Université de Montréal

Effect of Mindfulness Meditation on the Neural Substrates of Emotion Processing and Resting State in Experienced and Beginner Meditators

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Résumé

La méditation par le 'mindfulness' favorise la stabilité émotionelle, mais les mécanismes neuroneux qui sous-tendent ces effets sont peu connus. Ce projet investiga l'effet du 'mindfulness' sur les réponses cérébrales et subjectives à des images négatives, positives et neutres chez des méditants expérimentés et des débutants au moyen de l'imagerie par résonance magnétique fonctionnelle (IRMf). Le 'mindfulness' atténua l'intensité émotionelle via différents mécanismes cérébraux pour chaque groupe. Comparés aux méditants, les débutants manifestèrent une déactivation de l'amygdale en réponse aux stimuli émotifs durant le 'mindfulness'. Comparés aux débutants, les méditants exhibèrent une déactivation de régions du *réseau du mode par défaut* (RMD) pendant le 'mindfulness' pour tous stimuli (cortex médian préfrontal [CMP], cortex cingulaire postérieur). Le RMD est constitué de régions fonctionnellement connectées, activées au repos et déactivées lors de tâches explicites. Cependant, nous ne connaissons pas les impacts de l'entraînement par la méditation sur la connectivité entre régions du RMD et si ces effets persistent au-delà d'un état méditatif. La connectivité fonctionnelle entre régions du RMD chez les méditants et débutants au repos fut investiguée au moyen de l'IRMf. Comparés aux débutants, les méditants montrèrent une connectivité affaiblie entre subdivisions du CMP, et une connectivité accrue entre le lobule pariétal inférieur et trois regions du RMD. Ces résultats reflètent que les bienfaits immédiats du 'mindfulness' sur la psychopathologie pourraient être dûs à une déactivation de régions limbiques impliquées dans la réactivité émotionelle. De plus, les bienfaits à long-terme de la méditation sur la stabilité émotionelle pourrait être dûs à une déactivation de régions corticales et cingulaires impliquées dans l'évaluation de la signification émotive et une connectivité altérée entre régions du RMD à l'état de repos.

Mots clés : Méditation, Pleine conscience (‘mindfulness’), Régulation émotionnelle, Amygdale, Cortex préfrontal, Réseau du mode par défaut, Connectivité fonctionnelle

Abstract

Mindfulness meditation promotes emotional stability, yet little is known of the brain mechanisms through which this is achieved. The impact of mindfulness on the neural and subjective responses to negative, positive, and neutral pictures in experienced meditators and beginners was investigated using functional magnetic resonance imaging (fMRI). Mindfulness attenuated emotional intensity via distinct neural pathways for each group. For beginners, mindfulness induced a deactivation of the amygdala during emotional processing compared to meditators. For meditators (relative to beginners), mindfulness induced deactivations of areas involved in the evaluation of emotional significance and the *default mode network* (DMN) across all picture categories (medial prefrontal cortex [MPFC], posterior cingulate cortex). The DMN consists of functionally connected brain areas typically activated at rest and deactivated during goal-directed tasks. It remains unknown whether meditation training influences functional connectivity within DMN regions, and if so, whether these effects persist beyond a state of meditation *per se*. Functional connectivity within DMN regions at rest was examined using fMRI in beginners and meditators. Relative to beginners, meditators exhibited decreased connectivity between MPFC subdivisions, and increased connectivity between the right inferior parietal lobule and three other DMN regions. These findings may reflect that early beneficial effects of mindfulness on psychopathology are due to deactivations of limbic regions involved in emotional reactivity. On the other hand, long-term effects of meditation on emotional stability may occur through a down-regulation of prefrontal and cingulate regions involved in the evaluation of emotional significance, and altered functional connectivity within DMN regions at rest.

Keywords: Meditation, Mindfulness, Emotion Regulation, Amygdala, Prefrontal Cortex, Default Mode Network, Functional Connectivity

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List of Symbols and Abbreviations

η^2	Eta Squared Measure of Effect Size
Π	Partial Correlation Coefficient
ACC	Anterior Cingulate Cortex
AMY	Amygdala
BA	Brodmann Area
BOLD	Blood-Oxygen Level Dependent
cc	Correlation Coefficient
CORSICA	Correction of Structured noise using spatial Independent Component Analysis
d	Cohen's *D* Measure of Effect Size
DMN	Default Mode Network
DMPFC	Dorso-Medial Prefrontal Cortex
DR	Degree of Representativity
DU	Degree of Unicity
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
FWE	Family-Wise Error Rate

