation on attention, memory, response inhibition, self-regulation, and reward processing. In particular, Brefczynski-Lewis et al. (2007) found that the association between meditation and activation in the neural networks involved in sustained attention could be represented by an inverted U-shaped curve. Similarly, other researchers have demonstrated that expert meditators exhibit reduced brain activation in regions related to discursive thoughts and emotions (mainly in ventral attention network regions), and greater activation in regions related to response inhibition and attention (mainly prefrontal regions, basal ganglia, and sub-thalamic nuclei), suggesting that meditation practice can modify and enhance the mechanisms underlying cognitive control over automatic behaviors (also known as top–down neural activity) (Corbetta and Shulman, 2002; Ochsner et al., 2002; Aron and Poldrack, 2006; Carim-Todd et al., 2013). Moreover, Lazar et al. (2000) identified several functional brain regions that are active during meditation, such as the DLPFC, parietal cortex, temporal lobe, hippocampus and parahippocampus, striatum, and pregenual ACC. These areas are related to attention, memory, reward processing, and arousal/autonomic control. Xue et al. (2011) have also shown that even short-term meditation interventions can increase the network efficiency of the ACC, which is crucial for conflict monitoring and performance adjustment. Overall, these findings on the effects of meditation on cognitive processing on the neural level support the notion that meditation may improve several aspects of decision making. In summary, both behavioral and neural evidence of cognitive processing provide evidence that meditation affects decision making. We propose that meditation can enhance reflective decision making by improving cognitive control over habitual reactions and intuitive processing.

Emotion Regulation Reduces Intuitive Decisions

In addition to cognitive control, meditation can also affect emotion regulation, which can play a crucial role in decision making, especially in the social domain. Emotion regulation refers to a variety of strategies applied at different points during the generation of emotional responses that influence what, when, and how emotions arise, persist, and are experienced and expressed (Gross and Thompson, 2007). Notably, during meditation there is a particular awareness and non-judgmental acceptance of the present, which may enhance one's sensitivity to affective cues and lead to more timely emotion regulation, reactions, and hyper-vigilance (Block-Lerner et al., 2007). In such a way, meditation may modify decision making by promoting proper emotion regulation. In other words, we propose that meditation interventions may lead to better decisions by promoting better emotion regulation.

Evidence from behavioral and neuroimaging studies provide some support for the effects of meditation on decision making via emotion regulation. At the behavioral level, well-established research by Kiken and Shook (2011) has indicated that even short-term meditation interventions can reduce negativity bias and increase positive judgments. These effects, however, are mainly modulated by attention reallocation, the suppression of intuition, and executive control (Slagter et al., 2007; Kozasa et al., 2012). Research on structural brain changes associated with mindfulness have demonstrated a positive association between trait mindfulness and gray matter volume in the right anterior insula and the right amygdala, regions related to emotional/bodily states and intuitive responses. Taken together, these studies suggest that meditation may enhance decision making through the regulation of negative/positive emotions, thereby improving cognitive control over intuitive decisions.

Empathic Concern Facilitates Social Decisions

Empathy has been associated with increased helping and social support (Coke et al., 1978). In addition to the modulating effects of cognitive control and emotion regulation on decision making, we also found a crucial role of empathy in enhancing prosocial behavior during meditation training. Conceptually, meditation interventions, and compassion meditation and loving-kindness meditation in particular, involve training in understanding the feelings of others and a focus on alleviating their suffering. Empathy also elicits other-oriented emotions depending on the perceived well-being of others (Batson et al., 2011). Behaviorally, a number of social and developmental studies have demonstrated that short-term inductions of empathic concern can motivate prosocial behavior (Batson et al., 2007). Thus, it is possible that compassion or loving-kindness meditation can improve social decisions by promoting empathy and a better understanding of others.

Evidence from neuroimaging studies provides support for the effect of meditation on pro-social decisions through increased empathy. Mascaro et al. (2013) demonstrated that an 8-week compassion intervention improved empathic accuracy which is positively correlated with neural activity in the inferior frontal gyrus and dorsomedial prefrontal cortex. Structural neuroimaging studies have demonstrated that loving-kindness and compassion meditation altered the activation of circuits previously linked to empathy (insula and ACC) and theory of mind in response to emotional stimuli (amygdala, right temporo-parietal junction, and right posterior superior temporal sulcus) (Lutz et al., 2008a). These studies provided indirect evidence of the mediating role of empathy. Using a redistribution task combined with functional magnetic resonance imaging (fMRI) techniques, Weng et al. (2013) found that empathy-related brain networks are involved in the effects of meditation on prosocial decisions, suggesting a facilitating role of empathy on social decision making after meditation interventions. The psychological effects of meditation may depend not only basic cognitive processing and emotion regulation, but also on more advanced social capabilities, such as empathy.

Conclusions Regarding the Mechanisms of Meditation

Based on these previous studies, we propose one explanatory model for the effects of meditation on decision making that includes aspects of cognitive control, emotion regulation, and empathy. We have explored some of the neural mechanisms potentially underlying this model. We posit that the beneficial effects of meditation on decision making may be modulated by cognitive control, emotion regulation, and empathic concern, which are three important contributors to more rational decisions and prosocial behaviors. It should be noted that, in the current review, our model is mainly based on the extant relevant empirical studies. It is possible that additional mechanisms may be involved but have yet to be identified.

Limitations and Future Directions

Several important limitations in our review are worth mentioning. First, the current review focuses on three most studied types of meditation and their influence on decision making, but there many other forms of meditation, including concentrative meditation, transcendental meditation, Buddhist meditation and others. It remains unknown whether the different types of meditation result in similar effects and changes to decision making. Future studies may compare different forms of meditation in terms of their impact. Second, although we describe three distinct processes that may potentially underlie the effects of meditation, little direct evidence for the causal role of cognitive control, emotion regulation, and/or empathy has been provided. Using fMRI, future studies can further examine how meditation modulates activity in brain regions associated with cognitive control and emotion regulation in decision-making tasks. Additionally, in future research, other techniques like transcranial direct-current stimulation and transcranial magnetic stimulation may help to explore the function of specific brain areas on decision making during meditation training. Recent studies have shown that meditation experience modulates resting-state brain activity or functional connectivity in the default mode network, ACC, insula, and attention-related networks (Brefczynski-Lewis et al., 2007; Lutz et al., 2009a; Brewer et al., 2011; Xue et al., 2011). Research also shows that stimulating DLPFC can induce similar changes (Newberg et al., 2001). Third, we only briefly mentioned the separate influence of cognitive control, emotion regulation, and empathy on decision making following meditation interventions; however, some interaction effects may also exist. Thus, we suggest our model should be interpreted with caution and used as a guide for further studies to investigate such interactions. Finally, it is worth mentioning that there are only a small number of studies ($n = 13$) on the effects of meditation on decision making. More research is needed to better our understanding of how meditation shapes social decision making.

Conclusion

In this review, we have integrated findings on the effects of meditation on decision making, empathy, and prosocial behavior. This line of research has produced to promising data suggesting that meditation interventions may be effective in promoting good decision making and increasing prosocial behavior. However, an equally important direction for future research is to investigate the neural mechanisms underlying meditation interventions. In the present paper, we propose one explanatory model that accounts for the effects of meditation on decision making by way of changes to cognitive control, emotion regulation, and empathetic concern. This model has important implications for additional research and continues to shed light on the potential mechanisms underlying the effect of meditation on decision-making processes. More evidence is needed to test our explanatory model and explore the function of specific brain areas on decision making during meditation training. Finally, we address some limitations of the current review and indicate several future directions. This review provides a useful conceptual model of the significance of meditation for decision making in both social and non-social domains.

Author Contributions

SS, ZY, and JW wrote the first draft of the paper. SS, ZY, and RY edited drafts and contributed intellectually to the paper. All authors read and approved the final manuscript.

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The neural mediators of kindness-based meditation: a theoretical model

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Although kindness-based contemplative practices are increasingly employed by clinicians and cognitive researchers to enhance prosocial emotions, social cognitive skills, and well-being, and as a tool to understand the basic workings of the social mind, we lack a coherent theoretical model with which to test the mechanisms by which kindness-based meditation may alter the brain and body. Here, we link contemplative accounts of compassion and loving-kindness practices with research from social cognitive neuroscience and social psychology to generate predictions about how diverse practices may alter brain structure and function and related aspects of social cognition. Contingent on the nuances of the practice, kindness-based meditation may enhance the neural systems related to faster and more basic perceptual or motor simulation processes, simulation of another's affective body state, slower and higher-level perspective-taking, modulatory processes such as emotion regulation and self/other discrimination, and combinations thereof. This theoretical model will be discussed alongside best practices for testing such a model and potential implications and applications of future work.

Keywords: empathy, compassion, meditation, compassion meditation, loving-kindness meditation, oxytocin, simulation, mentalizing

INTRODUCTION

Over the last 25 years, research on meditation has advanced in domains both clinical and basic, motivated by an often implicit conviction that mindfulness and attention practices are effective interventions for remediating psychopathology and augmenting well-being and resilience, and may be used as tools to help scientists understand the human brain, body, and brain–body connections. More recently, researchers have turned their attention to kindness-based practices, frequently in search of answers to the dual questions of, "Can kindness be trained?" and "Are kindness-based practices good for us?" Increasingly, the answer to both of these questions appears to be yes.

There is a growing body of research on the effects and efficacy of kindness-based contemplative practices including compassion (CM) and loving-kindness (LKM) meditation [reviewed in Hofmann et al. (2011) and Galante et al. (2014)], a handful of which are studies exploring their effects on neural structure and function (Lutz et al., 2008a; Desbordes et al., 2012; Klimecki et al., 2013b,c; Mascaro et al., 2013b; Weng et al., 2013; Garrison et al., 2014). However, this sub-field remains in its infancy, and missing from this research are coherent theoretical models with which to test the mechanisms by which these meditation practices may alter the brain and body. We believe such models have dramatically increased the rigor of mindfulness research (Shapiro et al., 2006; Hölzel et al., 2011; Vago and Silbersweig, 2012), and what follows is meant as a first contribution toward building such a dialog for scaffolding future research on compassion and loving-kindness meditation.

A crucial starting place for such a model of the impact of CM and LKM on social cognition and neurobiology is with clear definitions and descriptions of both the contemplative practices in our focus and the social cognitive skills and traits in question, (for discussions of the importance of accurate construct definition, see Lutz et al., 2008b; Batson, 2009). In his review of historical trends surrounding the study of empathy, Davis (1996, p. 11) observed that "the study of empathy, as much as any topic in psychology, has been marked by a failure to agree on the nature of and relations among its core constructs." As a result of ongoing vacillations in the importance assigned to either cognitive or affective factors by researchers in the field, the confusion noted by Davis has diminished only slightly since the time of his writing (Batson, 2009; see **Table 1** for the relationship between terms used here and related terms). While not in complete agreement, social cognitive neuroscientists and social psychologists generally converge on a definition of *empathy* as an affective response that arises from the comprehension of another's emotional state and that is similar to what the other person is feeling (Eisenberg et al., 1991; de Vignemont and Singer, 2006). More recently, social cognitive neuroscientists have turned their attention to the related but arguably distinct construct, *compassion*, usually defined as the deep wish that another be free from suffering, coupled with the motivation to alleviate such suffering (Kim et al., 2009; Klimecki et al., 2013b). It is generally agreed that empathy and/or compassion can lead to

Table 1 | Associations between terms used here and related terms used in social cognitive neuroscience and social psychology (Preston and De Waal, 2002; Keysers and Gazzola, 2007; De Waal, 2008; Singer and Lamm, 2009; Preston and Hofelich, 2012; Zaki and Ochsner, 2012).

Current terms	Related terms
Perceptual/motor	Mirror simulation
Affective	Simulation
	Resonance
	Emotional contagion
Cognitive	Perspective-taking
	Theory of mind
	Mentalizing
Compassion	Sympathy
	Prosocial concern
	Empathic concern
Prosocial behavior	Altruism
	Empathic motivation

prosocial behavior or *altruism*, helping behavior directed at another in need or distress (De Waal, 2008).

In what follows, we will start with a brief treatment of traditional contemplative accounts of empathy and compassion found in Buddhist traditions, as well as a description of the primary meditation practices currently undergoing scientific scrutiny. Next, we will outline a theoretical model arising from current research in social psychology and social cognitive neuroscience, which proposes core neural components of empathy, compassion, and prosocial behavior, coupled with testable hypotheses regarding how compassion practices may alter these components. Finally, we will situate existing neurobiological studies within this testable model and end with a discussion of best practices for investigating the mechanisms of compassion and for targeting populations that may benefit from compassion and loving-kindness meditation.

CONTEMPLATIVE ACCOUNTS AND PRACTICES

With a relative torrent of recent research on the neurobiology supporting empathy, it is striking that social cognitive neuroscientists have only recently come to appreciate the distinction between empathy and compassion, with this development arising largely from its interaction with Buddhist contemplatives (for example, Davidson et al., 2002). According to the Indo-Tibetan Buddhist tradition, compassion is based upon the fundamental appreciation of interdependence and the illusory nature of the self (Wallace, 2001). Here, the granularity with which this contemplative tradition characterizes positive emotions is striking, as compassion is cultivated along with three other discrete qualities (loving-kindness, empathetic joy, and equanimity), which are together referred to as the *four immeasurables.* Loving-kindness, translated from the Pali term, *mettā,* is defined as the wish that others find genuine happiness and well-being. While empathy involves taking another's perspective in order to experience their emotional state and is a foundation of compassion, compassion is the wish that others be free from suffering (Wallace, 2001).

Our understanding of compassion and empathy has also been enriched by phenomenological accounts from contemplative adepts such as Matthieu Ricard. A renowned student and practitioner of the Nyingma school of Tibetan Buddhism, Ricard describes two distinct and refined states under his command during meditation practice: "So when I was immersing myself in empathic resonance, I visualized the suffering of these orphan children as vividly as possible. The empathic sharing of their pain very quickly became intolerable to me and I felt emotionally exhausted, very similar to being burned out... Subsequently engaging in compassion meditation completely altered my mental landscape. Although the images of the suffering children were still as vivid as before, they no longer induced distress. Instead, I felt natural and boundless love for these children and the courage to approach and console them" [in Klimecki et al. (2013a, p. 279)].

In addition to these Buddhist theoretical models and phenomenological accounts from contemporary Buddhist adepts, Buddhist texts are rich with practices offered for enhancing the four immeasurables. For example, the Tibetan practice of *tonglen* ("giving and taking") involves visualizing 'giving' one's joy and happiness to others as an expression of love and kindness, and 'taking' upon one's self the suffering of others to deepen one's compassion (Wallace, 2001). Another set of practices described by the Indian Buddhist monk, Shantideva, involves first meditating on the *equality* of self and other, with the goal of cultivating a cherishing attitude for one's self and others in an equal degree. Next, practitioners *exchange* their priorities to give preference to others' interests over one's own (Thompson, 2001; Tsong-Kha-Pa, 2004).

Currently, the most researched Buddhist kindness-based contemplative practice is Loving-Kindness Meditation. According to this practice, loving-kindness is first generated for oneself in order to remove negative emotions that might impede the generation of loving-kindness for others. Next, practitioners generate feelings of loving-kindness for someone whom it is typically easy, for example, someone who is acutely suffering or a close loved one. The practitioner progresses by extending this feeling to others for whom loving-kindness may be more challenging, first, to someone neutral, and ultimately to someone whom is challenging or difficult (Wallace, 2001; Salzberg, 2002). Currently, there are several adapted versions of LKM under investigation (Fredrickson et al., 2008; Johnson et al., 2011; Jazaieri et al., 2013, 2014).

A second practice currently being examined is Cognitively-Based Compassion Training (CBCT), based on the 11th century Tibetan Buddhist *lojong* ("mind training") tradition and heavily rooted in the seminal works of eight century Buddhist adept Shantideva. In its operationalization for novice populations, CBCT modifies standard *lojong* procedures in two important ways. First, the program is presented in a secular manner; thus, all discussions of soteriological or existential themes (e.g., the attainment of Buddhahood, Karma) are omitted. Second, rather than commencing with compassion-specific techniques, CBCT provides an introduction to foundational meditation practices; specifically, 1 week each of concentrative (i.e., *shamatha*) and open-presence practices at the beginning of the course. While these techniques are generally considered advanced according to the Tibetan tradition, they are often practiced alongside compassion practices and are thought to be necessary for establishing the focus and awareness necessary to engage in analytical practices (HHDL, 2001; Wallace, 2001). In contrast to the affective focus of LKM, CBCT uses analytical and didactic techniques to reorient the practitioner's perspective on his or her relationship with others. It is through this active analytical process and reorientation that empathy and compassion are cultivated (Ozawa-de Silva and Dodson-Lavelle, 2011). The instruction unfolds in the following order:

Module 1: Developing Attention and Stability of Mind
Module 2: Cultivating Insight into the Nature of Mental Experience
Module 3: Cultivating Self-Compassion
Module 4: Developing Equanimity
Module 5: Developing Appreciation and Gratitude for Others
Module 6: Developing Affection and Empathy
Module 7: Realizing Wishing and Aspirational Compassion
Module 8: Realizing Active Compassion for Others

Another contemplative program that incorporates analytic strategies is compassionate mind training (CMT) and its more encompassing psychotherapeutic application, Compassion-Focused Therapy (CFT; Gilbert, 2009). A clinically informed practice constructed as a therapeutic tool, CFT incorporates a Buddhist understanding of compassion alongside the cultivation of emotion regulation skills and the augmentation of secure attachment (Gilbert, 2013), with the idea that by instilling feelings of safety and decreasing negative emotions, the patient will grow their compassion, and in turn, their well-being (Gilbert, 2014a). We characterize CFT as an analytical practice for the purposes of this review given its connections with cognitive behavioral therapy and its use of reason and imagery to generate awareness in the practitioner of the importance of being a "compassionate self" (Gilbert, 2014b). However, it is important to note that CFT incorporates a wide array of practices to maximize its therapeutic potential (for a thorough description, see Gilbert, 2014b). Interestingly, CFT entrusts the therapist to model the components of compassion in a way that imparts those skills on their patient (Gilbert, 2009), and an intriguing hypothesis is that the therapist benefits alongside the patient. While several studies attest to the efficacy of CFT (Gale et al., 2014; Heriot-Maitland et al., 2014), the neural mediators, to the best of our knowledge, have remained unexplored.

Research on CBCT, LKM, and CFT/CMT presents an important opportunity not only to investigate the efficacy of the practices for enhancing well-being and prosocial concern, but also to examine whether the practices have differential effects on the brain, body, and behavior. Such research would improve our understanding of the active ingredients in each practice at the same time that it would prove a powerful tool for testing basic scientific models such as the one presented below. It is plausible that LKM explicitly targets the more affective components of empathy, while CBCT impacts the more cognitive components, and CFT may combine the effects of both LKM and CBCT.

Intriguingly, the aforementioned practices also have a common foundational thread, which is a fundamental realization that empathy and compassion are malleable and can be cultivated and optimized. In fact, while the third section of CBCT, *Cultivating Self-Compassion*, can be easily misunderstood as something akin to self-esteem, the teachings and practices are in actuality designed to help practitioners reflect on their innate ability to cultivate and shape their mind. Importantly, a recent line of research shows that individual differences in the belief that empathy can be shaped and developed predicts an individual's propensity to empathize in difficult situations (Schumann et al., 2014). This research suggests that one of the active ingredients in compassion meditation may be simply, but repeatedly, empowering practitioners with the understanding that empathy and compassion are traits that can be cultivated. If this is the case, we would expect to see similar effects on neural systems regardless of the practice, just as we might find that compassion meditation has a similar effect to other experimental inductions or interventions that engender beliefs in the malleability of empathy and compassion. A second prediction would be that the effects of all kindness-based practices would be most pronounced during situations when empathy is most challenging, and might lead to a positive feedback whereby new empathy "successes" reinforce the practitioners' confidence that their compassionate "muscles" are, in fact, malleable.

NEUROSCIENTIFIC ACCOUNT

Following the western scientific definition of empathy above, an empathic response is thought to have two crucial constituents: (1) an affective dimension that involves a shared affective experience, and (2) a cognitive dimension that includes the ability to understand or have some degree of conscious awareness that the affective experience is evoked by another. If either constituent is missing, the feeling becomes something else entirely. Should the cognitive piece be missing, the observer is instead experiencing *emotional contagion* or *simulation*. Should the affective dimension be absent, the observer is using their *theory of mind* or *perspective-taking* skills. Together these constituents combine to form a fully empathic response (de Vignemont and Singer, 2006; Eisenberg and Eggum, 2009).

Synthesizing almost a decade of functional neuroimaging research into a mechanistic model (**Figure 1**), it appears that three components underlie the neural bases of empathy: early and fast perceptual and motor simulation processes, affective simulation, and slower, cognitive processing. In addition to these core processes, empathy may require a self-other distinction and emotion regulation. All of these processes take place in, and are influenced by, a neuromodulatory milieu that, as we will see, takes cues from the environment and may serve as a powerful target for contemplative practices. Each of these three levels of neural influence and their possible control by meditation practices will be elaborated, but it is important to remember that this model is offered for heuristic purposes, with the acknowledgment that these processes and neural systems are multifaceted and likely influence one another in complex ways that are yet undiscovered. For example, several researchers have noted the important distinction between *capacity* and *propensity* when it comes to empathy (Klein and Hodges, 2001; Keysers and Gazzola, 2014), and it is likely that feelings of compassion alter an individual's propensity to empathize. It should also be noted, as many have before, that prosocial behavior does not necessarily rely on each or even any of these components (De Waal, 2008;

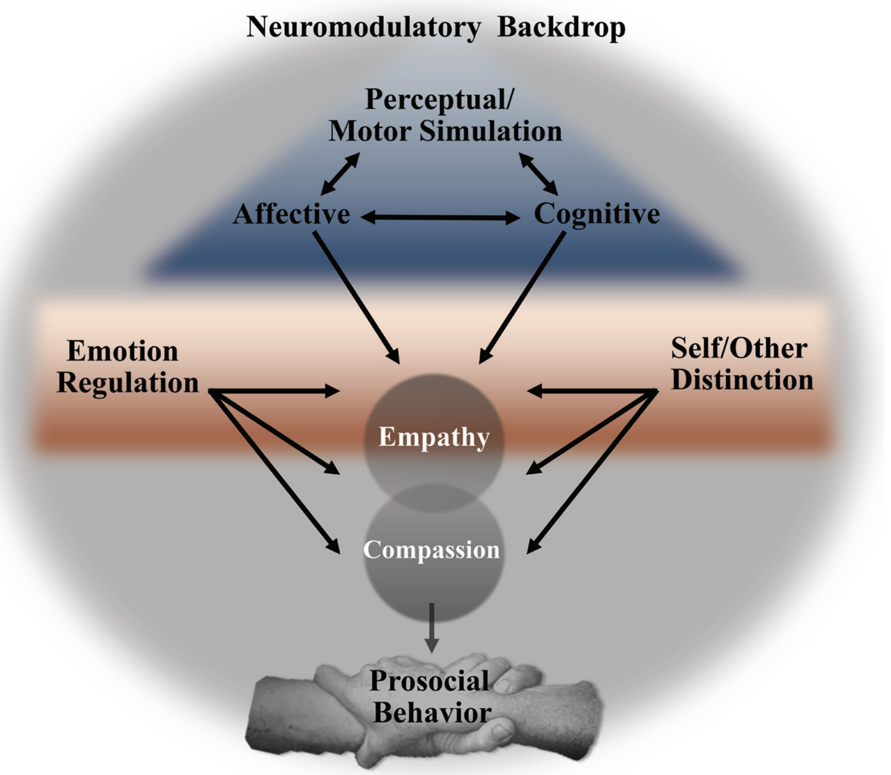

FIGURE 1 | Proposed model linking core neural processes, active amidst a neuromodulatory backdrop, leading to empathy, compassion, and prosocial behavior.

Preston and Hofelich, 2012; Decety and Cowell, 2014), just as compassion can likely occur in the absence of empathy, as will be discussed in more detail below. With these caveats in mind, we will detail the neural systems that contribute to empathy and compassion.

PERCEPTUAL/MOTOR

Though not consistently activated by many of the empathy-for-pain tasks utilized by functional neuroimagers (Fan et al., 2011; Lamm et al., 2011), the amygdala is arguably a core structure that subserves empathy and compassion. The first evidence supporting its importance for empathy came from studies of psychopaths, whose deficits in empathy form a core symptom of their disorder and who consistently have altered amygdala structure and function (Rilling et al., 2007; Blair, 2008; Marsh et al., 2013). Beyond its role in the etiology of psychopathy, recent studies also support the amygdala's role in empathy in healthy populations. For example, a recent study found that extreme altruists have greater amygdala volume and activity when viewing others' distressed faces (Marsh et al., 2014), and another study found that individuals that self-report high levels of affective empathy have greater functional connectivity between the amygdala and other limbic structures consistently implicated in empathic processing [anterior insula (AI); Cox et al., 2012].

However, the amygdala's implication in empathy rests in large part on correlational studies such as those referenced above [though see (Leigh et al., 2013) for the effects of acute amygdala lesion on affective empathy] and its exact role remains unclear. Some have argued that the importance of the amygdala in this context stems from its role in detecting the salience of, and learning about, social information based on sensory cues (Blair, 2008), which may be critically involved in the affective dimension of empathy (Hurlemann et al., 2010). For example, the amygdala plays a crucial role in detecting social information from others' eyes (Mosher et al., 2014) and in emotional processing of visual information (Pessoa and Adolphs, 2010; Wang et al., 2014), and it is well-placed to translate incoming sensory information into changes in arousal (Davis, 1992). It is possible that kindness-based meditation practices alter these early perceptual processes to direct an observer's attention and resources toward a target that is suffering.

A second early system that is often implicated in empathy is the putative 'mirror neuron system,' composed of the anterior part of the inferior parietal lobe and the inferior frontal cortex (Iacoboni and Dapretto, 2006). This system is thought to facilitate emotional understanding by mapping the target's emotive facial expression onto the observer's premotor repertoire. As such, neural activity related to motor simulation supports the ability to read emotional facial expressions (Carr et al., 2003; Jabbi and Keysers, 2008), and there is evidence that activity in this system precedes and may be causal to activity in the affective system described below (Jabbi and Keysers, 2008). In our longitudinal investigation of CBCT, we found that those randomized to meditation, compared to a health education control group, had enhanced scores on an empathic accuracy task. Increased scores were related to increased activity in the inferior frontal gyrus, a hub in the putative mirror neuron system, and the dorsomedial prefrontal cortex, a region that we will see below is important for thinking about others' mental states (Mascaro et al., 2012).

AFFECTIVE

A second component of empathy is often referred to as affective simulation, a process of matching limbic system activity with that of the target. Consistently, both the perception (auditory and visual) and contemplation of the suffering of another elicits activation in the anterior mid-cingulate cortex (aMCC), as well as bilateral AI and ventral frontal operculum, particularly on the right side (Lamm et al., 2011). Activity in the AI is thought to represent a simulated mapping of the observed individual's body state onto one's own (Fan et al., 2011; Bernhardt and Singer, 2012). Two studies have linked subsequent prosocial behavior with AI activity when viewing another's suffering (Hein et al., 2010; Masten et al., 2011). Importantly, these results were found using different paradigms, with one study inducing empathy in subjects by leading them to believe others were being excluded in a ball-tossing game (Masten et al., 2011) and the other had subjects watch others receive painful shocks and then gave them the choice to endure painful shocks on behalf of the other (Hein et al., 2010). In both cases, the finding that altruistic behavior was predicted by AI activity supports the idea that affective simulation is, at least in some cases, causal to compassion and prosocial behavior.

COGNITIVE

The third component of empathy is the cognitive element, often referred to as perspective-taking or mentalizing, which allows the observer to at some level understand that his or her affective state is related to someone else's affective state. Mentalizing consistently activates the medial and dorsomedial prefrontal cortex and the temporoparietal junction (TPJ), systems that are thought to subserve relatively controlled, reflective cognition (Lieberman, 2007). These neural regions are also activated by a diverse array of empathy-inducing tasks (Lamm et al., 2011; Morelli et al., 2012).

Given the analytical nature of CBCT, it is worth speculating that training augments regions of the brain important for mentalizing. Consistent with this, our longitudinal study found that enhanced empathic accuracy scores were in part related to enhanced activity in the dorsomedial PFC (Mascaro et al., 2012). An intriguing hypothesis is that these results reflect early effects of CBCT, and that with more extensive practice would come changes in the affective and motivational systems thought to subserve compassion, and described more fully below.

EMOTION REGULATION

Research from social and developmental psychology has convincingly demonstrated a difference, both in subjective feeling and in resultant behavior, between *empathy* and the related but distinct experience of *personal distress* (Batson et al., 1983; Eisenberg et al., 1998). Batson explains personal distress: "This state does not involve feeling distressed *for* the other or distress *as* the other. It involves feeling distressed *by* the state of the other." (Batson, 2009) As evidence, cross-cultural studies (Germany, Israel, Indonesia, and Malaysia) in preschool aged children consistently reveal a positive relationship between empathy (e.g., child shows features of sadness and has a soft voice toward an experimenter whose balloon had popped) and prosocial helping behavior. However, there was a negative relationship between self-focused distress (child turns away from victim, interpreted as avoidance of the distressing stimuli) and prosocial behavior (Trommsdorff et al., 2007). Interestingly, Buddhist contemplative accounts are consistent with this idea:

> "When one empathetically attends to another person who is unhappy, one naturally experiences sadness oneself. But such a feeling may actually lead instead to righteous indignation and the vengeful wish to exact retribution on the one who has made the other person unhappy. On the other hand, in the cultivation of compassion, empathetic sadness or grief acts instead as fuel for the warmth of compassion. One does not simply remain in a state of sadness or despair, but rises from this with the wish: 'May you be free of this suffering and its causes!'" (Wallace, 2001, pp. 11–12)

Taken together, these data suggest that becoming mired in personal distress is distinct from empathy and impairs prosocial behavior. It is likely, then, that emotion regulation plays an integral role in determining an individual's response to viewing another's suffering.

Defined as the initiation of new, or modulation of ongoing, emotional responses, emotion regulation varies in method and speed of processing from changes in attention to more cognitive reappraisal strategies (Ochsner and Gross, 2005). For example, simply shifting attention toward or away from social cues can up- or down-regulate empathic processes (Zaki, 2014), a regulatory process that arguably involves the amygdala, in some cases relying on it (Todd et al., 2012), in other cases modulating it (Larson et al., 2013). One testable hypothesis is that individuals motivated toward a compassionate response by meditation modulate their attention toward a suffering other in such a way to hover in a sweet spot, empathic but not over-aroused.

In addition to attention-shifting, cognitive reappraisal may modulate empathy by altering emotional responding. Zaki (2014) presents a detailed model of empathy-specific appraisals that are influenced by approach and avoidance motivations to determine empathy across contexts. In general, cognitive strategies activate the lateral (Ochsner et al., 2002) and ventromedial (Urry et al., 2006) prefrontal cortex. Interestingly, cognitive reappraisal strategies involving prefrontal regions are generally linked with *reduced* activation of the amygdala (e.g., Banks et al., 2007), suggesting that, while cognitive reappraisal is certainly not mutually exclusive with attention-shifting, the two different types of emotion regulation may have differing functional profiles in the amygdala. In addition to the prefrontal cortex, cognitive reappraisal strategies also engage the vagus nerve's parasympathetic influence over heart rate, as reflected by respiratory sinus arrhythmia (RSA; Butler et al., 2006; Segerstrom and Nes, 2007). Porges's (2003, 2007) Polyvagal theory posits that it is this vagal brake, shaped by evolutionary pressures for parental caregiving, that supports affiliative interactions. Researchers have found that compassionate responses appear to rely on parasympathetic dampening of the emotional response of witnessing another's suffering (Rockliff et al., 2008).

While emotion regulation is often hypothesized as an integral outcome of mindfulness meditation (e.g., Hölzel et al., 2011), few studies, to our knowledge, have directly investigated whether kindness-based meditation practices augment emotion regulation. However, a recent study found that LKM increased practitioners' vagal tone, an effect that moderated an increase in positive emotions, which in turn moderated even greater gains in vagal tone (Kok et al., 2013). Importantly, the positive spiral of increased vagal tone was mediated by increased feelings of social connectivity. While the researchers assessed vagal tone at rest, an interesting next step would be to examine whether these gains in vagal tone are evident during an empathy-inducing situation. Weng et al. (2013) randomized subjects to either 2 weeks of LKM or to a control course that taught emotional reappraisal strategies. Those randomized to LKM had increased neural activity while viewing photographs of others suffering in an area of the putative mirror-neuron system (inferior parietal lobe) and in a brain region important for emotion regulation [dorsolateral PFC (dlPFC)], and they exhibited more altruism during an economic game outside of the scanner. Functional connectivity between the dlPFC and the nucleus accumbens (NA) predicted greater altruistic behavior, a finding the authors interpreted as consistent with the idea that LKM enhances altruism by augmenting emotion regulation in the face of suffering.

Should kindness-based meditation augment prosocial emotions and behavior by enhancing emotion regulation and vagal tone in response to others' suffering, there may be mediating mechanisms in addition to the enhanced feelings of connectivity reported by Kok et al. (2013). For example, van Kleef et al. (2008) found that individuals who self-report higher-levels of social power exhibit less vagal tone and compassion in response to another's suffering, and it may be that compassion meditation alters feelings of social power by reminding practitioners of their interdependence and shared desire for happiness with others.

SELF/OTHER DISTINCTION

Nearly two decades of research from social psychology shows that excessive overlap between self and other may render the perceiver mired in personally oriented distress that, rather than leading to prosocial behavior, leads to disengagement from the victim (Batson et al., 1987; Batson, 1998). In addition to this cross-sectional research, Hoffman (2001) cites developmental research in support of the same idea. While young children display "egocentric empathic distress" causing them to seek personal comfort when they witness another in distress (for example, by crawling into their parent's lap), the development of a self-concept is concomitant with a child's tendency to make helpful advances toward the victim (Hoffman, 2001). Several studies have found that mirror-self recognition in children predicts later helping behavior during empathic distress (Zahn-Waxler et al., 1979; Johnson, 1982; Bischoff-Kohler, 1991). Based on these data, social cognitive neuroscientists have persuasively argued for the importance for empathy of a rigid self/other distinction (Decety and Grèzes, 2006), and experimental induction of a self-oriented versus other-oriented perspective reveals that taking the perspective of another who is suffering activates the posterior cingulate cortex and TPJ (Jackson et al., 2006).

Interestingly, the importance of a self/other distinction for empathy and compassion may be one topic where current neuroscientific theories differ from contemplative accounts that emphasize the importance of self/other exchange (Thompson, 2001; Wallace, 2001). To the best of our knowledge kindness-based meditation practices have not been shown to impact the TPJ or to increase the ability to take an other-oriented perspective; however, a recent study by Garrison et al. (2014) may lend support to the idea that loving-kindness meditation reduces self-oriented processing. In this study, experienced meditators practicing LKM in the fMRI scanner had reduced functional connectivity between nodes of the default mode network thought to be important for self-referential processing (Garrison et al., 2014).

COMPASSION

Clarifying the distinction between compassion and empathy may be highlighted as an example of the promise of functional neuroimaging, as recent studies of these discrete affective states reveal distinctly different patterns of brain activation. In fact, one of the first neuroimaging studies that purported to probe the neural correlates of compassion likely evoked empathy, and as such, the neural response to the empathy-inducing stimuli was characteristic of the core network described above (Immordino-Yang et al., 2009). However, Kim et al. (2009) found that adopting a true compassionate stance when viewing photographs of others suffering activated the mesolimbic dopamine (DA) system [ventral tegmental area (VTA) and ventral striatum] implicated in reward and motivation. A more recent study found that activity in the septal nuclei, another area important for reward and motivation, was commonly activated by several different empathy-inducing tasks and predicted helping behaviors (Morelli et al., 2012).

Interestingly, the research on compassion dovetails with that emerging from the investigation of the neurobiology of the parental brain. Animal models have long implicated both the septal area (Francis et al., 2000) and the DA system in supporting the motivation to proactively nurture offspring, with DA-producing cell bodies in the VTA projecting to the NA to motivate caregiving (Numan and Stolzenberg, 2009). Recent neuroimaging research suggests that this system may support human parents' motivation to nurture their offspring (Mascaro et al., 2013a; Rilling, 2013), which raises the intriguing possibility that it is this system that underlies the motivational quality of compassion (Preston and Hofelich, 2012).

In fact, there is accumulating evidence that LKM alters the reward and motivation system in ways that support compassion. Klimecki et al. (2013b) found that 1 day of training in a loving-kindness practice enhanced neural responses to viewing video vignettes of others suffering in key nodes of the DA system (VTA and orbitofrontal cortex) and augmented self-reported positive affect. In a second study, the same group compared changes in the neural response to the same vignettes and found differential effects of training depending on whether the individual was trained to share others' suffering (empathy) or in loving-kindness training. After the former, participants had enhanced activity in AI bilaterally and aMCC, whereas compassion training enhanced activity in the ventral striatum and medial orbitofrontal cortex (mOFC; Klimecki et al., 2013c).

NEUROMODULATORY BACKDROP

Innate immune system

Research from multiple domains supports the idea that empathy and compassionate behavior are diminished by both acute and chronic states of social disconnection. For example, experimental induction of social exclusion is linked to a reduction in empathy and less subsequent prosocial behavior toward others (DeWall and Baumeister, 2006; Twenge et al., 2007). A related body of literature reports a consistent negative relationship between empathy and depression (Cusi et al., 2011). Interestingly, psychoneuroimmunologists have proposed that chronic social isolation biases an individual's immune system toward the fast-acting innate immune response, characterized by deleterious pro-inflammatory signaling (Cole, 2009). In other studies, enhanced signaling in the innate immune system has been shown to further increase feelings of isolation and enhance amygdala responses to threatening social stimuli (Inagaki et al., 2012), as well as depression (Musselman et al., 2001). Taken together, these studies reveal a powerful cycle whereby isolation and depression enhance inflammation, which then further enhance subjective isolation and decrease empathy and compassion. The optimistic outlook on such a negative cycle is that compassion practices may present an equally powerful intervention that targets the cycle at multiple sites by augmenting both subjective feelings of social connectivity and the biological systems that support it (Pace et al., 2009, 2013). If this is true, then we would hypothesize that decreases in inflammation (e.g., pro-inflammatory cytokines) would mediate changes in social emotions and behavior and related neural functioning.

Desbordes et al. (2012) longitudinal investigation of CBCT in adults naïve to meditation found that, for individuals randomized to compassion meditation but not those randomized to attention meditation, meditation practice time predicted increased amygdala activation in response to compassion-inducing stimuli, though the effect was only marginally statistically significant. Importantly, the increased amygdala activation was associated with reduced levels of depression (Desbordes et al., 2012). This finding is consistent with studies reporting that CBCT reduces inflammatory biomarkers both at rest and in response to psychosocial stress (Pace et al., 2009, 2013), and with other studies showing compassion-based practices lead to decreased depression (Gilbert and Procter, 2006), and supports the idea that one active ingredient in compassion practices is the amelioration of depression and attendant activity of the innate immune response, essentially unmasking the underlying empathy and compassion that were impaired by the individual's own suffering.

Oxytocin

A rapidly burgeoning literature suggests that the oxytocin (OT) system plays an important role in empathy. Research on OT most recently points to a complex, but generally supportive role for OT in the generation of social emotions and behaviors such as trust, empathy, cooperation, social attention, eye gaze, as well as augmentation of the vagal system and dampening of the innate immune and sympathetic response to psychosocial stress [reviewed in Carter (2014)]. Taken together, these findings suggest that the OT system may be involved in mediating the effects of meditation on prosocial emotions and behavior. Moreover, oxytocin's role as a widely acting neuromodulator (Carter, 2014) might provide a parsimonious explanation for the multitude of effects of kindness-based meditation on both stress physiology and social cognition. However, to the best of our knowledge there is no current evidence that kindness-based meditation alters the OT system. This may be attributed to the fact that central nervous system levels of OT are notoriously difficult to assay and to the potential limitations of plasma measures, which may not accurately reflect OT levels affecting the brain and behavior (Kagerbauer et al., 2013). Beyond circulating levels of OT, the impact of oxytocin on social cognition will also depend on the brain's sensitivity to it as reflected in receptor density (Insel, 1990), and compassion meditation may up-regulate OT receptors. Unfortunately, a method for directly assessing this possibility *in vivo* does not currently exist, but another possibility, both intriguing and tractable for investigation, is that individual differences in OT receptor polymorphisms, such as those with known relationships with empathy (Rodrigues et al., 2009), may moderate the effects of compassion meditation.

In summary (**Table 2**), the model presented here proposes that empathy is composed of basic attentional, perceptual and motor simulation processes, simulation of another's affective body state, and slower and higher-level perspective-taking. These components are modulated by emotion regulation and self/other discrimination, and when infused with a motivational component, may become a compassionate response. At all levels in the process, neural systems are influenced by oxytocin and the pro-inflammatory immune system. Kindness-based meditation practices may influence each of these neural systems; however, to date the most consistent evidence supports the idea that LKM enhances the neural systems important for emotion regulation (dlPFC: Weng et al., 2013; vagal tone: Kok et al., 2013) and reward (VTA and mOFC: Klimecki et al., 2013b,c), whereas CBCT affects the perceptual/motor and cognitive processes (Desbordes et al., 2012; Mascaro et al., 2012), perhaps in part by modulating inflammation (Pace et al., 2009, 2013).

BEST PRACTICES AND FUTURE DIRECTIONS

As has been well-documented (Ospina, 2008; Sedlmeier et al., 2012), the major limitation to identifying mechanisms of action of meditation, including kindness-based practices (Galante et al., 2014), relates to general design weaknesses that, while not unique

Table 2 | Synopsis of model presented here.

Model	Neural systems involved
Perceptual/motor	Amygdala* (↑)
	Inferior frontal gyrus*
Affective	Anterior insula
	Anterior cingulate cortex
Cognitive	Dorsomedial PFC*
	Temporoparietal junction
Emotion regulation	Amygdala (↑* or ↓)
	Dorsolateral PFC*
	Vagus nerve*
Self/other distinction	Temporoparietal junction
Neuromodulatory backdrop	
Oxytocin system (↑)	
Pro-inflammatory immune system (↓)*	
Compassion	VTA*
	Medial OFC*
	Septal nuclei

Asterisk indicate regions of the brain that have been shown to be affected by loving-kindness or compassion meditation training.

to meditation research, are arguably especially problematic for it. First, there has been a frequent lack of appropriate comparator groups against which to measure the effects of any given style of meditation, and major confounds such as self-selection and non-specific effects of meditation training have often been left unaddressed. Second, we echo others' appeals for ecologically valid, objective and implicit assessments of empathy and compassion (Zaki and Ochsner, 2012), and believe that this is especially crucial for examining potential effects of kindness-based meditation practices given the likelihood that demand characteristics and practitioner social desirability render self-report assessments less than optimally reliable (for example, see Hutcherson et al., 2008). Third, researchers in the field of contemplative research, who are often personally committed to the practice of meditation, should be especially mindful to guard against the file drawer effect, or worse, the tendency to under-report findings that would paint meditation in a less positive light. The potential hazards of a research bias in meditation have been illuminated by the work of Willoughby Britton and colleagues (Rocha, 2014), and is supported by accounts in traditional contemplative literature. For example, with respect to compassion practices, Wallace notes that although the long-term effects of compassion are positive, it may be superficially unsettling or upsetting at times (Wallace, 2001). Similarly, the Buddhist scholar Dreyfus (2002, p. 43) has written of beginning bodhisattvas who "are often described as being overwhelmed by compassion. They can be deeply moved by compassion and sometimes cry." It is likely that similar difficulties may be revealed in studies of western practitioners embarking on compassion meditation, and if so, future research can examine the depth of grief and whether it is simply a necessary obstacle for the beginner to overcome, or rather is integral and motivational, in a sense vital for future outcomes.

It is our hope that the model proposed here will contribute to an ongoing discussion of how best to design, implement and interpret theoretically driven research on compassion and loving-kindness meditation. We suggest that for the field to continue moving forward it will be important to move beyond unitary, single-level outcome measures and rather to employ both peripheral and neural biomeasures, as well as socio-cognitive and behavioral outcome measures that allow testing of mechanistic models within an explicitly defined theoretical framework. Moreover, it will be important for the field to welcome the reporting of negative findings with the understanding that meditation may not be of benefit for all people in all times and places and is unlikely to be a panacea for the many physical and emotional problems that plague the modern world.