IC	Independent Component
ICA	Independent Component Analysis
INS	Insula
IPL	Inferior Parietal Lobule
ITC	Infero-Temporal Cortex
k	Clsuter Size (Number of Voxels)
LPFC	Lateral Prefrontal Cortex
MDD	Major Depressive Disorder
MFG	Medial Frontal Gyrus
MPFC	Medial Prefrontal Cortex
MSBR	Mindfulness-Based Stress Reduction Program
NEDICA	Network Detection using Independent Component Analysis
OFC	Orbito-Frontal Cortex
PC	Precuneus
PCA	Principal Component Analysis
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex

PHG	Parahippocampal Gyrus
PUT	Putamen
ROI	Region of Interest
SAD	Social Anxiety Disorder
T2*	Transverse Relaxation Time
TE	Echo Time
TMS	Transcranial Magnetic Stimulation
TR	Repetition Time
VMPFC	Ventro-Medial Prefrontal Cortex

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To Loïc,
Who teaches me
By example the Value of
Hard Work and Perseverance

To my Mother,
Who keeps showing me the Importance of
Resourcefulness, Strength and Determination
And Taught me that a Little Organization goes a Long Way

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General Introduction

Mindfulness meditation is an ancient spiritual practice which attenuates emotional reactivity and is beneficial to the treatment of emotion-related disorders (Baer, 2003). Yet the neural mechanisms through which this is achieved currently remain unknown. In this context, the principal aim of this thesis was to investigate the neural mechanisms through which mindfulness meditation influences the processing of emotional processing and a baseline state of rest. A brief overview of the empirical psychological literature on emotions and emotion regulation is presented, as well as an overview of findings from the neuroscientific literature on brain mechanisms involved in emotional processing (also known as affective behavioural neuroscience). Findings from studies investigating the relationship between meditation, emotional processing and brain function are then presented. Next, the literature on resting states using functional magnetic resonance imaging (fMRI) and findings demonstrating the involvement of the default-mode network in emotional processing as well as meditation are discussed. The specific objectives and hypotheses are stated, and the results of this thesis are presented within two articles (the first article has been published in the journal *NeuroImage*; the second article has been submitted to the journal *Social Cognitive and Affective Neuroscience*). Finally, the results presented in these articles are discussed, followed by concluding remarks.

Emotions and Emotion Regulation

As opposed to moods which are diffuse and long-lasting, emotions are generally short-lived experiences triggered by discrete events (either internal events such as thoughts, or concrete external events; Gross, 2007). Additionally, emotions are thought to depend on the *meaning* attributed to their triggering events in terms of their relevance to one's goals, values, and circumstances (Gross, 2007).

Specifically, the sequence of events preceding an emotional response has been described as: 1- the occurrence of a triggering event (external or internal), 2- the allocation of attention to this event, 3- the appraisal or assessment of the event with respect to one's goals and values, after which 4- the emotional response ensues (Gross, 2007). Thus, the *appraisal* of the triggering event is thought to play a crucial role in generating emotional responses. This sequence of events is often cyclical, such that one emotional response may constitute a triggering event generating a subsequent emotional response, etc. Additionally, emotional responses occur across several dimensions: subjective experience, behaviour, and physiology (involving central and peripheral nervous system processes). However, an important aspect of emotions is that they are not permanent; rather, emotions are in constant change and are *malleable*.

Indeed, given that we are primarily social beings, certain emotional responses cannot be expressed within every social context. For example, it would not be considered appropriate to burst out crying in the middle of a professor's class lecture, but it would be considered appropriate to do so at a funeral. In most cases, when experiencing an emotion arising in an incongruent context (grief from the death of a relative in the context of a classroom), an attempt is made to regulate, attenuate, or modulate this emotion in some way.

Emotion regulation refers to several types of processes (conscious, unconscious, voluntary, uncontrolled) which are intended to attenuate, maintain, or amplify an emotional response. Some types of emotion regulation strategies are focused on altering aspects of the response itself, such as performing physical exercise to attenuate anxiety before an exam. Other strategies are focused on regulating aspects of the appraisal process. As such, re-appraisal entails that the triggering event is re-interpreted in more neutral terms (Ochsner, Bunge, Gross, and Gabrieli, 2002). Since the regulation of emotion allows individuals to comply with social norms and to function effectively within the environment, failure to effectively regulate emotions can lead to detrimental psychosocial functioning, and is associated with a wide array of psychological disorders including major depression, anxiety disorders, psychopathy, and antisocial personality disorder (Phillips, Drevets, Rauch, and Lane, 2003a). It is therefore crucial to gain a better understanding of emotional experiences and emotion regulation. Specifically, the neural mechanisms underlying these processes have been increasingly studied using a variety of methods assessing brain function.

Affective Behavioural Neuroscience

A wide body of research suggests the involvement of two main cerebral systems in emotional processing: brain regions involved in lower-level subcortical affective appraisal, and brain regions involved in higher order top-down affective appraisal systems (Gross, 2007; Phan, Wager, Taylor, and Liberzon, 2004; Phan, Wager, Taylor, and Liberzon, 2002).