The model proposed here also reveals several outstanding questions within the field of social cognitive neuroscience that may be addressed within studies of meditation. Most obvious, this model suggests a dynamic progression of neural processes, but the timing and interrelationships between these dynamic processes remains unclear. A previous study used functional connectivity and causality modeling to determine the interaction between motor simulation in the inferior frontal gyrus and affective simulation in the AI while viewing emotional facial expressions (Jabbi and Keysers, 2008), and similar methodologies could be used to determine the role and relative timing of emotion regulation and self/other distinctions in the dynamic interplay between empathy and compassion. In addition, there is a debate arising within social cognitive neuroscience (Decety and Cowell, 2014) as well as popularized science journalism (Bloom, 2014) regarding the necessity of empathy for compassion, prosocial behavior, and morality, and investigating the outcomes of training the neural systems supporting these discrete aspects of cognition and behavior may be relevant to the discussion. For example, investigations of kindness-based meditation may uncover neural systems that have been up to this point underappreciated for empathy, such as those that underlie the courage or conviction to maintain compassion even when it conflicts with social norms or authority (Bègue et al., 2014).

In addition to theory driven research, we see several under-researched but important questions in the field of meditation research in general, and in compassion and loving-kindness meditation more specifically. As hinted above, the possibility that the effects of meditation practice are not linear, and rather, contain periods of ebb, flow, and even setback during which positive outcomes are less evident remains an underexplored, but crucial topic for basic scientists and clinicians, alike. In addition, research on kindness-based contemplative practices lends itself to the investigation of the ways in which context and meaning impact outcomes. Distinctly different modes of inquiry currently investigate these meditation practices: for individual well-being and therapeutic outcomes on the one hand (e.g., Braehler et al., 2013), and for enhanced social cognitive acuity and prosociality on the other (e.g., Klimecki et al., 2013b). It remains possible that these diverse contexts produce differential subject demand characteristics or otherwise influence outcomes. Similarly, research on mindfulness has benefited from the attention paid to the intentions of the practitioner (Shapiro et al., 2006), and one study has shown that Vipassana practitioner's goals impacted the outcome of their practice (Shapiro, 1992). Interestingly, our own research with compassion meditation is not consistent with the findings from Vipassana and mindfulness (Mascaro, 2011), as the effects of CBCT were not moderated by practitioner goals, and it may be that practitioner intentions and goals are more influential for particular contemplative practices.

Finally, it would seem obvious that kindness-based contemplative practices might be optimally useful for enhancing empathy and compassion in populations that may stand to benefit most, such as those with psychopathologies typified by empathy deficits (autism, as the most obvious example) or children with as yet under-developed empathic abilities. While this may certainly be the case, it will also be important to simultaneously investigate the real possibility that CM and LKM will be most difficult or least resonant for those that may benefit the most (Rockliff et al., 2008; Mascaro et al., 2014). One potentially fruitful line of research would investigate whether populations that have difficulty adopting a meditation practice are aided by pharmaceutical interventions, such as pre-treatment with oxytocin, that might make the practices more accessible or effective.

Taken together, the studies reviewed here support the idea that compassion and loving-kindness meditation practices alter neural systems thought to be important for empathy and compassion. Intriguingly, the pattern of results, though admittedly incomplete, hints at differential effects of affective and cognitively based practices. On the one hand, LKM appears to target the neural systems important for emotion regulation and reward, whereas CBCT may target the perceptual/motor and cognitive processes. Future work will reveal whether this pattern is indicative of genuine underlying differences in mechanisms of action of the practices, and if so, what such differential mechanisms mean for the behavior and well-being of the practitioner.

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Auditory driving of the autonomic nervous system: Listening to theta-frequency binaural beats post-exercise increases parasympathetic activation and sympathetic withdrawal

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Binaural beats are an auditory illusion perceived when two or more pure tones of similar frequencies are presented dichotically through stereo headphones. Although this phenomenon is thought to facilitate state changes (e.g., relaxation), few empirical studies have reported on whether binaural beats produce changes in autonomic arousal. Therefore, the present study investigated the effects of binaural beating on autonomic dynamics [heart rate variability (HRV)] during post-exercise relaxation. Subjects ($n = 21$; 18–29 years old) participated in a double-blind, placebo-controlled study during which binaural beats and placebo were administered over two randomized and counterbalanced sessions (within-subjects repeated-measures design). At the onset of each visit, subjects exercised for 20-min; post-exercise, subjects listened to either binaural beats (‘wide-band’ theta-frequency binaural beats) or placebo (carrier tones) for 20-min while relaxing alone in a quiet, low-light environment. Dependent variables consisted of high-frequency (HF, reflecting parasympathetic activity), low-frequency (LF, reflecting sympathetic and parasympathetic activity), and LF/HF normalized powers, as well as self-reported relaxation. As compared to the placebo visit, the binaural-beat visit resulted in greater self-reported relaxation, increased parasympathetic activation and increased sympathetic withdrawal. By the end of the 20-min relaxation period there were no observable differences in HRV between binaural-beat and placebo visits, although binaural-beat associated HRV significantly predicted subsequent reported relaxation. Findings suggest that listening to binaural beats may exert an acute influence on both LF and HF components of HRV and may increase subjective feelings of relaxation.

Keywords: auditory driving, autonomic, binaural-beat, exercise, heart rate variability, relaxation

INTRODUCTION

Binaural beating is an auditory illusion that is perceived when two or more pure-tone sine waves of similar but different frequencies (under 1500 Hz and less than 40 Hz apart) are presented dichotically via stereo headphones (Draganova et al., 2008). For example, if a 510 Hz pure tone is presented to a listener’s right ear while a 500 Hz pure tone is presented to the listener’s left ear, the listener perceives an illusory binaural beat with a frequency (perceived tempo) of 10 Hz. Binaural-beat perception originates in the brainstem’s inferior colliculi (Smith et al., 1975) and superior olivary nuclei (Oster, 1973), where sound signals from each ear are integrated, and continues as the neural impulses travel through the reticular formation up the midbrain to the thalamus (Swann et al., 1982), auditory cortices and other cortical regions (Draganova et al., 2008).

Research findings suggest that music and sound can modulate autonomic arousal through entrainment (Trost and Vuilleumier, 2013; Regaçone et al., 2014). Entrainment is a process through which two autonomous rhythmic oscillators with similar but different fundamental frequencies interact, resonate, and synchronize (Cvetkovic et al., 2009). Classic examples of entrainment include the synchronizing of human sleep-wake cycles to the 24-h cycle of light and dark (Clayton et al., 2005), the synchronization of a heartbeat to a cardiac pacemaker (Cvetkovic et al., 2009), and the use of rhythmic auditory stimulation in the rehabilitation of motor functions (Thaut and Abiru, 2010).

Numerous studies have reported positive effects of purported binaural-beat entrainment on clinically relevant outcomes including: heart rate, blood pressure, electrodermal response, and finger temperature (Kennerly, 2004), performance vigilance and mood (Lane et al., 1998), hypnotic susceptibility (Brady and Stevens, 2000), mental and physical relaxation (Foster, 1990), attention and memory (Kennerly, 1994), depression and mood regulation (Cantor and Stevens, 2009), generalized anxiety (Le Scouarnec et al., 2001), as well as pre-operative anxiety and intra-operative anesthesia requirements (Kliempt et al., 1999; Lewis et al., 2004; Padmanabhan et al., 2005; Dabu-Bondoc et al., 2010). Many of these studies employed the Hemi-Sync® auditory-guidance system (which combines binaural beats, music, pink noise, natural surf sounds, and verbal guidance) which is designed to employ 'brainwave entrainment' and facilitate ergotropic (increasing arousal) or trophotropic (decreasing arousal) changes in consciousness (Atwater, 2004). In spite of these prior positive findings, it remains uncertain whether binaural beats alone modulate autonomic arousal. In order to ascertain the clinical effectiveness of binaural beats, they must be experimentally isolated from possible confounding variables such as verbal guidance and instrumental music.

In the present study, we chose to employ theta-frequency (4–7 Hz) binaural beats to facilitate the post-exercise relaxation response. The relaxation response is an innate physiological response characterized by diminished sympathetic nervous system (SNS) activity and increased theta-brainwave activity (Benson et al., 1981). Interestingly, it has recently been shown that combining exercise—a practice known to produce anxiolytic effects (Raglin and Morgan, 1987) and improve long-term stress-resiliency (Salmon, 2001)—with subsequent relaxation training significantly reduced blood pressure and post-exercise blood pressure response to a laboratory stressor (Santaella et al., 2006). Therefore, exercise followed by conscious relaxation may provide for a deeper relaxation response than either intervention alone – a finding that might inform treatment for a wide-variety of stress-related conditions. In addition to the aforementioned positive effects of combined exercise and relaxation training, the decision to investigate binaural-beat effects post-exercise was made in an effort to capitalize on known autonomic effects of exercise and exercise-recovery (Parekh and Lee, 2005).

Briefly, exercise serves as an ergotropic stimulus which increases SNS activity (Bricout et al., 2010). In healthy populations, exercise elicits characteristic intensity- and duration-dependent effects which can interact with fitness level (i.e., VO_2max; Buchheit and Gindre, 2006). We aimed to induce sympathetic activation via exercise, and then compare the effects of binaural beats to those of a placebo on post-exercise autonomic arousal, as indicated by heart rate variability (HRV) – a sensitive probe of autonomic tone. HRV was chosen as an autonomic probe (opposed to other measures such as event-related potentials or skin conductance) due to the monitor's low-cost, minimal invasiveness, and portability. Generally, the effects of exercise include increased low-frequency (LF) power [a measure of both parasympathetic (PNS) and sympathetic (SNS) activity] and decreased high-frequency (HF) power (reflecting PNS activity) relative to pre-exercise values, with the net effect of increasing sympathetic dominance (i.e., LF/HF ratio; Parekh and Lee, 2005). Recovery from moderate/intense exercise normally involves an acute reduction in LF power and an increase in HF power, which then typically return to near baseline levels within 30-min to an hour – resulting in the eventual restoration of baseline sympathovagal balance (Terziotti et al., 2001; Gladwell et al., 2010). It is important to note that while exercise-induced increases in SNS activity can be inferred through the LF component of HRV, LF HRV signal is contributed to by both SNS and PNS components – making interpretations based on LF power alone somewhat dubious (Camm et al., 1996). HF HRV signal, however, is considered to be exclusively mediated by PNS. Post-exercise, heart rate decreases towards baseline levels, reputedly through a combination of SNS withdrawal and increased PNS activation (Pierpont and Voth, 2004). For heart rates above 100 bpm, SNS withdrawal dominates; as heart rate falls below 100 bpm, further reductions are primarily mediated by PNS activation (Pierpont and Voth, 2004).

First, we hypothesized that exercise would decrease parasympathetic activity (as measured through decreased HF HRV component) and increase sympathetic activity (as measured through increases in the LF HRV component). Second, we hypothesized that exposure to theta-frequency binaural beats (relative to placebo) would result in increased parasympathetic activity following exercise (increased HF HRV component). Third, we also hypothesized concomitant decreases in the LF HRV component (reflecting a combination of parasympathetic and sympathetic activity), as well as in overall LF/HF ratio – often referred to as sympathovagal balance. Lastly, we hypothesized that binaural beats would facilitate entry into a deeper state of relaxation, with participants reporting increased perceived relaxation during the binaural-beat condition relative to the placebo condition.

MATERIALS AND METHODS

SUBJECTS

Twenty-two college students were recruited by announcement and signed informed consent approved by Ithaca College's institutional research review board. Subjects remained naïve to the true nature of the experiment; they were told only that the study was designed to examine the effects of music on exercise recovery. Subjects' health-histories were assessed; exclusion criteria included high cardiovascular risk, habitual smoking, chronic alcohol usage, prescription medication usage or a history of diagnosed mental or physical illness. One subject's data were excluded from analyses due to failure to complete both sessions, resulting in an n of 21 for final analyses. Eleven subjects received placebo condition first and ten subjects received binaural-beat condition first; no significant differences between assignment groups for any variable were observed ($p > 0.05$). Baseline and post-exercise descriptive statistics for subjects are found in **Table 1**.

Cardiovascular measures and analyses

A Polar RS800CX heart rate monitor (Polar Electro Oy, Kempele, Finland) was used to record heart rate, as it has been previously demonstrated to provide reliable measures to calculate HRV (Wallén et al., 2011) – an important indicator of relaxation (Peng et al., 2004) and sympathovagal balance (Sharpley et al., 2000). Subjects' R–R interval data were sampled at a 1000 Hz sampling frequency, allowing for a 1-ms temporal resolution of HRV (Polar RS800CX User Manual, 2011). Heart rate data for each subject were uploaded to Polar ProTrainer 5 software (Version 5.40.172).

Acoustic equipment

A sound level meter (Model 33-2050, Radio Shack, Tandy Corporation, Fort Worth, TX, USA) was used with a C-weighted slow-response setting to calibrate a pair of Koss HQ1 collapsible full-size headphones (Milwaukee, WI, USA), and to standardize

Table 1 | Descriptive statistics for subjects' baseline and post-exercise data.

	Mean (*M*)	Standard Deviation (*SD*)
Age	20.33	2.69
Height (cm)	171.12	10.24
Weight (kg)	77.41	15.31
Body mass index	26.1	4.1
VO_2max (mL/kg/min)	48.3	6.5
ExRx-MPH	5.8	0.8
Sex (no.)	14 male/7 female	
Ethnicity (no.)		
White/Caucasian	16	
Black/African American	2	
Asian	1	
Hispanic/Latino(a)	1	
Unreported	1	

VO_2max = maximal predicted volume of oxygen consumption; ExRx-MPH = exercise prescription in miles per hour.

volume levels. Volume levels for both left and right earpieces, and for both placebo and binaural-beat audio tracks, ranged from 61 to 63 decibels (dB).

During the experimental session, multiple carrier tones were presented over a background of pink noise (20–20,000 Hz with power attenuated in non-audible frequency ranges) with a 7 Hz interaural frequency difference that was continuously varied by plus or minus 1.5 Hz over a 4-s period (i.e., looped from 7 to 8.5 to 7 to 5.5 Hz and back; The Monroe Institute, Faber, VA, USA). Over the course of a 20-min presentation, carrier tones were changed in seamless ten-second cross fades to facilitate listener vigilance. This 'wide-band' binaural-beat effect was created through the presentation of the following carrier tone chords: zero to 3-min, C-Major-seventh; 3-min to 5-min, C-Major; 6-min to 10-min, G-Major; 10-min to 15-min, D-Minor; and 15-min to 20-min, C-Major (Brady and Stevens, 2000). The audio tracks (placebo vs. binaural-beat) were designed to be perceptually indistinguishable from one another in naïve listeners. Both audio tracks were provided by The Monroe Institute, Faber, VA, USA (Atwater, unpublished manuscript). During the placebo session, subjects listened to pink noise with identical carrier tones as in the binaural-beat condition but with no varying interaural phase difference.

Perceived relaxation scales

At the end of each experimental session, subjects were asked to rate the degree of their perceived relaxation during the relaxation protocol on a scale of 1–10, with one indicating the least relaxed and 10 indicating the most relaxed. Single-item numeric rating scales have been previously used in the literature to measure subjective responses to music (Iwanaga et al., 2005; Tan et al., 2012) as well as to other interventions (Strauser, 1997).

PROCEDURES

Prior to each experimental session, subjects were emailed instructions to avoid strenuous exercise, alcohol, and over-the-counter medication for 24-h prior to the session, and caffeine within 3-h of the session. A 24-h history questionnaire was administered to each subject at the beginning of each experimental session to assess compliance with study instructions. Participants who failed to comply with all study requirements over the 24-h period prior to testing were excluded from participation (one subject due to medical reasons). To control for diurnal hormone fluctuations known to play a role in HRV, each subject was scheduled at the same time of day for each experimental session (Armstrong et al., 2011). Subjects were alternately assigned to A–B and B–A conditions to control for order effects and the researcher conducting the experiment was blinded to condition. Subjects returned within a 2-week period to complete the alternate condition. On subjects' first visit, height and weight were measured. Subjects were seated and instructed to complete paperwork required for a predicted VO_2max regression formula (Bradshaw et al., 2005). After completion, they were told to sit quietly and relax for 5-min. An exercise protocol was individually determined as per American College of Sports Medicine guidelines for moderate cardiovascular exercise (70% of predicted VO_2max; Thompson, 2010) with a 5-min warm-up and cool-down at 50% of prescribed workload. Subjects performed treadmill (Precor 956; Woodinville, WA, USA) exercise in order to elicit a strong sympathetic nervous system response. Heart rate was recorded continuously throughout the experiment. HRV was sampled during 2-min windows of quiet rest while in an upright position: at baseline, post-exercise, and at the beginning (RELAX-1), middle (RELAX-2), and end (RELAX-3) of the relaxation protocol (**Figure 1**).

After completion of post-exercise measurements, subjects were instructed to sit in a recliner, lights were dimmed, a curtain was drawn around the recliner, and the following short script was read:

> *"This relaxation period will last 20-min. I will close this curtain and leave the room so you can relax and have the space to yourself. I will return after 20-min and open the curtain and we will move back over to the other chair. Once you put on the headphones and begin listening to the music, I need you to close your eyes, focus attentively on the music and relax as deeply as you can. Do you have any questions?"*

Subjects attended two laboratory sessions: once while listening to binaural beats, once while listening to a placebo (carrier tones and pink noise only). Following 20-min of stimulus exposure via stereo headphones at a standardized volume, subjects were asked to rate their perceived degree of relaxation during the relaxation protocol. After completion of the study, subjects were debriefed (i.e., provided with information about binaural-beats).

DATA PROCESSING

All heart rate signal time series were inspected for artifacts using-Polar ProTrainer to ensure that no signal contained more than 2% artifacts (Camm et al., 1996; Bricout et al., 2010). Heart rate R–R interval data were subsequently processed in Kubios HRV (Version 2.1; Tarvainen and Niskanen, 2008). Time series for all subjects were detrended using a smoothness priors based

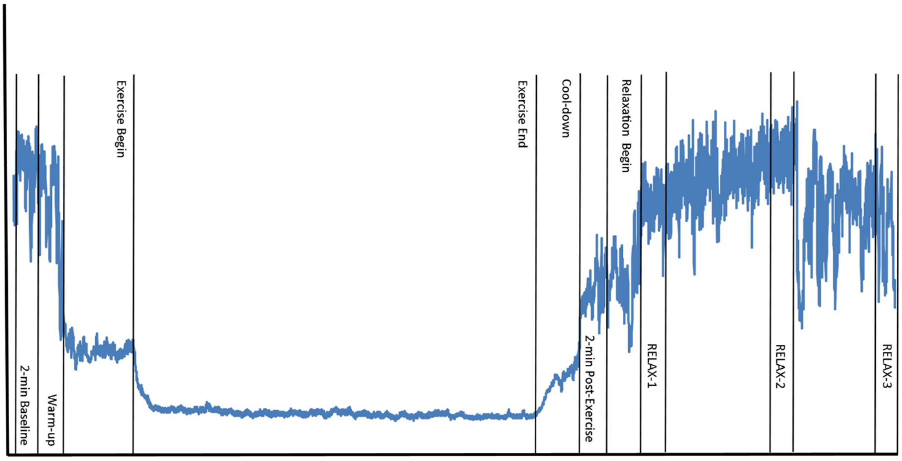

FIGURE 1 | Testing schedule and data collection time points. Wavy line represents example R–R interval time series over the course of one experimental session, including the following time points: 2-min baseline, 5-min warm-up, 20-min exercise, 5-min cool-down, 2-min post-exercise, 20-min relaxation [heart rate variability sampled during 2-min windows at beginning (RELAX-1), middle (RELAX-2), and last 2-min (RELAX-3) of relaxation].

detrending approach with $\lambda = 500$ (smoothing parameter with cut-off of 0.010 Hz times the sampling frequency), $f_c = 0.035$ Hz (estimated cut-off frequency of the filter). Detrending removes slow-trend (Schmidt et al., 2010), and non-linear trend (Manimmanakorn et al., 2011), components which can cause distortion in the signal. Next, a conservative interpolation artifact correction algorithm was employed, using a 'medium' level of correction which excluded all obvious artifacts from analysis (Tarvainen and Niskanen, 2008). No more than 0.78% of R–R time-series (32/4069 beats) were interpolated. Frequency-domain HRV indices were calculated using a Fast-Fourier Transform (FFT) based Welch's Periodogram method (Tarvainen and Niskanen, 2008), with a 256-s window width and a 50% window overlap. A standard setting with a 4 Hz interpolation rate was used with the following frequency bands: very-low frequency (VLF, 0–0.04 Hz), LF (0.04–0.15 Hz), and HF (0.15–1.0 Hz; Tarvainen and Niskanen, 2008). Consistent with prior exercise research, the extended HF band was included for analysis as so to include frequencies resulting from post-exercise tachypnea which might otherwise be missed (Brenner et al., 1998; Sumi et al., 2006). After detrending and applying artifact correction, each signal was cut into five 2-min samples (baseline, post-exercise, beginning, middle, and end of relaxation protocol) providing adequate duration to assess short-term spectral components (Camm et al., 1996).

DATA ANALYSIS

Preliminary analyses

First, all HRV variables were natural-log transformed to fulfill normality assumptions of parametric statistical testing. All data were then reverse-log transformed prior to reporting. Cohen's *d*, a non-biased measure of effect size, was calculated for significant within-subjects results based on a correction for dependent means (Morris and DeShon, 2002; Wiseheart, 2013). For significant interactions, η^2 is reported as an indicator of effect size. All analyses were two-tailed with $\alpha = 0.05$.

Repeated-measures ANCOVA were performed for all baseline and post-exercise measures of HRV to test for differences between conditions in pre-relaxation HRV values (**Table 2**). In an effort to isolate potential binaural-beat treatment effects from any confounding effect of exercise, delta scores for each session (2-min immediately post-exercise minus the 2-min baseline) were computed and included as nuisance covariates in all HRV analyses – the intended effect being to explain known variance in HRV at the onset of relaxation resulting from baseline and post-exercise differences in HRV between conditions. In order to control for known differences in vagal mediation of cardiac control due to aerobic fitness level, sex/gender, and age (Stein et al., 1997; Rossy and Thayer, 1998), VO_2max, sex, and age were included as nuisance covariates in all HRV analyses.

Given that the sample mean body mass index (BMI) was 26.1 (slightly overweight), additional correlational and ANCOVA analyses were performed to rule out a potentially confounding effect of BMI. To rule out a potentially confounding effect of condition order, this variable was included in all ANCOVA models as a between-subjects factor *post hoc*. When condition order was included in the ANCOVA models as a between-subjects factor, in each case significant findings became more significant and Condition × Time error was moderately reduced. No significant Condition × Time × Condition Order interactions were observed.

Primary analyses: Heart rate variability

To assess whether theta-frequency binaural-beats significantly altered sympathovagal balance (i.e., LF to HF normalized power ratio; LF/HF) over the course of the relaxation session (i.e., beginning, middle, and end), a 2 (Condition) × 3 (Time) repeated-measures analysis of covariance (RM-ANCOVA) was employed. Normalized LF and HF components were then assessed independently via 2 × 3 RM-ANCOVAs with the same covariates.

Table 2 | Baseline and post-exercise measures of heart rate variability.

	Placebo *M* (*SE*)	Binaural-beat *M* (*SE*)	*F (p)*
Baseline heart rate	71.88 (1.03)	69.55 (1.03)	0.49 (0.492)
Baseline LF power	66.62 (1.05)	57.86 (1.05)	4.00 (0.063)
Baseline HF power	27.61 (1.11)	31.41 (1.07)	4.43 (0.051)
Baseline LF/HF ratio	2.42 (1.17)	1.84 (1.11)	5.25 (0.035)*
Post-Ex heart rate	98.00 (1.04)	97.61 (1.03)	0.02 (0.884)
Post-Ex LF power	82.76 (1.03)	82.76 (1.03)	1.34 (0.255)
Post-Ex HF power	13.64 (1.16)	14.00 (1.15)	1.10 (0.310)
Post-Ex LF/HF ratio	6.07 (1.19)	5.91 (1.18)	1.17 (0.295)

*All power measures expressed in normalized units. Age, sex, and VO_2max included as covariates in model. *$p < 0.05$.*

Significant Condition × Time interactions were followed up with planned within-subjects repeated-measures contrasts (RELAX-1 to RELAX-2 and RELAX-2 to RELAX-3). To further characterize the nature of observed Condition × Time interactions, simple main effects of Time were assessed via within-subjects F-test within each condition separately; where significant F-statistics were observed, planned within-subjects contrasts were reported. Simple main effects of Condition were assessed at each time point, again via RM-ANCOVA. When observed, significant covariate interactions were explored by plotting said covariate against each condition's delta regressor (i.e., RELAX-3–RELAX-1). In order to rule out gross patterns of autonomic difference, mean heart rate was also evaluated at baseline, post-exercise, and at each relaxation time point using RM-ANCOVA. Given the short duration of HRV recording samples, time-domain, and non-linear measures were not explored.

Secondary analyses: Perceived relaxation

Perceived relaxation ratings were assessed through paired-samples t-test. Effects of baseline variability in HRV on perceived relaxation were assessed using RM-ANCOVA; marginal means for significant results were reported. Relationships between in-session HRV measures and perceived relaxation were explored using bivariate correlation, partial correlation and linear regression.

RESULTS

BASELINE AND POST-EXERCISE MEASURES OF HEART RATE VARIABILITY

After controlling for age, sex, and VO_2max, a significant difference was observed between conditions for baseline LF/HF ratio, with subjects exhibiting reduced baseline sympathovagal balance during the binaural-beat session (**Table 2**). No differences were observed between conditions for post-exercise HRV values, even after including baseline HRV values as covariates. Mean heart rate did not differ between conditions at any time point and was not significantly higher than baseline at RELAX-3 (all $p > 0.05$). Exercise significantly decreased HF power and increased LF and LF/HF powers during both conditions (all $p < 0.05$).

Body mass index was not correlated with any measure of HRV (i.e., HF, LF, or LF/HF components) during the relaxation protocol during either experimental condition (all $p > 0.05$). This remained the case after running partial correlations controlling for age, sex, and VO_2max. To assess group differences while maintaining statistical power, participants were categorically coded in to low (BMI $\leq$ 25; $n = 10$), high (BMI $\leq$ 30; $n = 8$), and very high (BMI > 30; $n = 3$). This categorical variable, 'BMI-level,' was then added into the general linear model for each ANCOVA as a between-subjects variable. For HF, LF, and LF/HF, within-subjects ANCOVA results still showed a significant Condition × Time effect (all $p < 0.05$) with no significant Condition × Time × BMI-level interactions (all $p > 0.05$).

EFFECTS OF BINAURAL-BEATS ON HEART RATE VARIABILITY

The effects of binaural-beats were assessed through three independent 2 × 3 RM-ANCOVAs for LF/HF, LF, and HF. Marginal means for HRV measures at the beginning (RELAX-1), middle (RELAX-2), and end (RELAX-3) of the relaxation protocol are shown in **Table 3**.

Low-frequency to high-frequency ratio

2 × 3 RM ANCOVA revealed a significant Condition × Time interaction for LF/HF, $F(2,30) = 5.130$, $p = 0.012$, $\eta^2 = 0.255$ (**Figure 2**). LF/HF ratio increased in the placebo condition but decreased in the binaural-beat condition from the beginning to the middle of the relaxation protocol (i.e., from RELAX-1 to RELAX-2), $F(1,15) = 5.427$, $p = 0.044$, $\eta^2 = 0.245$. No significant interactions between conditions were observed from the middle to the end of the relaxation protocol. There was a significant Condition × Time × VO_2max interaction observed for LF/HF, $F(2,30) = 3.793$, $p = 0.034$, $\eta^2 = 0.202$. However, the interaction of Time × VO_2max was not significant in either condition ($p > 0.05$). When VO_2max was regressed against delta (RELAX-3–RELAX-2) for the binaural-beat condition, $\beta = -0.268$; in the placebo condition, $\beta = 0.139$.

Follow-up simple main effects of Condition RM-ANCOVAs showed no significant difference between conditions for any time point (all $p > 0.05$; see **Table 3** above). No simple main effect of Time was observed for the placebo condition ($p = 0.270$); however a simple main effect of Time was observed in the binaural-beat condition [$F(2,32) = 3.866$, $p = 0.031$, $\eta^2 = 0.195$]. No

Table 3 | Marginal heart rate variability means at onset, middle, and end of relaxation protocol.

	Placebo *M* (*SE*)	Binaural-beat *M* (*SE*)	*F* (*p*)
Onset of relaxation			
RELAX-1 Heart Rate	85.03 (1.03)	84.35 (1.03)	0.03 (0.873)
RELAX-1 LF Power	66.89 (1.06)	61.62 (1.07)	7.93 (0.013)*
RELAX-1 HF Power	27.91 (1.11)	28.56 (1.14)	2.44 (0.139)
RELAX-1 LF/HF Ratio	2.4 (1.17)	2.16 (1.21)	4.03 (0.063)
Middle of relaxation			
RELAX-2 Heart Rate	77.56 (1.03)	77.09 (1.04)	0.00 (0.961)
RELAX-2 LF Power	65.04 (1.07)	61.37 (1.07)	0.095 (0.762)
RELAX-2 HF Power	26.41 (1.14)	30.17 (1.13)	0.678 (0.423)
RELAX-2 LF/HF Ratio	2.46 (1.22)	2.03 (1.19)	0.543 (0.473)
End of relaxation			
RELAX-3 Heart Rate	75.04 (1.03)	73.70 (1.04)	0.03 (0.858)
RELAX-3 LF Power	59.2 (1.07)	59.15 (1.07)	1.33 (0.267)
RELAX-3 HF Power	34.47 (1.12)	32.95 (1.11)	2.10 (0.169)
RELAX-3 LF/HF Ratio	1.72 (1.20)	1.8 (1.17)	2.03 (0.174)

All power measures expressed in normalized units. Age, sex, VO_2max, and ΔHRV (post-exercise – baseline; for each respective HRV variable) are included as covariates in the model. *$p < 0.05$.

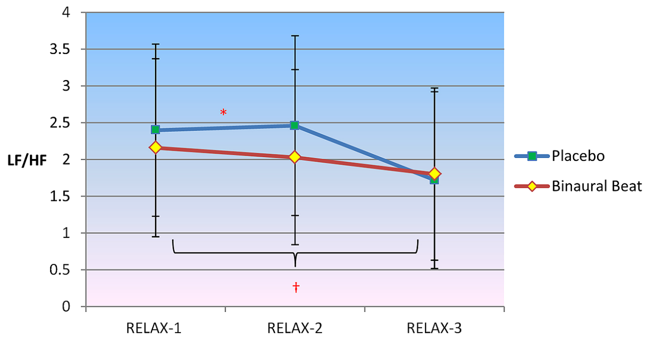

FIGURE 2 | Differences in sympathovagal balance (i.e., LF/HF) between binaural-beat and placebo conditions. Error bars represent ±1 SE of the marginal mean. *Condition × Time interaction is significant at $p < 0.05$. †Simple main effect of Time is significant at $p < 0.05$ (for binaural-beat condition only). *Interaction is significant at $p < 0.05$.

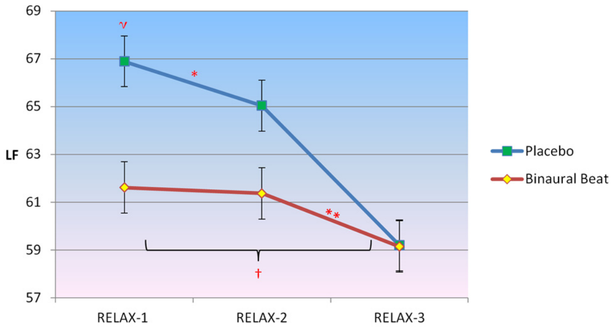

FIGURE 3 | Differences in the trajectory of low-frequency (LF) power (representing a combination of sympathetic and parasympathetic influences) over the course of relaxation between binaural-beat and placebo conditions. Error bars represent ±1 SE of the marginal mean. *Condition × Time interaction is significant at $p < 0.05$. $^{\eta}$Marginal means are significantly different at $p < 0.05$. †Simple main effect of time is significant at $p < 0.05$ (for binaural-beat condition only). **Within-subjects contrast from RELAX-2 to RELAX-3 is significant at $p < 0.05$.

within-subjects contrasts were significant in the binaural-beat condition (all $p > 0.05$).

Low-frequency normalized power

2 × 3 RM ANCOVA showed a significant Condition × Time interaction for LF, $F(2,30) = 7.202$, $p = 0.003$, $\eta^2 = 0.324$ (**Figure 3**). LF/HF ratio increased in the placebo condition but decreased in the binaural-beat condition from the beginning to the middle of the relaxation protocol (i.e., after 10-min of stimulus exposure), $F(1,15) = 5.427$, $p = 0.044$, $\eta^2 = 0.245$. No significant interactions between conditions were observed from the middle to the end of the relaxation protocol. There was a significant Condition × Time × VO_2max interaction observed for LF, $F(2,30) = 4.806$, $p = 0.015$, $\eta^2 = 0.243$. The interaction of Time × VO_2max was not significant in either condition ($p > 0.05$). When VO_2max was regressed against delta (RELAX-3–RELAX-2) for the binaural-beat condition, $\beta = -0.267$; in the placebo condition, $\beta = 0.272$.

Follow-up simple main effects of Condition RM-ANCOVAs showed no significant difference between conditions for any time point (all $p > 0.05$; see **Table 3** above). No simple main effect of Time was observed for the placebo condition ($p = 0.183$), however, a simple main effect of Time was observed in the binaural-beat condition [$F(2,32) = 4.057, p = 0.027, \eta^2 = 0.202$].

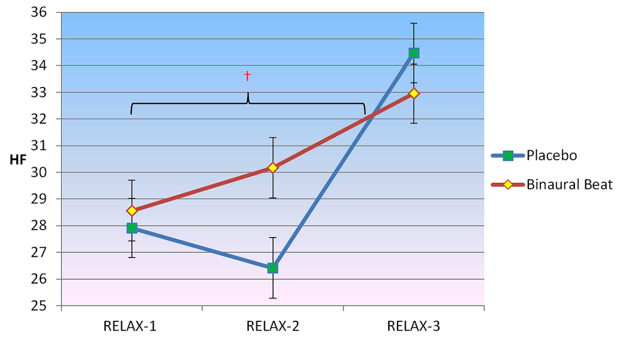

FIGURE 4 | Differences in the trajectory of high-frequency (HF) power (representing parasympathetic influence) over the course of relaxation between binaural-beat and placebo conditions. Error bars represent ±1 SE of the marginal mean. † Simple main effect of Time significant at $p < 0.05$ (for binaural-beat condition only).

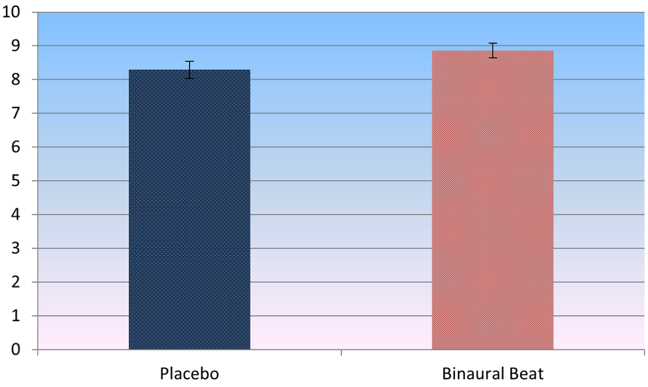

FIGURE 5 | Self-report ratings of perceived relaxation post-treatment ($t = 2.248$, $p = 0.036$, $d = 0.493$). Error bars represent ±1 SE of the marginal mean.

Within-subjects contrasts were significant in the binaural-beat condition from RELAX-2 to RELAX-3.

High-frequency normalized power

2×3 RM ANCOVA showed a significant Condition × Time interaction for HF, $F(2,30) = 3.811$, $p = 0.034$, $\eta^2 = 0.203$ (**Figure 4**). Planned follow-up within-subjects contrasts indicated an approach towards significance for HF, $F(1,15) = 3.305$, $p = 0.089$, from the beginning to the middle of the relaxation protocol. No significant interactions between conditions were observed from the middle to the end of the relaxation protocol. No Condition × Time × Covariate interactions were observed ($p > 0.05$).

Follow-up simple main effects of Condition RM-ANCOVAs showed no significant difference between conditions for any time point (all $p > 0.05$; see **Table 3** above). No simple main effect of Time was observed for the placebo condition ($p = 0.295$); however, a simple main effect of Time was observed in the binaural-beat condition [$F(2,32) = 3.269$, $p = 0.051$, $\eta^2 = 0.170$]. No within-subjects contrasts were significant in the binaural-beat condition (all $p > 0.05$).

EFFECTS OF BINAURAL BEATS ON PERCEIVED RELAXATION

Paired-samples t-test of post-treatment self-reported relaxation ratings revealed that subjects reported significantly more relaxation in the binaural-beat condition relative to the placebo condition ($p = 0.036$, $d = 0.493$; **Figure 5**). Importantly, this difference remained significant after including baseline LF/HF ratios as covariates in a RM-ANVOCA [$F(1,18) = 5.75$, $p = 0.027$, $\eta^2 = 0.242$]. This provides some support for the idea that differences in self-reported relaxation were driven by binaural-beat exposure, not by baseline differences in autonomic tone.

RELATIONS BETWEEN PERCEIVED RELAXATION AND HEART RATE VARIABILITY

In the binaural-beat condition (but not in the placebo condition), LF/HF during the middle of relaxation was negatively correlated with, ($r = -0.695$, $p < 0.001$), and significantly predictive of, [$F(1,20) = 17.786$, $p < 0.001$], reported relaxation at the end of the session (**Figure 6**). This was the case for LF, ($r = -0.640$, $p = 0.002$; $F(1,20) = 13.204$, $p = 0.002$) as well; whereas HF was positively correlated with ($r = 0.699$, $p < 0.001$), and predictive of [$F(1,20) = 18.203$, $p < 0.001$], relaxation at the end of the session. To rule out the possibility that baseline LF/HF was responsible for the observed differences in perceived relaxation, a regression model was performed for each condition between baseline LF/HF, RELAX-2 LF/HF, and perceived relaxation. While both conditions' baseline LF/HF values were significantly predictive of LF/HF mid-relaxation [$F(1,20) = 8.409$, $p = 0.006$ and $F(1,20) = 12.566$, $p = 0.002$, respectively], neither conditions' baseline LF/HF values were significantly predictive of self-reported perceived relaxation at the end of the study (all $p > 0.05$). Partial correlations remained significant after controlling for age, sex, VO_2max, and delta HRV regressor (all $p < 0.05$). Changes in self-reported relaxation between conditions were not correlated with changes in HRV between conditions or with changes in HRV from the beginning to the end of the relaxation sessions (all $p > 0.05$).

DISCUSSION

OVERVIEW OF HEART RATE VARIABILITY FINDINGS

The present study investigated the effectiveness of theta-frequency binaural beats in enhancing the post-exercise relaxation response, quantified as trophotropic modulation of autonomic nervous system dynamics (i.e., HRV), and perceived relaxation. We hypothesized that binaural beats would increase HF power and decrease LF power and LF/HF ratio in a manner consistent with the binaural-beat entrainment model (i.e., that theta-frequency entrainment would effect trophotropic changes in autonomic arousal).

Consistent with our hypotheses, results demonstrate that, relative to placebo, 20-min of exposure to binaural beats significantly increased HF power – a known marker of parasympathetic activation that is driven by activity in regions of the anterior cingulate and medial prefrontal cortex (Wager et al., 2009). Binaural-beat exposure also decreased LF power and LF/HF ratio. Initial response to binaural beats (i.e., within the first 2-min) was characterized by significantly reduced LF power relative to placebo, with no differences in HF power or LF/HF ratio. This was the only time

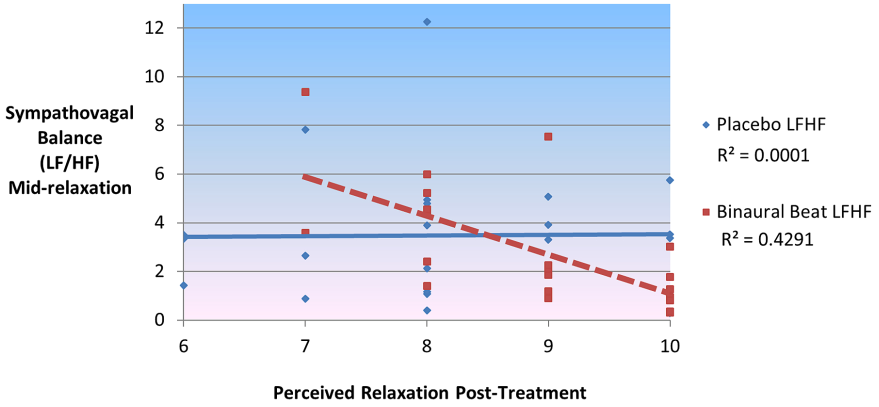

FIGURE 6 | Sympathovagal balance (LF/HF) mid-relaxation predicts 43% of variance in self-reported ratings of perceived relaxation in binaural-beat but not placebo condition.

point where subjects showed a significant difference in mean HRV between conditions. However, significant interactions indicated a differential response to binaural beats vs. placebo, with subjects exhibiting an increase in parasympathetic dominance while listening to binaural beats, but an increase in sympathetic dominance while listening to placebo. Subjects exhibited a decrease in LF power over the first 10-min of listening to placebo but showed no change during the same period while listening to binaural beats. These findings suggest that theta-frequency binaural beats initially modulate LF power post-exercise, followed by subsequent modulation of HF power, with an overall net effect of increasing parasympathetic dominance. It appears that even a brief administration (e.g., <2-min) of binaural beats may produce acute effects on autonomic nervous system response post-exercise.

Notably, subjects entered into the relaxation protocol with a mean post-exercise heart rate of 98 bpm, which did not vary significantly by condition. After 2-min of the relaxation protocol, mean heart rate had dropped to 85 bpm, which also did not differ by condition. Research has shown that post-exercise heart rate recovery is initially mediated by a combination of sympathetic withdrawal and parasympathetic activation, but as heart rate falls below 100 bpm, parasympathetic activation begins to dominate (Pierpont and Voth, 2004). Over the course of the relaxation period, mean heart rate dropped to 74 bpm. This suggests that initial decreases in heart rate may have resulted from a combination of sympathetic and parasympathetic modulation, while subsequent decreases were increasingly mediated by parasympathetic activation (i.e., increases in HF power as well as decreased LF and LF/HF ratio).

Somewhat unexpectedly, aerobic fitness level was found to significantly interact with both Time and Condition, producing differential LF and LF/HF responses to binaural-beat vs. placebo. Specifically, in the placebo condition, greater aerobic fitness was associated with larger change scores for LF and LF/HF – suggesting that fitter individuals exhibited less sympathetic withdrawal over the course of the placebo relaxation period. Conversely, while in the binaural-beat condition, aerobic fitness was negatively correlated with relaxation LF and LF/HF change scores, suggesting that fitter individuals exhibited greater sympathetic withdrawal while listening to binaural beats. In part, this explains why simple main effects of Time were observed for the binaural-beat condition but not for the placebo condition, when aerobic fitness was included as a covariate.

PERCEIVED RELAXATION FINDINGS

Interestingly, subjects' sympathovagal balance during the middle of the relaxation protocol significantly predicted 43% of the variance in self-reported relaxation while listening to binaural beats, but none of the variance during the placebo condition. Further, subjects also reported being significantly more relaxed while listening to binaural beats then while listening to the placebo. Findings from this double-blind placebo-controlled study may suggest a role for binaural beats in facilitating access to more restorative states of post-exercise relaxation with subtle, yet somewhat durable psychophysiological effects. These findings should be interpreted with caution, however, given that the change in HRV measures during relaxation were not correlated with the change in relaxation scores. Regardless, results may suggest that binaural-beat associated HRV may be coupled with subjective perceptions of relaxation more so than HRV associated with standard music perception.