Lower-order affective appraisal brain systems are thought to involve primary innate responses to emotion-triggering events, and consist mostly of subcortical limbic brain structures innervated via a direct pathway from primary sensory areas to the thalamus (Gross, 2007). These structures include the amygdala, the insula, the nucleus accumbens, and the basal ganglia (putamen, caudate nucleus), and play a role in encoding the affective value of environmental stimuli (Calder, Lawrence, and Young, 2001; Phillips, Drevets, Kauch, and Lane, 2003b).

According to evolutionary perspectives, these structures have important survival functions as they allow individuals to react quickly by signalling biologically relevant information, including potential environmental threats. Particularly, the amygdala has been shown to be activated in response to both aversive and fearful information (see, for instance, Ochsner et al., 2002; Ochsner, Knierim, Ludlow, Hanelin, Ramachandran, Glover, and Mackey, 2004; Whalen, Rauch, Etcoff, McInerney, Lee, and Jenike, 1998), as well as apetitve stimuli (Beauregard, Lévesque, and Bourgoin, 2001; Sergerie, Chochol, and Armony, 2008). In contrast, the basal ganglia (caudate nucleus and putamen) appear to be activated mainly in response to positive, pleasurable and addictive stimuli (Everitt, Parkinson, Olmstead, et al., 1999; Haruno et al., 2004; Naqvi and Bechara, 2010; Phillips and LeDoux, 1992; Prado-Alcala and Wise, 1984). In addition, the anterior portion of the insula has been shown to be involved in the anticipation of aversive events, and is thought to reflect greater awareness of interoceptive states (Craig 2004; Critchley, Mathias, and Dolan, 2001).

Nonetheless, primary affective appraisal systems have been shown to have afferent and efferent connections to higher-order cognitive and control areas of the prefrontal and cingulate cortices (Beauregard et al., 2001; Levesque, Eugene, Joanette, Paquette, Mensour, Beaudoin, Leroux, Bourgouin, and Beauregard, 2003; Ochsner et al., 2002; Ochsner et al., 2004). As such, the amygdala, which plays an important role in fear conditioning, has been shown to be densely connected to the prefrontal cortex, especially the medial prefrontal cortex (MPFC; BA 9 /10) and orbito-frontal cortex (OFC; BA 11 / 47; Amaral, Price, Pitkanen, and Carmichael, 1992; Davidson, 1998). These regions of the prefrontal cortex (PFC) have been shown to play a pivotal role in the extinction of conditioned fear and the dampening of negative affect (Amaral et al., 1992; Davidson, 1998).

Thus, higher-order areas of the PFC and cingulate cortex are thought to be mainly involved in the voluntary regulation of emotion, including the reappraisal of emotional events and the voluntary generation of emotional states (Beauregard et al., 2001; Levesque et al., 2003; Ochsner et al., 2002; Ochsner et al., 2004). In addition, the rostro-dorsal anterior cingulate cortex (ACC) appears to be involved in monitoring the extent to which regulation strategies actually affect the emotional response (Ochsner et al., 2002; Ochsner et al., 2004).

Finally, subdivisions of higher order PFC regions may also underlie distinct functions. For instance, dorsal regions of the MPFC (8), LPFC (8 / 9), and rostro-dorsal ACC (32) have been associated with description-based appraisal systems, mainly involved in mental descriptions of emotional states as well as the controlled appraisal of emotional states using beliefs and expectations (Gross, 2007). Ventral and orbital portions of the PFC and ACC have been defined as outcome-based systems (Gross, 2007), which are involved in learning basic stimulus-outcome contingencies. Extinction of conditioned learning appears to recruit these areas (Amaral et al., 1992; Davidson et al., 1998). With the use of a variety of brain mapping techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and transcranial magnetic stimulation (TMS), the study of the neural substrates underlying emotional processes has revealed considerable insight into clinical affect-related psychopathology.

Relevance to Psychopathology

Different neural processes relevant to emotional processing seem to distinguish clinical from healthy populations (Phillips et al., 2003b). With regard to this issue, hyperactivity of the amygdala has been observed in depressed and anxious patients (Drevets, 2000; Rauch et al, 1997). Depression has also been characterized by hypoactivity of the left PFC, a brain area which has been associated with positive emotions (Davidson, 2002). In addition, a theory has been put forth that hemispheric differences in parietal cortex activity play a role in arousal: greater left than right parietal activity is associated with low arousal, as observed in depressed individuals without an anxiety disorder; and greater right than left parietal activity is associated with increased arousal, as observed in depressed patients with an anxiety disorder (Bruder; Fong; Tenke; Leite; Towey; Stewart; McGrath, and Quitkin 1997; Davidson 1992; Davidson 2002). Since several mental disorders such as depression and anxiety disorders typically involve some form of emotional dysregulation (Gross, 2007), psychological treatments of clinical populations often focus on implementing and developing various emotion regulation skills.

Mindfulness Meditation and the Regulation of Emotion

One type of mechanism which appears to influence emotional responsiveness and to promote emotional stability (Arch et al., 2006; Baer, 2003; Broderick, 2005) is mindfulness meditation, a practice which is being increasingly studied under experimental psychological and neuroscientific frameworks.

Meditation originates from ancient Eastern traditions, and this spiritual practice dates back from more than two millenaries ago (Nataraja, 2008). Mindfulness is a type of meditation based on cultivating self-observation and present-moment awareness (Kabat-Zinn, 1994), as opposed to living in recollections of the past or in the anticipation of fears concerning the future. As such, Kabat-Zinn (1994) defines mindfulness as “paying attention in a particular way: on purpose, in the present moment, and non-judgementally”.

Mindfulness meditation is commonly practiced sitting down, and initiated by focusing on a particular object, often physical aspects or sensations related to the breath or posture. In doing so, “each thought, feeling, or sensation that arises in the attentional field is acknowledged and accepted as it is” (Bishop, 2004). After acceptance of these arising events, attention is re-directed to the initial object of focus. Eventually, the frequency of interfering internal thoughts decreases, and ultimately these thoughts cease to arise, at which stage attention is in complete contact with its direct environment. Importantly, during a state of mindfulness, events are not evaluated as good, bad, or assessed in terms of implications for the self (Bishop, 2004). Mindfulness therefore promotes a detached and objective manner of responding to emotional events, as opposed to other maladaptive practices such as avoidance or rumination (Broderick, 2005).

Mindfulness has indeed been shown to reduce ruminative thoughts as well as depressive symptoms (Deyo, Wilson, Ong, and Koopman, 2009). In addition, a focused-breathing manipulation, typically practiced during a state of mindfulness, was shown to reduce emotional volatility to affective slides (Arch and Craske 2006). It is therefore not surprising that this practice has widespread benefits for the treatment of emotion-related psychological disorders, including major depression, which is associated with excessive rumination on negative thoughts (Joormann, 2006), generalized anxiety disorder, which is associated with excessive worry and avoidance (Dugas, Freeston, Ladouceur, Rheaume, Provencher, and Boisvert, 1998), as well as substance use, chronic pain, and binge eating disorder (Baer, 2003). Nevertheless, the neural mechanisms through which mindfulness influences emotional responses remain unclear.

Mindfulness, Emotions, and the Brain

Few studies have examined the effects of mindfulness, the brain, and emotional processing. Lutz et al. (2008) have investigated the effect of compassion meditation (which involves generating a non-specific, unconditional state of compassion) on brain function in response to emotional aversive, positive and neutral sounds in experienced Buddhist meditators as well as novices. They found that compassion meditation induced increased anterior insula and rostro-dorsal ACC activity during the processing of aversive sounds, and this occurred to a larger extent in experienced meditators. Thus, according to these data, the insula and ACC play a role in generating compassion meditative and empathic states to sounds of distress. In addition, they found that across all valence categories, compassion meditation induced increased activity in the amygdala for the experienced meditators compared to novices. This may reflect general increased emotional arousal during a state of loving-kindness meditation (Lutz, Brefczynski-Lewis, Johnstone, and Davidson 2008).

In contrast, another study conducted by the same group (Brefczynski-Lewis, Lutz, Schaefer, Levinson, and Davidson, 2007) found that for experienced meditators (compared with novices), mindfulness meditation induced decreased activity of the amygdala during the processing of negative emotional sounds. The magnitude of this effect was also negatively correlated with the extent of meditation experience in the group of experienced meditators. Similarly, Grant et al (2011) found that during aversive painful stimulations, experienced Zen meditators had reduced amygdala activity compared to non-meditators, suggesting an attenuating effect of meditation experience on reactivity limbic systems. These results are consistent with evidence that after completing an eight-week mindfulness-based stress-reduction (MSBR) training, individuals with social anxiety disorder had decreased amygdala activity in response to negative self-beliefs (Goldin and Gross 2010).

There are inconsistencies in the literature with respect to the effect of meditation on lower-level appraisal systems such as the amygdala in response to emotional stimuli. Some reports suggest that meditation attenuates activity in this structure during negative emotional processing (Brefczynski-Lewis et al., 2007), consistent with the idea that meditation attenuates emotional reactivity. On the other hand, other evidence demonstrates a general increase in amygdala activity in response to emotional and non-emotional stimuli during a (compassion) meditative state (Lutz et al., 2008), consistent with the fact that emotions are accepted and unsuppressed during a state of meditation.