LIMITATIONS AND FUTURE DIRECTIONS

In summary, we present preliminary evidence for a role of binaural beats in acutely modulating autonomic arousal, as measured through HRV. We also provide evidence linking autonomic correlates of binaural-beat exposure with a subsequent behavioral measure – perceived relaxation. Given that our sample comprised young, healthy college students, it is important for future research to investigate how binaural beats might interact with autonomic activity in a broader demographic (e.g., high-stress and clinical populations, meditation practitioners). Future studies, outside of the exercise context, that include measures of control for baseline differences in autonomic tone are warranted in order to evaluate the putative beneficial effects of theta-frequency binaural beats on the facilitation of relaxation. Further, binaural-beat technology is often designed as a training device: to assist users in accessing various altered states of consciousness. Future research will need to ascertain the extent to which structured binaural-beat training might provide for a cumulative training effect.

Although these findings suggest that theta-frequency binaural beats may facilitate relaxation post-exercise, it is important to note that other factors may have contributed to these findings. First, no measure of relaxation was taken prior to the relaxation protocol; thus, it is uncertain whether or not the observed results were a direct result of binaural-beat exposure or some other factor affecting perceived relaxation. Second, at baseline, subjects exhibited significantly lower sympathovagal balance during the binaural-beat condition relative to the control condition. It is possible that this caused the timeline of the exercise-recovery period to be offset, potentially explaining the differential autonomic response observed during the relaxation protocol between conditions. However, baseline HRV differences were controlled for in our analyses, and as previously noted, baseline sympathovagal balance predicted mid-relaxation HRV, but did not predict self-reported perceived relaxation. Only HRV indices while listening to binaural beats predicted subsequent reported relaxation. Furthermore, exercise served to bring subjects into a comparable state of physiological arousal which did not significantly differ by condition. Third, the study's small sample size is an important limitation, although we attempted to offset this through our repeated-measures design. Future studies should attempt to replicate these findings with a sample larger than 30. Fourth, according to the BMI scale, our sample was, on average, classified as slightly overweight. It is important to note that BMI was not a primary independent variable, dependent variable, or covariate in our study. Height and weight were necessarily collected as they were used in the regression formula for predicted VO_2max. Further, it is also important to mention that many of our study's participants were collegiate athletes with elevated lean muscle mass, a demographic that is notoriously misclassified as 'overweight' or 'obese' by the BMI (Ode et al., 2007). Lastly, given that subjects showed an initial decrease in LF power while listening to the placebo, it is unclear to what extent the observed differences in LF power, and absence of placebo-associated changes in autonomic tone over the course of the relaxation protocol, are a result of binaural-beat assisted sympathetic withdrawal, or placebo-associated inhibition of sympathetic withdrawal. Further research with a 'no-music' condition will be needed to resolve this issue.

Crucially, however, the primary aim of this study was to evaluate the putative role of binaural beats in affecting autonomic nervous system activity in isolation from common confounds such as verbal guidance or instrumental music. Therefore, while the current study is not without limitations, when taking these limitations into consideration in our analytic strategy, we still demonstrated acute binaural-beat effects on parasympathetic activation and sympathetic withdrawal post-exercise.

CONCLUSION

Acute exposure to theta-frequency binaural beats in a young, healthy sample of college students resulted in increased parasympathetic activation, increased sympathetic withdrawal, and increased self-reported relaxation post-exercise. Binaural-beat-associated HRV appeared to be more tightly coupled with self-reported relaxation than placebo-associated HRV. These findings support the putative clinical effectiveness of binaural beats in their own right, the effects of which may be synergistically enhanced through combination with other therapeutic factors such as verbal guidance and music.

AUTHOR CONTRIBUTIONS

Patrick A. McConnell, Gary A. Sforzo and Jeffrey C. Ives were responsible for the study concept and design, and provided critical revision of the manuscript. Brett Froeliger and Eric L. Garland assisted with developing the data analysis strategy, interpreting findings, and provided critical revision of the manuscript. Patrick A. McConnell was responsible for all data collection, data analysis, drafting the manuscript, and interpreting the findings. All authors have made active contributions, critically reviewed content, and approved of the final version.

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Short-term meditation increases blood flow in anterior cingulate cortex and insula

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Asymmetry in frontal electrical activity has been reported to be associated with positive mood. One form of mindfulness meditation, integrative body-mind training (IBMT) improves positive mood and neuroplasticity. The purpose of this study is to determine whether short-term IBMT improves mood and induces frontal asymmetry. This study showed that 5-days (30-min per day) IBMT significantly enhanced cerebral blood flow (CBF) in subgenual/adjacent ventral anterior cingulate cortex (ACC), medial prefrontal cortex and insula. The results showed that both IBMT and relaxation training increased left laterality of CBF, but only IBMT improved CBF in left ACC and insula, critical brain areas in self-regulation.

Keywords: integrative body–mind training, cerebral blood flow, positive mood, frontal asymmetry, anterior cingulate cortex

INTRODUCTION

Mindfulness meditation has been shown to produce positive effects on psychological wellbeing (Hölzel et al., 2011). As an important benefit of meditation practice, changes in self-reported positive mood or emotion are often observed (Kabat-Zinn et al., 1992; Tang et al., 2007). In particular, one form of meditation, the integrative body-mind training (IBMT) that originates from traditional Chinese medicine, improves attention, self-regulation, and mood after only few hours of training in comparison with relaxation training in a random assignment design (Tang et al., 2007; Ding et al., 2014).

Since late 1970s, frontal EEG asymmetry has had widespread use in measuring individual differences in emotional state. In general, it is believed a left-sided frontal activation indicates a positive emotion, although the evidence is not always consistent with this view (Allen and Kline, 2004; Allen et al., 2004; Cacioppo, 2004; Travis and Arenander, 2004, 2006).

A number of EEG studies have examined the relationship between meditation and frontal asymmetry (Davidson et al., 2003; Moyer et al., 2011). For example, 8-weeks mindfulness-based stress reduction, in comparison to a wait-list control, increased left-sided lateralization of alpha power and decreased negative affect (Davidson et al., 2003). Another study suggested 5-weeks of meditation shifts EEG asymmetry toward a pattern associated with positive emotion compared to a waiting-list control although there was no significant difference between the two groups (Moyer et al., 2011).

However, previous studies have used EEG with low spatial resolution and have not involved an active control group. To our knowledge, only one single photon emission computed tomography (SPECT) imaging study reported a marginal significant left frontal asymmetry of cerebral blood flow (CBF) but this study involved a sample of 12 long-term meditators compared to normal controls (Newberg et al., 2010) and was not a randomized test with an active control. Thus, we set out to apply brain imaging to investigate the CBF asymmetry induced by short-term training in a relatively large sample of 40 undergraduates with a random assignment to IBMT or relaxation training groups. We hypothesize that IBMT could improve left frontal CBF at resting state, which may underlie the promotion of positive emotion.

MATERIALS AND METHODS

PARTICIPANTS

Forty right-handed Chinese undergraduates at Dalian University of Technology without any training experience and a history of psychiatric or neurological conditions were recruited. They were randomly assigned to IBMT or relaxation group (20:20 each group, age = 22.75 ± 2.02), a brief self-report mood scale, similar to short form of Positive and Negative Affect Schedule (PANAS) was used to measure positive (PA) and negative affect (NA; Moyer et al., 2011; Ding et al., 2014). A written informed consent was obtained and local IRB approved the study.

TRAINING

Participants received 30-min of IBMT or relaxation training from Monday through Friday, with a total of 2.5 h training. IBMT involves body relaxation, mental imagery, and mindfulness training, guided by an IBMT coach and compact disk. Cooperation between the body and the mind is emphasized in facilitating and achieving a meditative state. The trainees concentrated on achieving a balanced state of body and mind. The method stresses no effort to control thoughts, but instead a state of restful alertness that allows a high degree of awareness of body, mind, and external instructions (Tang et al., 2007, 2010; Tang, 2011). Relaxation training involves the relaxing of different muscle groups over the face, head, shoulders, arms, legs, chest, back, and abdomen, etc., guided by a tutor and compact disk. With eyes closed and in a sequential pattern, one is forced to concentrate on the sensation of relaxation such as the feelings of warmth and heaviness. This progressive training helps the participant achieve physical and mental relaxation and calmness (Tang et al., 2007, 2010).

IMAGE ACQUISITION AND ANALYSIS

Single photon emission computed tomography neuroimaging data were acquired on a double head detector of GE HAWK EYE SPECT system (Millenium VG, GE Healthcare) from all participants before and after a 5-days IBMT or relaxation training. Participants were instructed to stay in a quiet dark room with eyes closed and ears unoccluded for 10 min, and then they were injected with 25 mCi of $^{99\,\mathrm{m}}$Tc-ECD. Approximately 20 min following the injection, participants were scanned by SPECT system for 30 min (Tang et al., 2009; Newberg et al., 2010). Two different statistical methods were used to estimate CBF before and after training.

Statistical parametric mapping (SPM[1]) was applied to evaluate whole brain CBF differences between these two groups. All images were normalized to the SPECT template in SPM, and then 8 mm Gaussian kernel was used to smooth these images. Two groups' data were compared using two sample t-test with *ANCOVA* for removing global effect. The significance threshold was set at $p < 0.001$ (Tang et al., 2009; Newberg et al., 2010). The location and peaks of activation was identified by xjview[2].

Frontal asymmetry analysis was performed by SPSS (SPSS Inc., Chicago, IL, USA). CBF of the prefrontal regions, including inferior, middle, and superior frontal gyrus were extracted. All brain regions were identified by AAL atlas (Tzourio-Mazoyer et al., 2002). The laterality indexes were calculated by the following formula (Newberg et al., 2010):

$$\text{Laterality Index} = \frac{(\text{Right} - \text{Left})}{0.5 \times (\text{Right} + \text{Left})} \times 100$$

RESULTS

Consistent with our previous studies (Tang et al., 2007; Ding et al., 2014), no significant difference in mood was detected before training between two groups ($p > 0.05$). After training, the IBMT group showed significantly better scores in positive and negative affect in comparison with the RT group; IBMT group (not RT) also showed significant post vs. pre difference in PN and NA (all $p < 0.05$). These results suggested that short-term IBMT induced higher positive mood and lower negative mood states than relaxation training. However there was no significant time by group interaction.

Table 1 | Statistical parametric mapping (SPM) activation results in integrative body-mind training (IBMT) group (after vs. before).

Brodmann area	***p* value**
Left hemisphere	
BA 32	0.043
Insula	0.026
BA 10	0.001
Right hemisphere	
BA 25	0.005
BA 32	0.021

Imaging results showed that two groups did not differ in frontal CBF asymmetry before training ($p > 0.05$). However, the IBMT group (not relaxation group) had a significant CBF increase in subgenual/adjacent ventral anterior cingulate cortex (ACC; BA 25, BA 32), medial prefrontal cortex (BA 10) and insula after training (all $p < 0.05$). The group × session interaction was significant for BA 25 [$F(1,38) = 4.652$; $p < 0.05$], BA 10 [$F(1,38) = 10.652$; $p < 0.01$], and marginally significant for insula [$F(1,38) = 3.73$; $p = 0.06$], respectively. SPM activation results of Brodmann areas in IBMT group were shown in **Table 1** (after vs. before).

There were no significant differences in before vs. after laterality scores in frontal areas between the two groups. Instead, both groups showed significant differences favoring the left hemisphere in tIFG (triangular part of inferior frontal gyrus, $p = 0.033$) and oSFG (orbital part of superior frontal gyrus, $p = 0.045$) as shown in **Figure 1**. The IBMT group revealed larger laterality indexes that implied greater left frontal CBF lateralization, compared to relaxation group after training, but the group × session interaction was not significant.

DISCUSSION

Consistent with our previous studies, short-term IBMT improves CBF in the midfrontal lobe and insula compared to the relaxation training (Tang et al., 2007, 2009). This result is in line with the neural correlates of mindfulness meditation (Cahn and Polich,

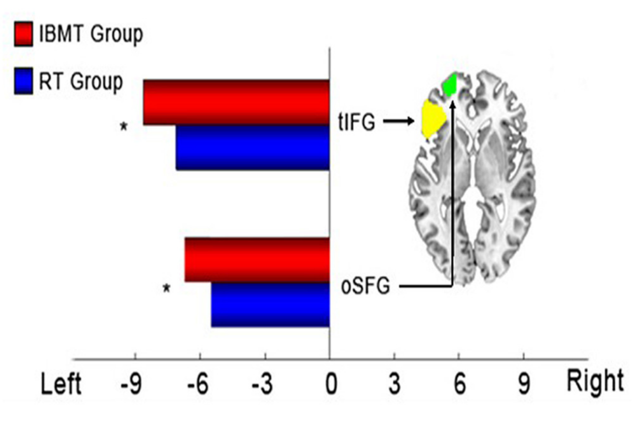

FIGURE 1 | Statistical results of laterality indexes in frontal regions. Left: significant frontal laterality differences in integrative body-mind training (IBMT) and relaxation groups. Right: axial section of two frontal regions ($z = -1$). tIFG, triangular part of inferior frontal gyrus; oSFG, orbital part of superior frontal gyrus. *$p < 0.05$.

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[1] http://www.fil.ion.ucl.ac.uk/spm/

[2] http://www.alivelearn.net/xjview8/

2006; Hölzel et al., 2011; Tang and Posner, 2014). The specific brain areas showing greater CBF following IBMT training suggests that IBMT works, in part, by improving self-regulation (Posner and Rothbart, 2006; Tang et al., 2007; Hölzel et al., 2011; Tang, 2011; Tang and Posner, 2014).

Our study, using the frontal asymmetry analysis, indicated only a few hours of training increases left-sided CBF asymmetry in both groups but IBMT's increase is greater than that of relaxation training.

In previous studies meditation training promoted positive emotions and degraded negative affect (Kabat-Zinn et al., 1992; Tang et al., 2007; Ding et al., 2014) Studies have found 8-weeks mindfulness meditation produced EEG frontal asymmetry and reduced negative mood state (Davidson et al., 2003). In our previous study of 80 Chinese undergraduates, a few hours of IBMT improved positive moods using a 65-item Profile of Mood States (POMS; Tang et al., 2007, 2009; Newberg et al., 2010; Tang, 2011). The current study did not repeat the POMS measures, instead, a brief self-report positive and negative mood scale was used before and after training (Moyer et al., 2011; Ding et al., 2014). After training a significant between-group differences were observed and IBMT group performed better in mood states than relaxation group. However, we did not find a significant difference in the group by time of testing interaction in mood. It is likely that that the brief measure of mood was not as sensitive as the POMS. These findings could also be due to power considerations and sensitivity of imaging techniques (Gatzke-Kopp et al., 2001), but with 20 participants per group our study has a larger number than most imaging studies.

Although studies have shown mindfulness meditation increased left-sided anterior activation, a pattern previously associated with positive affect (Davidson et al., 2003; Moyer et al., 2011) comparing to a wait-list control group, alternation of EEG frontal asymmetry was not detected during transcendental meditation, but the participants' emotion states were improved (Travis and Arenander, 2004, 2006). Given the low spatial resolution of EEG, it remains to be elusive whether the brain regions involved in these studies are the same. In our study both meditation and relaxation resulted in increased left lateralization, but only IBMT changed mood and brain activity in ACC and insula associated with self-control, consistent with our series of research (Tang et al., 2007, 2009, 2010). Since we did not detect the significant correlation between frontal asymmetry and mood using EEG, future studies will be needed to demonstrate the mechanisms of changes in frontal asymmetry and mood state using ERP/fMRI fusion approach.

Our study shows that few hours of IBMT increases resting CBF in specific brain areas often shown to be involved in attention and self-regulation (Posner and Rothbart, 2006; Tang et al., 2009, 2010; Hölzel et al., 2011; Tang, 2011). However, both IBMT and relaxation training increase frontal asymmetry significantly, although IBMT has a somewhat larger increase. The IBMT group has better overall mood state following training, but it is not clear if the brain differences found in this study are the cause of the changes in affect and mood.

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Time course of conflict processing modulated by brief meditation training

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Resolving conflict is a pivotal self-control ability for human adaptation and survival. Although some studies reported meditation may affect conflict resolution, the neural mechanisms are poorly understood. We conducted a fully randomized 5 h trial of one form of mindfulness meditation—integrative body-mind training (IBMT) in comparison to a relaxation training control. During the Stroop word-color task, IBMT group produced faster resolution of conflict, a smaller N2 and an earlier and larger P3 component of the event-related brain potentials. These results indicate that brief meditation training induces a brain state that improves the resolution of conflict.

Keywords: IBMT, conflict resolution, self-control, brain state, ACC, N2, P3

Introduction

Our previous randomized studies have shown that integrative body-mind training (IBMT) improves attention and self-regulation after short-term practice (Tang et al., 2007; Tang and Posner, 2009, 2014). Furthermore, 5 days of IBMT training can induce better conflict resolution in the flanker and Stroop task than same amount of relaxation training (RT; Tang et al., 2007; Fan et al., 2014). IBMT is one form of mindfulness meditation and originates from Eastern contemplative tradition and seems to work by increasing brain activity of self-regulation areas such as the anterior cingulate cortex (ACC) and improving its connection to the parasympathetic branch of the autonomic nervous system (Tang et al., 2009, 2012a; see more on Training Methods).

The Stroop effect has often been used as the gold standard for assessing conflict resolution (Stroop, 1935; MacLeod, 1991). The Stroop interference effect (or conflict resolution) refers to the longer time that it takes to name the ink color of a color-word when the ink color and printed color-word are incongruent (e.g., "RED" in blue ink, meaning the "conflict condition") as compared to congruent (e.g., "RED" in red). Long-term meditation training has been found to improve the efficiency of the executive attentional network measured by the paper Stroop task (Chan and Woollacott, 2007). Wenk-Sormaz (2005) showed that meditation practice led to a reduction in habitual patterns of response on the Stroop task, however, another study failed to find the same effects of mindfulness meditation (Anderson et al., 2007). Compared to a waiting list control, meditators showed better performance on Stroop task (Moore and Malinowski, 2009; Moore et al., 2012; Teper and Inzlicht, 2013); however, these studies were not randomized and could not provide conclusion on causality (Moore and Malinowski, 2009).

In an event-related potentials (ERPs) study of the manual Stroop task, P3 is defined as the largest positive peak following the N1-P2-N2 complex within a latency window between 280 and 600 ms (Ilan and Polich, 1999). P3 timing provides a measure of stimulus classification time that is independent of response processes. P3 amplitude reflects the amounts of attentional resources employed in a given task (Polich, 2007). Stroop interference occurs only after initial color and word processing and is most closely related to the response selection stage (Ilan and Polich, 1999; Rosenfeld and Skogsberg, 2006).

In a long-term meditator group with 2.5–40 years of experience, P3 amplitude was reduced for distracting stimuli in the oddball task, suggesting that meditators had a different attention allocation than non-meditators (Cahn and Polich, 2009). Studies have shown that the fronto-parietal N2 reflects conflict-related activity in the ACC (Van Veen and Carter, 2002; Rueda et al., 2004, 2005). Compared to a waiting list control, meditation training also influences N2 and P2 components, but the direction of these results are inconsistent (Moore et al., 2012; van Leeuwen et al., 2012). Taken together, ERP components can be modulated by meditative practice, although whether these findings are due to training or a pre-existing property of those who choose meditation remains unclear.

In the present study, we aimed to use ERPs to extend our previous behavioral findings and examine the time course of the neural correlates of processing conflict using a standard computerized Stroop task in a randomized design with 5 h of IBMT training. Prior to and following training, all subjects performed the standard Stroop word-color task while their brain activity was measured using ERPs. We hypothesized that (1) after 5 h training, IBMT group will have more reduced Stroop interference effect in reaction time than for relaxation group (2) IBMT will alter the N2 and P3 Stroop-related ERP components through the ACC. These new results will advance our understanding of brain mechanisms of conflict processing related to mental training.

Materials and Methods

Subjects and Task

Thirty-five healthy undergraduates (mean age = 21.31, 17 male) without any prior meditation or RT experience participated in this study. All subjects were right-handed, and had normal or corrected-to-normal vision. The experiment was approved by a local Institutional Review Board, and informed consent was obtained from each participant. The experiment consisted of neural, congruent, and incongruent stimuli programmed by E-prime (Psychology Software Tools, Sharpsburg, PA, USA). The congruent stimuli consisted of the three color words in Chinese (red, yellow, blue) written in the same color in which the stimulus was presented (e.g., the word red written in red color). The incongruent stimuli consisted of the same three words with display colors that do not match the word meaning (e.g., the word yellow written in red color). Each incongruent stimulus appeared in either of the two colors that does not match its meaning. In the neutral condition, two no-color words (ball, watch) were presented in one of the three colors.

Subjects were instructed to rest their right middle three fingers on the left three keys of the E-prime response box, and each finger represents one color. They were told that a gray cross would always appear first in the center of the screen serving as a fixation point, and then one word written in different colors would appear. The order is as follows: the fixation point appeared for 600 ms, the word appeared for 150 ms, and then the empty screen appeared for 1950 ms. Subjects were asked to identify the color in which the stimulus was written as fast and accurately as possible and responded by pressing the button of the corresponding color. The experiment was divided into a practice phase and a test phase. The test phase was about 3 min. The formal test consisted of three blocks of 90 trials (30 congruent stimuli, 30 neutral stimuli, 30 incongruent stimuli), each block was around 15 min. Participants were instructed to avoid blinking and eye movement of any sort and to keep their eyes fixated on the monitor rather than looking down at their fingers during task performance. Participants rested briefly after finishing one block. Before and after training, all subjects performed a Stroop word-color task while their brain activity was measured using a high-density electroencephalography system.

Training Methods

Integrative body-mind training involves body relaxation, mental imagery and mindfulness training, accompanied by selected music background. Cooperation between the body and the mind is emphasized in facilitating and achieving a meditative state (Tang et al., 2007, 2012b). The trainees concentrated on achieving a balanced state of body and mind guided by an IBMT coach. The method stresses no effort to control thoughts, but instead a brain state of restful alertness that allows a high degree of awareness of body, mind, and external instructions. RT involves the relaxing of different muscle groups over the face, head, shoulders, arms, legs, chest, back, and abdomen, guided by a qualified tutor. With eyes closed and in a sequential pattern, one is forced to concentrate on the sensation of relaxation, such as the feelings of warmth and heaviness. This progressive training helps the participant achieve a physical and mental relaxation and calmness (Tang et al., 2007, 2012b). Eighteen subjects had 10 consecutive IBMT sessions with about 30 min per day (5 h in total), 17 subjects were given the same amount of RT. These two training sessions were conducted in parallel.

Electrophysiological Recording and Analysis

Brain electrical activity was recorded using a 61-channel EasyCap with sintered Ag/AgCI electrodes (Brain Products system). The reference electrode was placed on the FCz, while ground was linked to the AFz. Signals were collected at 500 Hz samples and impedances kept below 5 kΩ. Vertical and horizontal electro-oculograms (EOG) were recorded by electrodes situated supra- and infra-orbital of the left eye and external canthi of both eyes, respectively.

The EEG was digitally low-pass filtered at 20 Hz, and transformed to an average reference. Trials with EOG artifacts (exceeding $\pm$ 70 μV), and those contaminated by other artifacts (amplifier clipping or peak-to-peak deflection exceeding 100 μV) were excluded before averaging. The averaged epoch for ERP was 1200 ms, and the first 200 ms before stimulus presentation served as baseline. Only segments with correct responses were averaged, and at least 52 trials were available for each subject and condition (incongruent, congruent, and neural).

Grand averages were computed to identify components and time windows for statistical analysis. Based on the ERPs grand averaged map and the Stroop-related scalp regions (Liotti et al., 2000; Qiu et al., 2006), the following three electrode points were chosen for statistical analysis: Fz, FCz, and Cz. The P2, N2, and P3 peak amplitudes, which were detected from individual ERPs, were measured within time windows of 150–250 ms, 250–400 ms, and 300–500 ms, respectively. The peak amplitude and peak latency data of each component were compared between two groups using between-group, repeated measure ANOVA with Greenhouse–Geisser correction. The significance level for all statistical tests was $p < 0.05$, marginally level was $p < 0.08$.

To map the brain location of ERPs, we used source analysis toolbox, the standardized low-resolution brain electromagnetic tomography software (sLORETA; Pascual-Marqui, 2002). Previous research showed that sLORETA can model and correctly localize the cortical sources of the P3 component at the ACC (BA 24, BA 32) and mesial temporal lobes (Pascual-Marqui et al., 2002; Lorenzo-López et al., 2008).

Results

Using reaction time and accuracy as dependent variables, we conducted a repeated measured ANOVAs comparing Group (IBMT and Relaxation), Session (Pre and Post) and Congruency (Congruent, Incongruent, and Neutral). The reaction time analysis revealed significant main effects of Session $[F(1,33) = 48.42, p < 0.001]$ and Congruency $[F(2,66) = 69.36, p < 0.001]$, as well as significant interactions for Session × Group $[F(1,33) = 15.38, p < 0.001]$ and Session × Congruency $[F(2,66) = 7.17, p < 0.01]$. A main effect for congruency $[F(2,66) = 47.97, p < 0.001]$ was the only significant result obtained for accuracy.

Post hoc analyses indicated that compared to the pre-training scores, both IBMT and relaxation groups showed significant reduction in the post-training reaction time for congruent, incongruent and neutral conditions (all $p < 0.01$). Conflict scores refer to the difference between congruent and incongruent conditions. The pre vs. post difference in conflict reaction time scores was significant only for IBMT group [t(17) = 6.949, $p < 0.001$]. Prior to training, the IBMT and relaxation groups did not differ in reaction times and accuracy scores ($P > 0.05$). After training, a t-test showed that the IBMT group demonstrated superior performance on the Stroop task, as indicated by significantly faster reaction times than relaxation group in the congruent [t(33) = 2.717, $p < 0.05$], the incongruent [t(33) = 3.745, $p < 0.01$], the neutral [t(33) = 2.632, $p < 0.05$] conditions, as well as smaller conflict scores [t(33) = 3.611, $p < 0.01$].

For accuracy analysis (at pre-session, Congruent 97.5% vs. Incongruent 94.0% in IBMT and 97.0 vs. 93.9% in relaxation; at post-session, Congruent 97.9% vs. Incongruent 95.3% in IBMT and 97.8 vs. 95.5% in relaxation), no significant differences were found between two groups at each session, nor between two sessions in each group (all $p > 0.05$). This suggested that the superior performance on Stroop reaction times at post-training was not due to participants responding less carefully. **Figure 1** shows a comparison of IBMT and relaxation groups in the Stroop task after training.

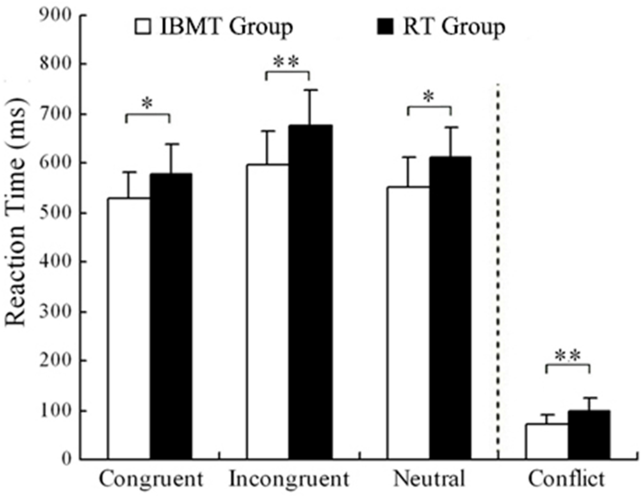

FIGURE 1 | Comparison of Reaction Time in Stroop task between two groups after training. Conflict is the result of incongruent reaction time minus the congruent reaction time (*$p < 0.05$, **$p < 0.01$). IBMT, integrative body-mind training; RT, relaxation training.

To examine the training effects on brain activity, we then computed differences in ERP components between the two groups at the post-training session. Four midline sites along the anterior-posterior axis (Fz, FCz, Cz, and Pz) were selected based on previous research findings that showed frontopolar, frontocentral, central, and parietal scalp regions have Stroop-related changes (Liotti et al., 2000; Markela-Lerenc et al., 2004; Qiu et al., 2006). Grand-average ERPs waveforms for both groups at Fz, FCz, Cz, and Pz were shown in **Figure 2**. We included the Pz data in **Figure 2** but restricted analysis to the anterior sites.

After training, the IBMT group showed significantly shorter P3 latency than the relaxation group at FCz in congruent $[F(1,33) = 6.584, p < 0.05]$ and incongruent $[F(1,33) = 10.605, p < 0.01]$ conditions; at Fz in congruent $[F(1,33) = 6.881, p < 0.05]$ and incongruent $[F(1,33) = 13.111, p < 0.01]$ conditions; and Cz [congruent: $F(1,33) = 5.126, p < 0.05$; incongruent: $F(1,33) = 3.359, p = 0.079$]. The P3 amplitudes were significantly larger in IBMT group than the relaxation group at FCz [congruent: $F(1,33) = 15.102, p < 0.01$; incongruent: $F(1,33) = 16.365, p < 0.01$], Fz [congruent: $F(1,33) = 10.264, p < 0.01$; incongruent: $F(1,33) = 10.838, p < 0.01$], and Cz [congruent: $F(1,33) = 2.892, p = 0.101$; incongruent: $F(1,33) = 11.801, p < 0.01$].

Source analysis using sLORETA showed that the P3 localized bilaterally to the dorsal part of the ACC (BA 24/BA 32, $p < 0.05$; Pascual-Marqui et al., 2002; Lorenzo-López et al., 2008; **Figure 3**). There was no significant difference between two groups for the N2 latency, and the effect is mainly observed in the amplitude of the component. The N2 amplitudes were smaller in IBMT group than the relaxation group at FCz [congruent: $F(1,33) = 7.508, p < 0.05$; incongruent: $F(1,33) = 15.651, p < 0.01$], Cz [congruent: $F(1,33) = 7.270, p < 0.05$; incongruent: $F(1,33) = 13.248, p < 0.01$], and Fz [congruent: $F(1,33) = 3.521, p = 0.07$; incongruent: $F(1,33) = 5.709, p < 0.05$]. Inspection

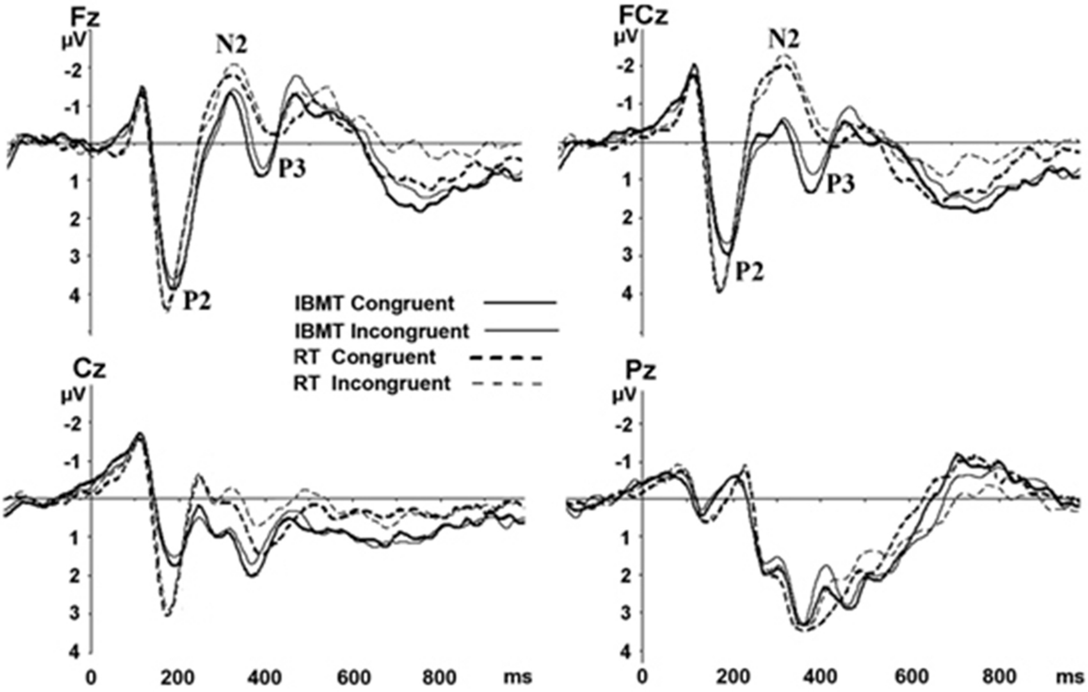

FIGURE 2 | Grand-average ERPs for congruent and incongruent conditions at Fz, FCz, Cz, and Pz between two groups after training. The letters F, C, P, and O stand for frontal, central, and parietal lobes, respectively. A "Z" (0) refers to an electrode placed on the midline. IBMT, integrative body-mind training; RT, relaxation training.

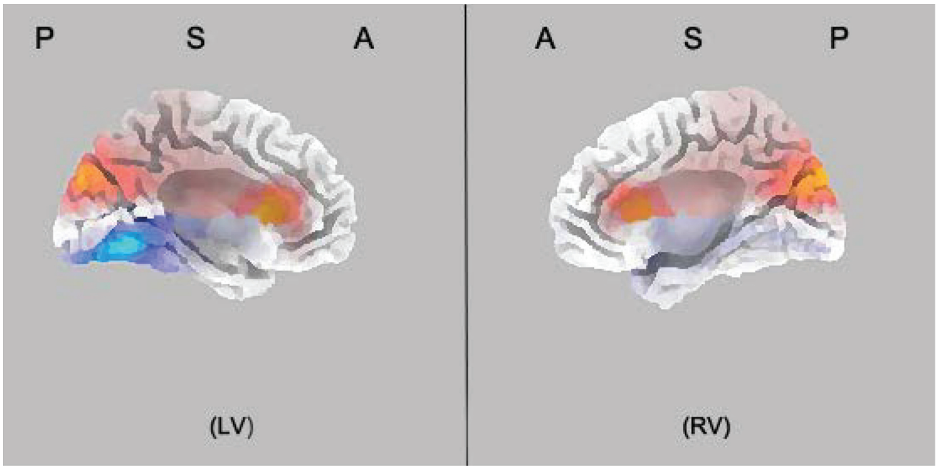

FIGURE 3 | sLORETA statistical non-parametric maps for the incongruent conditions for P3 ERP component. P3 localized bilaterally at the dorsal part of the anterior cingulate cortex (ACC; BA 24/BA 32, $p < 0.05$). The time window is 400–500 ms. The letters P, S, A stand for posterior, superior, and anterior view of brain portion, respectively. LV, left view; RV, right view. The warm colors mean increased activity and cold colors represent decreased activity.

of the topographical voltage map for N2 component in the incongruent condition indicated that group differences were mainly over frontal midline and left temporo-parietal scalp regions.

The IBMT group also showed significantly delayed P2 latency and smaller P2 amplitudes than relaxation group at frontal midline (FCz and Cz) and other brain regions (all $p < 0.05$).

Discussion

Using the classic Stroop task, 5 h of IBMT improved the ability to resolve conflict compared to an active relaxation control. This result supported our previous findings using the attention network test to measure conflict resolution (Tang et al., 2007; Fan et al., 2014).

A series of behavioral and imaging studies have established that IBMT can improve attention and self-control after only 2 h of practice through increased activation in the ACC accompanied by improved connectivity to the parasympathetic system (Tang et al., 2007, 2009, 2010; Tang and Posner, 2009, 2014). These measures were obtained at rest and thus reflect a change in brain state (Tang et al., 2012b). This change in brain state is not achieved by RT which served as a control condition in these studies (Tang et al., 2009).

In the current study, we found significant differences between two groups in brain electrical activity over frontal midline ACC regions after training. The P3 amplitude is thought to reflect the amounts of attentional resources employed in a given task (Polich, 2007). Our study is consistent with the idea that meditation practice affects attentional resource allocation and increases the efficiency of conflict resolution (Cahn and Polich, 2006; Sarang and Telles, 2006; Slagter et al., 2007; Kozasa et al., 2012). The shorter P3 latency also agrees with the faster overall reaction time following IBMT.

These findings provide a likely account of how a change in brain state influences the ability to resolve conflict. Posterior brain potentials did not differ between two groups but the frontal midline N2, which has often been related to the effort to monitor conflict, was greatly reduced in the IBMT, especially in the more dorsal part of the ACC. Thus, the smaller N2 may suggest less effort needed to monitor conflict after meditation training and quicker resolution as shown by both reaction time and P3 latency. These results are consistent with our series of randomized studies that IBMT changes brain state and resolves conflict with less effort and more efficiency (Tang et al., 2007, 2012b; Tang and Posner, 2009, 2014; Xue et al., 2014).

P3 latency is proportional to stimulus evaluation time and individual differences for P3 latency are correlated with mental functions, such that shorter latencies are related to superior cognitive performance (Ilan and Polich, 1999; Rosenfeld and Skogsberg, 2006; Polich, 2007). The neuropsychological tests that produce the strongest correlation between P3 latency and cognitive capability assess how rapidly subjects can allocate attentional resources. In addition, P3 latency increases with normal aging and cognitive impairment (Polich, 1996; Neuhaus et al., 2007). In the current study, after training, IBMT decreased P3 latency at Fz and FCz compared to relaxation in both congruent and incongruent conditions. These findings may be consistent with increased attention, creativity and working memory in our studies, and may indicate that IBMT increases cognitive capability through the reorganization of attention resources in midline cortices (Tang et al., 2007; Ding et al., 2014a,b).

In a 16-week breathing meditation study using Stroop task (Moore et al., 2012), meditation group showed increased N2 (160–240 ms) component than a waiting list control group at left medial and lateral occipitotemporal areas, and decreased P3 (310–380 ms) component at right lateral occipitotemporal and inferior temporal areas respectively. These results involved the same components, but different direction and localization from what we found using IBMT. This raises the possibility that meditation type or length of practice may affect the brain processing involved in conflict resolution (Cahn and Polich, 2009; Tang and Posner, 2013). However, the use of a waiting list control could mean that factors other than the training were involved in the specific findings.

A recent fMRI study compared the performance of meditators and matched controls in the Stroop task. There were no differences in the Stroop task interference effect between the groups, but non-meditators showed greater activity than meditators in the right medial frontal, middle temporal, precentral and postcentral gyri and the lentiform nucleus during the incongruent conditions (Kozasa et al., 2012). Authors explained that less brain activity following meditation training indicated increased brain efficiency in the task. However, this could have been a property of those who chose meditation rather than being cause by training.

In sum, 5 h of IBMT induces a brain state that modulates the activity of ACC and improves information processing including the resolution of Stroop conflict. These findings are compatible with the idea that IBMT improves cognitive flexibility and reduces habitual response via enhanced self-control (Tang et al., 2015).

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Mindfulness meditation modulates reward prediction errors in a passive conditioning task

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Reinforcement learning models have demonstrated that phasic activity of dopamine neurons during reward expectation encodes information about the predictability of reward and cues that predict reward. Self-control strategies such as those practiced in mindfulness-based approaches is claimed to reduce negative and positive reactions to stimuli suggesting the hypothesis that such training may influence basic reward processing. Using a passive conditioning task and fMRI in a group of experienced mindfulness meditators and age-matched controls, we tested the hypothesis that mindfulness meditation influence reward and reward prediction error (PE) signals. We found diminished positive and negative PE-related blood-oxygen level-dependent (BOLD) responses in the putamen in meditators compared with controls. In the meditator group this decrease in striatal BOLD responses to reward PE was paralleled by increased activity in posterior insula, a primary interoceptive region. Critically, responses in the putamen during early trials of the conditioning procedure (run 1) were elevated in both meditators and controls. Overall, these results provide evidence that experienced mindfulness meditators are able to attenuate reward prediction signals to valenced stimuli, which may be related to interoceptive processes encoded in the posterior insula.

Keywords: fMRI BOLD, mindfulness, reward processing, conditioning, classical, interoceptive awareness

INTRODUCTION

The inability of individuals to use self-control gives rise to a range of adverse health consequences, conferring great personal and societal costs (Mokdad et al., 2004; Schroeder, 2007). Only recently have studies in cognitive neuroscience begun to address the issue of the underlying neural mechanisms involved in self-control (Hare et al., 2009; Kirk et al., 2011a; Hutcherson et al., 2012). The clinical and social importance of self-control (Moffitt et al., 2011), as well as the possibility that sustained self-control techniques such as those practiced in mindfulness-based approaches, may be acquired and impact distinct domains of human reward processing and decision-making, provides urgency and relevance to this nascent field of study.

There is reason to expect a fundamental involvement of the dopaminergic pathways in an inability to exert self-control. The neurotransmitter system most strongly implicated in value-based decision-making is dopamine, and the mesolimbic dopaminergic system, the key substrate of the brain's reward system, has been implicated in conditions with learning and decision-making deficits such as addiction (Montague, 2007). Despite advances in understanding how the brain assigns value to the expectancy and predictability of rewards (Montague et al., 1996; Schultz et al., 1997), a purported interaction between mindfulness-based approaches and valuation of reward prediction signals remains poorly understood.

One behavioral therapy that seems to provide systematic training in self-control and emotion management is mindfulness (Vago and Silbersweig, 2012). Mindfulness teaches practitioners to step back from emotions by enabling practitioners to experience "space between one's perception and response" (Shapiro et al., 2006), Indeed, recent work have shown using a cross-sectional design that long-term mindfulness practice impacts an individual's ability to regulate anticipatory responses towards monetary gains or losses in a financial incentive task by a dampening of the mesolimbic dopaminergic system, specifically the caudate nucleus (Kirk et al., 2014b). Recent studies have shown that mindfulness training enhances interoceptive awareness through practices such as breath monitoring (Farb et al., 2007, 2013b; Daubenmier et al., 2013; Kirk et al., 2014a). These reports link nicely up to the conceptual content of the actual mindfulness exercises. For example in one canonical exercise mindfulness practitioners are instructed to attend to physical sensations of breathing in a non-evaluative manner and to notice the occurrence of thoughts, emotions, sounds, and other stimuli as they arise. Once practitioners become distracted or lost in thought, attention is directed back to the breath. In a recent study involving a randomized design with 8 weeks of mindfulness training on an initially naïve subject cohort, we studied the impact of mindfulness on behavior and neural responses during value computation using both a primary and a secondary reward task (Kirk et al., 2014a). In contrast to an active control group, the mindfulness group decoupled activity in the ventromedial prefrontal cortex (vmPFC) during value computation, reflected by a suppression of vmPFC activity in this group. Instead, the mindfulness group recruited value signals that scaled linearly with preference in the left mid/anterior insula. This brain region has been proposed to play a role in attending to self-reference in the present moment (Farb et al., 2007, 2010, 2013b) and attending to internal bodily states (Critchley et al., 2004; Craig, 2009) as well as the homeostatic state of the body (Craig, 2003; Seth et al., 2011). It has recently been proposed that interoceptive functioning contributes to value-based decision-making (Gu and FitzGerald, 2014). These findings argue for the possibility that in the Kirk et al. (2014a) study the mindfulness group were able to maintain interoceptive awareness (e.g., attending to internal bodily states and presumably breath monitoring), by integrating such signals during value computation. The results further showed a decoupling between the posterior insula, and the vmPFC valuation systems in the mindfulness group in the context of both the primary and secondary reward tasks, suggesting a specific interaction mediated by mindfulness training between interoceptive networks and value computation systems. In related studies by Farb et al. (2007, 2013b), changes associated with interoceptive awareness were reported in relation to mindfulness training. Specifically, increased activation of the somatosensory and posterior insula was found in a mindfulness group when attending to present-moment experience. Farb et al. (2007) showed that present-moment experience, as a function of mindfulness training, was associated with increased activation of viscerosomatic regions, including the insula and somatosensory cortex, and reduced activation of the medial prefrontal cortex encompassing the vmPFC. In addition, mindfulness practice time has been positively correlated with activation in the posterior insula during respiratory awareness tasks (Farb et al., 2013a,b), but not all studies have found such a relationship (Kirk et al., 2011b, 2014a,b). Based on this evidence we propose that the elevated activity in posterior insula, presumably reflecting interoceptive awareness of respiration or breath monitoring, may be one basis by which mindfulness training promotes adaptive decision-making.