With respect to higher-order PFC systems involved in emotional processing, Grant and colleagues (2011) found that experienced meditators exhibited deactivations in the medial PFC (MPFC), a brain region involved in evaluating self-relevance and emotional value to stimuli. In contrast, non-meditators recruited the dorso-lateral PFC, which is involved in the voluntary regulation of emotion (Ochsner et al., 2004). These findings were interpreted as reflecting that meditation practice attenuates the emotional impact of stimuli by *deactivating* brain areas involved in the cognitive evaluation of emotional stimul. In other words, mindfulness meditation may be associated with *'no regulation'* or '*no appraisal'* due to acceptance of emotional states (Grant et al., 2011). Inherently, as suggested by Grant and colleagues, this may translate into a passive decoupling of PFC-amygdala pathways via deactivation of cortical appraisal systems.

The MPFC deactivations observed in experienced meditators in response to painful stimuli (Grant et al., 2011) are consistent with previous research (Farb, Segal, Mayberg, Bean, McKeon, Fatima, and Anderson, 2007). Indeed, Farb and colleagues (2007) found that an experiential focus condition (evaluating the self in terms of moment-to-moment monitoring of the environment) was associated with decreased activity in the dorsal and ventral MPFC relative to a narrative self condition (evaluating the self in terms of trait-like descriptors). This effect was observed to a larger extent in participants having completed an 8-weeek MSBR program than in novices. Together, the results from Grant et al (2011) and Farb and colleagues (2007) regarding decreased activity in the MPFC associated with meditation - are relevant to the fact that the MPFC is also one of the key structures involved in the so-called '*default mode network' (DMN).*

The Default Mode Network

The DMN consists of spatially remote brain regions with correlated temporal dynamics. This network is typically actived during rest, and deactivated during specific goal-related tasks (Buckner, Andrews-Hanna, and Schacter, 2008). Though the mental processes related to the DMN remain unclear, it has been proposed that activity in this network during rest (or in the absence of engagement in activities with the external world) reflects mentation about the self (Northoff, Heinzel, de Greck, Bermpohl, Dobrowolny, and Panksepp, 2006), simulations of past and future scenarios, and the planification of future actions (Buckner, Andrews-Hanna, and Schacter, 2008). The core brain regions in the DMN are located within posterior portions of the brain (inferior parietal lobule [IPL], precuneus, posterior cingulate cortex [PCC]), the temporal lobe (lateral and mid-temporal cortex, and the parahippocampal formation), and the prefrontal cortex (dorso-medial PFC [DMPFC] and ventro-medial PFC [VMPFC]).

Specifically, DMN function has been widely studied using fMRI, by recording brain activity during ‘resting states’ (typically, sessions of several minutes during which participants are instructed to rest and not to engage in any explicit goal-related task). These studies have provided valuable insight into clinical disorders, such as marked differences in DMN functioning in patients with Alzheimer’s Disease (who show decreased connectivity between DMN structures and the hippocampus; Greicius; Srivastava; Reiss, and Menon 2004) and major depression (who exhibit increased connectivity between DMN structures and the subgenual ACC; Greicius, Flores, Menon, Glover, Solvason; Kenna, Reiss, and Schatzberg 2007).

The DMN has also been shown to be related to emotional processing (Sheline, Barch, Price, Rundle, Vaishnavi, Snyder, Mintun, Wang, Coalson, and Raichle, 2009). Indeed, Sheline and colleagues (2009) demonstrated that depressed patients failed to deactivate DMN regions (IPL [BA 39], VMPFC [BA 10], and lateral temporal cortex [BA 21]) during the passive viewing and re-appraisal of negative pictures. This was interpreted as reflecting greater interference from internal emotional states. In parallel with these findings, there is also evidence that compassion meditation is associated with increased activity in some regions of the DMN, such as the right IPL, precuneus, and parahippocampal gyrus (Lutz et al., 2008). Enhanced activity in these areas has been interpreted as reflecting greater compassion and understanding of others' intentions. Other reports have demonstrated increased DMN function during a focused-breath induction after viewing negative self-beliefs in social anxiety disorder (SAD) patients in precuneus, IPL and parahippocampal gyrus (Goldin et al, 2010). Finally, Brefczynski-Lewis and colleagues (2007) investigated brain function during concentration meditation, which is similar to mindfulness as it involves focusing attention on one particular object and gently bringing it back to this object when distracted. They found that during a state of concentration meditation, there was a negative correlation between activity in DMN regions (MPFC and PCC) and the number of hours of meditation experience. Therefore, it appears that there is a relationship between the DMN, meditation, and emotional processing. However, the DMN is thought to operate as a coherent network during rest, since the spatially remote regions within this network are functionally connected (i.e. the time-courses between regions are correlated). Yet, to date, the impact of meditation training on functional connectivity between DMN regions during rest remains completely unknown.

Principal Objectives

The central objectives of this research project were twofold. First, given the premise that mindfulness meditation promotes affective balance (Kabat-Zinn 1994; Bishop, 2004; Arche et al., 2006; Broderick, 2005) and benefits the treatment of affective and anxiety disorders (Baer, 2003), a central goal of this thesis was to determine the effects of mindfulness on the neural responses to emotional information. This question was addressed in Study #1, in which brain activity using fMRI was recorded while experienced and beginner meditators viewed emotional (positive and negative) as well as neutral pictures. Subjective emotional intensity ratings were also recorded immediately following the presentation of each picture. There were two conditions, one in which pictures were viewed in a meditative state, and the other condition involved viewing pictures in a normal (non-meditative) state.

Second, given evidence of altered DMN function associated with emotional processing (Sheline et al., 2009) and meditation (Brefczynski-Lewis et al., 2007), another main objective of this research project was to investigate the relationship between mindfulness training and functional connectivity within DMN regions during a restful state. This question was addressed in Study #2, in which brain activity was recorded during a state of rest (6-minute fMRI sessions in the absence of any goal-related or specific mental activity) in experienced and beginner meditators. This was investigated using data-driven connectivity analysis approaches (spatial independent component analysis) to identify a DMN group map, after which pair-wise correlations and partial correlations between DMN regions were examined and compared between groups.

Hypotheses

In Study #1, it was hypothesized that the mindful condition would attenuate subjective emotional intensity perceived from emotional pictures. From a neural circuitry perspective, it was hypothesized that mindfulness would induce reduced amygdala activity in response to emotional stimuli, and more so in experienced vs. beginners (Brefczynski-Lewis et al., 2007; Grant et al., 2011). Finally, based on the MPFC deactivations associated with meditation (Farb et al., 2007; Grant et al., 2011), it was hypothesized that mindfulness would induce reduced activity in prefrontal areas involved in controlled regulation of emotion, and to a larger extent in experienced than in beginner meditators.

In Study #2, it was hypothesized that mindfulness training would be associated with weakened connectivity between MPFC and other DMN structures at rest. This hypothesis was also based on MPFC deactivations associated with mindfulness meditation (Farb et al., 2007; Grant et al., 2011), and on the premise that mindfulness is associated with reduced appraisal of emotional events (Bishop, 2004).

Article 1

Title: Impact of Mindfulness on the Neural Responses to Emotional Pictures in Experienced and Beginner Meditators

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Author Contributions

V.T. wrote the manuscript, and conducted all of the statistical analyses on the data presented in this article. J.G. actively participated in the writing process, as well as giving feedback on the experimental design, analyses, and interpretations. V.D. was responsible for coordinating and collecting the data included in this research project. G.S. assisted V.D. in the data collection. S. R.-V. and E.B. contributed to the setup of experimental design and tasks. J.C. contributed to the experimental design as well as the recruitment of participants. A.S.L. helped in some of the data acquisition. M.B. extensively revised and edited the manuscript into its final form.

Impact of Mindfulness on the Neural Responses to Emotional Pictures in Experienced and Beginner Meditators

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Abstract

There is mounting evidence that mindfulness meditation is beneficial for the treatment of mood and anxiety disorders. Little is known regarding the neural mechanisms through which mindfulness modulates emotional responses. A central objective of this functional magnetic resonance imaging study was to investigate the effects of mindfulness on the neural responses to emotionally laden stimuli. Another major goal of this study was to examine the impact of the extent of mindfulness training on the brain mechanisms supporting the processing of emotional stimuli. Twelve experienced (with over 1000 hours of practice) and 10 beginner meditators were scanned as they viewed negative, positive, and neutral pictures in a mindful state and a non-mindful state of awareness. For both groups, pictures viewed in a mindful state were subjectively perceived as less intense than when viewed in a non-mindful state. Compared with experienced meditators, mindfulness led to a down-regulation of the left amygdala during emotional (negative and positive) processing in beginners. Compared with beginners, mindfulness was associated with a down-regulation of activity in brain areas involved in responsiveness to emotional stimuli, self-referential processing, and the default mode network (medial prefrontal and posterior cingulate cortex) in experienced meditators across all valence categories. These results are consistent with the view that mindfulness attenuates emotional reactivity and influences neural mechanisms involved in emotion processing. These findings have implications for emotion-related psychological disorders.