In the current study we set out to study if long-term meditators were able to exert self-control by focusing on interoceptive awareness while exposed to primary reward (fruit juice) and reward predicting cues (yellow circle) in a conditioning paradigm. If long-term meditators were able to control their reward response, then BOLD responses measured with fMRI in the mesolimbic dopaminergic system should exhibit a modulation compared with a control group. Specifically, based on previous reports we had *a priori* hypotheses targeting bilateral putamen (McClure et al., 2003). In addition we expected that the influence of interoceptive awareness on prediction error (PE) signaling would be encoded by elevated activity in posterior insula in the meditator group.

To test our experimental predictions, we recruited 58 participants (30 controls and 28 Buddhist meditators) and used a classical conditioning procedure that has been previously used to study reward prediction and cues that predict reward (McClure et al., 2003; Salas et al., 2010). Specifically, participants were presented with a yellow light cue (1 s), which predicted the time of reward delivery (juice). Training consisted of reliably pairing a light cue (presented centrally in participants' visual field) with oral juice delivery 6 s later. After 45 of such normal events divided into two runs (run 1 = 23 events; run 2 = 22 events), 6 catch events were introduced in run 3 and another 6 catch events in run 4, randomly spaced in between 12 normal events. In the catch events, juice delivery was delayed 4 s beyond the time expected from training events (**Figure 1A**). Throughout the conditioning procedure juice delivery remained constant (0.8 ml). This conditioning procedure is known to generate two types of PEs during catch events: (1) no juice delivery at expected times generates a negative PE (less than expected), and (2) juice delivery at an unexpected times generates a positive PE (more than expected).

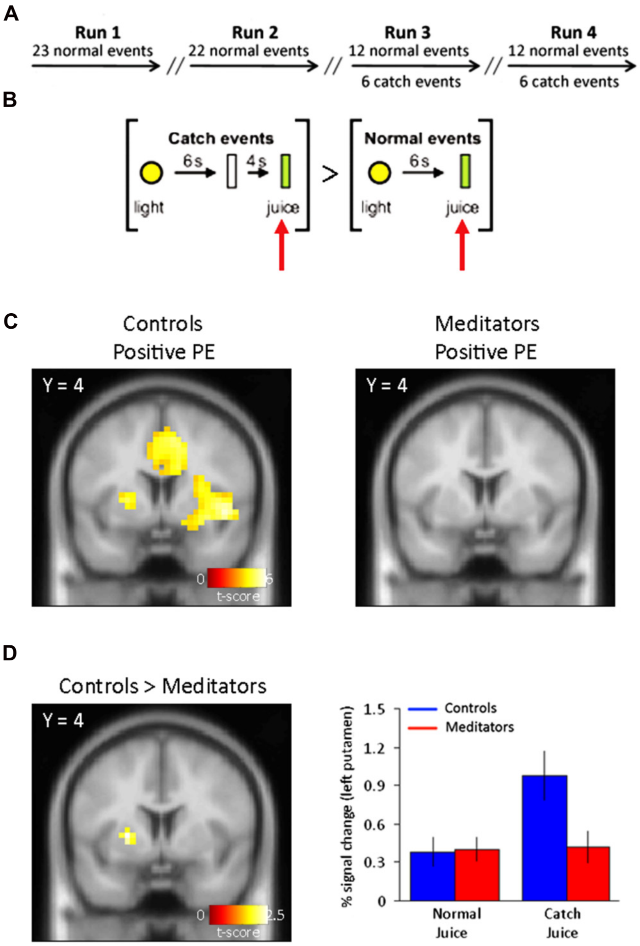

FIGURE 1 | Task outline and positive PE signals. (A) Outline of the conditioning task. fMRI scanning consisted of four separate sessions/runs. Catch events were interspersed among the normal events in run 3 and run 4. Run 1 and run 2 consisted on normal (training) trials only. **(B)** Normal events consisted of a yellow light (1 s) predicting the oral delivery of fruit juice (0.8 ml) 6 s later. Catch events designed to capture a positive reward PE consisted of presentation of the light cue (1 s) and juice delivery 10 s later at an unexpected time. The specific contrast designed to capture the positive PE was: [Juice delivered (unexpected) > Juice delivered (expected)]. **(C)** Left panel, positive PE for controls display activity in bilateral putamen. Right panel, positive PEs in meditators did not yield significant voxels in the putamen (see **Table 1** for complete list of activations). **(D)** Left panel, group differences to positive reward PEs show SVC-corrected activity in left putamen in controls. Right panel, parameter estimates for the significant voxels in left putamen show an increase in the BOLD signal at times when juice was not expected but delivered. Controls shown in blue and meditators in red. Error bars indicate SE.

NEUROIMAGING RESULTS

BOLD SIGNALS REFLECT PREDICTION ERRORS IN CONTROLS

We first focused our analysis on neural effects in catch vs. normal events in run 3 and 4. In the control group, we found significant activity for unpredicted juice delivery compared with predicted delivery, [Juice delivered (unexpected) > Juice delivered (expected)] (**Figure 1B**) corresponding to a positive PE in bilateral putamen (Right: 24 4 8; $z = 4.16$. Left: –24 4 4; $z = 5.48$), significant at $p < 0.05$ false discovery rate (FDR) corrected (**Figure 1C**, left panel). No regions showed significantly greater responses to predicted delivery compared to unpredicted juice delivery [Juice delivered (expected) > Juice delivered (unexpected)].

In catch trials where juice was expected but not delivered compared to normal trials in which juice was not expected and not delivered [Juice not delivered (expected) > Juice not delivered (unexpected)](**Figure 2A**), we found significant activity, corresponding to a negative PE, in bilateral putamen (Right: 24 4 8; $z = 3.54$. Left: –24 4 4; $z = 4.76$) significant at $p < 0.05$ FDR-corrected (**Figure 2B**, left panel). No brain regions demonstrated significantly greater changes in brain responses during normal non-delivery minus catch events [Juice not delivered (unexpected) > Juice not delivered (expected)].

REDUCED BOLD RESPONSES TO PREDICTION ERRORS IN MEDITATORS

In the meditator group, we did not observe significant activity with PE signals either positive [Juice delivered (unexpected) > Juice delivered (expected)], or negative [Juice not delivered (expected) > Juice not delivered (unexpected)] in the striatum even at $p < 0.001$, uncorrected (**Figure 1C**, right panel and **Figure 2B**, right panel). Only when dropping the threshold substantially did we observe PE-related signals in bilateral putamen ($p < 0.05$, uncorrected). No regions showed significantly greater responses to predicted delivery compared to unpredicted juice delivery [Juice delivered (expected) > Juice delivered (unexpected)]. And finally, no brain regions demonstrated significantly greater changes in brain responses during normal non-delivery minus catch events [Juice not delivered (unexpected) > Juice not delivered (expected)].

In a whole brain analysis, we show all regions that survived whole brain correction at $p < 0.05$ (FDR-corrected) in both groups for PE-related contrasts (**Table 1**).

GROUP DIFFERENCES IN PREDICTION ERROR-RELATED ACTIVITY IN PUTAMEN

In a direct statistical comparison between positive PEs in the control and meditator group (Controls > Meditators), we found that controls showed significantly greater positive PE-related activity in the left putamen (−24 4 4; $z = 2.42$), but not the right putamen, compared with meditators (**Figure 1D**, left panel). This analysis was significant at $p < 0.05$, uncorrected, and at $p < 0.05$ FDR-corrected threshold after small volume correction (SVC; Worsley et al., 1996) of the *a priori* defined putamen. Parameter estimates of the direct comparison between controls and meditators extracted from the left putamen are shown (**Figure 1D**, right panel). The opposite contrast (Meditators > Controls) did not result in significant activity at $p < 0.001$, uncorrected.

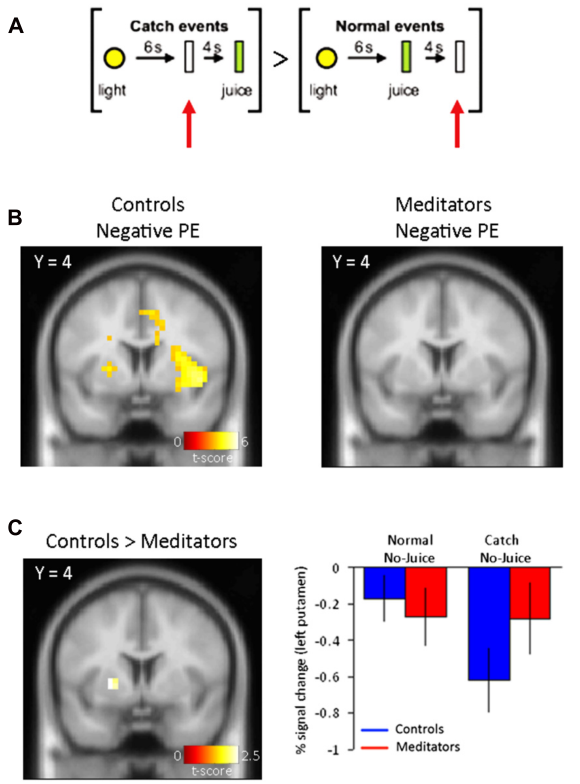

FIGURE 2 | Negative PE signals. (A) Normal events consisted of a yellow light (1 s) and no juice delivery 10 s following the light cue. Catch events designed to capture a negative reward PE consisted of presentation of the light cue (1 s) and no juice delivery at the expected time at 6 s following the light cue. The specific contrast designed to capture the negative PE was: [Juice not delivered (expected) > Juice not delivered (unexpected)]. **(B)** Left panel, negative PEs for controls display activity in bilateral putamen. Right panel, negative PEs in meditators did not yield significant voxels (see **Table 1** for complete list of activations). **(C)** Left panel, group differences to negative reward PEs show activity in left putamen in controls. Right panel, parameter estimates for the significant voxels in left putamen display a drop in the BOLD signal at times when juice was expected but not delivered. Controls are shown in blue and meditators in red. Error bars indicate SE.

Furthermore, in a comparison between negative PE-related activity in the control and meditator group (Controls > Meditators), we found significant activity in the left putamen (−22 4 2; $z = 2.28$). This contrast was significant at $p < 0.05$, uncorrected, and at $p < 0.05$ FDR-corrected threshold after SVC of the *a priori* defined putamen (**Figure 2C**, left panel). Parameter estimates of the direct comparison between controls and meditators extracted from the left putamen are shown (**Figure 2C**, right panel). The opposite contrast for negative PE-related activity (Meditators > Controls) did not result in significant activity at $p < 0.001$, uncorrected.

INCREASED POSTERIOR INSULA ACTIVITY PARALLEL DECREASED PREDICTION ERRORS IN MEDITATORS

The reduced reliance on PEs in meditators expressed as reduced BOLD responses in the putamen, suggests a process whereby mindfulness meditation enables the brain to diminish the impact of PEs on behavior. If such a process is indeed at play in

Table 1 | Summary of brain regions in both groups displaying prediction error-related contrasts.

Region	Laterality	x	y	z	*z*-score
Control catch juice > Control normal juice					
Putamen	R	24	4	8	4.16
Putamen	L	−24	4	4	5.48
Cingulate gyrus	R\L	4	0	40	4.85
Thalamus	R\L	4	−16	8	4.77
Control catch no-juice > Control normal no-juice					
Putamen	R	24	4	8	3.54
Cingulate gyrus	L	−24	4	4	4.76
Thalamus	R\L	4	2	38	3.71
Meditator catch juice > Meditator normal juice					
Thalamus	R/L	4	−4	8	3.87
Meditator catch no-juice > Meditator normal no-juice					
None					

Activations thresholded at p < 0.05, FDR. Extent threshold > 5 voxels.

this group of meditators, there should also be a corresponding increase in brain regions that mediate the implementation of reduced PE signaling. To determine which brain regions may enable the effects of reduced PEs, we conducted an exploratory analysis to localize potential brain areas where activation to juice reward (independent of modality, i.e., normal or catch trials) was greater for meditators compared with controls. We focused on juice delivery independent of modality because our previous analyses did not identify differences between catch and normal juice delivery in meditators. We computed the main effect at juice delivery time in run 3 and run 4 (Meditators > Controls). This analysis revealed activity in the right posterior insula at $p < 0.001$, uncorrected (**Figure 3A**). Parameter estimates extracted from this region demonstrated that the meditator group showed elevated activity in the posterior insula compared to controls at juice delivery both during normal juice delivery and during catch juice trials in run 3 and 4 (**Figure 3B**).

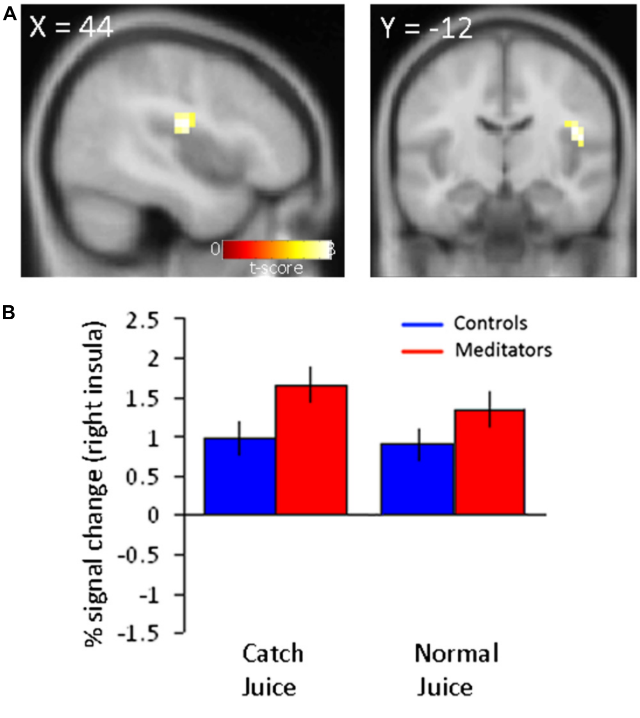

FIGURE 3 | Increased neural activity in right posterior insula to juice delivery in meditators. (A) Main effect of juice delivery collapsed across modality (normal/catch) in (Meditators > Controls) resulted in activity in the right insula (44 -12 20; $z = 3.35$; $p < 0.001$, unc.). **(B)** Parameter estimates extracted from the right posterior insula region are displayed for both groups and separated into trial types corresponding to averaged responses from run 3 and 4. Error bars indicate SE.

REGIONS OF INTEREST ANALYSIS DURING TRAINING (RUN 1): PUTAMEN

Next we tested if the differences in reward processing in the striatum was induced by the conditioning procedure or alternatively was task-independent and a pre-existing difference between the meditators and controls. We modeled the (unexpected) juice delivery time during run 1 in both groups. The contrast was computed at juice delivery 6 s after cue vs. baseline 5 s prior to cue (23 events). We found significant activity at the FDR-corrected level in bilateral putamen in both controls (Left: −24 4 12; $z = 4.58$. Right: 24 4 4; $z = 4.45$) and meditators (Left: −23 4 6; $z = 4.58$. Right: 28 0 4; $z = 4.51$). The beta estimates in the putamen did not differentiate between the two groups during unexpected juice delivery in run 1 (**Figure 4B**). In a direct comparison between the two groups at the time of (unexpected) juice delivery in run 1 we did not observe any differences between groups at $p < 0.001$, uncorrected (**Figure 4A**). These results demonstrate that mediators and controls exhibit non-differential striatal responses to unexpected juice delivery in run 1.

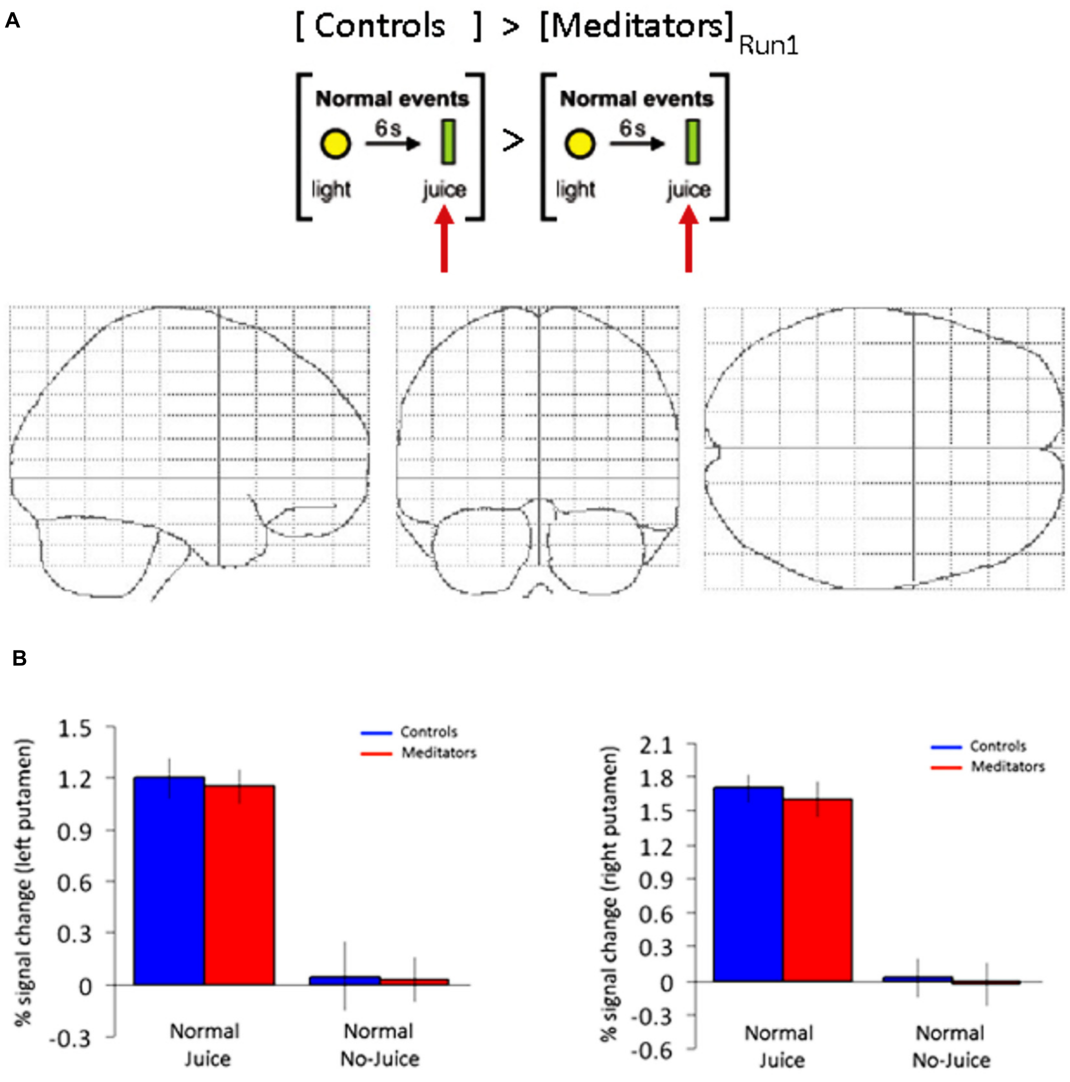

FIGURE 4 | ROI putamen: no group-specific differences during training events (run 1). (A) Main effect of juice delivery (Controls > Meditators) averaged across run 1 display no differential activity in a whole brain analysis at $p < 0.001$, uncorrected. **(B)** ROI in left and right putamen. Beta estimates display significant activity in both groups, but non-differential reward activity across groups at the time of juice delivery during run 1 as displayed in **(A)**. Error bars indicate SE.

REGIONS OF INTEREST ANALYSIS: VISUAL CORTEX

Furthermore, we tested if differences in visual cortical areas in run 3 and 4 would account for differences in PE signaling between groups. We observed activity in primary visual cortex to the light cue in both groups (**Figure 5**), and no significant differences were found in a direct comparison (Figure not shown). These findings demonstrate that the participants in both groups were processing the visual components of the task non-differentially, and argues against the possibility that the meditator group were simply disengaged from the task.

DISCUSSION

In this study we found that long-term meditators were better able to dampen the impact of reward PEs encoded in the ventral striatum. The findings suggest that elevated activity in posterior insula, presumably reflecting interoceptive awareness of respiration or breath monitoring, may be one basis through which mindfulness training exerts a behavioral impact on value-based decision-making. Alas, since the current design was cross-sectional, further longitudinal designs are required to complement these findings before a firm link between mindfulness training and striatal PE-related activity may be made.

Recent work using cognitive strategies such as emotion regulation have observed dampening of the striatum to reward expectancy of secondary reward (Delgado et al., 2008) and in anterior insula to fictive reward predicting errors (Gu et al., 2014). Different from emotion regulation (Ochsner and Gross, 2005), mindfulness takes an objective or outside perspective on one's experiences, rather than changing the content (distraction) or context (reframing) of those experiences. It seems plausible that with

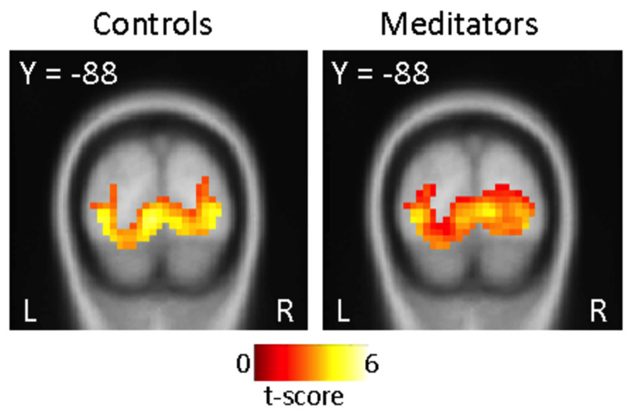

FIGURE 5 | ROI visual cortex: no group-specific differences during cue onset (run 3 and 4). Significant activity in visual cortical areas related to light cue onset in run 3 and 4 in both controls (left panel) and meditators (right panel) displayed at $p < 0.001$, uncorrected. Direct contrast between groups (Controls > Meditators) at cue onset display no significant differences in activity at $p < 0.001$, uncorrected. The opposite contrast (Meditators > Controls) did not results in significant activity at $p < 0.001$, uncorrected.

a mindful stance the practitioner adopts emotion regulation using different mechanisms; specifically mindfulness training seems to enhance interoceptive awareness through practices such as breath monitoring (Farb et al., 2007, 2013b; Daubenmier et al., 2013; Kirk et al., 2014a).

Mindfulness has informed a number of psychoeducational interventions where popular versions include Mindfulness Based Stress Reduction (MBSR; Kabat-Zinn, 1990) and Mindfulness Based Cognitive Therapy (MBCT; Segal et al., 2001). Mindfulness as taught in such interventions differs from recent formulations of emotional regulation in three main ways. First, rather than averting attention away from difficult thoughts, mindfulness training has participants notice or accept such thoughts without reacting to them. The idea is that simply registering and staying with the moment-to-moment attention of the particular thought or feeling is a non-habitual way of responding (as oppose to reacting) to a given thought or feeling. Second, mindfulness is non-judgmental, which limits the elaborative processes mediating the appraisal of emotionally relevant experience. Third, the meta-cognitive awareness cultivated through mindfulness training promotes an experience of negative thoughts or feelings as simply mental events, rather than as real events that are self-relevant and to be acted upon. This form of training is hypothesized to have long-lasting and potent effects on economic decision-making (Kirk et al., 2014b) and cooperative exchange (Kirk et al., 2011b), however, this remains to be tested empirically and modeled quantitatively in longitudinal and experimental studies. Indeed, one limitation of the current results is that we used a cross-sectional rather than longitudinal design. Hence, it was not possible to compare the behavior of the subjects before and after they started practicing mindfulness. Without this information, we cannot determine whether the meditators actually acquired a different behavioral profile through meditation experience.

A separate line of research may offer an interpretation to the current results. Evidence suggests that mindfulness may impact mind wandering. Specifically, people who report higher trait mindfulness demonstrate less mind wandering (Mrazek et al., 2012). In addition, it has recently been found that only 2 weeks of mindfulness training decrease mind wandering and improves GRE scores (Mrazek et al., 2013). One interpretation of the current results may be that focusing on interoceptive awareness in the present moment may decrease mind wandering and thus reduce the tendency to focus on the future or past. This may have the consequence that any future state would have the same value as the current state for mindfulness practitioners, which would result is flat value functions, i.e., PE signals in this group. Indeed this interpretation seems in line with recent work suggesting that mindfulness training may accomplish reduction is bias effects by drawing the practitioners focus away from the future and past in the context of sunk cost economic decisions (Hafenbrack et al., 2013).

In summary, we found that experienced meditators exhibited reduced neural responses to reward PEs. The data suggest that the reward system in this group is not by default attenuated in that we observed significant and non-differential activity in the ventral striatum during reward delivery (juice) during the training trials (run 1) of the conditioning procedure. This argues against the simple interpretation that the meditators exhibit trait-specific reward sensitivity. Our results rather argue that interoceptive awareness processed in the posterior insula decreases the impact of the reward system. It is noteworthy that meditators were not given instructions to meditate during the scanning sessions. Participants in both groups were instructed to focus on the light cue and swallow juice as it was delivered, and no reference was made to the cue/juice pairings. Our cross-sectional design and thus preliminary data suggest that mindfulness may be an intrinsic mechanism for altered reward processing with potential clinical benefits, which would be interesting to investigate in future studies. Despite advances in understanding how the brain assigns value to the expectancy of rewards, it is poorly understood how to control or regulate hyper-valuation of reward prediction signals. The current results suggest that meditators may systematically train strategies that allow regulation and deploy self-control to primary reward predicting stimuli.

MATERIALS AND METHODS

SUBJECTS

Fifty eight subjects participated in the study. Subjects were recruited in two groups. One group ($n = 30$) consisted of controls. The second group ($n = 28$) consisted of expert meditators. The expert group was selected primarily from a southwestern Zen center in the US and were recruited based on the criterion of maintaining a regular mindfulness-integrated meditation practice (minimum three sessions of 20 min per week). In addition, all participants in the meditation group had completed at least one meditation retreat of min 3 days duration. Both groups maintained a normal secular lifestyle. We did not collect data on the specific form of meditation (e.g., open awareness or focused attention). The groups were matched on age, gender, socioeconomic status (education and income levels), depressive symptoms

(Beck Depression Inventory; Beckham and Leber, 1985) and anxiety symptoms (Beck Anxiety Inventory; Beck and Steer, 1993; **Table 2**).

All subjects had normal or corrected-to-normal vision, and none had a history of neurological or psychiatric disorders, and no current use of psychoactive medications. All procedures were conducted in accordance with the Institutional Review Board at Baylor College of Medicine.

EXPERIMENTAL PROCEDURES

The classical conditioning task had four scanning runs. The sequence in run 1 and 2 consisted of a yellow light cue of 1 s duration which was followed by juice delivery 6 s later (normal events). The time between individual pairings was randomly selected from between 4 and 14 s (at 2 s increments). In run 1 there were 23 such events and in run 2 there were 22 events. In the subsequent runs 3 and 4 there were 18 events in each run of which 6 events were catch events. For these catch events, the time from light cue to juice delivery was increased to 10 s. The light cues were presented and responses collected using NEMO (Human Neuroimaging Lab, Baylor College of Medicine). The stimuli were back-projected via an LCD projector onto a transparent screen positioned over the subjects' head and viewed through a tilted mirror fixed to the head coil. Juice delivery was accomplished using a computer-controlled syringe pump (Harvard Apparatus, Holliston, MA, USA). Juice delivery consisted of 0.8 ml juice per event. Post-scanning, subjects reported enjoying the taste of the juice.

FMRI DATA ACQUISITION

The anatomical and functional imaging was performed using 3 Tesla Siemens Trio scanners. High-resolution T1 weighted scans were acquired using an MPRAGE sequence (Siemens). The first five scans were discarded to allow for T1 equilibration effects. Functional imaging used an EPI sequence with a repetition time (TR) of 2000 ms, echo time (TE) = 25 ms, flip angle = 90°, 220 mm field of view (FOV), 64 × 64 matrix. Functional slices were oriented 30° superior-caudal to the plane through the anterior and posterior commissures in order to reduce signal drop-out due to magnetic field in-homogeneities (Deichmann et al., 2003). Each functional image was acquired in an interleaved way, comprising 37.4 mm axial slices for measurement of the BOLD effect (Ogawa et al., 1990), yielding 3.4 mm × 3.4 mm × 4.0 mm voxels.

Table 2 | Summary of demographic and behavioral variables.

	Controls ($n = 30$)	Meditators ($n = 28$)
Mean age	32.4 (9.3)	33.7 (11.2)
Female:Male ratio	14:16	13:15
Meditation experience	–	10.3 (8.1)
Education (years)	14.9 (1.6)	14.7 (1.8)
Income	2.6 (1.4)	2.7 (1.2)
BDI	4.8 (5.7)	2.8 (3.9)
BAI	4.2 (4.7)	3.1 (4.1)
MAAS	63.5 (13)	75.8 (9.8)*

*Mean demographic variables were compared using two-sample t-tests assuming unequal variance. SD in parentheses. *Indicate significant differences ($p < 0.05$) between controls and meditators. BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; MAAS, Mindful Attention Awareness Scale. Yearly income levels were coded as 1 = < $20K; 2 = 20–35K; 3 = 35–50K; 4 = 50–75K; 5 = 75–100K; and 6 = > 100K.*

FMRI DATA ANALYSIS

Image pre-processing and data analysis was performed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Motion correction to the first functional scan was performed using a 6 parameter rigid-body transformation (Friston et al., 1996). The average of the motion-corrected images was co-registered to each individuals structural MRI using a 12 parameter affine transformation. Slice timing artifact was corrected, after which images were spatially normalized to the Montreal Neurological Institute (MNI) template provided in SPM8. Images were then spatially filtered with an 8 mm isotropic Gaussian kernel and for the analysis a high pass filter with a cut-off frequency at 1/128 Hz was applied. Following pre-processing a general linear model (GLM) was applied to the fMRI time-series where each event was modeled as single impulse response functions at light cue onset and at juice delivery onset (for runs 1 and 2). For runs 3 and 4 the model included the light cue, juice delivery during normal events, juice delivery during catch events, the absence of juice delivery at 6 s during catch events, and the absence of juice delivery during normal events (10 s after light cue). The model was convolved with the hemodynamic response function (HRF) including its temporal derivative to account for slight discrepancies in juice delivery time and duration. Residual effects of head motion were corrected for by including the 6 estimated motion parameters for each subject as regressors of no interest. The mean images from the first level analysis were entered into a second-level, random effects (RFX) analysis accounting for the between subject variance. An ANOVA model using the beta-estimates of the regressors of interest was used. Equal variance was not assumed, and thus non-sphericity correction was applied (Glaser and Friston, 2004). Using t-contrasts allowed us to test for correlations of the fMRI BOLD signal and the parameters of interest. The resulting t maps were subsequently transformed to the unit normal z-distribution to create a statistical parametric map for each contrast. The statistical results given were based on a single-voxel t-statistic corresponding to $p < 0.05$ corrected for multiple comparisons (FDR-corrected). The coordinates of all activations are reported in MNI space. SVC were applied in the *a priori* region in the bilateral putamen, where coordinates for the putamen was derived from McClure et al. (2003), specifically (−18, 4, 8) and (18 4 8), by applying 10 mm spheres around the peak MNI coordinates. Using the coordinates of the study cited above, we placed a 10 mm spherical ROI in the bilateral putamen and extracted beta estimates for normal and catch trials in each group for run 3 and run 4.

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Mindfulness meditation and explicit and implicit indicators of personality and self-concept changes

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The scientific interest on mindfulness meditation (MM) has significantly increased in the last two decades probably because of the positive health effects that this practice exerts in a great variety of clinical and non-clinical conditions. Despite attention regulation, emotional regulation, and body awareness have been argued to be critical mechanisms through which MM improves well-being, much less is known on the effects of this practice on personality. Here we review the current state of knowledge about the role of MM in promoting changes in practitioners' personality profiles and self-concepts. We first focus on studies that investigated the relations between mindfulness and personality using well-known self-report inventories such as the Five-Factor model of personality traits and the Temperament and Character Inventory. Second, based on the intrinsic limitations of these explicit personality measures, we review a key set of results showing effects of MM on implicit, as well as explicit, self-representations. Although the research on MM and personality is still in its infancy, it appears that this form of meditative practice may notably shape individuals' personality and self-concept toward more healthy profiles.

Keywords: mindfulness meditation, personality inventory, character, self-concept, explicit-attitude, implicit-attitude

INTRODUCTION

Meditation originated several centuries BCE in Hinduism and Buddhism healing and spiritual traditions. Since then, various forms of meditation are followed to cultivate well-being and cognitive/emotional balance (Wynne, 2007; Lutz et al., 2008; Fabbro, 2010). Over the past 30 years, an important form of meditation has taken hold in the West, in both clinical and non-clinical contexts, namely mindfulness meditation (MM; Kabat-Zinn, 1982, 1990, 2003). Mindfulness meditation relies upon techniques of mental training that suggest that non-judgmental awareness of here-and-now mental or somatosensory experience positively influences accurateness of perception and acceptance of one's own life experiences. The mindful practitioner thus amalgamates a focused attention component with a non-judgmental attitude of openness and receptivity when trying to intentionally pay attention, and non-reactively monitor, the content of present-moment experience (Brown and Ryan, 2003; Lutz et al., 2008).

The growing interest in MM is probably due to its well-documented beneficial effects on physical and psychological health, which have been obtained in different clinical contexts on individuals of various age ranges and with slightly different formalizations of mindfulness-based therapies (Baer, 2003, 2010; Didonna, 2009). Moreover, another important dimension of MM is its potential in promoting personal development such as equanimity, self-compassion, and perspective taking (Neff, 2003; Baer, 2010; Birnie et al., 2010; Hölzel et al., 2011) and in undermining self-critical tendencies (Hayes et al., 2004; Segal et al., 2004).

Together with the body of knowledge pointing to the health benefits of MM, another research line has aimed at identifying the mechanisms of action through which MM exerts its effects. Thus, the role of a series of interrelated components such as attentional control, emotion regulation, body awareness, and change in perspective on the self has been recognized (Hölzel et al., 2011). Nevertheless, while several studies have focused on the relation between MM and enhancement of attention and emotion regulation skills (e.g., Jha et al., 2007; Lutz et al., 2008, 2014; Malinowski, 2013; for a recent review see Lippelt et al., 2014), relatively little empirical research has investigated whether MM promotes changes in the perspective on the self and, more generally, in personality traits (Hölzel et al., 2011; Campanella et al., 2014). However, a central tenet of MM is that the practitioner learns to experience the transient nature of all mental phenomena including the sense of self, gaining distance (detaching) from identification with a static sense of self that, instead, would be experienced as an event. Experiencing the transitory nature of the sense of self has been suggested to lead to the "deconstruction of the self" (Epstein, 1988; see in Hölzel et al., 2011), which presumably may promote modifications in personality. Moreover, it is also generally assumed that the practice of MM aims at developing new ways to experience and face life events (Kabat-Zinn, 1990; van den Hurk et al., 2011) and this may also lead to changes in personality. From this perspective, the empirical study of the relation between MM and personality is of some importance as it is reasonable to expect modifications in personality traits as due to MM practice.

MINDFULNESS MEDITATION AND EXPLICIT MEASURES OF PERSONALITY AND SELF-CONCEPT CHANGES

One of the first studies documenting a change in individuals' self-concept as due to MM has been that of Emavardhana and

Tori (1997; see also Nystul and Garde, 1977 and Turnbull and Norris, 1982 for two older studies), who reported higher self-acceptance, increases in overall self-esteem and a more positive self-representation (measured with the Tennessee Self-Concept Scale; Roid and Fitts, 1988), in two large groups (overall $n = 438$) of 18-years old participants attending a 1-week mindfulness retreat (i.e., vipassana meditation) vs. a control group of young participants ($n = 281$).

More recently, several studies have further investigated the relationship between MM and personality relying on well-known personality inventories. Many of these studies have tried to link dispositional (trait) mindfulness (globally reflecting the disposition to persist in mindful states over time irrespective of meditation practice; Brown et al., 2007), rather than MM practice, with personality traits using the Five-Factor model of personality (e.g., Costa and McCrae, 1992). For example, Thompson and Waltz (2007) employed the Mindful Attention Awareness Scale (MAAS, Brown and Ryan, 2003), a 15-item mindfulness scale regarding levels of attention and awareness in daily life, finding that greater mindfulness scores were negatively related with the neuroticism trait (propensity toward anxiety, worrying, moodiness, impulsiveness, and self-criticism) but positively related with the agreeableness (the tendency to be trustworthy and altruistic) and conscientiousness (the inclination to be efficient, organized and to show high self-discipline) traits. Similarly, Barnhofer et al. (2011) have shown that dispositional mindfulness [measured in this study with the Five-Facet Mindfulness Questionnaire (FFMQ), Baer et al., 2006] moderated the relation between depressive symptoms and neuroticism, which were positively related only at low or medium, but not at high levels of dispositional mindfulness. Other studies have documented negative correlations between dispositional mindfulness or self-compassion and neuroticism (Brown and Ryan, 2003; Neff et al., 2007; Ortner et al., 2007; Zabelina et al., 2011), while in one of these studies it was also found that state mindfulness (the moment-to-moment awareness of one's experience; a state that can be enhanced by practices such as brief MM exercises) facilitated creative elaboration among individuals with high levels of neuroticism. This was proposed to occur via a role of mindfulness in reducing tendencies toward self-criticism and behavioral inhibition (Zabelina et al., 2011). These and other data linking mindfulness and personality traits have recently been subjected to meta-analysis (Giluk, 2009) involving 29 studies addressing the relationship between dispositional mindfulness (e.g., trait MAAS, FFMQ) and the Big-Five personality traits (conscientiousness, agreeableness, extraversion, openness-to-experience, and neuroticism). Overall, this meta-analysis confirmed that trait mindfulness negatively correlates with neuroticism but positively with conscientiousness.

Although valuable, these studies interested in the relationship between everyday mindfulness and personality leave open the question of the impact of regular MM practice on mindfulness and personality variables, for instance during an 8-week intervention or in expert practitioners. Of importance, a recent study by van den Hurk et al. (2011) has recently made an important step toward understanding the contribution of MM practice. In this cross-sectional study the authors compared the personality profiles (using the NEO-Five-Factor Inventory; Costa and McCrae, 1992) of two groups of healthy participants (age range, 27–75 years) with ($n = 35$; mean meditation experience: 13.2 years, 3.0 h a week) and without ($n = 35$) MM experience. Meditators showed higher openness-to-experience scores (reflecting dispositional curiosity, creativity) than non-meditators but lower conscientiousness scores than the latter. Moreover, the practice of MM was negatively related to neuroticism and positively related to openness-to-experience and extraversion (the tendency to experience positive emotions and being sociable). Although the cross-sectional nature of the study may limit the interpretation of the results, the authors concluded that MM practice is associated with positive affect and increased levels of curiosity and openness-to-experience. Furthermore, it helps to reduce moodiness and worrying, also leading to a reduced focus on achievements (related to the conscientiousness trait).

Another well-known personality inventory refers to the psychobiological model of Temperament and Character (TCI; Cloninger et al., 1993, 1994). This model combines the posited neurobiological and genetic bases of personality (four temperamental traits: Novelty Seeking, Persistence, Reward Dependency, and Harm Avoidance) with their interaction with life experiences (character). The character consists of three dimensions measuring the maturity of the self at the levels intrapersonal (Self-Directedness that maps on concepts such as self-esteem and self-efficacy), interpersonal (Cooperativeness expressing the capacity to be empathic, tolerant, compassionate), and transpersonal (Self-Transcendence measuring the tendency toward spirituality and creativeness). Thus, the character refers to one's own self-evaluation and is responsible for efficient behavioral self-regulation; indeed, character profiles are useful to diagnose personality disorders, in that individuals with immature character (e.g., with low Self-Directedness and Cooperativeness) are at higher risk of developing personality disorders than individuals with better character maturity (Svrakic et al., 1993, 2002).

Only a few studies have used the TCI to investigate the relationship between dispositional mindfulness or MM practice and personality traits. Haimerl and Valentine (2001) compared cross-sectionally the TCI character profiles of three groups of Buddhist meditators with varying levels of meditation experience (28 naïve individuals; 58 beginners with less than 2 years of practice; and 73 experts with more than 2 years of experience). Indicative of greater overall self-maturity, expert meditators obtained higher scores in all three aspects of the character profile compared to naïve subjects and they also scored higher than beginners on the cooperativeness trait. Moreover, beginners scored higher than naïve individuals on the self-transcendence scale. This study thus showed that progresses in meditation experience led to positive growth in the character components of personality (see Smalley et al., 2009 for similar findings obtained considering dispositional mindfulness rather than MM practice).

Similarly to the conclusions that can be drawn from the studies using the Five-Factor model of personality, the correlative and cross-sectional nature of these previous studies considering the

TCI may limit the possibility of linking MM with the changes in the perspective on the self. Nevertheless, a recent longitudinal study by Campanella et al. (2014) was able to test more directly the effects of MM practice on individuals' TCI personality profiles. This was done in three groups of meditation-naïve healthy subjects (overall $n = 41$, age range: 21–58 years) who participated in three replicates of an 8-week MM course inspired by the mindfulness-based stress reduction. In this study, there was also a control group of healthy individuals ($n = 15$, age range: 26–69 years) not involved in any meditation training. Notably, the authors reported increased scores in all three character scales after vs. before the MM course in two of the three meditation groups (groups 1 and 3 in Campanella et al., 2014, Figure 1). In the remaining meditation group (group 2 in Campanella et al., 2014, Figure 1) and in the control group the TCI profiles remained unaltered across the two testing sessions. Remarkably, it was found that the individuals in the two meditation groups who showed an increment in the character scores had meditated more frequently than those in the meditation group who did not show any character change during the course (4–5 vs. 2–3 days per week, respectively; see Figure 2A in Campanella et al., 2014).

Overall, the reviewed studies above suggest that MM may indeed promote positive changes in individuals' self-concept and personality. This may help further characterizing the change in the perspective on the self as an important mechanism of action through which MM exerts its beneficial health effects. In particular, this change in perspective could be supported by a mindfulness-related increased ability to start experiencing the sense of self as a transitory event rather than as a constant and unchanging entity (Hölzel et al., 2011; see Introduction). The detachment from identification with a static sense of self may provide MM practitioners with a better capacity for objectivity about their own internal experience that, in turn, could help them experience more authentic ways of being and reduce psychological suffering (Shapiro et al., 2006; Hölzel et al., 2011).

Tellingly, recent functional imaging studies have identified the putative neurofunctional signatures of the change in the perspective on the self brought about by MM. In particular, it has been claimed that during MM states detachment from identification with a static sense of self associates with a diminished self-referential, narrative/autobiographical, processing paired with enhanced present-based, experiential processing of the self (Farb et al., 2007). In the brain, this has been shown to reflect in decreased activity in self-referential cortical midline structures (e.g., medial prefrontal cortex; see Northoff and Bermpohl, 2004; Northoff et al., 2006) and enhanced activity in lateral structures such as the insula and the somatosensory cortex associated more with momentary interoceptive and exteroceptive self-awareness (see Hölzel et al., 2011 for a discussion of other relevant neuroimaging studies; see also Tomasino et al., 2013).

MINDFULNESS MEDITATION AND IMPLICIT MEASURES OF PERSONALITY AND SELF-CONCEPT CHANGES

People have two sources of self-evaluative tendencies. The first relies on propositional processes of intentional reasoning that shapes individuals' explicit attitudes through well-articulated beliefs and motivations. By contrast, the second source roots in associative and automatic processes in which intuitive feelings and evaluations, that one could or could not be aware of, shape individuals' implicit attitudes (Gawronski and Bodenhausen, 2006; Jordan et al., 2007). While explicit attitudes can be measured through self-report questionnaires (e.g., TCI), implicit attitudes can be inferred from individuals' performance on reaction times measures such as the Implicit Association Test (IAT). The IAT is one of the most common tests used to compute the strength of automatic concept-attribute associations that could underlie specific aspects of personality (Greenwald and Farnham, 2000; Schnabel et al., 2008). Relative to self-report measures, implicit tests do not require the intent to self-evaluate on the part of the respondent and are thus more difficult to fake or to control (Greenwald and Farnham, 2000; Crescentini et al., 2014a). Of importance, experiencing psychological conflicts between intuitive feelings and more reflective evaluations is common in daily life decisions, with such conflicts also affecting more personal spheres, such as self-attitudes and self-representations (Emmons and King, 1988; Greenwald and Banaji, 1995; Gawronski and Bodenhausen, 2006). Notably, while concordance between implicit and explicit self-representations is important for psychological health, incongruities between the two forms of self-evaluation have been put into relation with different forms of psychological distress. For example, unhealthy forms of perfectionism may occur when one shows high implicit self-esteem but low explicit self-esteem (Zeigler-Hill and Terry, 2007; see also Bosson et al., 2003; Briñol et al., 2006; Schröder-Abé et al., 2007a,b).