Originating from ancient Eastern traditions (Nataraja, 2008), meditation is an increasingly prominent object of study within the fields of clinical psychology and behavioral neuroscience. Mindfulness is a form of meditation which has been operationally defined as “a kind of nonelaborative, nonjudgmental, present-centered awareness in which each thought, feeling, or sensation that arises in the attentional field is acknowledged and accepted as it is.” (Bishop, 2004). The detached observation state which is adopted during mindfulness is thought to promote an objective and adaptive manner of responding to emotional triggers in contrast to a habitual pattern of emotional reactivation typically driven by past experiences, fears and preconceptions (Bishop, 2004). Consistent with this view, it has been demonstrated that mindfulness-based clinical interventions have beneficial outcomes on the treatment of affect-related psychopathology, including major depression (Bondolfi et al., 2010; Teasdale et al., 2000) and anxiety disorders (Bondolfi, Jermann, der Linden, Gex-Fabry, Bizzini, Rouget, Myers-Arrazola, Gonzalez, Segal, Aubry, and Bertschy, 2010; Goldin and Gross, 2010; Kabat-Zinn;, Massion, Kristeller; Peterson, Fletcher; Pbert, Lenderking, and Santorelli, 1992; Kim, Lee, Choi, Suh, Kim, Kim, Cho, Kim, Yook, Ryu, Song, and Yook, 2009).

To date, a few studies have examined the effects of meditation on the processing of emotional stimuli. Focused-breathing typically practiced during mindfulness has been shown to promote emotional self-regulation by reducing reactivity to emotionally laden pictures (positive and negative) (Arch et al., 2006). Mindfulness meditation practiced following a sad mood induction was also shown to decrease dysphoria (Broderick, 2005). Additionally, Brefczynski-Lewis and colleagues (2007) found a negative correlation between the number of hours of meditation training and right amygdala activation during concentration meditation in a group of experienced meditators while processing negative emotional sounds. In another study (Farb, Anderson, Mayberg, Bean, McKeon, and Segal, 2010), the MBSR program led to reduced activation in regions associated with autobiographical memory and increased activity in the right insula (Farb et al, 2010). Finally, Lutz and colleagues (2008) investigated the effects of compassion meditation on the processing of emotional auditory stimuli. They found increased right insula activation for experienced meditators, relative to beginner meditators, during a state of compassion meditation while listening to negative emotional sounds (compared to emotionally positive sounds). This brain region plays an important role in awareness of interoceptive states (Craig, 2004; Critchley, Wiens, Rotshtein, Ohman, and Dolan, 2004). Compassion meditation also induced increased amygdala activation while listening to emotional and neutral sounds for experienced meditators relative to beginners. It is noteworthy that since compassion meditation involves maintaining a non-referential state of compassion, different brain processes may be involved in mindfulness meditation during emotional processing as opposed to compassion meditation.

Emotional self-regulation strategies, such as cognitive distancing and reappraisal, have commonly been associated with the recruitment of prefrontal cortical areas critically involved in executive control functions (e.g., lateral prefrontal cortex [LPFC], medial prefrontal cortex [MPFC], and anterior cingulate cortex [ACC]), and decreased activation in subcortical structures implicated in emotional processing (e.g., amygdala) (Beauregard et al., 2001; Levesque et al., 2003; Ochsner et al., 2002; Ochsner et al., 2004). Convergent with neuroimaging studies of emotional self-regulation, there are some reports that meditative states are associated with increased activation in various prefrontal cortical areas. Such heightened prefrontal activation has been interpreted as reflecting increased recruitment of attentional resources during meditation (Newberg, Alavi, Baime, Pourdehnad, Santanna, and d'Aquili, 2001). Interestingly, mindfulness was shown to be associated with increased MPFC/LPFC activation and reduced amygdala activation during affect labelling, which is commonly employed during meditation in order to identify emotional states (Creswell, Way, Eisenberger, and Lieberman, 2007). In this study, Creswell and collaborators (2007) found that participants high in trait mindfulness also had negative correlations between areas of the PFC (MPFC and LPFC) and the right amygdala, but not those low in trait mindfulness. These findings are consistent with evidence that the MPFC, through its inhibitory downstream connections to the amygdala, is implicated in the extinction of conditioned fear as well as the dampening of negative affect (Amaral et al., 1992; Davidson, 1998). Similar results were found in clinical populations. For example, Goldin and Gross (2010) reported that patients with social anxiety disorder (SAD) exhibited decreased right amygdalar activation after viewing phrases of negative self-beliefs, and increased activation in regions relevant to the control of attention (including regions of the parietal cortex) after having completed an 8-week mindfulness-based stress reduction program (MBSR). Goldin and Gross (2010) interpreted these results as indicating that mindfulness meditation helps to reduce avoidance-related behavior to threatening stimuli in SAD patients by enhancing the recruitment of brain regions involved in attentional control.

From a phenomenological perspective, it should be noted that cognitive distancing and reappraisal differ to a large extent from mindfulness. Indeed, these emotional self-regulation strategies aim at altering emotional states, whereas mindfulness is based on accepting emotional states as they are (Kabat-Zinn, 1994).