On the basis of these premises, it seems important to investigate the impact of MM upon changes in the perspective on the self also at the implicit level of self-representation. This appears critical for at least two reasons. First, linking mindfulness with implicit self-concept, namely a specific type of implicit cognition, may help to "cross-validate" findings from self-report measures of personality. Explicit measures may indeed be susceptible to desirable responding and are clearly subjective in nature (Schwarz, 1999; Jordan et al., 2007). Second, these studies could test whether mindful awareness promotes a coherent self in which implicit and explicit self-representations become better integrated with each other. Despite intuition and implicit cognition are likely important aspects of mindfulness, as this practice is believed to foster self-insights and greater acceptance of one's own internal states, we should note that most of the studies on the impact of everyday mindfulness or MM practice on personality and self-concept have only considered explicit self-report measures.

Nevertheless, a few relevant exceptions exist, being represented by studies focusing on the impact of mindfulness on psychological dimensions such as implicit affective states, self-esteem, and motivation (Brown and Ryan, 2003; Levesque and Brown, 2007; Koole et al., 2009; Sauer et al., 2011; see Hutcherson et al., 2008 and Strick et al., 2012 for similar issues in the context of Loving-Kindness meditation and Zen meditation). Overall, these studies have been particularly interested in the putative effects of dispositional mindfulness or transient state mindfulness on implicit and explicit self-representations and/or their potential concordance. Thus, in their pioneering study, Brown and Ryan (2003, Study 3) measured individuals' emotional well-being using both self-report measures (explicit level) and an IAT (implicit level). They found that MAAS scores predicted concordance between implicit and explicit affect. In particular, there was a closer relation between explicit and implicit affective experience in meditation naïve individuals ($n = 78$) with high versus low MAAS scores. Another important study has recently extended these findings to self-esteem (Koole et al., 2009). In particular, it was shown that brief MM exercises, carried out by young naïve participants (overall $n = 188$), led to greater congruence between explicit and implicit measures of self-esteem specifically when they were executed before, rather than after, completing the two types of self-esteem.

Notably, these studies interested in dispositional or state mindfulness left unaddressed the issue of whether regular MM practice, for instance during an 8-week mindfulness-based intervention, directly affects implicit as well as explicit self-concepts. This is an important issue that was addressed by our research group in a recent study (Crescentini et al., 2014b). In particular, we assessed the changes in explicit (e.g., Self-Transcendence in the TCI) and implicit [using an IAT for religiousness/spirituality (RS); Crescentini et al., 2014a] RS self-representations in meditation-naïve individuals participating in an 8-week MM program. Remarkably, we found that MM led to widespread increases in explicit RS and to more circumscribed increases in implicit RS occurring in the individuals with low pre-existing implicit RS (i.e., before the MM training). Moreover, the two RS measures globally tended to increase congruently after vs. before the training.

Generally, the reviewed studies suggest that MM may have an impact on implicit self-concepts. This is important if one considers that implicit attitudes may be more difficult to transform than explicit attitudes; while the latter may represent recently acquired self-representations coexisting with the former, implicit attitudes could reflect more stable and older evaluative representations that have their origins in long-term personal experiences (Wilson et al., 2000; Gawronski and Bodenhausen, 2006). Development of mindful awareness thus appears able to impact responding at an automatic level and it could therefore be involved in gradually transforming patterns of automatic and habitual reacting and self-evaluation (Chambers et al., 2008). More generally, the reviewed data suggest that this practice fulfills important self-regulatory functions, for instance by letting intuitive self-attitudes to be more easily attuned and integrated into explicit self-attitudes, thus contributing to a more coherent self-image (Koole et al., 2009; Crescentini et al., 2014b).

CONCLUSION

The aim of this study was to review findings of researches investigating the relationship between MM and changes in personality and in the perspective on the self. Most of these studies addressed changes occurring at an explicit level using self-report measures of personality and self-concept changes. However, a few studies also focused on changes occurring at a deeper, implicit level. Although the research on MM and personality is still in its infancy, warranting further investigations on both levels of explicit and implicit self-concepts, the reviewed studies suggest that, operating on aspects such as sense of responsibility, authenticity, compassion, and self-acceptance, this form of mental training may significantly shape individuals' personality toward a more coherent and healthy sense of self and identity.

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Meditation reduces pain-related neural activity in the anterior cingulate cortex, insula, secondary somatosensory cortex, and thalamus

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Recent studies have shown that meditation inhibits or relieves pain perception. To clarify the underlying mechanisms for this phenomenon, neuroimaging methods, such as functional magnetic resonance imaging, and neurophysiological methods, such as magnetoencephalography and electroencephalography, have been used. However, it has been difficult to interpret the results, because there is some paradoxical evidence. For example, some studies reported increased neural responses to pain stimulation during meditation in the anterior cingulate cortex (ACC) and insula, whereas others showed a decrease in these regions. There have been inconsistent findings to date. Moreover, in general, since the activities of the ACC and insula are correlated with pain perception, the increase in neural activities during meditation would be related to the enhancement of pain perception rather than its reduction. These contradictions might directly contribute to the 'mystery of meditation.' In this review, we presented previous findings for brain regions during meditation and the anatomical changes that occurred in the brain with long-term meditation training. We then discussed the findings of previous studies that examined pain-related neural activity during meditation. We also described the brain mechanisms responsible for pain relief during meditation, and possible reasons for paradoxical evidence among previous studies. By thoroughly overviewing previous findings, we hypothesized that meditation reduces pain-related neural activity in the ACC, insula, secondary somatosensory cortex, and thalamus. We suggest that the characteristics of the modulation of this activity may depend on the kind of meditation and/or number of years of experience of meditation, which were associated with paradoxical findings among previous studies that investigated pain-related neural activities during meditation.

Keywords: MEG, EEG, fMRI, pain matrix, Yoga

INTRODUCTION

Some highly trained meditators reported that they did not feel pain during meditation, and in an attempt to demonstrate this, they stuck needles into their tongues and cheeks. This phenomenon suggests that meditation may affect higher functions of the central nervous system, and indicates the existence of specific neural mechanisms to inhibit or relief the perception of pain through long-term meditation training. Several studies using psychological methods demonstrated that meditators had lower pain sensitivity and experienced analgesic effects during mindful states (Grant and Rainville, 2009; Perlman et al., 2010; Zeidan et al., 2010). Recent studies have attempted to clarify this by using neuroimaging methods, such as functional magnetic resonance imaging (fMRI), and neurophysiological methods, such as magnetoencephalography (MEG) and electroencephalography (EEG) (Kakigi et al., 2005a; Orme-Johnson et al., 2006; Brown and Jones, 2010; Grant et al., 2011; Zeidan et al., 2011; Gard et al., 2012; Lutz et al., 2013; Villemure et al., 2014). These studies provided evidence of modulation regarding pain-related neural activity during meditation. However, the characteristics of this modulation were not consistent among these studies, which will be introduced in Section "Neural Activity of Pain Perception during Meditation" in detail. Thus, these neural mechanisms have been considered as the 'mystery of meditation.'

In this review, we attempted to elucidate the neural mechanisms involved in the effects of meditation on human pain perception based on published findings with neuroimaging and neurophysiology. To the best of our knowledge, there have been few systematic reviews in the scientific literature on this topic, even though many research reviews have focused on the neural mechanisms of pain perception (Kakigi et al., 2003, 2005b; Apkarian et al., 2005; Tracey and Mantyh, 2007; Wiech et al., 2008b; Inui and Kakigi, 2012; Garcia-Larrea and Peyron, 2013; Moayedi and Davis, 2013) and meditation (Cahn and Polich, 2006; Lutz et al., 2008; Tang and Posner, 2013a,b; Marchand, 2014). Zeidan et al. (2012) and Grant (2014) recently published a review on the brain mechanisms involved in pain relief during meditation. They discussed the underlying mechanisms based on their previous findings and other fMRI studies; however, we considered that additional standpoints were needed for a better understanding.

We firstly overviewed brain regions during meditation and the anatomical changes that occurred in the brain with long-term meditation training. We then reviewed the findings of previous studies that examined pain-related activity during meditation. We also described the brain mechanisms responsible for pain relief during meditation, and the reason for paradoxical evidence among previous studies. These processes and ideas were not accessed in previous reviews by Zeidan et al. (2012) and Grant (2014). We believed that the reappraisal of this effect may be associated with an understanding of the mechanisms underlying sensory, cognitive, or affective pain modulation along the lines of perceived control over pain.

Regarding the methodology of this research, we performed several PubMed searches with terms including meditation, mindfulness, pain, fMRI, EEG, MEG, VBM, DTI, ERP, voxel-based morphometry, distraction, placebo, review, electroencephalography, magnetoencephalography, diffusion tensor imaging, and event-related potentials.

NEURAL ACTIVITY OF PAIN PROCESSING

Pain is a conscious experience, an interpretation of the nociceptive input influenced by memories, as well as emotional, pathological, genetic, and cognitive factors (Tracey and Mantyh, 2007). Thus, the central nervous system in the human brain possesses complex pain-related neural networks, involving sensory-discriminative, affective-motivational, and cognitive-evaluative components, at least partially dissociable in terms of the underlying neural networks (Apkarian et al., 2005; Grant et al., 2011). Neuroimaging and neurophysiological studies provided evidence for these neural networks, which include multiple brain regions often referred to as the ‘pain matrix.’ The pain matrix generally includes the primary somatosensory cortex (SI) contralateral to side of the stimulation, as well as the bilateral secondary somatosensory cortex (SII), insula, anterior cingulate cortex (ACC), and thalamus. The prefrontal cortex (PFC) has been linked to the evaluation and anticipation of pain sensations (Coghill et al., 1999). Previous studies defined the pain matrix as including two systems: lateral and medial systems (see the review by Treede et al., 1999). The lateral system is projected to the cortical level with SI, SII, and the thalamus and is involved in the sensory-discriminative component of pain (stimulus localization, intensity discrimination, and quality discrimination). The medial system involves the ACC and insula, and is associated with the affective-motivational component, which is an essential part of pain (emotional reactions, arousal, attention to the pain stimulation, and escape response). Moreover, recent studies have suggested the existence of a descending pain modulation system, which includes activities in the PFC, ACC, and periaqueductal gray (PAG) of the brainstem (see reviews, Tracey and Mantyh, 2007; Wiech et al., 2008b). Afferent signals related to noxious stimuli are attenuated by the release of opioids from the PAG.

BRAIN REGIONS DURING MEDITATION

BRAIN REGIONS DURING MEDITATION

Based on the findings of studies conducted over the last three decades, meditation practices have been shown to have many ameliorative effects on the symptoms of disorders, including anxiety, depression, substance abuse, eating disorders, and chronic pain, and also improve well-being and quality of life (Kabat-Zinn et al., 1992; Teasdale et al., 2000; Hölzel et al., 2011). Meditation is also known to have lasting effects on respiratory control, including respiration rate and oxygen consumption, and the long-term practice of such forms of meditation may induce structural changes in brain regions involved in basic autonomic regulation (Vestergaard-Poulsen et al., 2009). A number of studies investigated brain activation during meditation by utilizing neurophysiological and neuroimaging methods in order to clarify the neural mechanisms during meditation. The characteristics of background EEG activities have often been examined during meditation (for a review, see Cahn and Polich, 2006). One characteristic is the increase of theta and alpha activation associated with proficiency in the meditative technique. Frontal midline activity is generated from the ACC, medial prefrontal cortex (mPFC), and dorsolateral prefrontal cortex (DLPFC; Asada et al., 1999; Ishii et al., 1999), and the activity is correlated with a continuous concentration of attention. Neuroimaging methods including fMRI, PET, and single photon emission computed tomography (SPECT) revealed the brain regions activated during meditation (for a review, see Cahn and Polich, 2006). fMRI studies reported significant activation in the inferior frontal gyrus (IFG), mPFC, ACC, posterior cingulate cortex (PCC), basal ganglia, supplementary motor area (SMA), precentral gyrus, midbrain, inferior parietal lobule (IPL), precuneus, and hippocampus (Lazar et al., 2000; Hölzel et al., 2007; Baerentsen et al., 2010; Davanger et al., 2010; Engström et al., 2010; Ives-Deliperi et al., 2011), while deactivation was observed in the primary (VI) and secondary (VII) visual cortices, PFC, precuneus, insula, ACC, PCC, and occipito-parieto-temporal area (Herzog et al., 1990; Baerentsen et al., 2010; Ives-Deliperi et al., 2011). Newberg et al. (2001) using SPECT showed that regional cerebral blood flow was significantly increased in the cingulate gyrus, inferior, and orbital frontal cortex, DLPFC, and thalamus. Yamamoto et al. (2006) using MEG and EEG simultaneously identified the source of alpha activity in eight meditators during meditation, and localized dipole sources in both the mPFC and ACC.

Sperduti et al. (2012), using a meta-analysis of previous neuroimaging studies on brain regions during meditation, recently reported the core cortical system shared by different kinds of meditation. Prominent activations were detected in the parahippocampal formation, basal ganglia, and mPFC. They hypothesized that the parahippocampal formation evaluated and controlled the stream of mental scenes (thoughts monitoring system), and also that the basal ganglia were responsible for the onset and maintenance of a background attentional set characterized by lower distractibility from irrelevant stimuli (interference control system). They also suggested that mPFC supported the inner engagement of attention and enhanced self-awareness (self-monitoring system).

BRAIN ACTIVITIES IN DIFFERENT FORMS OF MEDITATION

There are two broad categories of meditation styles; focused attention (FA) meditation and open monitoring (OM) meditation (for a review, see Lutz et al., 2008), involving different attentional, cognitive monitoring, and awareness processes. Lutz et al. (2008) reported that FA meditation entailed the voluntary focusing of attention on a chosen object. The characteristics of this type involve directing and sustaining attention on a selected object (e.g., breath sensation), detecting mind wandering and distractors (e.g., thoughts), disengagement of attention from distractors and shifting attention back to the selected object, and cognitive reappraisal of the distractor (e.g., 'just a thought,' 'it is okay to be distracted'). On the other hand, OM meditation reflects non-reactive monitoring of the content of experience from one moment to the next. This includes no explicit focus on objects, non-reactive metacognitive monitoring (e.g., for novices, the labeling of experience), and non-reactive awareness of automatic cognitive and emotional interpretations of sensory, perceptual, and endogenous stimuli.

According to the findings of Lou et al. (1999), the activity pattern of meditation differed according to the meditative content. For example, meditation on the sensations of the weight of limbs and other body parts, presumably related to motor attention, was mainly supported by parietal and superior frontal activities, abstract sensations of joy by left hemisphere parietal and superior temporal (i.e., Wernicke area) activities, and visual imagery by strong activation of the occipital lobe, with sparing of the VI region, and the parietal lobe. Meditation on symbolic representation of the self was supported by bilateral parietal activity.

Shimomura et al. (2008) identified differences in the activated regions of BOLD signals between the Nembutsu, which voices the hope of rebirth into Amida's Pure Land in the Buddhists, and Sutra. The task of repeating the Nembutsu activated the superior/medial frontal gyrus, while the task of reciting the Sutra activated the lateral middle frontal gyrus, angular gyrus, and supramarginal gyrus.

Manna et al. (2010) compared brain activities between FA and OM meditations within the same subjects. They detected larger activated regions in the DLPFC, precuneus, superior parietal lobule (SPL), insula, IFG, and transverse temporal gyrus during OM meditation than FA meditation, while larger activated regions were observed in the mPFC and ACC during FA meditation than OM meditation.

Wang et al. (2011) also reported differences in brain activation between focused-based and breath-based practices. They demonstrated that the breath-based practice activated many regions in the hippocampus, parahippocampus, amygdala, insula, IFG, superior temporal gyrus (STG), and fusiform gyrus, whereas focused-based practice was associated more closely with activation of the precentral gyrus, precuneus, and insula.

These studies using neuroimaging methods suggested the existence of different neural networks depending on the style of meditation. Based on these findings, OM meditation may activate larger brain regions including the limbic system than FA meditation.

NEUROPLASTICITY OF BRAIN STRUCTURES WITH LONG-TERM MEDITATION

Several studies focused on the neuroplasticity of brain structures in relation to the long-term practice of meditation. One approach used to analyze neuroplasticity was comparing the thickness of the cerebral cortex between meditators and non-meditators, with an anatomical MRI scan (Fischl and Dale, 2000). The cortical thickness is estimated as the distance between the gray/white boundary and outer cortical surface. The segmentation procedure uses both intensity and continuity information from three-dimensional high-resolution MRI, including the coronal, axial, and sagittal planes (Salat et al., 2004). A second approach was voxel-based morphometry (VBM). VBM has frequently been used to clarify differences in the gray matter (GM) between different subject groups, as well as changes in GM within the same subject between pre- and post-training (i.e., longitudinal study). For example, this method has been utilized to examine the long-term effects of training on the volumes of GM, such as juggling skills (Draganski et al., 2004; Boyke et al., 2008; Scholz et al., 2009), golf (Bezzola et al., 2011), large-scale space (Maguire et al., 2000), bilingualism (Mechelli et al., 2004), arithmetic (Aydin et al., 2007), music (Han et al., 2009; Hyde et al., 2009), and revising for exams (Draganski et al., 2006). In a study by Draganski et al. (2004) involving juggling training for 3 months, they showed a transient and selective structural change in brain areas associated with the processing and storage of complex visual motion in the mid-temporal area (hMT/V5) and left posterior intraparietal sulcus. This study suggested that long-term training led to neuroplasticity in human brains, which was related to functional rather than anatomical changes. Thus, it is likely that similar neuroplasticity occurs in meditators on long-term training in meditation. A third approach was diffusion tensor imaging (DTI). DTI has been used to evaluate the anatomical connectivity of white matter (WM) with fractional anisotropy (FA; Taubert et al., 2012). Similar to VBM, DTI has been employed to clarify structural changes in WM with long-term training such as music (Bengtsson et al., 2005; Imfeld et al., 2009; Oechslin et al., 2010) and physical activity (Tseng et al., 2013; Herting et al., 2014). Just like GM, the WM density may also be affected by long-term training in meditation. Indeed, several studies reported that both GM and WM were changed by long-term training, such as in juggling skills (Scholz et al., 2009), suggesting that the WM changes underlie behavioral improvements by altering the conduction velocity and synchronization of nervous signals, which are regulated by myelin.

We briefly introduced previous studies that examined neuroplasticity through long-term meditation training in the next subsection, and these are listed in **Table 1**.

CORTICAL THICKNESS AND MRI VOLUME

Lazar et al. (2005) compared cortical thicknesses between 20 participants with extensive training in insight meditation and 15 control participants. The right anterior insula (AI), right PFC, left STG, and left SI were significantly thicker in meditators than in controls.

Grant et al. (2010) investigated cortical thicknesses in 19 Zen meditators and 20 controls. Meditators were found to have a thicker cortex in the bilateral ACC, bilateral SII, bilateral insula, bilateral parahippocampal gyrus, bilateral SI, and bilateral PFC. Furthermore, when assessed in all subjects, lower pain sensitivity was associated with a thicker cortex in affective, pain-related regions including the ACC, bilateral parahippocampal gyrus, and AI.

Kang et al. (2013) employed a whole-brain cortical thickness analysis in the brains of 46 experienced meditators and 46 matched

Table 1 | Brain regions altered by long-term meditation training.

Authors	Measurement	Brain regions altered by long-term meditation training
Lazar et al. (2005)	Cortical thickness	Right AI, right PFC, left STG, and left SI
Pagnoni and Cekic (2007)	VBM	Left putamen
Hölzel et al. (2008)	VBM	Right AI, left ITG, and right hippocampus
Luders et al. (2009)	VBM	Right OFC, right hippocampus, and left ITG
Vestergaard-Poulsen et al. (2009)	VBM	Brainstem
Grant et al. (2010)	Cortical thickness	Bilateral ACC, bilateral SII, bilateral insula, bilateral parahippocampal gyrus, bilateral SI, and bilateral PFC
Hölzel et al. (2010)	VBM	Right amygdala
Tang et al. (2010)	DTI	ACC
Hölzel et al. (2011)	VBM	Left hippocampus, PCC, left TPJ, and the cerebellum
Luders et al. (2011)	DTI	Commissural pathways, association pathways, corticospinal tract, temporal component of superior longitudinal fasciculus, and uncinate fasciculus
Tang et al. (2012)	DTI	Genu and body of the corpus callosum, bilateral corona radiata, left anterior corona radiata, and left superior longitudinal fasiculus
Luders et al. (2012a)	DTI and MRI	Corpus callosum
Luders et al. (2012b)	Gyrification	Bilateral AI, left pre/postcentral gyrus, left central sulcus, left ITG, left angular gyrus, left parieto-occipital fissure, right parietal operculum, right fusiform gyrus, and right cuneus
Murakami et al. (2012)	VBM	Right AI, and right amygdala
Luders et al. (2013a)	MRI volume	Bilateral hippocampi
Luders et al. (2013b)	VBM	Bilateral hippocampi
Kang et al. (2013)	Cortical thickness	Bilateral MTG/ITG, bilateral OFC, bilateral PFC, bilateral superior frontal cortex, bilateral PPC, right PCC, right cuneus, right fusiform gyrus
	DTI	Bilateral cuneus, bilateral ITG, bilateral temporal pole, left forceps minor, left frontal pole, left precuneus, left lateral occipital cortex, left precental cortex, left parahippocampal gyrus, left PCC, right insula, right ACC, right subcallosal cortex, right superior corona radiation, right OFC, and right anterior thalamic radiation
Leung et al. (2013)	VBM	Right angular gyrus, right parahippocampal gyrus, left ITG, and left MTG
Pickut et al. (2013)	VBM	Bilateral TPJ, left lingual gyrus, left cuneus, left thalamus; bilateral hippocampi, right amygdala, and bilateral caudate nucleus
Wells et al. (2013)	Connectivity	Connectivity between PCC and bilateral PFC, and between PCC and left hippocampus
	MRI volume	Bilateral hippocampi
Kurth et al. (2014)	VBM	Superior parietal lobule
Singleton et al. (2014)	VBM	Brainstem

VBM, voxel-based morphometry; DTI, Diffusion tensor imaging; AI, anterior insula; PFC, prefrontal cortex; STG, superior temporal gyrus; SI, primary somatosensory cortex; ITG, inferior temporal gyrus; OFC, orbito-frontal cortex; ACC, anterior cingulate cortex; SII, secondary somatosensory cortex; PCC, posterior cingulate cortex; TPJ, temporo-parietal junction; MTG, middle temporal gyrus; PPC, posterior parietal cortex.

control volunteers. Cortical thickness was significantly greater in meditators than in controls in the bilateral middle temporal gyrus (MTG)/inferior temporal gyrus (ITG), bilateral orbito-frontal cortex (OFC), bilateral PFC, bilateral superior frontal cortex, bilateral posterior parietal cortex (PPC), right PCC, right cuneus, and right fusiform gyrus.

In a study performed by Luders et al. (2013a), high-resolution structural MRI data from 30 long-term meditators and 30 controls were analyzed to explore hippocampal features in the framework of meditations. Bilateral hippocampal volumes were larger in meditators than in controls, and significantly so for the left hippocampus.

Wells et al. (2013) randomized 14 adults with mild cognitive impairments into mindfulness-based stress reduction (MBSR) or usual care interventions, and recorded brain morphometry before and after the intervention. MBSR participants had higher functional connectivity between the PCC, bilateral mPFC, and left hippocampus than that of the controls. MBSR participants also had trends of less bilateral hippocampal volume atrophy than the controls.

These studies indicated that long-term meditation increased cortical thickness in several brain regions, such as SI, SII, PFC, temporal gyrus, PPC, ACC, and hippocampus, and the connectivity was also enhanced among PCC, PFC, and hippocampus.

VOXEL-BASED MORPHOMETRY

Pagnoni and Cekic (2007) employed VBM in 13 regular practitioners of Zen meditation and 13 matched controls, and a significant difference was observed in GM in the left putamen.

Hölzel et al. (2008) investigated the MRI brain images of 20 mindfulness (Vipassana) meditators and compared regional GM concentrations to those of non-meditators. The findings obtained revealed greater GM concentrations for meditators in the right AI, left ITG, and right hippocampus.

Luders et al. (2009) detected significantly larger GM volumes in the right OFC, right hippocampus, and left ITG in 22 meditators than in 22 controls.

Vestergaard-Poulsen et al. (2009) showed that there were structural differences in the brainstem regions, which were associated with cardiorespiratory control, between 10 long-term practitioners of meditation and 10 controls.

Hölzel et al. (2010) conducted a longitudinal MRI study to investigate the relationship between changes in perceived stress with changes in amygdala GM density following 8 weeks of MBSR. Following the intervention, participants reported significantly reduced perceived stress, and reductions in perceived stress positively correlated with decreases in right amygdala GM density.

Hölzel et al. (2011) performed a longitudinal study on 16 meditation naïve participants to investigate pre–post changes in brain GM concentrations attributable to participation in an 8-week MBSR program. The VBM analysis showed increases in GM concentration within the left hippocampus, PCC, left temporo-parietal junction (TPJ), and the cerebellum.

Murakami et al. (2012) applied VBM to investigate the relationship between brain structures and each facet as measured by the Five Facet Mindfulness Questionnaire (FFMQ). The findings obtained showed a positive association between the describing facet of mindfulness on the FFMQ and GM volume in the right AI and right amygdala.

Luders et al. (2013b) examined GM characteristics in a large sample of 100 subjects (50 meditators and 50 controls), in which meditators had been practicing for approximately 20 years on average. A standard, whole-brain VBM approach was applied and revealed significant meditation effects in the vicinity of the hippocampus, showing that the volume of GM was greater in meditators than in controls as well as positive correlations with the number of years practiced.

Leung et al. (2013) demonstrated that the GM volume was greater in the right angular gyrus, right parahippocampal gyrus, left ITG, and left MTG in experts of loving-kindness meditation, than in controls.

Pickut et al. (2013) compared differences in the GM density between 14 patients with Parkinson's Disease (PD) following an 8-week MBSR and 13 patients with PD following usual care. GM density was higher in the MBSR group than in the usual care group in the bilateral TPJ, left lingual gyrus, left cuneus, left thalamus, bilateral hippocampi, right amygdala, and bilateral caudate nucleus.

Kurth et al. (2014) investigated differences in GM asymmetry as well as correlations between GM asymmetry and years of meditation practice in 50 long-term meditators and 50 controls. They observed significant differences between meditators and controls with respect to GM asymmetry in the SPL.

Singleton et al. (2014) showed that the scores on five psychological well-being (PWB) subscales as well as the PWB total score increased significantly over the MBSR course. In addition, these changes positively correlated with GM concentration increases in two symmetrically bilateral clusters in the brainstem, which contained the area of the pontine tegmentum, locus coeruleus, nucleus raphe pontis, and sensory trigeminal nucleus.

Luders et al. (2012b) examined cortical gyrification in a large sample ($n = 100$) of meditators and controls. Cortical gyrification was established by calculating the mean curvature across 1000s of vertices on individual cortical surface models. Gyrification in meditators was prominent within the bilateral AI, left pre/postcentral gyrus, left central sulcus, left ITG, left angular gyrus, left parieto-occipital fissure, right parietal operculum, right fusiform gyrus, and right cuneus.

As shown in VBM studies, long-term meditation increased the GM volume in the OFC, PPC, temporal gyrus, lingual gyrus, cuneus, thalamus, insula, PCC, cerebellum, hippocampus, amygdala, basal ganglia, and brainstem. Thus, GM in both the cerebral cortex and the limbic system may be larger in meditators than in controls.

DIFFUSION TENSOR IMAGING

Tang et al. (2010) examined all brain areas showing FA changes between pre- and post-training with 11 h of integrative body–mind training. They demonstrated significantly greater FA in the anterior corona radiata associated with the ACC.

Luders et al. (2011) investigated WM fiber characteristics in a well-matched sample of long-term meditators and controls. The findings obtained showed more pronounced structural connectivity in meditators than in controls throughout the commissural pathways, association pathways, corticospinal tract, temporal component of the superior longitudinal fasciculus, and uncinate fasciculus.

Luders et al. (2012a) analyzed differences in the corpus callosum between 30 meditators and 30 controls. Callosal measures, particularly in anterior callosal sections, were larger in long-term meditators than in controls, indicating the greater connectivity of hemispheric integration involving prefrontal regions.

Tang et al. (2012) reported different patterns of FA increases in brain regions following 4 weeks of integrative body–mind training. The first pattern was a decrease in both radial diffusivity (RD) and axial diffusivity (AD) accompanied by increased FA, and occurred in six brain regions involving the genu and body of the corpus callosum, bilateral corona radiata, left anterior corona radiata, and left superior longitudinal fasiculus. The second pattern was a decrease in RD accompanied by increased FA, and was detected in the body of the corpus callosum, left corona radiata, left anterior corona radiata, and left superior longitudinal fasiculus.

In addition to whole-brain cortical thickness analyzes, Kang et al. (2013) used DTI. Direct comparisons of FA values between meditators and controls revealed significant differences in most of the anterior portion of the brain, with higher FA values in the cuneus, precuneus, and occipital regions as well as the ventromedial PFC in the meditator group. In contrast, meditators showed lower FA values in the right MPFC, PCC, and right occipital regions than those in the controls.

These previous findings using the DTI method revealed that long-term meditation enhanced the anatomical connectivity of WM including the corona radiata, superior longitudinal fasciculus, and uncinate fasciculus, and corpus callosum.

NEURAL ACTIVITY OF PAIN PERCEPTION DURING MEDITATION

As described in the Section "Introduction," recent studies using neuroimaging and neurophysiological methods demonstrated that meditation reduced pain perception. We have introduced these studies in this section. We initially considered why meditation modulated pain perception. Previous studies reported the modulation of pain perception and pain-related neural activities during distraction (Yamasaki et al., 1999, 2000; Qiu et al., 2004), placebo (Petrovic et al., 2002; Wager et al., 2004), voluntary movements (Kakigi and Shibasaki, 1992; Kakigi et al., 1993; Nakata et al., 2004, 2009), odors (Villemure et al., 2003), emotion (Roy et al., 2009), and religious contemplation (Wiech et al., 2008a). We suggested three possible hypotheses; (1) an attention effect (distraction away from pain itself); (2) placebo effect; and (3) modulation of neural activity in the 'pain matrix.' Regarding hypothesis 1, MEG and EEG studies previously showed that brain activity relating to pain perception decreased during distraction tasks, and linked processes with attentional control. For example, Yamasaki et al. (1999) reported that MEG responses that peaked approximately 160 ms after a painful CO_2 laser stimulation to the right forearm were not affected during a distraction task (calculating), whereas sequential EEG responses that peaked at 240–340 ms were markedly affected. They also confirmed this effect with MEG and EEG by using a painful electrical stimulation to the right index finger (Yamasaki et al., 2000). Qiu et al. (2004) also recorded MEG and EEG following the stimulation of a small surface area with a CO_2 laser, which elicited brain activity for the selective activation of the C afferent sensory terminal, and compared activities between resting control and distraction tasks (calculating). In that study, the strength of equivalent current dipoles (ECDs) in six brain regions, which included the SI contralateral to the side of the stimulation, bilateral SII, bilateral the medial temporal area, and the cingulate, was significantly smaller during the distraction task than during the resting control task. These studies using MEG and EEG indicated that the strength of neural activities relating to pain perception decreased during distraction tasks. In addition to the distraction effect, the placebo effect on pain perception has been examined, and is often referred to as placebo analgesia. Previous reviews described the neural mechanisms underlying placebo analgesia (Wiech et al., 2008b; Qiu et al., 2009), and indicated that pain-related neural activity, such as that in the thalamus, ACC, and insula, decreased during the placebo condition, while the magnitudes of these decreases correlated with subjective pain relief afforded by the placebo. Prefrontal activation has also been observed prior to a noxious stimulation, indicating an interplay between expectations and reappraisal in the placebo effect (Wiech et al., 2008b). A stereotypical image regarding meditation already exists in participants before experiments are performed. This state should be associated with a similar effect to that of placebo analgesia. However, we speculated whether the effects of meditation on pain perception could be simply explained by the distraction and placebo effects. We subsequently considered specific neural mechanisms; the modulation of neural activity for the 'pain matrix' during meditation. Some published findings supported this notion.

PREVIOUS FINDINGS USING NEUROPHYSIOLOGICAL METHODS

The first study using neuroimaging and neurophysiological methods to show the effects of meditation on pain perception was ours. We recorded brain activity relating to pain perception in a Yoga master by utilizing MEG and fMRI, and compared differences in this activity between meditation and non-meditation (Kakigi et al., 2005a). This study consisted of only one person, and, as such, was a case report for the effects of meditation on pain perception. The Yoga master that participated in this study was very special because he had achieved the title of Yoga Samrat, indicating the highest level of proficiency, from the Indian Yoga Culture Federation in 1983. We identified several characteristics during meditation. We analyzed background MEG activity, and found that the power of alpha frequency bands peaking at approximately 10 Hz was larger during meditation than non-meditation in the occipital, parietal, and temporal regions. Cortical activities in the SI and SII detected by MEG were also very weak or absent during meditation following a painful laser stimulation applied to the dorsum of the left hand. BOLD signals in fMRI data revealed marked changes in the levels of neural activities in the thalamus, SII-insula, and cingulate cortex between meditation and non-meditation. Activities in these regions increased during non-meditation, which was similar to that observed in normal subjects. On the other hand, these activities decreased during meditation (**Figure 1**). In addition, activities in other regions such as frontal lobe, parietal lobe, and midbrain involving PAG increased during meditation. This study revealed marked changes in multiple regions related to pain perception during meditation.

Brown and Jones (2010) compared event-related potentials (ERPs) related to anticipatory processing before pain stimuli and pain processing after the stimulation between meditator and control groups. More experienced meditators perceived the pain as being less unpleasant than the controls, with meditation experience correlating inversely with unpleasantness ratings. The amplitude of ERPs for anticipatory processing was significantly smaller in the meditator group than in the control group, whereas no significant difference was observed in the peak amplitude of the P2 component for pain processing between groups. Low-resolution electromagnetic tomography (LORETA), which was performed to analyze the ERP source for anticipation, showed that activation of the mid-cingulate cortex (MCC) and inferior parietal

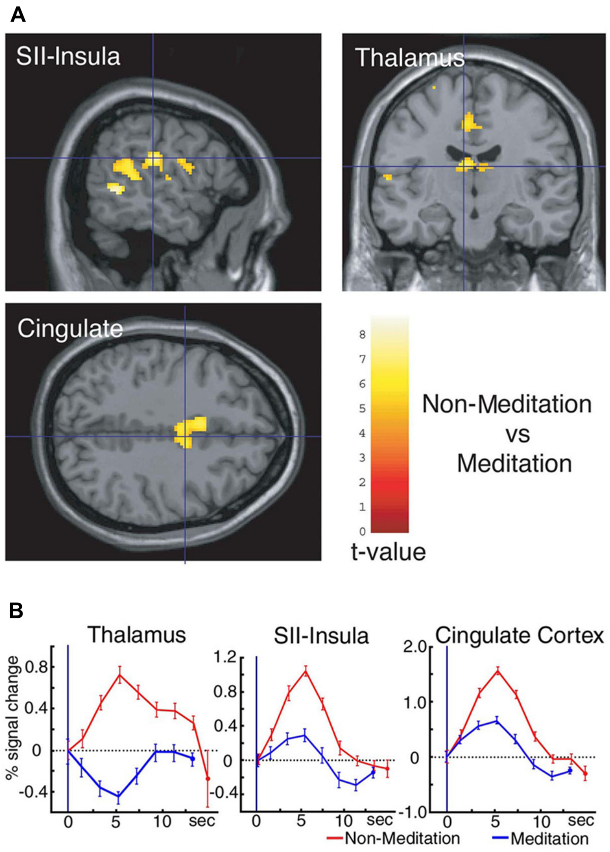

FIGURE 1 | (A) Significant differences were observed between non-meditation and meditation in three regions, the thalamus, SII-insula, and cingulate cortex. **(B)** Time course of the hemodynamic response (HDR) in the thalamus, SII-insula, and cingulate cortex during both non-meditation and meditation in the Yoga Master following a noxious YAG laser stimulation applied to the dorsum of the left foot. Activities in these regions decreased during meditation, and levels were lower than the baseline in the thalamus. Error bars indicate the SD of trials. Adopted from Kakigi et al. (2005a).

cortex during late anticipation was lower in meditator group than in the control group. In addition, activity in the MCC was positively correlated with pain unpleasantness in the meditator group, but not in the control group. Activity in the ventromedial-PFC (vmPFC) correlated negatively with pain unpleasantness in the meditator group and positively in the control group. Activity in the SII and posterior insula (PI) after the pain stimulation was lower during meditation, in spite of no significant difference in the peak amplitude of P2. These findings indicated that meditation reduced anticipation for the pain stimulation; however, its effects on pain-evoked activity were less clear.

PREVIOUS FINDINGS USING NEUROIMAGING METHODS

Orme-Johnson et al. (2006) recorded fMRI responses to thermal pain stimuli, and used two groups for the experiments. One group comprised healthy control subjects, who had trained in meditation for 5 months. fMRI was recorded pre- and post training. The other group included age-matched healthy long-term meditators who had practiced meditation techniques for a mean of approximately 31 years. In the pre-training period, the long-term meditators showed 40–50% lower responses than the healthy controls in the thalamus, PFC, and ACC for the thermal pain stimulation. Moreover, after learning and practicing meditation techniques for 5 months, brain responses in the healthy control group decreased by 40–50%, with no significant changes being observed in the long-term meditators. All fMRI recordings in their study were conducted outside the meditation period, not during it. Thus, distractions from pain by meditation were not relevant. One limitation of this study was that they only investigated neural activities in the thalamus, PFC, and ACC, and not in other brain regions such as the SI, SII, insula, and amygdala.

Grant et al. (2011) used a thermal stimulator to induce pain, and compared pain-related activity with fMRI between Zen meditators and controls. Neural activity in the PFC, amygdala, and hippocampus was decreased, whereas activation of the ACC, thalamus, and insula was increased in Zen meditators. In contrast, activation of the DLPFC, amygdala, middle frontal gyrus, hippocampus, and med-PFC/orbitofrontal cortex (OFC) was stronger in the controls. However, paradoxically, a correlation was noted between pain-related activation and meditation experience. In other words, the most experienced practitioners showed lower responses in the ACC, thalamus, and insula, which was consistent with the findings of Kakigi et al. (2005a).

Zeidan et al. (2011) also investigated pain-related brain activity using fMRI before and after meditation training for 4 days. They showed that meditation reduced pain-related activation of the SI contralateral to the thermal pain stimulation, which was a region associated with the sensory-discriminative processing of nociceptive information (Coghill et al., 1999). Meditation-induced reductions in pain intensity ratings were associated with increased activity in the ACC and AI. Reductions in pain unpleasantness ratings were associated with OFC activation and thalamic deactivation. These findings suggested that meditation modulated multiple brain activities that alter the construction of the subjectively available pain experience from afferent information.

Gard et al. (2012) recorded fMRI in meditation practitioners and control subjects during meditation and mindfulness and control conditions following unpleasant electric stimuli. Pain unpleasantness was 22% less and anticipatory anxiety was 29% less in meditation practitioners during meditation, but not in control subjects. This reduction was associated with decreased activation of the PFC and increased activation of the right PI during the stimulation, as well as increased activation of the ACC during the anticipation of pain.

Lutz et al. (2013) used fMRI and detected differences in neural activation patterns associated with pain, its anticipation, and habituation between expert meditators and novices. Three main findings were reported: Expert practitioners gave lower unpleasantness ratings, and had stronger BOLD activity in the left AI and MCC during pain, than novices. Experts had less anxiety-related baseline activity in these clusters and in the amygdala prior to pain. Experts had faster neural habituation to pain and its anticipation; the smaller the anticipatory activity in the amygdala, the faster the neural habituation in response to pain in the MCC.

RELATIONSHIP BETWEEN BRAIN STRUCTURE AND PAIN PERCEPTION

Villemure et al. (2014) investigated thermal detection and pain thresholds as well as cold pain tolerance in experienced North American Yoga practitioners and controls subjects. To clarify the underlying neuroanatomical mechanisms of perceptual changes, they also examined structural differences in brain GM and WM between the yogis and controls by using VBM in MRI recording. They found that insular GM correlated with pain tolerance. Insular GM volumes in yogis positively correlated with Yoga experience, suggesting a causal relationship between Yoga and insular size. Yogis also had higher left intrainsular WM integrity. These findings suggested that the regular and long-term practice of Yoga improved pain tolerance by changing insular brain anatomy and connectivity.

The pain-related brain regions modulated by meditation are listed in **Table 2**.

Table 2 | Pain-related brain regions affected by meditation.

Authors	Effects of meditation on brain activity
Kakigi et al. (2005a)	Increase: left SMI, right SPL, right DLPFC, bilateral SFG, and bilateral midbrain
	Decrease: bilateral thalamus, bilateral SII-insula, and cingulate cortex
Orme-Johnson et al. (2006)	Increase: absent
	Decrease: thalamus, PFC, and ACC
Brown and Jones (2010)	Increase: absent
	Decrease: left MCC, right IPL, right SII, and left PI
Grant et al. (2011)	Increase: bilateral ACC, bilateral thalamus, left insula, and left SII
	Decrease: bilateral DLPFC, bilateral amygdala, right OFC, and right hippocampus
Zeidan et al. (2011)	Increase: ACC, right AI, and OFC
	Decrease: SI and thalamus
Gard et al. (2012)	Increase: right PI and ACC
	Decrease: PFC, cerebellum, and STG
Lutz et al. (2013)	Increase: left AI and MCC
	Decrease: amygdala

SMI, primary sensorimotor cortex; SPL, superior parietal lobule; DLPFC, dorsolateral prefrontal cortex; SFG, superior fronal gyrus; SII, secondary somatosensory cortex; ACC, anterior cingulate cortex; MCC, midcingulate cortex; IPL, inferior parietal lobule; PI, posterior insula; SI, primary somatosensory cortex; AI, anterior insula; OFC, orbito-frontal cortex; STG, superior temporal gyrus.

DISCUSSION

A review of previous studies using EEG, MEG, and fMRI on the effects of meditation effect on pain-related neural activity revealed difficulties in interpreting their findings due to paradoxical evidence. Some studies reported increases in neural responses to pain stimuli during meditation in the ACC and insula (Grant et al., 2011; Zeidan et al., 2011; Gard et al., 2012; Lutz et al., 2013), whereas others showed a decrease (Kakigi et al., 2005a; Orme-Johnson et al., 2006; Brown and Jones, 2010; **Table 2**). In general, since the activities of the ACC and AI were correlated with pain perception (Wiech et al., 2008b), increases in neural activities during meditation may be related to enhancements rather than reductions in pain perception. This contradiction may directly contribute to the 'mystery of meditation,' and we proposed two possible hypotheses.

HYPOTHESES

One was the number of years of experience of the meditation. Grant et al. (2011) reported difference in the strength of neural activities in the ACC, DLPFC, and mPFC/OFC that were dependent on the number of years of experience of the meditation. Interestingly, pain activation in the ACC and insula was lower with higher meditation experience. In the study conducted by Kakigi et al. (2005a), as described above, a Yoga master who had achieved the highest level of proficiency had lower pain-related neural activity in the thalamus, SII-insula, and cingulate cortex. That is, the neural activities through long-term training might be related to its spent time. For example, 3 weeks of daily practice on finger movements evoked significantly larger activation of the MI than the control, untrained sequence (Karni et al., 1998). However, long-term physical training (e.g., 10 years) may evoke decreases in neural activities in the MI rather than increases. Such a phenomenon has been reported in musicians and athletes, who often started training very early in childhood, throughout their entire careers (Münte et al., 2002; Nakata et al., 2010), and has frequently been referred to as neural efficiency (Del Percio et al., 2008). Based on the theory of motor learning and neural efficiency, the strength of the neural response in the ACC and insula to pain stimulation during meditation may reflect the proficiency of meditators, even if the unpleasantness of pain and anticipatory anxiety were lower in meditators in novices.

The second hypothesis was the kind of meditation. There are several meditation methods, such as Yoga, Zen, mindfulness of breathing, and Samatha. Thus, differences in the meditation style may be associated with pain-related brain responses. As described in Section "Brain Regions during Meditation," there are two styles of meditation: FA and OM meditation. Perlman et al. (2010) published behavioral findings from a comparison between novice and long-term meditation practitioners using these techniques. Self-reported unpleasantness, but not the intensity, of painful stimuli while practicing OM were significantly lower in long-term meditators than in novices. No significant effects were found for FA.

Meditation may mainly affect the medial system of pain perception, which involves the ACC, and insula, even though activation or deactivation occurred. Based on the findings of Zeidan et al. (2011), since meditation-induced changes in SI did not specifically correlate with reductions in either pain intensity or unpleasantness, meditation did not affect the lateral system in the SI. On the other hand, pain-related activity in the SII, which belongs to the lateral system, may be affected by meditation. Some studies found stronger activation of the SII during meditation (Grant et al., 2011), while others observed its deactivation (Kakigi et al., 2005a; Brown and Jones, 2010). The modulation of neural activity in the SII may be similar to that in the ACC and insula, even if activation or deactivation occurred. Thus, the effects of meditation on pain processing may be different between the strength of the SI and SII.

Furthermore, regarding activity in the thalamus, three studies showed its deactivation (Kakigi et al., 2005a; Orme-Johnson et al., 2006; Zeidan et al., 2011). Grant et al. (2011) reported that the pain-related neural activity in the thalamus of a Yoga master with the highest level of proficiency was reduced. Deactivation of the thalamus may also be important for understanding the effects of meditation on pain perception, and may be related to a filtering function and the modulation of ascending pain sensory information.

Taking previous findings into consideration, OM meditation rather than FA meditation should attenuate pain-related neural activity in the SII, ACC, insula, and thalamus.

UNDERLYING MECHANISMS IN MODULATION OF PAIN PERCEPTION

Previous findings revealed increased brain activation in some regions even in meditators with more experience of meditation. For example, Kakigi et al. (2005a) reported that the left foot region of the primary sensorimotor area (SMI), SPL, superior frontal gyrus (SFG), DLPFC, and tectum mesencephali were activated during meditation following laser stimulation of the dorsum of the left foot in a meditator with the highest level of proficiency. The activation of these brain regions was not detected during non-meditation. One possibility for this finding is the specific attention system during meditation. It should be noted that activation was greater in the foot region in SMI. As described in Section "Neural Activity of Pain Perception during Meditation," if an attention effect and/or placebo effect exists during meditation, activation should be decreased. Moreover, activation was greater in SPL, and SFG/DLPFC, which is consistent with brain regions in the fronto-parietal network related to the attention system (for a review, see Chica et al., 2013). Therefore, we inferred the existence of a specific attention system during meditation that may modulate pain perception during meditation.

In addition to the attention system, meditation affects cognitive control, emotional regulation, cardiorespiratory control, and thinking patterns, because **Table 1** shows many brain regions altered by long-term meditation training. The human brain contains many neural networks, and it may be necessary to consider the functional mechanisms over the simple pain matrix to interpret the 'mystery of meditation.' For example, several studies reported that default mode network was changed with long-term meditation training (Taylor et al., 2011; Berkovich-Ohana et al., 2012). The default mode network has been identified to occur during task-induced deactivations, or during brain activity associated with a passive fixation baseline condition related to specific attention-demanding visual tasks (Gusnard and Raichle, 2001; Spreng, 2012). This network involves the medial frontal gyrus, medial and lateral parietal areas, and posterior cingulate (Fox et al., 2005), and is related to active cognitive processing that includes mind-wandering (Mason et al., 2007), and autobiographical remembering (Spreng and Grady, 2010). Thus, modulation in the neural activity of the default mode network with long-term meditation training reflects the changing of automatic processes, such as automatic thoughts, unconscious awareness, and passive attention. Moreover, some studies have also shown that meditation training improves emotional regulation, involving the amygdala (Taylor et al., 2011; Reva et al., 2014). The amygdala function is impaired in many disorders including depression, anxiety, and post-traumatic stress disorders, and attention system and emotional regulation are interactively affected (Desbordes et al., 2012). Therefore, other brain functions including attention, the resting state, and emotional regulation should be related to underlying neural mechanisms for the modulation of pain-related neural activity.

CONCLUSION

As described in the Section "Introduction," many studies have examined neural activities associated with pain perception and meditation. However, the neural mechanisms responsible for the effects of meditation have yet to be elucidated in detail. After a thorough literature search, we hypothesized that meditation mainly attenuated the medial system of pain perception including brain regions in the ACC and insula, as well as the lateral system in the SII and thalamus. We speculated that the characteristics of the modulation of this activity depended on the number of years of experience of meditation and/or the kind of meditation, which were associated with paradoxical findings among previous studies that investigated pain-related neural activities during meditation.

In addition, further studies are necessary to improve our understanding of the neurophysiological and psychological mechanisms underlying the effects of meditation on pain perception. For example, the descending pain modulatory system at the level of the brainstem may play an important role in pain relief during modulation (Tracey and Mantyh, 2007; Wiech et al., 2008b). These findings may be related to other neural mechanisms involved in the 'mystery of meditation.'

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Mechanisms of white matter change induced by meditation training

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Training can induce changes in specific brain networks and changes in brain state. In both cases it has been found that the efficiency of white matter as measured by diffusion tensor imaging is increased, often after only a few hours of training. In this paper we consider a plausible molecular mechanism for how state change produced by meditation might lead to white matter change. According to this hypothesis frontal theta induced by meditation produces a molecular cascade that increases myelin and improves connectivity.

Keywords: theta rhythm, myelination, diffusion tensor imaging, meditation, fractional anisotropy (FA)

In recent years there have been many reports of changes in white matter induced by training of human adults (see Zatorre et al., 2012 for a summary). Such changes usually involve training of specific networks involved in sensory discrimination, motor activity, or working memory. We call this form of training network training because it uses a specific task to induce changes in the underlying brain network. A different form of training involves training the brain state as occurs in the use of aerobic exercise or meditation, which we call state training (Tang and Posner, 2009; Tang et al., 2012b).

Our studies used a form of mindfulness meditation, integrative body-mind training (IBMT) in comparison with relaxation training (RT), which served as an active control (Tang et al., 2007). We used diffusion tensor imaging (DTI) before and after 4 weeks of training with IBMT and RT (Tang et al., 2010). We found significantly greater increases in fractional anisotropy (FA) following IBMT than after the RT control. The training effect was in white matter pathways connecting the anterior cingulate cortex (ACC) to other brain areas (Tang et al., 2010). We also found that after 2 weeks the FA change was entirely due to axial diffusivity (AD), which declined significantly more following IBMT than RT (Tang et al., 2012a). AD is thought to relate to changes in axonal density (Kumar et al., 2010, 2012). After 4 weeks FA involved changes in both axial and radial diffusivity (RD). RD is thought to reflect myelination (Song et al., 2002, 2003). This evidence suggests that meditation can influence brain areas known to be involved in self control in children and adults (Posner and Rothbart, 2007).

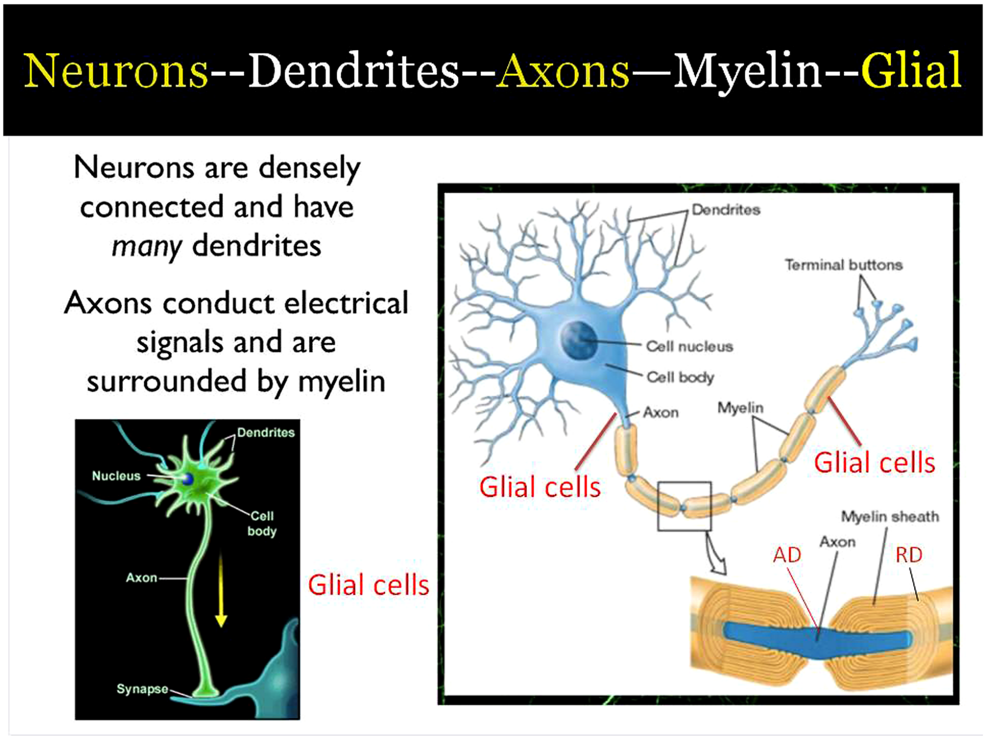
How can white matter change in as little as 2–4 weeks of training in meditation? In this paper we use evidence from a variety of human and animals studies to examine how meditation influences frontal brain rhythms, and the consequence of these rhythms on protease secretion that influence glial cells in forming the basis of white matter change. These mechanisms are summarized in **Figure 1** and elaborated below. We believe that they represent one way changes in brain state induced by meditation could lead to the observed changes in white matter as shown by DTI.

INCREASED FRONTAL THETA

Frontal theta has been regarded as a mechanism for recognizing the need for cognitive control and providing information to other brain areas (Cavanagh and Frank, 2014). The meditative state produces an increase in the EEG theta rhythm over frontal electrodes consistent with a generator in the anterior cingulate (Cahn and Polich, 2006; Chiesa and Serretti, 2010). Increased frontal midline theta is thought to reflect positive emotional state, internalized attention and autonomic nervous activity. Using IBMT with 1 week of training we recently replicated this result in frontal midline electrodes consistent with ACC activation (Tang et al., 2009; Xue et al., 2014). Theta oscillations may also induce changes in posterior alpha rhythms in humans (Song et al., 2014).

Theta rhythm in the ACC is also triggered by the violation of expectation such as when a person is presented with a novel event (Berger, 2012, p. 30). It has also been found that presenting a novel event within a visual search paradigm tends to recruit the ACC (Shulman et al., 2009). We have speculated that the presentation of a novel visual event may serve to foster the connectivity of the ACC, which has been found to increase during development of infants and young children (Posner et al., 2012).

Bursts of transcranial magnetic stimulation (TMS) in the theta range have been shown to induce changes in plasticity in the human motor cortex that outlast the stimulation (Huang et al., 2006). Recently theta burst rTMS was shown to increase cortical excitability and resting state connectivity in the motor system in a dose dependent manner (Nettekoven et al., 2014). Similar



Neurons--Dendrites--Axons—Myelin--Glial

Neurons are densely connected and have *many* dendrites

Axons conduct electrical signals and are surrounded by myelin

FIGURE 1 | Summary cartoon of major areas of change in the formation of white matter due to training. (AD, axial diffusivity; RD, radial diffusivity).

theta burst TMS has been shown to influence cognitive control networks including the ACC (Gratton et al., 2013). In a rat model repeated theta burst stimulation induced changes in calbindin protein in the frontal lobe thus reducing inhibitory control of neuronal spiking (Volz et al., 2013). These findings may provide the opportunity to test the role of theta in animal models.

INDUCTION OF PROTEASE CALPAIN

How can theta activity in mid frontal brain areas be related to changes in white matter connecting the ACC to other brain areas? Bouts of high frequency neuronal firing synchronized to theta are known to activate the calcium sensitive protease calpain, an event that causes substantial changes to the neuronal submembrane cytoskeleton (Vanderklish et al., 1995, 2000). Because they are structural in nature, the modifications produced by the protease can be very long lasting. These effects are usually discussed in terms of synapses and the extraordinarily persistent long-term potentiation effect (Lynch, 1998). This role for calpain in learning and memory through inducing synaptic plasticity has been disputed, but recent studies seem to indicate that it plays an important role in learning and memory (Zadran et al., 2010). Studies of drugs reducing calpain in mice (Amini et al., 2013) show impairment of dendritic spines and of long term potentiation.

The evidence for the role of calpain in learning and memory supports the observation that it can induce axonal growth and thus foster brain connectivity. Notably, calpain is also found in axons where it appears to play an important role in growth (Qin et al., 2010). It has been known for some time that action potentials trigger an influx of calcium into axons (e.g., Zhang et al., 2006), with recent work demonstrating activity-driven stimulation of calpain (Huff et al., 2011). The latter event, which modifies the same primary membrane cytoskeletal protein affected by theta bursts at synapses (Vanderklish et al., 2000), is followed by a substantial change to the myelin sheath (Huff et al., 2011).

Moderate stimulation of the protease during repeated, prolonged episodes of theta could, therefore, (i) foster brain connectivity and (ii) alter the axon-glia relationship; together, these lasting effects constitute plausible contributors to the results obtained with DTI. Of interest, recent work emphasizes the possibility that changes in oligodendrocytes contribute importantly to memory and cognition (Fields, 2013).

RAPID WHITE MATTER CHANGES

Traditionally white matter has been thought not to change after the period in development when axonal migration and myelination have taken place. However, this concept has been changing. For example, adult mice show reduced myelin thickness in prefrontal cortex induced by social isolation (Liu et al., 2012). The loss of myelin in the isolated mice, was associated with the presence of oligodendrocytes with immature nuclear chromatin. Beirowski (2013) argues that in adults axons are enwrapped by glia, including oligodendrocytes, with which they closely interact to form a unique symbiotic unit, a key contributor to the normal function of axonal connections. Indeed parts of the glia may respond to axonal damage within a few minutes (Guertin et al., 2005). Two key components of this final pathway could be axonal transport failure and calcium influx that among other targets activate cysteine proteases such as calpains whose inhibition also confers protection of injured axons *in vitro* and *in vivo* (Ma, 2013; Ma et al., 2013). While calpains are often associated with rapid release after axonal injury, they have also been associated with axonic growth within the axon rich intermediate zone of the cortex (Spira et al., 2003; Yang et al., 2011). Moreover, blocking of these molecular events interferes with this growth (Yang et al., 2011). Spira et al. (2003, p. 311) suggest "in light of the present findings, it would be interesting to examine the role of calpain ... in events that lead to morphological restructuring of neurons in relation to plasticity such as in learning and in memory acquisition processes." To our knowledge these critical studies have not yet been done, but as described above, calpain provides a viable possibility for white matter changes in brain state training.

Changes in axonal growth or myelination via calpain are not the only molecular route to alteration of myelin. For example, in one study mutant mice without erbB signaling from Neuregulin 1 showed demyelination and thinner myelin sheaths as adults (Chen et al., 2006). As expected these mice showed slower conduction velocities that would result in slower reaction times. However, these effects depend upon a mutation and would not result from learning. In any case, our goal is more to describe one possible route between training effects and white matter changes and we think other mechanisms are likely. Other potential mechanisms of white matter change are discussed in a recent review (Zatorre et al., 2012), but they are not clearly related to meditation effects.

TRAINING INDUCED WHITE MATTER CHANGES

Magnetic resonance imaging (MRI) cannot examine molecular events. However, the directionality of water molecules along white matter pathways (FA) can be measured and is believed to reflect the efficiency of connections. Changes in FA found in many learning studies can be linked to a plausible set of events including increased frontal theta and activation of the protease calpain which in turns works through glia cells to change myelin. Moreover the ability to impose the theta rhythm by brain stimulation may allow testing of its effects without extensive training.

A number of recent learning studies have shown FA changes that may take advantage of the molecular cascade that we have been describing. Most of these studies have involved learning of specific networks, for example, working memory training (Takeuchi et al., 2010), or juggling (Scholz et al., 2009). The periods of training run from a few hours to many months. In most studies of network training these effects are said to lead to an increase in myelination and changes in RD. However, our studies of meditation have shown that within 2 weeks of training there are changes in AD, most often associated with axonal density, and after 4 weeks both AD and RD are changed, suggesting both axonal density and myelin changes. We do not know if the differences between studies relate to state training vs. network training or other differences. It is possible that the study of calpain and other possible pathways for inducing these rapid changes will provide a better understanding of the time course of various forms of increased efficiency in the connectivity between brain areas.

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Forever Young(er): potential age-defying effects of long-term meditation on gray matter atrophy

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While overall life expectancy has been increasing, the human brain still begins deteriorating after the first two decades of life and continues degrading further with increasing age. Thus, techniques that diminish the negative impact of aging on the brain are desirable. Existing research, although scarce, suggests meditation to be an attractive candidate in the quest for an accessible and inexpensive, efficacious remedy. Here, we examined the link between age and cerebral gray matter re-analyzing a large sample ($n = 100$) of long-term meditators and control subjects aged between 24 and 77 years. When correlating global and local gray matter with age, we detected negative correlations within both controls and meditators, suggesting a decline over time. However, the slopes of the regression lines were steeper and the correlation coefficients were stronger in controls than in meditators. Moreover, the age-affected brain regions were much more extended in controls than in meditators, with significant group-by-age interactions in numerous clusters throughout the brain. Altogether, these findings seem to suggest less age-related gray matter atrophy in long-term meditation practitioners.

Keywords: aging, brain, gray matter, meditation, mindfulness, MRI, VBM

INTRODUCTION

Life expectancy around the world has risen dramatically, with more than 10 years of life gained since 1970. While this demonstrates major advances in healthcare and public health, it also presents major challenges: The human brain starts to decrease in volume and weight from our mid-twenties onwards (Fotenos et al., 2005; Walhovd et al., 2011; Oh et al., 2014). This structural deterioration leads progressively to functional impairments and is accompanied by an increased risk of mental illness and neurodegenerative disease (Fotenos et al., 2005; Kooistra et al., 2014). With an aging population, the incidence of cognitive decline and dementia has substantially increased in the last decades. In this light, it seems essential that longer life expectancies do not come at the cost of reduced life qualities, so that individuals can spend their increased lifetime living as healthy and satisfying as possible. Naturally, this requires a better understanding of the pathological mechanisms leading to brain aging but also the identification of factors which are protective of cerebral health and particularly those that can have incremental effects across the lifespan. Much research has focused on the identification of risk factors, but relatively less attention has been turned to positive approaches aimed at enhancing cerebral health.

Meditation might be a possible candidate in the quest for such a positive approach as there is ample evidence for its beneficial effects for a number of cognitive domains, including attention, memory, verbal fluency, executive function, processing speed, overall cognitive flexibility as well as conflict monitoring and even creativity (Lutz et al., 2008, 2009; Colzato et al., 2012; Gard et al., 2014; Lippelt et al., 2014; Marciniak et al., 2014; Newberg et al., 2014). This wealth of cognitive studies did not only further support the idea that the human brain (and mind) is plastic throughout life but also lead to a number of relevant concepts and theories, such as that meditation is associated with an increasing control over the distribution of limited brain resources (Slagter et al., 2007) as well as with process-specific learning, rather than purely stimulus- or task-specific learning (Slagter et al., 2011). Nevertheless, studies exploring the actual brain-protective effects of meditation are still sparse. As recently reviewed (Luders, 2014), there are only three published studies examining if correlations between chronological age and cerebral measures are different in meditators and controls. The first study (Lazar et al., 2005) focused on cortical thickness in two predetermined[1] brain areas. The second study (Pagnoni and Cekic, 2007) focused on whole-brain as well as voxel-wise gray matter. The third study (Luders et al., 2011) focused on fractional anisotropy, an indicator of white matter fiber integrity, in 20 predefined[2] fiber tracts. The outcomes from all three studies seem to suggest that meditation may slow, stall, or even reverse age-related brain degeneration, as

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[1] The two areas were defined based on outcomes of a preceding analysis comparing meditators and controls with respect to cortical thickness: significant group differences were observed within the right insula and right frontal cortex.

[2] The twenty tracts were defined based on applying a white matter tractography atlas, which includes the following tracts: anterior thalamic radiation, corticospinal tract, uncinate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus (two sections: main/temporal component), cingulum (two sections: cingulate gyrus/hippocampus), as well as forceps major and forceps minor.

there were less pronounced negative correlations and even positive correlations in meditators compared to controls (for a more detailed summary see Luders, 2014).

To further expand this field of research, we set out to examine the link between age and brain atrophy using an approach similar to the one used in one of the aforementioned studies (Pagnoni and Cekic, 2007). However, while Pagnoni and Cekic collected valuable data in a relatively small sample of 25 subjects (12 meditators/13 controls) with a mean age in the thirties, the present study included a large sample of 100 subjects (50 meditators/50 controls) with a mean age in the fifties. Using the present sample spanning a wide age range (24–77 years), we calculated the group-specific age-related correlations and tested for significant group-by-age interactions with respect to whole-brain gray matter volumes (hereafter referred to as *global* gray matter) as well as voxel-wise gray matter volumes (hereafter referred to as *local* gray matter). We expected reduced negative correlations in meditation practitioners compared to age-matched control subjects.

METHODS

SUBJECTS AND IMAGING

Our study included 50 meditation practitioners (28 men, 22 women) and 50 control subjects (28 men, 22 women). Meditators and controls were closely matched for chronological age, ranging between 24 and 77 years (meditators [mean ± SD]: 51.4 ± 12.8 years; controls [mean ± SD]: 50.4 ± 11.8 years). Meditators were recruited from various venues in the greater Los Angeles area. Years of meditation experience ranged between 4 and 46 years (mean ± SD: 19.8 ± 11.4 years). A detailed overview with respect to each subject's individual practice is provided in Supplementary Table 1. Brain scans for the control subjects were obtained from the International Consortium for Brain Mapping (ICBM) database of normal adults (http://www.loni.usc.edu/ICBM/Databases/). The majority (89%) of study participants was right-handed; six meditators and five controls were left-handed. Importantly, all subjects were scanned at the same site, using the same scanner, and following the same scanning protocol. Specifically, magnetic resonance images were acquired on a 1.5 Tesla Siemens Sonata scanner (Erlangen, Germany) using an 8-channel head coil and a T1-weighted magnetization-prepared rapid acquired gradient echo (MPRAGE) sequence with the following parameters: 1900 ms repetition time, 4.38 ms echo time, 15° flip angle, 160 contiguous sagittal slices, 256 × 256 mm field-of-view, 1 × 1 × 1 mm voxel size. All procedures pertaining to this study were reviewed and approved by UCLA's Institutional Review Board; all subjects gave their informed consent.

DATA PROCESSING AND ANALYSES

All T1-weighted images were processed in Matlab (http://www.mathworks.com/products/matlab/) using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and voxel-based morphometry (VBM) standard routines as implemented in the VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm.html), as previously described (Luders et al., 2013a). Briefly, images were corrected for magnetic field inhomogeneities (bias correction) and tissue-classified into gray matter, white matter, and cerebrospinal fluid (segmentation). Importantly, the tissue segmentation algorithm accounted for partial volume effects, which is crucial for the accurate estimation of tissue volumes (Tohka et al., 2004). To generate the input for the *global* gray matter analysis, we used the resulting gray matter partitions in their native dimensions and calculated the individual gray matter volumes (in ml) by summing up the voxel-wise gray matter content (across the entire brain) and multiplying it by voxel size. In order to characterize the group-specific direction and magnitude of age-related associations with respect to global gray matter, we first calculated the Pearson's correlations separately within meditators and controls, while removing the variance associated with sex (see **Figure 1**). Then, we tested if the correlations between age and global gray matter were significantly different between meditators and controls (group-by-age interaction), again, while co-varying for sex. All statistical analyses pertaining to global gray matter were conducted in Matlab using the Statistics Toolbox (http://www.mathworks.com/products/statistics/).

In parallel, to generate the input for the *local* gray matter analysis, we used the segmented gray matter partitions and normalized them spatially to the DARTEL template (provided with the VBM8 Toolbox) applying linear 12-parameter transformations and non-linear high-dimensional warping (Ashburner, 2007). The normalized gray matter segments were then multiplied by the linear and non-linear components derived from the normalization matrix (modulation) and convoluted with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel (smoothing). These modulated, smoothed gray matter segments constitute the input for the subsequent statistical analyses: Mirroring the global gray matter analysis, we first calculated the correlations between age and local gray matter separately within meditators and controls in order to get a sense of the

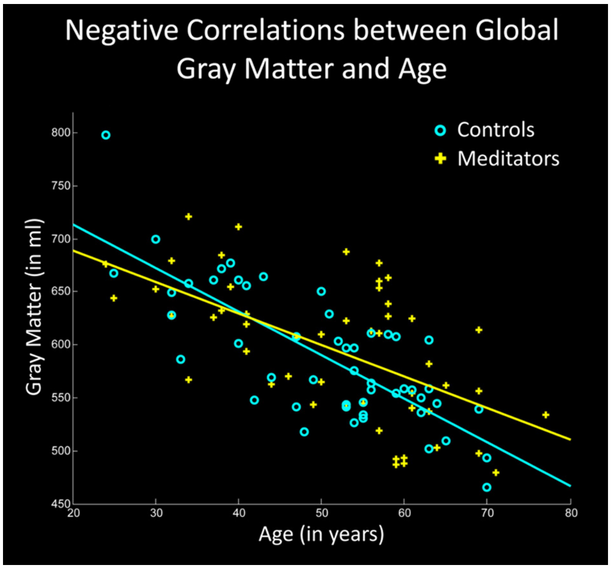


FIGURE 1 | Negative correlations between global gray matter and age. The X-axis displays the chronological age (in years); the Y-axis displays the global gray matter volume (in ml). Note the less steep slope of the regression line in meditators (yellow) compared to controls (cyan).

direction and extent of the age-related associations. For this purpose, we generated a series of maximum intensity projections within controls and meditators separately (see **Figure 2**). Then, we tested for significant group-by-age interactions (see **Figure 3**). For both analyses, group-specific correlations and group-by-age interactions, we removed the variance associated with sex and applied a significance threshold of $p \leq 0.05$, corrected for multiple comparisons via controlling the family-wise error (FWE) rate. FWE-corrections resulted in a lack of significance clusters for the group-by-age interaction, but given that such interactions have been reported previously, we repeated the analysis without the rather conservative FWE-corrections. To discriminate real effects from spurious noise, we applied an appropriate spatial extent threshold (corresponding to the expected number of voxels per cluster) calculated according to the Gaussian random fields theory. All statistical analyses pertaining to local gray matter were conducted in Matlab using SPM (http://www.fil.ion.ucl.ac.uk/spm).

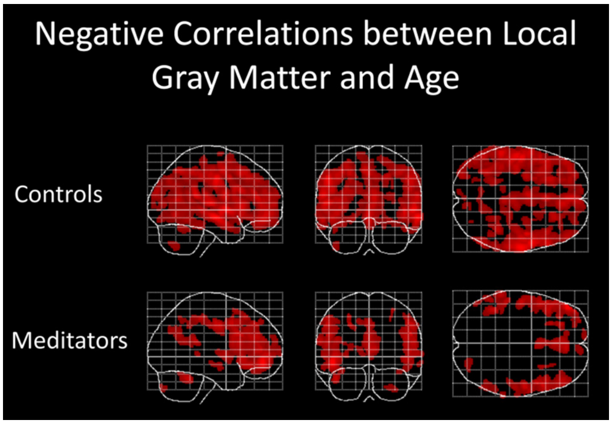


FIGURE 2 | Negative correlations between local gray matter and age. Displayed are maximum intensity projections superimposed onto the SPM standard glass brain (sagittal, coronal, axial). Shown, in red, are significant negative age-related correlations within controls **(top)** and meditators **(bottom)**. Significance profiles are corrected for multiple comparisons via controlling the family-wise error (FWE) rate at $p \leq 0.05$. Note the less extended clusters in meditators compared to controls.

RESULTS

GLOBAL GRAY MATTER

Examining the link between age and *whole-brain* gray matter, we observed a significant negative correlation in controls ($p < 0.001$) as well as in meditators ($p < 0.001$), suggesting age-related gray matter decline in both groups. However, as shown in **Figure 1**, the slopes of the regression lines were considerably steeper in controls than in meditators. Moreover, the group-specific correlation coefficients were higher in controls ($r = -0.77$) than in meditators ($r = -0.58$). The group-by-age interaction was highly significant ($p = 0.003$), altogether suggesting less age-related gray matter decline in meditators than in controls.

LOCAL GRAY MATTER

Examining the link between age and *voxel-wise* gray matter, significant negative correlations were evident in controls ($p < 0.05$, FWE-corrected) as well as in meditators ($p < 0.05$, FWE-corrected), suggesting age-related gray matter decline in both groups. However, as shown in **Figure 2**, age-affected brain regions were much more extended in controls than in meditators. In other words, echoing the global gray matter effect, the age-related decline of local gray matter was less prominent in meditators. Significant positive correlations were absent in both groups.

When mapping local group-by-age interactions applying a cluster size minimum of 1039 voxels (i.e., the expected number of voxels per cluster calculated according to the Gaussian

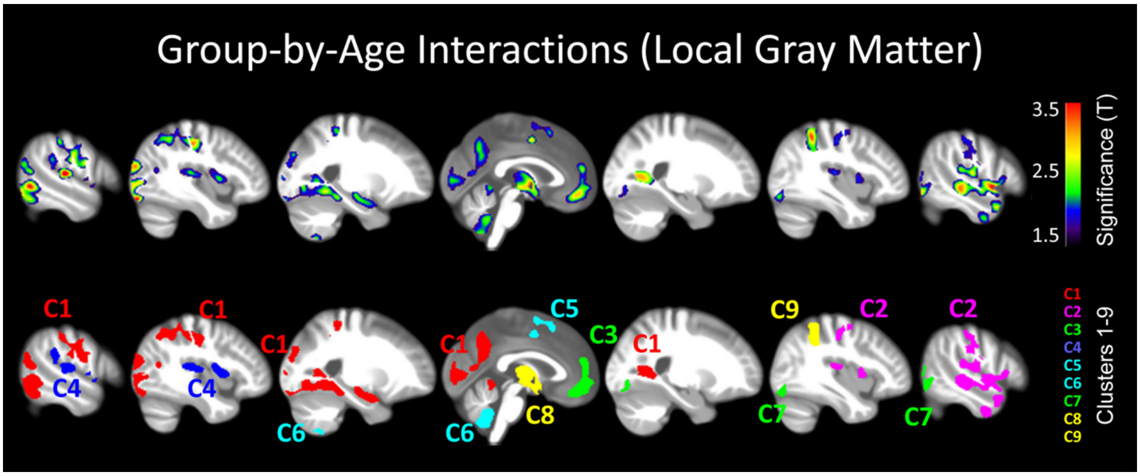
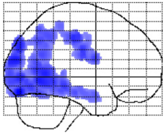
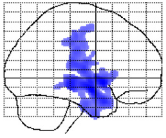
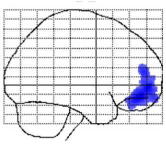
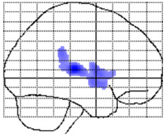
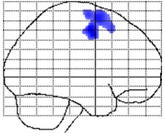
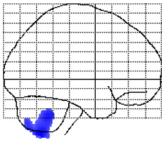
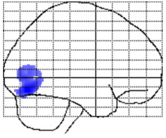
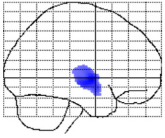
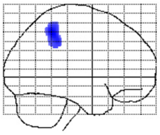


FIGURE 3 | Group-by-age interactions (local gray matter). The results are projected onto sagittal sections of the mean image derived from all subjects ($n = 100$). The clusters indicate areas where correlations between local gray matter and age are significantly different between meditators and controls (group-by-age interactions). Shown are clusters significant at $p \leq 0.05$ with a spatial extent threshold of $k \geq 1039$ voxels. **Top Row**: the different colors encode the T-statistic at the voxel level. **Bottom Row**: the different colors depict the nine clusters (C1–C9), as detailed in **Table 1**.

Table 1 | Cluster-specific details for significant group-by-age interactions (local gray matter).

Cluster	Number of voxels	Volume (ml)	Significance maximum (*T*)	Significance maximum (*x, y, z*)	Brain regions
C1 	20,019	67.56	3.89	−42, −84, −17	Hippocampus/amygdala (L) Medial (B) lateral (L) occipital cortex Medial (L) lateral (L) parietal cortex Posterior cingulate (L) Central sulcus (L)
C2 	8,539	28.82	3.59	60, −4, −12	Sylvian F. w/operculum + insula (R) Lateral temporal cortex (R) Inferior parietal cortex (R) Central sulcus (R)
C3 	2,986	10.08	2.99	2, 48, −12	Orbital gyrus (B) Anterior cingulate gyrus (B) Medial superior frontal gyrus (B)
C4 	2,825	9.53	3.91	−52, −24, 10	Sylvian F. w/operculum + insula (L) Temporo-parietal junction (L)
C5 	1,856	6.26	3.19	−6, −4, 51	Mid cingulate gyrus (B) Medial superior frontal (B)
C6 	1,542	5.20	2.70	−18, −61, −60	Cerebellum (B)
C7 	1,368	4.62	3.25	51, −75, −12	Lateral occipital cortex (R)
C8 	1,360	4.59	3.47	2, −4, −2	Hypothalamus (B) Medial thalamus (B)
C9 	1,131	3.82	3.42	38, −45, 49	Lateral parietal cortex (R)

L, left hemisphere; R, right hemisphere; B, both hemispheres.

random fields theory), we revealed nine significance clusters (C1–C9), as illustrated in **Figure 3** and also **Table 1**. The largest cluster (C1) contains 20,019 voxels (corresponding to 68 ml of gray matter) traveling from the left hippocampus / amygdala posteriorly toward the left and right medial and left lateral occipital cortex, and then anteriorly toward the left medial and left lateral parietal cortex, from which it further expands toward the left central sulcus. The significance maximum of C1 is located at $x = -42$; $y = -84$; $z = -17$ (MNI space). **Table 1** provides the details for all significance clusters (C1–C9) including the number of voxels, the cluster volume, the T-value and the MNI coordinates of the significance maximum, as well as the brain regions affected.

DISCUSSION

We investigated the link between chronological age and gray matter in a large sample of long-term meditators and control subjects closely matched on age and sex. We observed that the age-related gray matter loss was less pronounced in meditators than in controls, both globally and locally. As summarized recently (Luders, 2014), there are only a few previous studies that were directed at exploring age-related brain atrophy in the framework of meditation (Lazar et al., 2005; Pagnoni and Cekic, 2007; Luders et al., 2011).

CORRESPONDENCE WITH PRIOR RESEARCH

In terms of the specific methods applied and cerebral features analyzed, our current analyses are most comparable to those done by examining gray matter. With respect to *global* gray matter, Pagnoni and Cekic (2007) reported a trend for a significant group-by-age interaction "with an estimated rate of change of −4.7 ml/year for the control group vs. +1.8 ml/year for the meditators group" (Pagnoni and Cekic, 2007). Our significant group-by-age interaction with respect to *global* gray matter seems to confirm these prior findings. Interestingly, however, while the aforementioned study (Pagnoni and Cekic, 2007) exposed a marginally significant negative correlation in the control group ($r = -0.54$) and a non-significant positive correlation in the meditation group ($r = 0.006$), our study revealed significant negative correlations between age and gray matter both in controls ($r = -0.77$) and in meditators ($r = -0.58$). The lack of positive correlations in meditators and the comparably stronger age-related decline in controls might be attributable to our considerably older cohort (with a mean age in the early-fifties), contrasting Pagnoni and Cekic's relatively young sample (with a mean age in the mid-thirties). Similarly, different mean ages—but also slightly different significance and spatial extent thresholds—might account for diverging findings between the two studies with respect to *local* gray matter: while Pagnoni and Cekic (2007) detected one significant cluster in the region of the putamen, the current study detected nine significant clusters spread throughout the entire brain (albeit none of them in the putamen).

The nine significance clusters, indicating different age-related correlations in meditators, are spanning large areas of the brain and include several structures where prior studies—although not focusing on aging effects *per se*—had revealed meditation effects, either as cross-sectional group differences and/or as longitudinal changes. For example, resembling the spatial location of previous observations, we detected significant group-by-age interactions within the left hippocampus [C1] (Holzel et al., 2011; Luders et al., 2013a,b), left and right insula [C2, C4] (Lazar et al., 2005; Holzel et al., 2008; Luders et al., 2012), left posterior cingulate gyrus [C1] (Holzel et al., 2011), right anterior cingulate gyrus [C3] (Grant et al., 2010, 2013), left and right superior frontal lobe, including precentral gyrus and central sulcus [C1, C2, C3, C5] (Lazar et al., 2005; Luders et al., 2009, 2012; Grant et al., 2013; Kang et al., 2013; Kumar et al., 2014), left and right inferior frontal lobe, including orbital gyrus [C3] (Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Kang et al., 2013), left and right parietal lobe, including supramarginal gyrus, angular gyrus, and secondary somatosensory cortex [C1, C2, C4, C9] (Grant et al., 2010, 2013; Leung et al., 2013), right middle/inferior temporal cortex [C2] (Kang et al., 2013), left temporo-parietal junction [C4] (Holzel et al., 2011), right thalamus [C8] (Luders et al., 2009), as well as left and right cerebellum [C6] (Vestergaard-Poulsen et al., 2009; Holzel et al., 2011).

POSSIBLE UNDERLYING MECHANISMS

In general, engaging the brain in intense mental activities has been suggested to stimulate dendritic branching and/or synaptogenesis (Greenwood and Parasuraman, 2010; Birch et al., 2013). These micro-anatomical changes might manifest on the macro-anatomical level as increased gray matter. Over time, such activity-induced gray matter gain may "mask" the gray matter loss that is normally observed in aging. In other words, the potential meditation-induced tissue increase might counteract the normal age-related decrease. In support of this stream of thought, evidence for increases in cerebral gray matter due to meditation has been provided (Holzel et al., 2011), where significant effects were detected within the hippocampus, posterior cingulate cortex, temporo-parietal junction, and cerebellum (i.e., all regions where our study also revealed significant effects; see clusters C1, C4, and C6). The fact that we detected significant group-by-age interactions in several additional regions might be attributable to our unique study population, which included expert meditators with a mean practice of close to 20 years, rather than meditation-naïve participants as examined in the aforementioned study (Holzel et al., 2011). Unfortunately, due to feasibility constraints, there is still a lack of longitudinal studies exploring the long-term effects of meditation.

An alternative (or complementary) mechanism to practice-induced gray matter *gain* might be practice-accompanying gray matter *conservation* over time (i.e., an actual deceleration of the gray matter loss itself). For example, meditation might conserve cerebral gray matter by reducing stress levels and thus modulating the potentially harmful effects of immune response genes expression (Irwin and Cole, 2011), HPA axis hyperactivity (McEwen, 2008), down-regulation of neurogenesis (Varela-Nallar et al., 2010), activation of pro-inflammatory processes and the production of reactive oxygen species (Swaab et al., 2005). Direct or indirect effects of stress reduction might manifest, especially in regions that are known to be particularly vulnerable against stress (e.g., the hippocampus; see cluster C1) and/or directly involved in the regulation of stress (e.g., the hypothalamus; see cluster C8). As an alternative to this stress-related mechanism, tissue preservation might also be the result of better health in general, perhaps a consequence of healthier habits related to eating, sleeping, working, physical exercise, and/or resulting from higher levels of (self-)awareness, intelligence, socioeconomic status, etc. However, given that none of these aforementioned factors has been systematically assessed for the entire sample, all this is merely conjecture. On this note, we also wish to emphasize that, given the cross-sectional design of our study, it is impossible to draw any clear causal inferences. In addition to the factors discussed above, the diminished age-related tissue loss as well as the meditation practice itself may be a consequence of certain personal traits and/or practice-promoting circumstances. For example, in order to keep meditating for close to 20 years, individuals need to possess a minimum level of discipline and commitment, a well-organized life that allows them the spare time, an awareness of the possibility to control their own life, perhaps even a calm nature to begin with. Clearly, not everyone has these traits, desires, and possibilities, and thus there might be a selection bias in our sample of long-term meditators. Future studies may thus further advance this field of research by capturing (and accounting for) characteristics unique to meditation samples.

CONCLUSION AND ADDITIONAL IMPLICATIONS FOR FUTURE RESEARCH

Altogether, our findings seem to add further support to the hypothesis that meditation is brain-protective and associated with a reduced age-related tissue decline. Nevertheless, it is important to acknowledge that the observed effects may not only be a consequence of meditating but also of other factors allowing for (or accompanying) a successful long-term practice. Moreover, given the cross-sectional nature of the present data with explicit focus on gray matter, further research—ideally using longitudinal data and perhaps exploring additional cerebral attributes—is necessary to establish the true potential of meditation to maintain our aging brains. Along these lines, future studies may also want to consider exploring possible differential effects of various meditation styles in the framework of brain aging. Similarly, as previously mentioned (Luders, 2014), it may be worthwhile to determine what constitutes the critical amount of meditation—preferably not only in terms of the number of practice hours or years in total, but also with respect to the length, frequency, and regularity of individual practice sessions—in order to accomplish desirable effects. In parallel, it remains to be defined what "desirable" actually means (for whom and in which context). Furthermore, given that the vast majority of older adults experience at least some deterioration in cognitive function, it seems valuable to extend purely anatomical analyses to investigations of cognitive abilities and decline. Knowing if (and how) the actual preservation of brain tissue is related to the preservation of mental skills, will add crucial insights to this emerging, but still understudied, research field "at the intersection of gerontology and contemplative sciences" (Gard et al., 2014). Accumulating scientifically solid evidence that meditation has brain (and mind) altering capacities might, ultimately, allow for an effective translation from research to practice, not only in the framework of healthy aging, but also pathological aging, such as is evident in mild cognitive impairment or Alzheimer's disease.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fpsyg.2014.01551/abstract

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Larger hippocampal dimensions in meditation practitioners: differential effects in women and men

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On average, the human hippocampus shows structural differences between meditators and non-meditators as well as between men and women. However, there is a lack of research exploring possible sex effects on hippocampal anatomy in the framework of meditation. Thus, we obtained high-resolution magnetic resonance imaging data from 30 long-term meditation practitioners (15 men/15 women) and 30 well-matched control subjects (15 men/15 women) to assess if hippocampus-specific effects manifest differently in male and female brains. Hippocampal dimensions were enlarged both in male and in female meditators when compared to sex- and age-matched controls. However, meditation effects differed between men and women in magnitude, laterality, and location on the hippocampal surface. Such sex-divergent findings may be due to genetic (innate) or acquired differences between male and female brains in the areas involved in meditation and/or suggest that male and female hippocampi are differently receptive to mindfulness practices.

Keywords: brain, gender, hippocampus, meditating, mindfulness, MRI, sex

INTRODUCTION

Meditation-specific features of the hippocampus, including its connecting fiber tracts, have been examined using different imaging modalities, such as magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). Outcomes of these imaging studies point to greater hippocampal dimensions in meditators, such as bigger hippocampal volumes, larger hippocampal distances, more hippocampal gray matter (GM), as well as a higher fractional anisotropy in fibers connecting to the hippocampus (Holzel et al., 2008; Luders et al., 2009b, 2011, 2013a,b; Murakami et al., 2012; Leung et al., 2013). Moreover, these cross-sectional findings are complemented by outcomes from longitudinal analyses suggesting an increase of hippocampal GM as a result of meditating (Holzel et al., 2011).

This solid body of literature on hippocampus-specific meditation effects is matched by an at least equally significant body of literature on hippocampus-specific differences between male and female brains. For example, there are reports of sex differences in hippocampal anatomy (Filipek et al., 1994; Goldstein et al., 2001; Szabo et al., 2003; Mouiha and Duchesne, 2011; Han et al., 2013; Perlaki et al., 2014; Persson et al., 2014), hippocampal function (Mackiewicz et al., 2006; Goldstein et al., 2010), hippocampal development (Benes et al., 1994; Giedd et al., 1996; Suzuki et al., 2005; Hu et al., 2013; Lin et al., 2013) as well as hippocampal pathology and age-related atrophy (Murphy et al., 1996; Briellmann et al., 2000; Exner et al., 2008; Li et al., 2014).

The aforementioned meditation effects and sex differences within the hippocampus raise the question of whether hippocampus-specific meditation effects manifest differently in male and female brains. The lack of research addressing that question might be due to the rather small number of subjects included in many meditation studies and/or the unequal distribution of male and female subjects. We therefore conducted the present study leveraging an existing data set consisting of 15 male and 15 female meditators as well as 15 male and 15 female control subjects. Specifically, we set out to investigate the modulating effects of biological sex on hippocampal anatomy in the framework of meditation. For this purpose, we combined a traditional volumetric approach (assessing global hippocampal volumes) with a modern surface-based mapping technique (assessing local hippocampal distances) and tested for significant group-by-sex interactions followed by mapping meditation effects in men and women separately.

MATERIALS AND METHODS

SUBJECTS

The study included 30 meditators and 30 control subjects, where the sample was identical to the one analyzed previously (Luders et al., 2012b, 2013b). Meditators were recruited by distributing study flyers at meditation centers, by postings on center-specific e-mail lists, or by word of mouth through meditators who had already participated in our study. Interested subjects contacted the lab and were subsequently pre-screened for eligibility via e-mail or phone. Subjects who met study inclusion criteria were scheduled for a 2-h appointment on the University of California, Los Angeles (UCLA) campus (for details on subject-specific meditation styles and practices, refer to Luders et al., 2012b). The final composition of the meditation sample ultimately determined the composition of the control sample. More specifically, for each meditator, we selected one control subject from an existing database[1] aiming at the closest pair-wise match with respect to sex, handedness, and age. The maximum allowed age difference within a sex-matched pair was 2 years. Criteria for eligibility and procedures to screen the control subjects are detailed elsewhere (Mazziotta et al., 2009).

The two resulting samples (meditators/controls) each contained 15 males and 15 females and consisted of 28 right-handers and two left-handers (all left-handers were males). Handedness was determined based on preferences for selected activities, such as writing, throwing, holding, opening, etc., using a modified version of the Edinburgh Inventory (Oldfield, 1971). Age ranged from 24 to 64 years, with a mean age of 47.3 years for meditators and also 47.3 years for controls (SD: ± 11.7 and 11.8, respectively). Within the meditation sample, years of meditation practice ranged from 5 to 46 years, with a mean practice duration of 20.2 years (SD: ± 12.2 years). The practice duration did not differ significantly between male meditators (mean ± SD: 19.9 ± 11.5 years) and female meditators (mean ± SD: 20.5 ± 13.3 years). All subjects gave informed consent according to institutional guidelines and the study was approved by the Institutional Review Board of the UCLA.

DATA ACQUISITION AND IMAGE PREPROCESSING

All subjects (meditators/controls) were scanned on the same site, using the same scanner, and following the same scanning protocol. Specifically, magnetic resonance images were acquired on a 1.5 Tesla Siemens Sonata scanner (Erlangen, Germany) using an 8-channel head coil and a T1-weighted MPRAGE sequence (1900 ms TR, 4.38 ms TE, 15° flip angle, 160 contiguous sagittal slices, 256 mm × 256 mm FOV, 1 mm × 1 mm × 1 mm voxel). The obtained structural brain images were then corrected for intensity inhomogeneities and linearly transferred into a standard space using six-parameter (rigid-body) normalizations, as previously detailed (Luders et al., 2013b).

TOTAL BRAIN VOLUME MEASURES

Prior to our hippocampal analyses, we set out to address if male meditators and male controls (female meditators and female controls, respectively) differ in total brain volume. For this purpose, all image volumes were tissue-classified into GM, white matter (WM), and cerebrospinal fluid (CSF) using SPM8[2] and the VBM8 toolbox[3], as described elsewhere (Luders et al., 2009a). Tissue volumes were determined based on the respective tissue-classified partitions (i.e., GM, WM, and CSF) in native space. Total brain volume was calculated (in ml) by adding GM, WM, and CSF volumes. Male meditators and male controls did not show significant differences in total brain volume (mean ± SD: 1514.02 ± 111.96 versus 1514.93 ± 111.12), and neither did female meditators relative to female controls (1378.03 ± 112.49 versus 1360.08 ± 99.13).

HIPPOCAMPUS ANALYSES

Labeling and reliability

The hippocampus was labeled manually in contiguous coronal brain sections, as previously described (Luders et al., 2013b). To determine intra-rater reliability, the hippocampus was labeled twice, by the same rater, in five randomly selected brains revealing intra-class correlations for hippocampal volume of $r_I = 0.95$. In addition, the hippocampus was labeled five times, by the same rater, within one randomly selected brain revealing a volumetric overlap of 85% for all labels. The overlap was defined as the volume of the intersection of the five labels, divided by the mean volume of these labels, multiplied by 100.

Global measures

Global left and right hippocampal volumes were established (in mm^3) based on the dimensions and number of voxels constituting the hippocampal labels. Left and right global hippocampus measures were statistically compared between groups defined by meditation status (meditators/controls) and biological sex (men/women). More specifically, we used a general linear model with the left and right hippocampal values as dependent variables, group as fixed factor, and sex as covariate. As a safeguard against type I error, Bonferroni corrections were applied using a threshold of $p \leq 0.025$ to account for the two (left/right) dependent variables. A significant group-by-sex interaction was followed by *post hoc* comparisons within men and women, separately.

Local measures

First, the manually outlined hippocampal labels (described above) were converted into three-dimensional shape representations of the left and right hippocampus. Then, parametric surface meshes (Thompson et al., 1996a,b) were generated automatically, precisely following the outer contours of the hippocampal shapes. As described previously (Luders et al., 2013b), these parametric surface meshes "resemble a gridded surface of equally spaced points, where the array of these points is standardized across all subjects establishing a point-by-point correspondence." For each left and right hippocampal mesh, a medial curve was defined along the long axis of the hippocampus threading down the hippocampal center. The radial distances (in mm) from this medial curve to each hippocampal surface point were measured and subsequently used in the statistical analysis. For more methodological details, including illustrations of the surface mesh modeling and radial distance mapping, please refer to a previous publication (Thompson et al., 2004). The local hippocampal distances were compared between groups using the general linear model, as detailed above for the global analyses. However, to explore differential effects across the hippocampal surface, the exact locations of significant group-by-sex interactions as well as any *post hoc* effects were mapped using uncorrected thresholds at $p \leq 0.05$.

RESULTS

GLOBAL MEASURES

Descriptively, left and right hippocampal volumes were larger, on average, in male meditators compared to male controls; they were also larger in female meditators compared to female controls

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[1] http://www.loni.usc.edu/ICBM/

[2] http://www.fil.ion.ucl.ac.uk/spm

[3] http://dbm.neuro.uni-jena.de/vbm.html

Table 1 | Hippocampal volumes (mean ± SD) in mm^3.

Left hippocampus		Right hippocampus	
Male meditators 3638.20 ± 316.85	Male controls 3346.00 ± 333.23	Male meditators 3600.87 ± 436.05	Male controls 3533.93 ± 593.56
Female meditators 3404.73 ± 311.18	Female controls 3192.80 ± 239.73	Female meditators 3568.40 ± 381.43	Female controls 3397.73 ± 480.72

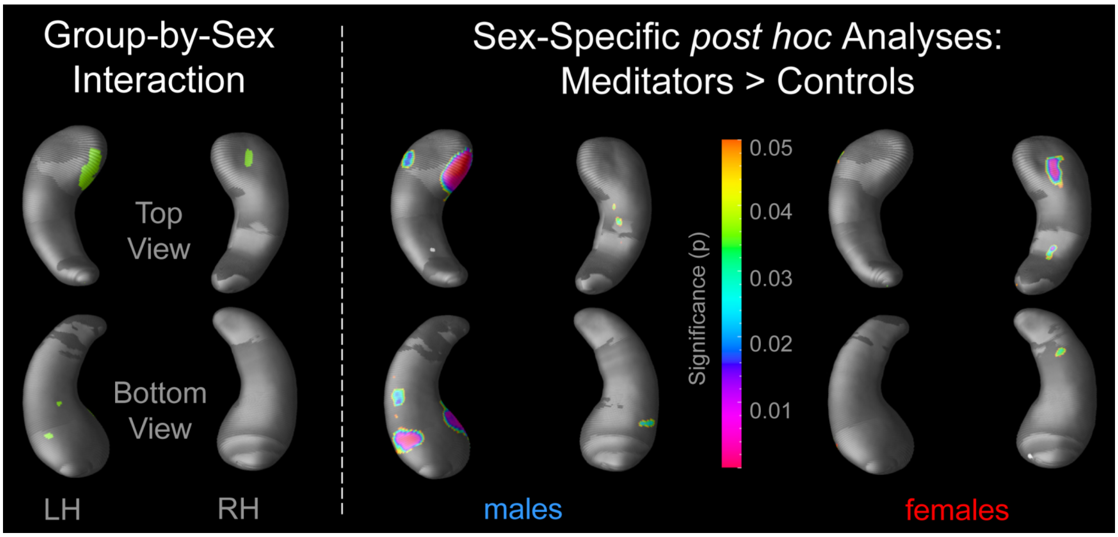

FIGURE 1 | Significant hippocampal differences. The left panel depicts significant group-by-sex interactions ($p \leq 0.05$). The right panel illustrates where *post hoc* analyses revealed significant group differences (meditators > controls), separately within males and females. The color bar encodes the significance (p) of the group differences. Hippocampal regions in gray indicate where no significant group differences were observed. LH, left hippocampus; RH, right hippocampus.

(see **Table 1**). The group-by-sex interaction was significant for the left hippocampus ($p = 0.002$) but not for the right hippocampus ($p = 0.46$). Conducting *post hoc* comparisons separately within males and females, left hippocampal volumes were significantly larger in male meditators than male controls ($p = 0.02$) as well as in female meditators than female controls ($p = 0.046$). Significant meditation effects with respect to right hippocampal volumes were not detectable in males ($p = 0.722$) or in females ($p = 0.291$).

LOCAL MEASURES

There were significant group-by-sex interactions, both within the left and right hippocampus (**Figure 1**, left). Conducting *post hoc* comparisons within males, radial distances were significantly larger in male meditators than in male controls. Significance clusters were evident in both hemispheres but stronger within the left hippocampus, with most pronounced effects in the hippocampal head (**Figure 1**, middle). Conducting *post hoc* comparisons within females also revealed significantly larger radial distances in female meditators than in female controls. However, in contrast to the laterality effect observed within males, significance clusters within females were almost exclusively detectable in the right hippocampus (**Figure 1**, right). Neither within males nor within females was there any hippocampal region where controls had significantly larger radial distances than meditators.

DISCUSSION

To our knowledge, this is the first study examining potential modulating effects of biological sex on hippocampal anatomy in the framework of meditation. Our analyses were applied in a well-matched sample of 30 meditators (15 men/15 women) and 30 controls (15 men/15 women), where meditators had, on average, more than 20 years of experience (with a minimum of 5 years), thus constituting true long-term practitioners. In accordance with the outcomes of our previous study of meditation effects on hippocampal anatomy by pooling male and female brains together (Luders et al., 2013b), we observed that hippocampal dimensions were enlarged both in male and in female meditators when compared to sex- and age-matched controls. In addition, our current analyses revealed that meditation effects, albeit present in both sexes, differ between men and women in terms of the magnitude of the effects, the laterality of the effects, and the exact location of the effects detectable on the hippocampal surface.

The observed group-by-sex interactions and sex-divergent effects are intriguing and perhaps reflective of differential (innate) conditions in male and female brains, as also implied by the large number of reports on sex differences within the hippocampus (see Introduction). At the same time, it is possible that male and female meditators may require (or employ) different amounts or elements of practice to experience desired effects. Both possibilities, independently or interacting with each other, might be accompanied by a sex-specific engagement of certain hippocampal subsections during meditation. Such a sex-specific hippocampal engagement might result in a sex-specific impact on hippocampal anatomy, where additional effects may manifest if male and female hippocampi are differently susceptive to the practice. Future research is clearly necessary, not only to uncover the rather complex underlying mechanisms but also answer the age-old question if meditation induces (sex-specific) brain changes or if a (sex-specific) unique brain anatomy preceded the meditation practice, as further discussed elsewhere (Luders et al., 2012a, 2013b). Both options are likely and not necessarily mutually exclusive, at least with respect to the hippocampus: biological sex as well as (sex-specific) experiences seem to play an integral role, not only in activating hippocampal functions but also shaping hippocampal structure, including adult hippocampal neurogenesis (Mitsushima, 2010; Galea et al., 2013). However, at this point, given the cross-sectional nature of our study, definite conclusions on the causality of the observed group-by-sex interactions and sex-specific group differences are not warranted.

CORRESPONDENCE WITH PREVIOUS STUDIES

Our current observations are in line with prior reports of sex differences in hippocampal function, development, atrophy and pathology (Benes et al., 1994; Giedd et al., 1996; Murphy et al., 1996; Briellmann et al., 2000; Suzuki et al., 2005; Mackiewicz et al., 2006; Exner et al., 2008; Goldstein et al., 2010; Hu et al., 2013; Lin et al., 2013; Li et al., 2014), which in turn may be linked to sex differences in hippocampal anatomy (Filipek et al., 1994; Goldstein et al., 2001; Szabo et al., 2003; Mouiha and Duchesne, 2011; Han et al., 2013; Perlaki et al., 2014). Moreover, our current observations are in line with prior reports of altered hippocampal features in meditators compared to controls (Holzel et al., 2008; Murakami et al., 2012; Leung et al., 2013).

Although existing mindfulness research seems to lack sex-specific analyses—at least with respect to addressing brain anatomy—the observed group-by-sex interactions seem to be in accordance with a recent study reporting sex-divergent outcomes when assessing the impact of a mindfulness intervention on behavioral measures/psychological constructs (de Vibe et al., 2013). More specifically, administering a 7-week mindfulness-based stress reduction (MBSR) program, that study detected significant changes in mental distress, study stress and well-being in female students but not in male students. Contrasting such lack of an effect in one sex, the current study observed meditation effects in both sexes (meditators > controls). So, at first sight, there seems to be a partial divergence between the outcomes of the aforementioned study (de Vibe et al., 2013) and our current observation, as one might expect a lack of meditation effects on hippocampal anatomy in males. However, de Vibe et al. (2013) also emphasize that males did experience a small effect on mental distress but that "this effect was not statistically significant, possibly due to the fact that there were significantly fewer men in the intervention group than the control group." Furthermore, given that 118 women but only 26 men received the MBSR intervention in de Vibe's study, the resulting statistical power (i.e., disadvantageous in men) might have caused the lack of significance within men. Since our study was gender-balanced with equal morphometric variance across groups (i.e., affording the same statistical power within men and women) this may explain why meditation effects were observed in both sexes. Nevertheless, the nature of the effect was still different in male and female meditators, which seems to agree with de Vibe's findings. Given the lack of other publications in this specific field, it seems tempting to (overly) relate both studies and find plausible explanations for convergences and divergences. However, as both studies are extremely different in many respects—not only in ages of the subjects, type of meditation, and duration of practice but also the actual study design and outcome measures—caution is warranted to not over-interpret apparent correspondences and discrepancies. Follow-up studies using more highly powered samples and gender-balanced designs are clearly necessary to further expand this currently understudied field of research.

IMPLICATIONS FOR FUTURE RESEARCH

Importantly, the hippocampus is not a single homogeneous structure but regionally segregated by architecture, connectivity, and functional relevance (Amunts et al., 2005). Our refined local measures (i.e., radial hippocampal distances) already provide substantial additional detail beyond more conventional global measures (i.e., hippocampal volumes), which ultimately were sufficient to uncover differential meditation effects across the hippocampal surface and the sex-specific significance profiles. However, future studies with methods that directly assess hippocampal subdivisions (and thus functional units) will be helpful and necessary to reveal the specific cellular anatomy and underlying mechanisms of the observed group-by-sex interactions and sex-divergent effects. Along these lines, future studies in sufficiently powered samples may also want to follow up on the seemingly sex-specific laterality effects by testing statistically for a significant sex-by-group interaction that varies across hemispheres. At the same time, it will be desirable to extend the array of targeted brain structures beyond the hippocampus altogether, eventually complementing measures of brain structure with measures of brain function, cognition, behavior and/or psychological constructs. Moreover, while cross-sectional analyses are an excellent starting point for exposing links between meditation and brain structure, longitudinal studies with biological sex as a moderator variable will be necessary to determine the relative (and perhaps sex-specific) contribution of nature and nurture to altered brain dimensions in male and female meditators. Altogether, this will not only add to a growing body of literature suggesting a sex-divergent brain organization, but also broaden our horizons concerning sex-specific links between meditation and cerebral features as well as cognitive and behavioral parameters—perhaps even clinical outcome measures when taking meditation or mindfulness practices into patient populations (Sequeira and Ahmed, 2012; Clayton and Collins, 2014; Newberg et al., 2014).

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Mindful Reading: Mindfulness Meditation Helps Keep Readers with Dyslexia and ADHD on the Lexical Track

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This study explored the effects of a Mindfulness-Based Stress Reduction (MBSR) intervention on reading, attention, and psychological well-being among people with developmental dyslexia and/or attention deficits. Various types of dyslexia exist, characterized by different error types. We examined a question that has not been tested so far: which types of errors (and dyslexias) are affected by MBSR training. To do so, we tested, using an extensive battery of reading tests, whether each participant had dyslexia, and which errors types s/he makes, and then compared the rate of each error type before and after the MBSR workshop. We used a similar approach to attention disorders: we evaluated the participants' sustained, selective, executive, and orienting of attention to assess whether they had attention-disorders, and if so, which functions were impaired. We then evaluated the effect of MBSR on each of the attention functions. Psychological measures including mindfulness, stress, reflection and rumination, life-satisfaction, depression, anxiety, and sleep-disturbances were also evaluated. Nineteen Hebrew-readers completed a 2-month mindfulness workshop. The results showed that whereas reading errors of letter-migrations within and between words and vowel-letter errors did not decrease following the workshop, most participants made fewer reading errors in general following the workshop, with a significant reduction of 19% from their original number of errors. This decrease mainly resulted from a decrease in errors that occur due to reading via the sublexical rather than the lexical route. It seems, therefore, that mindfulness helped reading by keeping the readers on the lexical route. This improvement in reading probably resulted from improved sustained attention: the reduction in sublexical reading was significant for the dyslexic participants who also had attention deficits, and there were significant correlations between reduced reading errors and decreases in impulsivity. Following the meditation workshop, the rate of commission errors decreased, indicating decreased impulsivity, and the variation in RTs in the CPT task decreased, indicating improved sustained attention. Significant improvements were obtained in participants' mindfulness, perceived-stress, rumination, depression, state-anxiety, and sleep-disturbances. Correlations were also obtained between reading improvement and increased mindfulness following the workshop.

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Thus, whereas mindfulness training did not affect specific types of errors and did not improve dyslexia, it did affect the reading of adults with developmental dyslexia and ADHD, by helping them to stay on the straight path of the lexical route while reading. Thus, the reading improvement induced by mindfulness sheds light on the intricate relation between attention and reading. Mindfulness reduced impulsivity and improved sustained attention, and this, in turn, improved reading of adults with developmental dyslexia and ADHD, by helping them to read via the straight path of the lexical route.

Keywords: dyslexia, ADHD, MBSR, mindfulness meditation, attention, lexical route, surface dyslexia

INTRODUCTION

In this study, we explore the unsolved riddle of the relation between attention and reading through a novel window: that of mindfulness meditation. We examine whether mindfulness meditation, which improves various aspects of attention, can have an effect on reading. We do so by exploring the effect of mindfulness on specific types of developmental dyslexia and on specific types of reading errors. The rationale is that if certain aspects of attention improve following mindfulness practice, and lead to improvement in certain aspects of reading, these aspects of reading may be related to attention. Furthermore, this may help define the conditions in which mindfulness can function as an effective treatment for reading difficulties.

The Reading Process and Dyslexia

The reading process is a multi-component process, which leads from the first orthographic-visual analysis of a written sequence of letters to sound and meaning. The model for single word reading that we assume here is the dual-route model (Morton and Patterson, 1980; Shallice and Warrington, 1980; Ellis and Young, 1996; Coltheart et al., 2001; Friedmann and Coltheart, in press). According to this model (depicted in **Figure 1**), the first stage of the process is a primary visual-orthographic analysis, in charge of letter identification, coding of the relative order of letters within the word, and binding letters to the words they appear in (Ellis and Young, 1996; Friedmann and Coltheart, in press). The results of this first visual analysis are then held in a short-term graphemic memory buffer, the graphemic input buffer.

Following this initial stage, the reading process divides into two routes: the lexical route, which allows efficient and rapid reading of words that the reader already knows, and which are stored in the orthographic input lexicon (the written form of the word), and the phonological output lexicon (its phonological form). Reading words that are not stored in these lexica requires the second route – the sublexical route, where reading is done via grapheme-to-phoneme conversion. This route is slower, and is inaccurate when reading words that do not unambiguously obey the grapheme-to-phoneme conversion rules.

Impairments in different stages and components of this process result in various types of dyslexia, each characterized by a different pattern of errors (Warrington and Shallice, 1980; Castles and Coltheart, 1993; Castles et al., 2006; Friedmann and Coltheart, in press). A deficit in letter identification causes *letter identity dyslexia*, which results in letter substitutions; a deficit in the encoding of letter position within a word causes *letter position dyslexia* (LPD, Friedmann and Gvion, 2001; Friedmann and Rahamim, 2007, 2014; Friedmann and Haddad-Hanna, 2012, 2014; Kohnen et al., 2012; Kezilas et al., 2014), characterized by letter migrations within words (such as reading *clam* as *"calm,"* and *flies* as *"files"*); a deficit in the allocation of letters to words results in *attentional dyslexia*, characterized by migrations of letters between neighboring words (Shallice and Warrington, 1977; Davis and Coltheart, 2002; Mayall and Humphreys, 2002; Friedmann et al., 2010b); a deficit in the identity of letters on one of the sides of a word, resulting in letter omission, substitution, or additions, is called *neglect dyslexia* (Ellis et al., 1987; Vallar et al., 2010). Impairments in the lexical route result in *surface dyslexia* (Marshall and Newcombe, 1973; Coltheart et al., 1983; Coltheart and Funnell, 1987; Howard and Franklin, 1987; Castles and Coltheart, 1993, 1996; Temple, 1997; Friedmann and Lukov, 2008). Readers with this dyslexia cannot use the lexical route, and they therefore have to rely on the sublexical route for reading aloud, and read words through grapheme-to-phoneme conversion. In this case, reading will be slower than usual, and, importantly for the current study, also inaccurate: reading of irregular words, namely, of words that do not obey the grapheme-to-phoneme conversion rules, will be incorrect. For example, the word *walk* may be read with a pronounced *l*, the word *knight* may be read with pronounced *k* and *g,* and the word *shoe* may be read as "show." Furthermore, words with ambiguous conversion from graphemes to phonemes may also suffer— a word like *bear* may be read like "beer," and *now* may be sounded out as "know."

A deficit in the sublexical route also gives rise to impaired reading: disordered grapheme-to-phoneme conversion results in a situation whereby the readers can only read words they already know and fail to read new words and non-words. This is called *phonological dyslexia* (Temple, 1997).

Recently, another type of dyslexia has been reported, which involves a selective impairment in the sublexical route, which specifically affects the reading of vowel letters, *vowel dyslexia*. Individuals with vowel dyslexia make migrations, substitutions, omissions, and additions of vowel letters when they read via the sublexical route, almost without errors in consonants (Khentov-Kraus and Friedmann, 2011)[1].

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[1] Additional types of dyslexia exist, but we present here the types that were most relevant for the current study. For a fuller exposition of dyslexia types, please see Coltheart and Kohnen (2012) and Friedmann and Coltheart (in press)

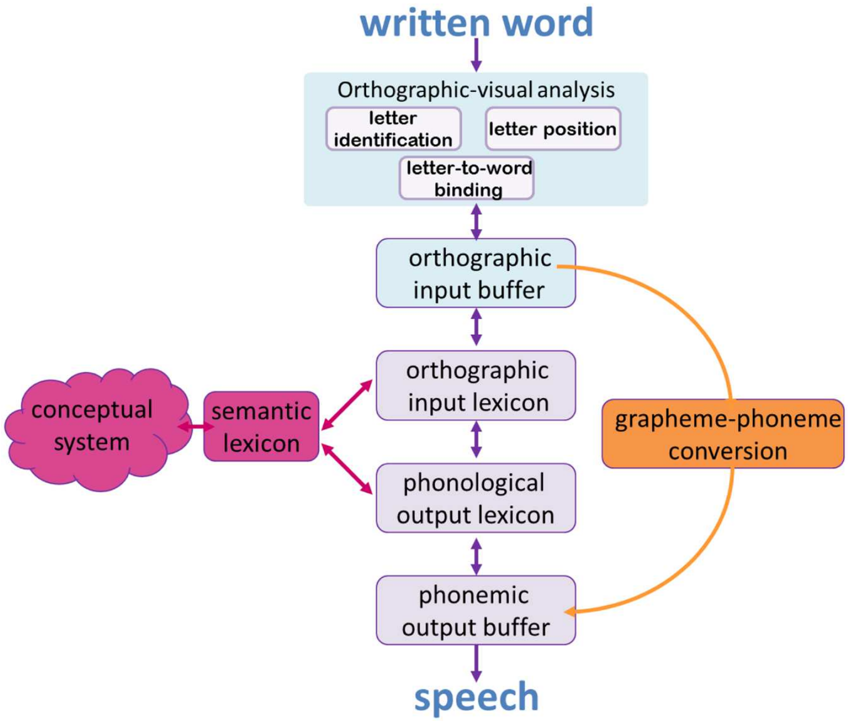

FIGURE 1 | The dual-route model for single word reading. The straight, purple path denotes the lexical route, the orange path is the sublexical grapheme-to-phoneme conversion route.

What Do We Know about the Relation between Reading and Attention Disorders?

The question of the relation between reading in general, and specific dyslexias on the one hand, and attention on the other is still an open one.

Epidemiological studies among children (Hinshaw, 1992) and adolescents (Hari et al., 1999, 2001; Goldston et al., 2007) report co-occurrence of diagnoses of ADHD and reading difficulties, and increased occurrence of poor reading in individuals with ADHD (August and Garfinkel, 1990; Dykman and Ackerman, 1991; Shalev-Mevorach et al., 2011). Some studies show poorer reading performance in the ADHD group in comparison to control participants without ADHD (Brock and Knapp, 1996; Miller et al., 2013). These findings are in line with the growing recognition that attention plays a crucial role in fluent reading (e.g., Cestnick and Coltheart, 1999; Reynolds and Besner, 2006; Shaywitz and Shaywitz, 2008; Ruffino et al., 2010). Recently, studies have shed more light on the relationships between specific attention functions and reading in skilled and dyslexic readers, emphasizing correlations between selective (Facoetti et al., 2006, 2010; Menghini et al., 2010), sustained (Menghini et al., 2010), and executive (Shalev-Mevorach et al., 2011) attention functions and successful reading.

However, the exact relation and mechanism of causality between ADHD and reading is not clear: text reading, for example, is a task that requires multiple skills, and many of them may be affected by attention. Performance in word and non-word reading tasks may also be affected by multiple factors. Furthermore, these studies have not examined the effect of attention on specific types of dyslexia or on specific types of errors in reading. As we have seen above, various types of dyslexias exist. Some of them may be thought to be associated with specific impairments to attentional processes: LPD, where letter migrations within words could result from inattention to middle letters; attentional dyslexia, where a difficulty in attenuating irrelevant neighboring words may be the cause for letter migrations between them; and neglect dyslexia, where attention allocating to one side of word or text may be the source for the neglect of that side in reading (see discussion in Lukov et al., 2015). However, various findings suggest that these dyslexias do not stem from attention disorders. Lukov et al. (2015) examined the relation between attention deficits and developmental LPD, attentional dyslexia, neglect dyslexia, surface dyslexia, and vowel dyslexia by systematically looking for dissociations between these dyslexia types and specific attention difficulties. They reported on 110 individuals who showed clear dissociations and double dissociations between these dyslexias and attention disorders, suggesting that attention disorders do not underlie these dyslexias.

Additionally, several studies found dissociations between the reading of words and that of numbers or symbols. Individuals with developmental neglect dyslexia who made neglect errors on the left side of words did not make errors on the left side of numbers (Friedmann and Nachman-Katz, 2004; Nachman-Katz and Friedmann, 2008). In addition, individuals with LPD, who made a considerable amount of transpositions of letters within words did not make more migrations of digits in multi-digit numbers compared to the normal rate (Friedmann et al., 2010a). In the same vein, adults with developmental dyslexia characterized by letter position errors and migration between words (which characterize LPD and attentional dyslexia, respectively) did not perform such errors among symbol strings (Collis et al., 2013). Had the reading errors in LPD, neglect dyslexia, or attentional dyslexia resulted from a general visuo-spatial attention deficit, we would expect this attention deficit to affect number reading as well. The findings that numbers are unimpaired in these dyslexias indicates that general visuo-spatial attention disorder does not underlie these dyslexias.

Relatedly, Salner et al. (2013) tested the effect of manipulations of spatial attention on letter transpositions in individuals with LPD using a Posner (cost-benefit) task. They found that the attentional manipulation did not affect letter transpositions. This result further corroborates the conclusion that LPD may reflect a specific impairment in letter position encoding, rather than a general attentional deficit.

Finally, Keidar and Friedmann (2011) found that methylphenidate, which is the most commonly prescribed drug for treating ADHD, relieved attentional deficits, but did not affect reading accuracy among individuals with ADHD and developmental dyslexia (all with LPD and many with attentional dyslexia). These findings further support the idea that these types of dyslexia are orthographic-specific and are not the result of a general attentional deficit.

Thus, whereas there are some indications for points of connection and disconnection between attention and reading, the exact relation and mechanism of causality between them are still an open question. By assessing the effect of mindfulness on specific attention functions and specific error types in reading we hope to learn more about the nature of the relation between reading and attention.

Mindfulness

A promising direction for the treatment of attention difficulties and possibly also of reading difficulties is the practice of mindfulness meditation. Among mindfulness practices, one of the most studied protocols is Mindfulness-Based Stress Reduction (MBSR). This protocol, developed by Kabat-Zinn (1990), is a well-established clinically oriented group-based meditation program, which has been widely used in the last few decades in various contexts. The foundation of MBSR is mindfulness meditation, defined operationally as "the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment" (Kabat-Zinn, 2003). Mindfulness training has been shown to be beneficial for clinical and non-clinical populations, causing a decrease in anxiety (Kabat-Zinn et al., 1992), depression (Kumar et al., 2008), stress (Chiesa and Serretti, 2009), avoidance and rumination (Kumar et al., 2008), cognitive reactivity (Raes et al., 2009), and sleep disturbances (Carlson and Garland, 2005; Winbush et al., 2007), among others.

Importantly, mindfulness has a strong conceptual relation with attention, as a fundamental aspect of mindfulness practice is attentional training, and the role of attention is being emphasized in mindfulness instructions (e.g., Jha et al., 2007). Mindfulness practice has been shown to enhance attentional functioning, including sustained, selective, and executive attention (e.g., Valentine and Sweet, 1999; Wenk-Sormaz, 2005; Jha et al., 2007; Zylowska et al., 2008; Hodgins and Adair, 2010), however, some studies did not find such effects (McMillan et al., 2002; Heeren et al., 2009; MacCoon et al., 2014). Mindfulness was also found to improve other cognitive abilities, such as working memory (Chambers et al., 2008; Zeidan et al., 2010; Mrazek et al., 2013). Recently, Mrazek et al. (2013) reported undergraduate students to significantly increase their GRE reading comprehension scores following a 2-week mindfulness training program. The effects of mindfulness have also been reported to influence brain function (e.g., Davidson et al., 2003; Creswell et al., 2007; Goldin and Gross, 2010).

The positive effect of mindfulness on psychological measures can be helpful also in the context of people with dyslexia. During school years, reading deficiencies are often associated with embarrassment, frustration, lack of motivation and low self-esteem (Maughan, 1995; McNulty, 2003). Furthermore, recent data indicate that individuals with poor reading suffer from higher rates of psychiatric disorders, including anxiety and affective disorders (the rates of anxiety disorders, especially social phobia and generalized anxiety disorder, are significantly higher even when accounting for the presence of ADHD, Goldston et al., 2007). Therefore, it would be important to examine whether MBSR can relieve these effects in dyslexic individuals.

Combining existing knowledge on the role of attention in reading with the accumulating evidence of enhanced attention following mindfulness practice, we hypothesized that mindfulness can be used to improve reading among people with dyslexia. Moreover, the reported positive effects of mindfulness on other cognitive abilities as well as on practitioners' wellbeing further suggest that this technique can serve as a highly beneficial intervention for this population. Thus, the aim of the present study was to investigate the effects of MBSR training on reading, attention, and psychological wellbeing among individuals with dyslexia and/or attention deficits. Specifically, we will ask whether reading errors decrease following mindfulness practice, whether specific types of reading errors are differentially affected by mindfulness, and which attention functions are sensitive to mindfulness practice. We will also explore the correlations between the effects of mindfulness on reading errors and on attention functions, to learn about the mechanism that ties reading and attention.

MATERIALS AND METHODS

Participants

Twenty-four adults started the MBSR workshop. Among them, 17 participants had dyslexia and 14 had ADHD (seven participants had both dyslexia and ADHD). The participants were students in diverse academic fields. They were recruited in various ways: some were approached through the students' dean's office, who are in contact with students with learning disabilities, others were recruited via flyers that were posted in Tel Aviv University, inviting individuals with dyslexia and/or ADHD to participate in the study, and some were former participants of the lab's studies who were invited to participate in this study.

The participants paid a symbolic fee for participating in the MBSR workshop, and committed to attend the meetings and exercise the workshop's tasks at home. Twenty participants completed the workshop. One participant was excluded from the analyses due to a history of stroke. None of the other participants had a history of brain injuries or neurological problems. The final group of participants included 12 students with dyslexia and 13 with ADHD (six had both). All participants had normal or corrected-to-normal vision. Main demographic characteristics of the participants are presented in **Table 1**.

The study was approved by the Tel Aviv University ethics committee, and written informed consents were obtained from all participants prior to the testing.

In order to determine the reading and attention profiles, we administered to each of the MBSR participants a battery of reading, attention and psychological tests, which we describe below.

Materials and Procedure

Reading Assessment

For the initial assessment of reading, we used the TILTAN screening test (Friedmann and Gvion, 2003). This test uses oral reading of 128 single words, 30 word pairs, and 30 non-words. The word list in the screening test included words of various types that can reveal the different types of dyslexia: 67 migratable words – words in which middle letter migration creates another existing word, for the identification of LPD; 104 words for which omission, substitution, migration, or addition of a vowel letter creates another existing word, for the identification of vowel letter dyslexia; 128 words for which neglect of the left side of the word yields another existing word, for the identification of neglect dyslexia, and 108 words for which right neglect errors create an existing word; 84 irregular words and potentiophones for the identification of surface dyslexia (notice that given that in Hebrew there are no words that can be unambiguously converted to a single phonological string via grapheme-to-phoneme conversion, in fact all words in the test were sensitive to surface dyslexia); 57 morphologically complex words for deep dyslexia and phonological dyslexia; and 26 abstract nouns and 28 function words, for deep dyslexia. All the words were sensitive to visual dyslexia, as each word had more than six orthographic neighbors.

TABLE 1 | Main demographic characteristics of experimental and control groups.

Age mean (SD)	30.6 (5)
Gender	10 females 16 males
Handedness	4 left, 22 right
Mother tongue	23 Hebrew, 1 Hebrew and English, 1 English, 1 Russian
Years of education mean (SD)	15.2 (1.4)

The 30 non-words were included for the identification of impairments in the sublexical route, phonological dyslexia, vowel dyslexia, and deep dyslexia, but also contained migratable non-words and non-words that created existing words by substitution, omission, or addition of letters, and were hence also sensitive to various impairments at the orthographic-visual analyzer (visual dyslexia, neglect dyslexia). The list of 30 word pairs was created so that between-word migrations created other existing words, for the identification of attentional dyslexia.

On the basis of this test, we determined, according to a comparison of the error rate of each participant to an age-matched control group of 372 skilled readers, whether she or he had dyslexia. If the participants had dyslexia, we determined which type(s) of dyslexia they had, on the basis of the types of errors they made and the factors that affected their reading – the types of stimuli that were most prone to reading errors and the factors that affected their reading (frequency effect, word length effect, lexicality effect, etc.). This diagnosis of the type of dyslexia guided the additional tests that we administered to each participant, in order to further establish the dyslexia type.

For example, participants who made mainly regularizations errors in irregular words in the screening task were suspected to have surface dyslexia and were therefore administered the continuation tests for surface dyslexia (see **Appendix A**); individuals who made a significant rate of letter transpositions within words in the screening task were further tested with the LPD tests, etc.

The performance of each of the participants in the screening test and in each of the reading tests was compared with the performance of a control group (372 adults) that was tested throughout the development of the test batteries. Each participant's performance was compared to the control group using the Crawford and Howell's (1998) *t*-test for the comparison of the performance of a participant with a control group. An impaired performance was defined as performance that was significantly below the control, with $p < 0.05$. The type of dyslexia was determined using the same procedure and statistical test, applied to each error type. We determined that a participant had a certain dyslexia if s/he made significantly more errors of the relevant type compared to the control group, and performed significantly poorer than the control group in the relevant reading tests. We only included individuals in the no-dyslexia group if they performed within the normal range in all the reading tests.

Letter position dyslexia was determined according to the number of letter position errors (consonant migrations) in reading migratable words; **attentional dyslexia** was determined according to the number of between-word errors, including between-word migrations and between-word letter omissions, in reading migratable word pairs; **surface dyslexia** was determined according to the number of reading errors that resulted from reading via the sublexical route rather than via the lexical route, which caused regularization errors in irregular words and potentiophones; **vowel dyslexia** was determined according to the number of vowel letter errors (migrations, substitutions, omissions, and additions) in words and non-words;

and **phonological dyslexia** was determined according to a significantly larger number of errors (substitutions, omissions, and additions) in non-words compared to words. See **Appendix A** for details on the tests that we administered to further establish the diagnosis of each type of dyslexia.

The analyses of error rates before and after the workshop were done for each participant out of the tests that s/he did, according to their dyslexia.

Surface dyslexia errors were analyzed from the screening test as well as an additional task of potentiophone reading, in which the participant read aloud 78 potentiophonic words, 2–6 letters long (mean = 3.7 letters, *SD* 0.8). Potentiophones are words whose reading via grapheme-to-phoneme conversion creates another existing word (like *now*, which can be read via grapheme-to-phoneme conversion to sound like "know," Friedmann and Lukov, 2008). Such words are the most sensitive stimuli to detect surface dyslexia because when a person reads them via the sublexical route, s/he does not know that the word was read erroneously, because another word was produced.

Letter position errors were calculated out of the migratable words that the participant read in the screening test and in an additional test of reading aloud of 232 migratable words of 4–7 letters (mean = 4.9, *SD* 0.9). Migratable words are words for which migration of middle letters within the words creates another existing word (such as *bread-beard, sings-signs*); 87 of these words had a lexical potential for a migration that involves a vowel letter, and 163 had a potential for a migration that involves only consonant letters. (For an English example, the word *sings* has a potential for transposition of two consonant letters- *n* and *g*, whereas the word *snag* has a potential for migration that involves a vowel – a transposition of *a* and *n*.)

Migrations between words were calculated out of the word pairs in the screening test as well as the additional task of reading aloud of 120 migratable word pairs of 2–7 letters (mean = 4.8, *SD* 1.0). All the word pairs were migratable, namely, for each of them, migration of a letter from one word to the other, preserving the within-word position, creates another existing word (such as *mild wind* in which between-word migration can create *wild mind*).

Vowel letter errors were calculated out of the non-words in the screening test as well as a test of reading aloud of 60 non-words, 3- to 6-letter long (mean = 4.45, *SD* 0.67). The non-word list was constructed so that for each non-word at least two different vowel errors would create existing words (a parallel example in English would be the non-word *bron*, which, with a vowel error could be read as *born*, *bran*, and *baron*.)

Each individual was tested separately, in a quiet room, and the reading tests were administered with no time limit. The resulting diagnoses of the participants are presented in **Table 2**.

Attention Assessment

We used four attention tasks that were developed to test each of the four functions of attention model, proposed by Tsal et al. (2005) in the context of ADHD. The model includes: *(a) sustained attention* – the ability to allocate attentional resources to a non-attractive task over time while maintaining a constant level of performance; *(b) selective (spatial) attention* – the ability to focus attention on a relevant target while ignoring adjacent distractors; *(c) orienting of attention* – the ability to direct attention over the visual or auditory field according to sensory input, and to disengage and reorient efficiently; and *(d) executive attention* – the ability to resolve conflicts of information and/or responses. We assessed the four functions of attention by using four computerized neuropsychological tasks, serving as indicators of performance in each of the attention functions. All four tasks were established by Tsal et al. (2005), where they were used to assess attention functioning in children with and without ADHD. Each attention test started with a short practice block and lasted approximately 12 min.

For *sustained attention*, we used a Continuous Performance Test (CPT). Participants were presented with a long series of stimuli and were instructed to respond to a single reoccurring pre-specified target (a red square) while withholding responses to all other, non-target stimuli. There were four possible shapes (square, circle, triangle, and star) and four possible colors (red, blue, green, and yellow). As soon as a target appeared, the participants were requested to press the spacebar. Using a low rate of target stimuli (30%) and varying the inter-stimulus interval (ISI) with an average ISI of 1750 ms, this task maintains a high demand on sustained attention but minimizes the involvement of other cognitive factors (Shalev et al., 2011; Stern and Shalev, 2013). The standard deviation of the participant's reaction times (RTs) indicates her/his ability to consistently maintain attention to the task over time. Thus, low standard deviation of RTs reflects high level of sustained attention, whereas a high standard deviation indicates inattention. The percent of commissions (responses to trial without target) depicts impulsivity.

For *selective attention*, we used a conjunctive search task (Tsal et al., 2005). Participants were instructed to search for a target stimuli appearing among distracters. The displays varied in their size (4, 8, 16, or 32 distractors), enabling estimation of the effect of attentional load on performance. Participants were instructed to fixate on a fixation point, which was followed by a display of items. Participants were requested to decide whether the display contained the target – a blue square – among the distractors (blue circles and red squares). The target appeared in 50% of the displays. If a target was detected, the participant had to press the 'L' key in the computer's keyboard and if the target was absent then s/he had to press the 'A' key. To assess performance on this task both RTs and accuracy rates were recorded; however, selective attention is usually represented in this kind of task by the slope of the search function. Thus, the performance measure was defined as the search slope. This measure reflects the efficiency of the search process and is based on the increase in response time and decrease in accuracy observed as a function of the increase in search load – the number of stimuli (geometric shapes) in each cluster. This measure is extracted for target-present trials only.

For *orienting of attention*, we used a cost-benefit paradigm with peripheral cueing (Posner et al., 1980) with an exogenous cue (Jonides, 1981). Participants had to discriminate a stimulus – a triangle or a circle – (at either the left or the right of a fixation point) preceded by an abrupt onset of a cue at either the target's location (a highlighted rectangle enclosing the stimulus – valid cue) or the opposite side of fixation (invalid cue). When the target

TABLE 2 | Diagnoses of reading and attention skills of MBSR participants and indicator of completion of workshop.

Participant	Diagnosis		Completion of workshop
	Dyslexia type(s)	Attention deficit(s)	
AO	LPD, attentional, surface	–	Yes
ALE	LPD, surface, attentional, vowel	–	No
EZ	–	Sustained attention	Yes
NG	LPD	–	Yes
ON	–	Sustained attention	Yes
YH	LPD, surface, attentional	–	No
SG	LPD, attentional, vowel, surface	Sustained attention	Yes
RC	Vowel	Sustained attention	Yes
YS	–	Orienting of attention, executive attention	Yes
RA	LPD, attentional	–	Yes
GA	LPD, surface	Sustained attention	Yes
OR	LPD, vowel, attentional, surface	Sustained attention	Yes
AF	LPD	–	Yes
TL	–	Sustained attention, orienting of attention	Yes
ET	LPD, vowel, surface	–	Yes
RS	Vowel	–	Yes
RB	LPD, vowel, attentional, surface	–	No
GS	Vowel, LPD, surface	Sustained attention	Yes
YK	LPD, surface	Selective attention	Yes
JO	–	Orienting of attention	Yes
ALU	Attentional, LPD	–	No
SY	–	Sustained attention	Yes
MS	–	Sustained-, selective-, executive- and orienting of attention	Yes
OT	Phonological	Sustained attention	No

was a triangle, the participant had to press the 'L' key and when the target was a circle s/he had to press the 'A' key. Both RTs and accuracy rates were recorded, and the difference in performance between valid and invalid trials was used to indicate the ability to efficiently orient attention (Tsal et al., 2005).

For *executive attention*, we used a Location-Direction Stroop-like task (Stroop, 1935) with a spatial aspect. Participants had to respond either to the location or the direction of an arrow (in different blocks) appearing on the screen, while ignoring the other irrelevant dimension. Half of the stimuli were congruent trials (i.e., the location on the screen and the direction of the arrow matched; e.g., an arrow presented below fixation pointing downward) and half of them were incongruent (i.e., an arrow presented above fixation pointing downward). In the first two blocks of the task, the participants were requested to judge the location of the arrow (relative to the fixation point; if it was presented above the fixation they had to press 'L' and if it was presented below the fixation they had to press 'A') and in the last two blocks they were requested to judge its direction (Tsal et al., 2005). Performance in this task was assessed by mean RTs and accuracy rates, and by subtracting congruent RT divided by accuracy rate from incongruent RT divided by their accuracy rate. The widely used interference effect in this task reflects the extent to which conflicting irrelevant information is effectively suppressed. Due to technical failures, the post-workshop data is missing for three participants in executive attention, for two in orienting of attention, and for one in selective and sustained attention.

We analyzed each participant's baseline performance in each of the attention tasks in order to determine the existence and nature of attention deficits. The resulting diagnoses of the participants are presented in **Table 2**.

Resistance of the Tools to Training Effects

Because we examine the performance before and after the meditation workshop using the exact same tools, we needed to establish that the tools we used were not sensitive to training effects. We therefore administered the reading and attention tests twice, 3 months apart, to a group of students who did not participate in the MBSR workshop. The students in this group had learning disabilities that were similar to the ones we examined in this study.

Reading tests: control group without MBSR

In the reading tests of the non-MBSR control group, out of 16 dyslexics (who had types of dyslexia that were similar to the MBSR dyslexia group: LPD, attentional dyslexia, vowel dyslexia, and surface dyslexia), nine made more errors in the second assessment than in the first assessment, while seven made fewer errors. The average error rate in the reading tests did not change [before 16.6% (*SD* 12.1%); after 16.6% (*SD* 13.6%)]. This was true also when analyzing words and non-words separately. For existing words the average error rate was 13.4% (*SD* 10.5) in the first assessment, and 13.2% (*SD* 11.1%) in the second, $p = 0.86$. The average error rate in reading non-words was 29.8% (*SD* 21.2) in the first assessment, and 30.6% (*SD* 25.7) in the second, $p = 0.83$. The consistency in the percent of errors over time also held in the analysis of surface errors alone ($p = 0.93$). Namely, neither general error rate nor surface errors benefitted from the repetition of the same reading tests after 3 months.

Attention tests: control group without MBSR

Eighteen participants in the control group performed the attention tests twice, without MBSR in the middle, two of them had missing data in the CPT test.

In **the sustained attention** test, no significant reduction was obtained in the standard deviation of reaction times (RTs) in the CPT task (first measure: 111.1 ms [*SD* 51.3], second measure: 100.7 ms [*SD* 46.9], $p = 0.29$). Overall, 69% of participants (11 out of 16) had larger standard deviations compared to the norm in this measure in the first assessment (>77 ms), and also in the second one. No significant difference was found in the measure of commissions between the two assessment points (first measure: 1.1% [*SD* 0.9%], second measure: 0.6% [*SD* 0.8%], $p = 0.09$).

For **selective attention**, repeated measures ANOVAs with the within-subjects factors of time (first/second measurement), target (with/without target), and number of distracters (4, 8, 16, or 32) in the conjunctive search task, were performed separately for RTs and accuracy. The analyses yielded only a significant effect of time in RTs (first measure: 934.1 ms [*SE* 53.6], second measure: 854.4 ms [*SE* 39.6], $F(1,17) = 9.52, p = 0.01, \eta_p^2 = 0.36$). No significant time effect was obtained in accuracy ($p = 0.97$), and no significant differences were obtained for the search slope ($p = 0.42$).

For **orienting of attention**, two repeated measures ANOVA were performed with the within-subjects factors of time (first/second measurement) and target (valid/invalid cue) in the peripheral cueing paradigm, one for RTs and one for accuracy. An approaching significance reduction was found in RTs (first measurement: 667.0 ms [*SE* 46.5], second measurement: 595.2 ms [*SE* 18.8], $F(1,17) = 4.3$, $p = 0.054$, $\eta_p^2 = 0.20$). No significant overall improvement in accuracy was obtained ($p = 0.91$). The difference between valid and invalid conditions did not change significantly between the two time points ($p = 0.97$).

For **executive attention**, two repeated measures ANOVAs were performed with the within-subjects factors of time (first/second measurement), kind of task (location/direction) and congruency (congruent/incongruent) in the location-direction Stroop-like task. No significant differences in RTs nor in accuracy or interference were obtained ($p = 0.86$ and $p = 0.88$, respectively). The difference between the interference effect in the two time points was also not significant ($p = 0.94$).

Thus, in the attention tests too, the main attention measures (apart from RT) were unaffected by the repetition of the same tests after 3 months, without MBSR training in between.

Psychological Measures

Eight psychological domains were assessed among the MBSR participants using a battery of seven questionnaires. Participants filled out the questionnaires through an online site[2] before and after the workshop, when they were available, at home, and free from other activities. The battery included the following questionnaires:

Mindfulness

This 26-item questionnaire was developed by Friedman (2006), based on two mindfulness questionnaires: the Mindful Attention Awareness Scale (MAAS; Brown and Ryan, 2003) and the Kentucky Inventory of Mindfulness Skills (KIMS; Baer et al., 2004). The questionnaire contains statements describing mindful and mindless experiences (e.g., "I tend to walk quickly to get where I'm going without paying attention to what I experience along the way"), each responded to on a 7-point scale, running from 1 (*not at all*) to 6 (*very much*). The original questionnaire has a Cronbach's alpha of 0.79. In the present study, Cronbach's alphas were 0.85 and 0.9 in the first and second administrations, respectively.

Perceived stress

The Perceived Stress Scale (PSS; Cohen et al., 1983) contains 14 items that describe emotions and feelings regarding stressful situations in one's life (e.g., "In the last month, how often have you felt that you were unable to control the important things in your life?"). The participants were requested to respond on a 5-point scale ranging from 0 (*never*) to 4 (*very* often), according to their experience in the past month. The questionnaire is scored as the sum across all items, after reversing the positive ones. The instrument was translated to Hebrew by Drory (1989), and was reported to have an internal consistency of 0.77 in its Hebrew version. In the present study, this questionnaire had a Cronbach's alpha of 0.9 and 0.91 in the first and second administration, respectively.

Reflection and rumination

The Rumination–Reflection Questionnaire (RRQ; Trapnell and Campbell, 1999) is a 24-item instrument consisting of two 12-item subscales: Reflection, addressing the degree of the person's self-focusing that stems/derives from curiosity and interest in the self (e.g., "I love exploring my 'inner' self"); and Rumination, addressing the degree of the person's self-focusing that stems/derives from threat, loss or injustice caused to her/him (e.g., "I spend a great deal of time thinking back over my embarrassing or disappointing moments"). Each item is responded on a 1 (*strongly disagree*) to 5 (*strongly agree*) scale. The questionnaire was translated to Hebrew by Margalit (2003). In the present study, the Reflection subscale had a Cronbach's alpha of 0.93 in the first administration and an alpha of 0.92 in the second, while the Rumination subscale had a Cronbach's alpha of 0.89 in the first administration and an alpha of 0.91 in the second.

Life satisfaction

The Satisfaction with Life Scale (SWLS; Diener et al., 1985) contains five statements referring to judgments of global satisfaction with one's life (e.g., "so far I have gotten the important things I want in life"), each responded to on a 7-point scale ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). The score

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[2] www.tfasim.org.il

was the items' mean ratings. The English version was reported to have highly favorable psychometric properties, with a test–retest correlation coefficient of 0.82, an alpha coefficient of 0.87 and a mean correlation of 0.61 with other measurements of life satisfaction (Diener et al., 1985). The score was the items' mean ratings. The questionnaire was translated to Hebrew by Shmotkin (P.C., 17.3.2011). In its translated version, the instrument's alpha coefficient was reported to be 0.76 (Shmotkin and Lomranz, 1998). In the present study, this questionnaire had a Cronbach's alpha of 0.84 in the first administration, and an alpha of 0.81 in the second.

Depression

The Center for Epidemiologic Studies – Depression Scale (CES-D scale; Radloff, 1977) is composed of 20 items (e.g., "I thought my life had been a failure"), each responded to regarding the degree of experiencing them in the past week on a 4-points scale running from 1 (*rarely or never [less than 1 day]*) to 4 (*most or all of the time [5–7 days]*). A test–retest reliability of the instrument was reported as 0.83 (Radloff, 1977). The questionnaire's score was calculated as the respondent's mean rating, with positive items reversed. The Hebrew version was reported to have a Cronbach's alpha of 0.88 (Shmotkin et al., 2003). In the present study, this questionnaire had a Cronbach's alpha of 0.9 in the first administration, and an alpha of 0.88 in the second.

Anxiety

The State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) was used to measure state anxiety. This scale contains 20 items (e.g., "I feel nervous"), each responded to on a 1 (*not at all*) to 4 (*very much*) scale, relating to the present moment. The state anxiety scale was reported to have a Cronbach's alpha of 0.89 in its English version (Spielberger et al., 1970). The questionnaire was translated to Hebrew by Teichman and Melineck (1978), who reported the English and Hebrew versions to have correlations of 0.77–0.84 between them. In the present study, this questionnaire had a Cronbach's alpha of 0.94 in the first administration, and an alpha of 0.95 in the second.

Sleep disturbances

The mini-Sleep Questionnaire was developed in Hebrew at the Technion Sleep Laboratory by Zomer et al. (1985). The questionnaire comprises 10 items tapping both insomnia and excessive daytime sleepiness. Each item is scored on a 7-point Likert scale ranging from 1 (*never*) to 7 (*always*). In the present study, this questionnaire had a Cronbach's alpha of 0.81 in the first administration, and an alpha of 0.83 in the second.

The MBSR Workshop

The Mindfulness-Based Stress Reduction (MBSR) is a structured group program developed by Kabat-Zinn (1990). According to its protocol, the participants attended eight weekly 2.5-hour classes and a half-day retreat with intensive practice during the sixth week. During these sessions, participants received training in mindfulness through body scan meditation, where participants bring attention to each body part, observe their sensations, and if pain or unpleasant sensations are felt, try to describe them objectively and then intentionally relax each body part; sitting meditation, where participants are instructed to sit in a relaxed, upright posture and to direct their full attention to the sensations of breathing, attending to and simply acknowledging any sensations that arise in the body, and non-judgmentally witnessing whatever thoughts arise, trying to merely label them and restoring attention to the breath; mindful stretching exercises, based on Hatha yoga, and mindful eating, where participants are instructed to be non-judgmental and fully aware, with all senses, of different aspects of the food that they eat (usually a raisin). The integration of mindfulness into everyday life and the application of mindfulness as a method for noticing habitual reactions to stressful situations and more creatively responding are greatly discussed in the group (Kabat-Zinn, 1990). In addition to the practice in the class, participants were asked to engage in mindfulness meditation practice for 45 min per day, guided by CDs and MP3 files that were provided. The workshop took place in a suitable auditorium and was instructed by a female clinical psychologist trained to teach MBSR by Jon Kabat-Zinn.

Statistical Analyses

To assess the effects of the workshop on reading, attention skills, and psychological measures among the MBSR participants, all tests were administered twice to each participant, once prior to the workshop and once during the week after the workshop ended. To assess changes in reading ability, we first compared overall change in number of reading errors using a paired t-test. Next, to assess the effect of the workshop on the reading of each participant, we counted each participant's number of errors typical of his/her dyslexia type/s (for example, migrations between words for participants with attentional dyslexia) made in the oral reading tests before and after the workshop, and calculated an improvement index for each participant as: (number of errors before – number of errors after)/number of errors before. Using this measure, we then tested the mean individual change using a paired t-test. Paired t-tests were also used for assessing changes in the main attention measures as well as for the psychological indexes. As sustained attention is the most prominent deficit among ADHD individuals, and in order to compare the improvement after the workshop between ADHD and non-ADHD participants, a repeated measurement ANOVA with the within-subjects factor of time of measurement and the between-subjects factor of ADHD diagnosis (present vs. absent) were performed on the standard deviation of RT's. In order to assess changes in selective attention, orienting of attention, and executive attention, repeated-measures ANOVAs were performed. Only main effects of time of measurement (before vs. after the workshop) or interactions with it were reported and further explored, as other effects or interactions are related to general characteristics of the tasks and are not part of the scope of the present study (e.g., main effect of number of distracters in the conjunctive search task with longer reaction times on larger displays). Significant interactions were followed by Tukey honest significant differences (HSD) *post hoc* comparisons. T-tests are reported with means and standard deviations (in square parentheses), and repeated measures-ANOVAs are reported with means and standard errors. Finally, in order to assess whether the improvement in reading was correlated to improvements in attentional and psychological measures, Pearson correlations were calculated between the differences in these measures, calculated as: measure before the workshop – measure after the workshop. In order not to inflate the number of correlations calculated, only overall accuracy measures were used for the conjunctive search, cost-benefit, and Stroop-like tasks, and commissions percentage was used for the CPT task. Furthermore, we controlled for multiple tests type I error by applying the Benjamini and Hochberg (1995) false discovery rate (FDR) separately for the correlations of each type.

RESULTS

Reading

The Effect of MBSR on the Whole Group of Participants with Dyslexia, and on Various Types of Reading Errors

Calculation of individual improvement indices revealed that most dyslexics (10 out of 12, $\chi^2 = 5.33$, $p = 0.02$) made fewer reading errors following the workshop, out of all the words that they read (6 of them significantly, McNemar's tests, $p < 0.01$). The average error rate in all the reading tests decreased significantly from 12.7% (*SD* 6.4%) before the workshop to 9.7% (*SD* 4.5%) after it. This yielded a mean improvement of 3% (*SD* 3.9%), which formed 18.5% of the errors the group of dyslexic participants made before the workshop. This overall improvement was significant at the group level, $t(11) = 2.60$, $p = 0.02$, Cohen's $d = 0.75$.

When analyzing words and non-words separately, this improvement was significant only for the existing words. Error rate in word reading decreased significantly from 12.1% (*SD* 6.4%) before the workshop to 9.2% (*SD* 4.5%) after it, yielding a mean improvement of 2.9% (*SD* 3.8%), $t(11) = 2.65$, $p = 0.03$, Cohen's $d = 0.76$). The decrease in error rate in non-word reading was not significant (before: 18.0%, *SD* 15.8%, after: 14.3%, *SD* 10.9%, mean improvement 3.7%, *SD* 8.9%, $t(11) = 1.43$, $p = 0.18$).

Possibly the most important finding comes from the analysis of improvement separately for each type of error. When we analyze, for the group, the improvement in each type of error out of the relevant words for this error type, we see that surface errors showed a significant decrease following the MBSR training, and that they were the only type of error that showed this significant improvement (see **Table 3**). Namely, following meditation, the dyslexic participants read words more consistently via the lexical route rather than via grapheme-to-phoneme conversion. This finding is also consistent with the finding that the improvement was significant only for words but not for non-words: if the mindfulness workshop affected reading by leading readers to read words via the lexical, rather than the sublexical route, this is not expected to affect non-words, which are read exclusively via the sublexical route.

To examine our assumption that the reduction in reading errors is modulated by the effect of mindfulness on attention, we compared the effect of mindfulness on dyslexic participants who had ADHD ($n = 6$, all but one of them had sustained attention impairment) and dyslexic participants without ADHD ($n = 6$). We analyzed the reduction in the percent of reading errors separately for each sub-group. In spite of the small power of such tests, the results suggest that the reduction in reading errors stems from dyslexic participants who also had ADHD (Without ADHD a reduction from 10.7% [*SD* 5.7%] to 8.6% [*SD* 2.9%], $t(5) = 1.16$, $p = 0.30$; with ADHD a reduction from 14.7% [*SD* 6.9%] to 10.9% [*SD* 5.8%], $t(5) = 2.71$, $p = 0.04$). In line with the idea that the effect on the total number of errors is through improved ability to read via the lexical route, rather than occasional slipping to the sublexical route, the significant reduction in reading errors in the dyslexia+ADHD group was only present in reading words, $t(5) = 2.92$, $p = 0.03$, and was not present in reading non-words, $t(5) = 1.57$, $p = 0.18$.

The Effect of MBSR on Specific Dyslexia Types

To examine whether the MBSR training affected specific types of dyslexia, we examined, for each type of dyslexia that our participants had, the effect of MBSR on the relevant error type. The analyses were performed on the percentage of errors out of all possible errors that participants could have performed within the words they read. **Table 4** summarizes the results of the reading tests of each of the 12 participants with dyslexia who completed the workshop in words that target their specific type(s) of dyslexia before and after the workshop.

This analysis did not yield any significant specific reduction of errors for any of the dyslexia types. The effect on LPD was assessed by the measure of reduction in letter migrations within words in reading 345 migratable words before and after the workshop for the 10 participants with LPD who participated in the workshop. This analysis yielded no significant reduction:

TABLE 3 | Comparison of reading errors of the various types before and after the MBSR workshop for the whole group of dyslexic participants: average % (SD) of the various error types, before and after the MBSR workshop and *t*-test for dependent samples.

	% Errors before MBSR	% Errors after MBSR	Comparison before and after
All errors in words	12.1% (6.4%)	9.2% (4.5%)	$t(11) = 2.65$, $p = 0.03$
All errors in non-words	18.0% (15.8)	14.3% (10.9%)	$t(11) = 1.43$, $p = 0.18$
Surface errors	9.9% (7.9%)	6.9% (6.3%)	$t(11) = 3.09$, $p = 0.01$
Migrations within words	8.0% (3.1%)	6.1% (3.4%)	$t(11) = 1.90$, $p = 0.08$
Migrations between words	14.2% (12.3%)	12.1% (14.3%)	$t(11) = 0.82$, $p = 0.43$
Vowel letter errors in non-words	9.9% (10.4%)	7.6% (7.4%)	$t(11) = 1.73$, $p = 0.11$

Shaded cells indicate a significant improvement between before and after the MBSR training.

TABLE 4 | Number of reading errors made by dyslexic participants before and after the workshop, separately for each error type; mean overall change per participant across types [(errors after – errors before)/(errors before)]; the number of words each participant read that could detect each error type (migratable words for migration errors, irregular words for surface errors, etc.); and total number of words read in all tests assessed at each timepoint.

Participant	Number of errors								Mean change of all errors (%)	Total number of words that are sensitive to errors relevant to the dyslexias diagnosed	Total number of words and non-words read
	LPD		Vowel		Attentional		Surface				
	Before	After	Before	After	Before	After	Before	After			
AO	50	25			44	27	16	7	–45%	658	698
NG	27	18							–8%	345	698
SG	17	29	15	17	12	16	47	33	2%	826	936
RC			12	2					–77%	90	464
RA	16	12			2	4			–24%	327	458
GA	35	22					54	33	–25%	586	776
OR	64	50	22	11	38	16	22	19	–35%	688	698
AF	19	32							–26%	297	458
ET	31	19	34	32			15	14	–31%	558	696
RS			19	10					–30%	90	618
GS	17	12	12	11			3	1	–6%	528	618
YK	21	22					20	24	85%	468	536

Note that the overall change is based on the number of unique errors in all tests, which do not correspond to the sum of the four specific error types.
LPD: middle letter transposition within a word.
Vowel: substitution, omission, addition, or migration of a vowel letter.
Attentional: migration of a letter between words.
Surface: error resulting from reading via the sublexical route instead of the lexical route – phonologically plausible errors.

reduction from 9.0% (*SD* 4.5%) to 7.4% (*SD* 3.3%), $t(9) = 1.44$, $p = 0.18$.

The effect on attentional dyslexia was assessed by the measure of reduction in letter migrations between words in reading 150 migratable word pairs before and after the workshop for the four participants with attentional dyslexia who participated in the workshop. This analysis also yielded a reduction from 17.3% migrations between words (*SD* 11.7%) to 13.2% (*SD* 3.5%), which was not significant, $t(3) = 0.80$, $p = 0.48$).

The analysis of the reduction of surface errors in surface dyslexia was made out of the phonologically legal reading of 241 irregular and potentiophonic words. This yielded a reduction from 12.7% surface errors before the workshop (*SD* 6.5%) to 9.5% (*SD* 5.2%) after it, which approached significance, $t(6) = 2.26$, $p = 0.06$.

Finally, the effect on the reading errors of the participants with vowel letter dyslexia was evaluated via the rate of vowel letter errors (substitutions, additions, migrations, and omissions of vowel letters) out of the 60 non-words they read. This yielded a reduction from 29.3% vowel letter errors [*SD* 23.4%] to 19.4% [*SD* 14.0%], which was, again, non-significant, $t(5) = 1.70$, $p = 0.15$.

Attention Tests

Sustained Attention

A significant reduction was found in the standard deviations of reaction times (RTs) in the CPT task (before: 117.5 ms [*SD* 50.3], after: 69.5 ms [*SD* 22.2], $t(17) = 4.37$, $p < 0.001$, Cohen's $d = 1.29$). Overall, 72% of participants (13 out of 18) had larger standard deviations compared to the norm in this measure before the workshop (>77 ms), while only 28% (five participants) performed above the norm after it. Repeated measurements ANOVA for the difference in standard deviations of reaction times between ADHD and non-ADHD participants revealed a significant time (pre–post intervention) by ADHD diagnosis interaction [$F(1,16) = 9.21$, $p = 0.008$, $\eta_p^2 = 0.37$]. As can be seen in **Figure 2A**, Tukey HSD *post hoc* comparisons revealed that the workshop had significantly improved ADHD participants' sustained attention (standard deviations of reaction times) by 54.2% (before: 144.8 ms [*SD* 51.12], after: 66.3 ms [*SD* 17.01], *Tukey HSD*: $p = 0.0003$, Cohen's $d = 2.17$). The improvement of 24.6% among non-ADHD participants was not statistically significant (before: 95.6 ms [*SD* 39.3], after: 72.1 ms [*SD* 26.2], *Tukey HSD*: $p = 0.25$, Cohen's $d = 0.72$).

An additional significantly reduction was found in the measure of commissions: the participants had significantly fewer commissions after the workshop (before: 1.9% [*SD* 2.7%], after: 0.4% [*SD* 0.6%], $t(17) = 2.69$, $p = 0.015$, Cohen's $d = 0.80$).

Selective Attention

Two repeated measures ANOVA's were performed with the within-subjects factors of time (before/after the workshop), target (with/without target) and number of distracters (4, 8, 16, or 32) in the conjunctive search task, one for RTs and one for accuracy. As can be seen in **Figure 2B**, a significant reduction after the workshop was found in RTs (before: 1002.6 ms [*SE* 65.3], after: 898.9 ms [*SE* 60.1], $F(1,17) = 7.53$, $p = 0.01$, $\eta_p^2 = 0.31$). No significant interactions with time were obtained, and the change in accuracy after the workshop was non-significant (before: 95.9% [*SE* 1.0%], after: 97.7% [*SE* 0.8%], $F(1,17) = 2.39$, $p = 0.14$). No significant differences were obtained for the search slope, $t(17) = 0.83$, $p = 0.42$).

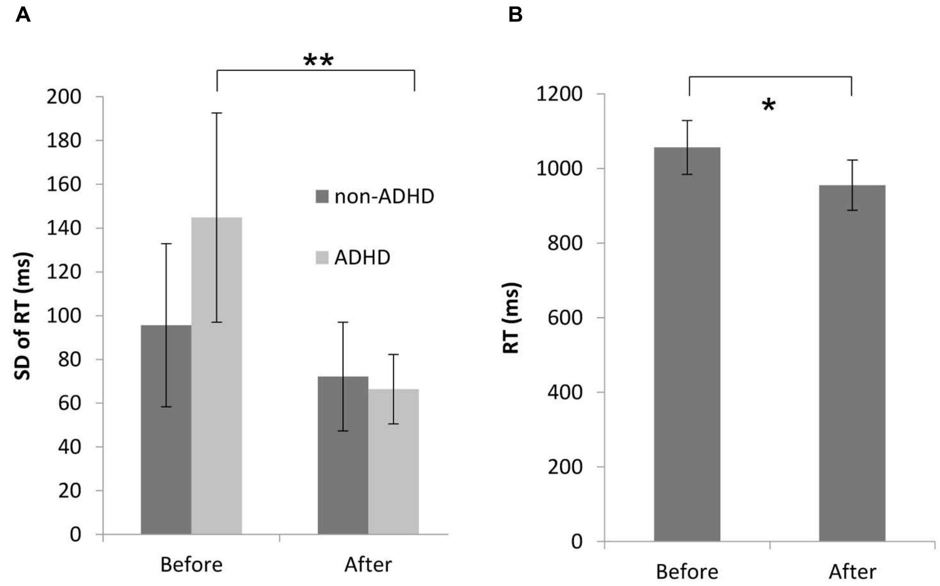

FIGURE 2 | Improvement in sustained attention among ADHD and non-ADHD participants (A) and in selective attention (B). $^*p < 0.01$, $^{**}p < 0.001$.

Orienting of Attention

Two repeated measures ANOVAs were performed with the within-subjects factors of time (before/after the workshop) and target (valid/invalid cue) in the peripheral cueing paradigm, one for RTs and one for accuracy. A significant reduction was found in RTs (before: 757.4 ms [*SE* 54.9], after: 632.6 ms [*SE* 44.9], $F(1,16) = 10.55$, $p = 0.005$, $\eta_p^2 = 0.40$). In addition, a significant overall improvement in accuracy was obtained (average of valid and invalid trials, before: 92.1% [*SE* 1.9%], after 96.4% [*SE* 0.9%], [$F(1,16) = 5.31$, $p = 0.035$, $\eta_p^2 = 0.25$]. The difference between valid and invalid conditions did not change significantly between before and after the workshop, $t(16) = 0.27$, $p = 0.79$.

Executive Attention

Two repeated measures ANOVAs were performed with the within-subjects factors of time (before/after the workshop), kind of task (location/direction), and congruency (congruent/incongruent) in the location-direction Stroop-like task. A significant reduction in RTs (overall location and congruity) was obtained (before: 708.1 ms [*SE* 48.4], after: 605.0 ms [*SE* 43.03], $F(1,15) = 6.81$, $p = 0.02$, $\eta_p^2 = 0.31$). In addition, a significant overall improvement in accuracy was obtained (before: 95.0% [*SE* 1.1%], after: 97.5% [*SE* 0.6%], $F(1,15) = 4.53$, $p = 0.05$, $\eta_p^2 = 0.23$). The difference between the interference effect before and after the workshop was not significant, $t(15) = 1.83$, $p = 0.09$.

Psychological Measures

The means and standard deviations of the participants' scores on the various questionnaires are presented in **Table 5**. Paired *t*-tests revealed significant improvements in most of the assessed dimensions. Following the workshop, there was an increase in participants' self-reported mindfulness ($p < 0.001$), and a

TABLE 5 | Scores of psychological measures among MBSR participants, before and after the workshop, and the *t*-tests for dependent samples their *p*-values, and Cohen's *d* effect sizes comparing before and after.

	Before		After		*n*	*t*	*p*	Cohen's *d*
	Mean	*SD*	Mean	*SD*				
Mindfulness	2.88	0.68	3.39	0.75	19	–4.28	<0.001	0.98
Perceived stress	2.39	0.76	1.55	0.79	19	4.75	<0.001	1.09
Rumination	3.67	0.92	3.26	0.81	18	2.49	0.02	0.59
Depression	2.12	0.53	1.90	0.52	18	2.46	0.02	0.58
Sleep disturbances	3.07	1.16	2.73	1.16	19	2.21	0.04	0.51
Reflection	3.98	0.71	3.77	0.71	18	1.91	0.07	0.45
State anxiety	2.33	0.64	2.08	0.66	19	1.74	0.10	0.40
Life satisfaction	3.52	1.30	3.83	1.13	18	–1.39	0.18	0.33

Shaded cells indicate a significant improvement between before and after the MBSR training.

decrease in their perceived stress ($p < 0.001$), rumination, depression, and sleep disturbances (p's < 0.05).

Correlations

The overall improvement in reading errors was significantly correlated with the improvement in the rate of commissions in the CPT ($r = 0.71$, $p = 0.01$), and with the improvement in self-reported mindfulness ($r = -0.71$, $p = 0.009$).

Significant correlations were obtained between the improvements in selective attention accuracy and improvement in life satisfaction ($r = 0.71$, $p = 0.01$) and sleep disturbances ($r = -0.74$, $p = 0.009$); between improvements in the cost-benefit task accuracy and improvement in sleep disturbances ($r = -0.80$, $p = 0.003$); and between reduction in commissions in the CPT task and improvement in rumination ($r = 0.74$, $p = 0.009$) and life satisfaction ($r = -0.77$, $p = 0.005$).

DISCUSSION

This study aimed at evaluating the effects of mindfulness meditation on reading, attention, and psychological measures in adults with reading and/or attention impairments. The main question regarded the nature of the relationships within the triangle of mindfulness meditation, attention, and specific functions of the reading process. Mindfulness practice was found to improve the reading of the dyslexic participants, as expressed by a general reduction in their reading errors rate. Importantly, this effect stemmed from a specific effect of mindfulness that encouraged reading via the lexical route, leading to a reduction in errors resulting from reading by grapheme-to-phoneme conversion, especially for the participants with ADHD.

In the domain of attention functions, mindfulness practice was found to reduce impulsivity and enhance sustained attention, as well as shorten reaction times to tasks measuring selective, sustained, executive, and orienting of attention functions. Self-reports indicated that the participants also felt improvement in most of the psychological domains that were evaluated, most prominently in mindfulness and perceived stress. Significant correlations indicated that the reading improvement was related to a decrease in impulsivity (fewer commissions in the CPT test). Additional significant correlations were found between psychological and attention changes following the workshop.

Possibly the most important finding of this study, and one that sheds light on the nature of the effect of mindfulness practice on reading, is the specific effect mindfulness had on errors. Reading can proceed via two different routes: a lexical route, which employs knowledge of words, where reading proceeds via identification of the whole word in the orthographic lexicon, which then activates the phonological output lexicon. The other route is a sublexical route, where words are read via grapheme-to-phoneme conversion. The lexical route is the more accurate, efficient and rapid route, whereas reading words via the sublexical route is slow, and often leads to inaccurate reading. For example, reading the word *talk* via the sublexical route may result in pronouncing the *l*, reading it as "talc." Such reading is phonologically plausible, but is an inaccurate reading of the target word, and this is the error type that benefitted the most from mindfulness practice. Importantly, this applied when we looked at all the participants, not only for the ones who had the relevant type of dyslexia, and the effect was in place mainly for the dyslexic participants who also had attention disorders (all but one of them had impaired sustained attention).

This result suggests that mindfulness practice keeps reading "on the right track" – in this case, the lexical route. Thus, whereas attention disorders as well as temporary inattention may allow diversion onto the sublexical route, mindfulness assists the reader in keeping reading on the mindful route. This finding is also consistent with the finding that the improvement was significant only for words but not for non-words: if the mindfulness workshop affected reading by leading readers to read words via the lexical, rather than the sublexical route, this would not be expected to affect non-words, which are read exclusively via the sublexical route.

In line with our hypothesis, the MBSR workshop was also found to improve the functioning of sustained-, selective-, orienting-, and executive attention functions, similar to previous findings (e.g., Jha et al., 2007; Zylowska et al., 2008; Jensen et al., 2012; Morrison et al., 2014). The improvement in attentional functioning was expressed via decreased reaction times in all four functions. Importantly, MBSR had a specific effect on sustained attention beyond response times: it significantly reduced commission errors, which are indicative of impulsivity, and it reduced the variation in reaction times in the CPT task, indicating improved sustained attention. In fact, more than half of the participants who performed above the norm before the intervention performed normally after it. Additionally, faster responses of participants were not accompanied by decreased accuracy rates (in fact, accuracy in the orienting of attention and executive attention even significantly improved), thus providing evidence for a more efficient attentional performance.

The picture that emerges with respect to the relation between attention and reading is quite intricate. Firstly, the results of the current study not only indicate that MBSR helped our dyslexic participants who had sustained attention disorder to stay on the lexical route; they also show that MBSR did not have a specific effect on any type of dyslexia, nor did it have an effect on any specific error type beyond surface errors. These results join previous studies that have shown the independence of dyslexias and attention: Lukov et al. (2015) showed double dissociations between various types of dyslexia and each of the attention functions: they reported individuals with LPD who did not have any attentional deficit, as well as individuals with attentional deficit who did not have LPD; similarly, they reported double dissociations between attentional dyslexia and attention; between vowel dyslexia and attention; between phonological buffer dyslexia and attention; between neglect dyslexia at the word level and attention; and between surface dyslexia and attention. Overall, it seems these dyslexias do not stem from attention disorders. Additionally, drugs that help (some) individuals with attention disorders do not reduce reading errors in dyslexia. Lukov and Friedmann (2007) and Keidar and Friedmann (2011) tested individuals with dyslexia and ADHD whose attention disorders were relieved with methylphenidate. Their reading errors were not affected by methylphenidate, supporting the independence between reading and attention disorders. Finally, reports of dyslexias that selectively affect the reading of words and not of numbers or other signs (c.f., Friedmann and Nachman-Katz, 2004; Friedmann et al., 2010a; Collis et al., 2013) further support the point that general attention cannot underlie dyslexia.

The current study thus adds a piece to the puzzle, by clarifying that whereas attention problems do not underlie dyslexia, they may allow the diversion of reading to the sublexical route, which, in turn, may result in inaccurate reading – surface errors. This aspect of the relation between (sustained)[3] attention and reading is the one that the current study suggests can be amended via mindfulness meditation, which helps the reader stay on the right, lexical track.

It should be noted that reading via the sublexical route not only causes slow and inaccurate reading, but it may also affect reading comprehension: when the word *now*, for example, is read via the sublexical route, it stands the risk of being read like "know," and hence also comprehended as such. The same with homophones, such as *which, write,* and, for some speakers, also *route* (and root). Reading comprehension is, no doubt, an orchestrated effort of various cognitive and linguistic skills, including lexical, syntactic, and semantic abilities, as well as decoding, motivation, and many others (Wasserman, 2012; Szterman and Friedmann, 2014). We may cautiously suggest that one of the sources of the effect of attention on reading comprehension (e.g., Solan et al., 2003; Kieffer et al., 2013) may be the effect of attention on the use of the right route (or the write root).

The increased ability to stay on the lexical track was correlated with self-reported mindfulness. The attentional aspect that most likely led to the increased ability to stay on the lexical track, and which mediated the effect of mindfulness on reading, is the reduction of impulsivity (as measured by the number of commission errors in the CPT task). The overall reduction in reading errors was significantly correlated with the reduction of commissions in the CPT task, and the reduction of reading errors was mainly present in the dyslexic participants who also had a sustained attention deficit. The mediating role of sustained attention in improving reading performance is consistent with Lam and Beale (1991), who claimed that poor reading comprehension is partly a result of poor sustained attention.

The reduction in surface errors and the improvement in attention measures cannot be ascribed to training effects that result from administering the same tests twice, 3 months apart. We administered the exact same tests twice, 3 months apart, to participants with similar characteristics of dyslexia and attention who did not participate in a meditation workshop, and they showed no improvement in reading error rates or in attention measures.

Consistent with previous reports (e.g., Kabat-Zinn et al., 1992), MBSR was also found to have significant positive effects on the participants' psychological wellbeing, including the relief of stress and depression. These benefits are also important to the application of mindfulness for individuals with dyslexia or ADHD, as it may successfully address some of the psychological distress experienced by many of them. To date, most interventions are either built on the training of a cognitive deficit that presumably underlies the reading deficiency (e.g., phonology based-training, Shaywitz et al., 2002; Simos et al., 2002), or designed to match the individual's specific dyslexia type. Examples of the latter include tracking letters with the index finger for LPD (Friedmann and Rahamim, 2014), using colored lines or blinking lights to the left of the word for neglect dyslexia (Nachman-Katz and Friedmann, 2010), or using a word-sized window for attentional dyslexia (Ellis and Young, 1996; Shvimer et al., 2009; Friedmann et al., 2010b). Despite the usefulness of existing interventions, none of them address other domains of difficulty experienced by many dyslexic individuals, such as inattention, heightened stress, and negative views of the self. The advantage of mindfulness practice is that, beyond keeping the readers on the lexical track, it also helps related cognitive and affective processes over the long term.

The psychological improvements related to MBSR were found to be correlated with attentional measures. The strongest correlation was between the improvement in orienting of attention and the reduction of sleep disturbances. In agreement with McCarthy and Waters (1997), Sanders and Reitsma (1982), and Mander et al. (2008) who found sleep deprivation to cause impairments in orienting of attention, it is suggested that the observed reduction in sleep disturbances found among participants following the mindfulness practice contributed to enhanced functioning of this attention system.

This study is the first to show that mindfulness training can improve reading aloud of single words. This improvement in reading following mindfulness practice is in accordance with the results of Mrazek et al. (2013), who demonstrated an improvement in GRE reading comprehension scores among healthy participants after eight mindfulness meetings of 45 min four times a week for 2 weeks. The positive effect of mindfulness practice on individuals with reading and/or attention problems opens promising new directions for intervention in these populations. It should be noted, however, that our observations rely on a small and heterogeneous sample, and as such, should be treated as preliminary.

CONCLUSION

Our study provides support to the idea that mindfulness-based interventions can be used to significantly improve reading as well as the quality of life of individuals with dyslexia and ADHD.

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[3] Most of the participants with attention disorders and dyslexia in our study had a sustained attention impairment. The finding that the main effect of keeping the reader on the lexical route happened with these participants, and the significant correlations between improved reading and reduced commissions suggest that lexical reading was modulated by reduced impulsivity and improved performance in the CPT task. Cestnick and Coltheart (1999) discussed a different aspect of relation between reading and attention: the need for orienting of visual–spatial attention in reading via grapheme-to-phoneme conversion. It might be that people who are specifically affected by orienting of attention deficit would show a different picture than the participants in the current study, with improved non-word reading.

The effectiveness of this technique, as well as its simplicity, offer these individuals a new hope for addressing their experienced difficulties, with suggested long-term effects. It also sheds important light on the intricate relation between attention and reading, suggesting that mindfulness assists readers in staying on the lexical track for reading.

AUTHOR CONTRIBUTIONS

NF, ZB, and RT conceived the idea for the study and the research questions. RT was in charge of the meditation practice. NF created the reading tasks, tested the reading of the participants (together with Rakefet Keidar, whom we thank very much) and analyzed the reading data (together with Lilach Khentov-Kraus, and Liora Lopez Morsian, whom we wholeheartedly thank). ZB ran the attention and psychological tests before and after the workshop as part of her MA thesis. Mainly RT, but also ZB and NF, did the statistical analyses. RT and NF wrote together the final manuscript.

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APPENDIX A: FURTHER READING TESTS TO ESTABLISH THE DIAGNOSIS OF THE DYSLEXIA TYPE

To establish the diagnosis of each type of dyslexia, we further ran tests of reading aloud as well as lexical decision and written word comprehension, with stimuli sensitive to each type of dyslexia. In these additional tests, reading aloud was done without time limit, and the participants were requested to read aloud as accurately and as quickly as possible, and the first responses were counted, even when they were later self-corrected. In the lexical decision and the comprehension tasks, the participants were requested to perform the tasks in silent reading, without sounding out the words they read.

The results of each participant in each of the further reading tasks was compared to those of age-matched controls. In the reading aloud tasks, the number of errors of each type (reading via the sublexical route, vowel omission, substitution, addition, migration, consonant omission, substitution, addition, migration, migrations between words, voicing errors, semantic errors) was compared to the number of these errors in the control group. In the lexical decision and comprehension tasks, the percentage of correct responses was compared to that of the age-matched controls.

Letter Position Dyslexia

To establish the diagnosis of letter position dyslexia, which is characterized by letter migrations within words, we used, beyond the oral reading tasks of migratable words described above, also tasks that tested the participants' silent reading of words that are most sensitive to this dyslexia– migratable words.

Additional tasks involved **same-different decision** in which the participant was presented with 60 word pairs, half of which differed in middle letter order (clam–calm), and was requested to determine whether the words in the pair are same or different; **lexical decision task**, in which the participants saw 60 items, half of them words and half migratable non-words (pecnil) and were requested to determine whether the item was a word; and a **reading comprehension task** that included 50 triads. Each triad consisted of a target migratable word, and two words to choose from: one word that is semantically associated with the target word, and one that is semantically associated with a word that can result from a transposition of middle letter (dairy → milk, notebook). The participants were requested to circle the word that is semantically associated with the target word.

Attentional Dyslexia

To establish the diagnosis of attentional dyslexia, characterized by migrations of letters between neighboring words (and by omissions of an instance of a letter that appears in two neighboring words in the same position), beyond the two word-pair reading tests, the participants read aloud an additional list of non-word pairs.

The **migratable non-word pair** list included 30 3-letter non-word pairs in which letter migration between words would result in existing words. A large number of migration errors between words in these tasks indicates that the reader has attentional dyslexia.

Surface Dyslexia

Each participant with suspected surface dyslexia was tested, in addition to the screening test and the potentiophone reading task, with a lexical discrimination task of pseudo-homophones, and a homophone comprehension task.

Pseudo-homophone Lexical Decision

The lexical decision task contained 66 word pairs. Each pair included a word spelled correctly and its pseudo-homophone (e.g., knife-nife). For each pair, the participants were requested to circle the word that was spelled correctly.

Homophone–Potentiophone Reading Comprehension

The reading comprehension task included 40 triads. Each triad consisted of a target word, and two words to choose from: one word that is semantically associated to the target word, and a homophone or a potentiophone of the associated word (e.g., bottle – bear beer). The participants were requested to circle the word that is semantically associated with the target word.

Vowel Dyslexia

To establish the diagnosis of vowel dyslexia, characterized by substitutions, omissions, additions, and migrations of vowel letters, the participants read in addition to the non-word lists, another word list, and performed two additional tasks of lexical decision and word comprehension.

Reading Words

The word list included 100 words, 3- to 8-letter long (mean = 4.17, *SD* 0.56). Words in this list were selected so that each word had at least two lexical options for vowel letter errors, namely, at least two vowel errors made in each target word create other existing words. (For example, a relevant word in English would be the word "form," which can be read with a vowel migration as *from*, with a vowel substitution as *firm* or *farm*, and with a vowel addition as *forum*.)

Lexical Decision

The vowel dyslexia lexical decision task contained 80 items: 45 non-words in which a vowel error creates existing Hebrew words and 35 existing words – 16 of which included a vowel letter and 19 without vowel letters. The items in the task were 2–8 letters ($M = 4.8$, *SD* 1.13). The participants were requested to silently read each word and to circle the words that exist in Hebrew.

Reading Comprehension

The reading comprehension task for vowel dyslexia included 52 triads. Each triad consisted of a target word (3–6 letters long, $M = 4.4$, *SD* 0.75), and two to four words to choose from: one word that is semantically associated with the target word, and the rest are words that are semantically associated with words that can result from a vowel error in the target word (form → shape, to, ranch). The participants were requested to circle the word that is semantically associated with the target word.

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