Consistent with this view, some neuroimaging studies suggest that long-term mindfulness meditation training can lead to decreased activation in prefrontal cortical areas, particularly the MPFC (Farb et al., 2007; Grant et al., 2011). In one of these studies, Farb and colleagues (2007) found that an experiential focus condition (monitoring the self in terms of present-moment circumstances) was associated with deactivations of the ventral and dorsal MPFC compared with a narrative self-focus task (monitoring the self in terms of self-descriptive traits). This effect was more pronounced and widespread in individuals having completed an 8-week MSBR program compared to a control group. A similar pattern of results has recently been reported in Zen meditators experiencing emotionally salient painful stimuli (Grant et al., 2011). In this study, when normally attending to painful stimulations, experienced meditators exhibited decreased activation in several brain regions involved in executive control and emotional appraisal, including the MPFC, LPFC, and amygdala compared to non-meditators. These decreased activations found in executive control areas have been proposed to reflect that meditation training is associated with a reduction in cognitive elaboration of aversive stimuli (Grant et al., 2011).

Clearly, however, methodological discrepancies in meditative and control tasks, as well as the different strategies or cognitive processes employed and the level or type of expertise in meditators may account for the inconsistencies in the literature. Nevertheless, the premise that meditation stabilizes emotion by not evaluating or appraising salient stimuli is in line with the prefrontal deactivations reported during mindfulness (Farb et al., 2007; Grant et al., 2011). Yet to date, little is known regarding the brain mechanisms through which mindfulness meditation modulates the processing of emotional stimuli.

In this context, a central goal of the present functional magnetic resonance imaging (fMRI) study was to investigate the neural mechanisms mediating the effect of this form of meditation on the processing of emotionally laden stimuli. Another major goal of this study was to examine the impact of the duration of mindfulness meditation training on the brain mechanisms supporting the processing of emotional stimuli. Thus, the effect of mindfulness was measured in a group of experienced meditators and a group of beginner meditators. Participants were scanned while they viewed negative, positive, or neutral pictures in a mindful state and a regular (non-mindful) state of awareness. They also rated stimuli on the emotional intensity they experienced when viewing the pictures. We hypothesized that the emotional stimuli viewed during mindfulness would be perceived as less emotionally intense than those viewed in a non-mindful state of awareness.

Moreover, we hypothesized that mindfulness would lead to decreased activation in cerebral structures involved in emotional processing, such as the amygdala. Based on previous research (Brefczynski-Lewis et al., 2007), this was predicted to occur to a greater extent in experienced meditators relative to beginners, since the former may attain a more sustained meditative state allowing them to more effectively attenuate emotional reactivity. Finally, due to the lack of evaluative processes maintained during mindfulness meditation, we hypothesized that during emotional processing, mindfulness would lead to reduced activation in prefrontal cortical areas. We also hypothesized that beginner meditators would exhibit a smaller reduction of prefrontal activation since they may have a greater need for effortful concentration while meditating.

Methods

Participants

Before being selected for the study, potential participants underwent preliminary telephone screening and were not included if they had any current or previous psychiatric or neurological disorders, consumed any psychotropic drugs, or had any severe medical condition. The group of experienced meditators consisted of 12 individuals with more than 1000 hours of experience in Zen meditation (7 females, 5 males; 11 right-handed, 1 left-handed; 25 - 60 yrs of age, $M = 46$, $SD = 11$), and were recruited from meditation centers located in Montreal (Quebec, Canada). One participant from this group had 45 000 hours of meditation practice experience, and deviated in the number of hours of experience from the rest of the group (which ranged from 1000 – 3000 hours, $M = 1709$, $SD = 694$). Therefore, the analyses reported below were also conducted without the inclusion of this participant, and the results remained essentially unchanged. Given this, to avoid losing statistical power, this participant was kept in the statistical analyses.

The group of beginner meditators consisted of 10 individuals (4 females, 6 males; 10 right-handed, 1 ambidextrous, 1 left-handed; 22 - 54 years of age, $M = 34$, $SD = 12$) with no prior experience in meditation or similar practices such as yoga. There were no significant between-group differences with respect to age ($p > 0.05$) or to the ratio of male/female participants ($p > 0.05$). In addition, to ensure that age and sex did not interact with any other experimental factors, the analyses reported below were also conducted by adding age and sex as covariates, and the results remained essentially unchanged. These factors were therefore dropped from the analyses and are not discussed further. The level of education was similar across groups, with all participants having completed a minimum of undergraduate university studies (except for one participant in the group of experienced meditators who had not studied beyond a highschool education, and two participants in the group of beginners whose highest level of education completed were CEGEP studies).

The beginner meditators were recruited from Université de Montréal and the Centre de recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM) through advertisement posters. They were given detailed instructions on how to practice mindfulness meditation based on various sources (Ricard, 2008; Kabat-Zinn, 1994; Thich Nhat Hanh, 1994). They were also given a written record of these instructions as well as a compact disc on which a guided mindfulness meditation session was recorded by the experimenters. Based on this guided session, beginners were instructed to practice mindfulness meditation 20 minutes per day, for 7 days before the fMRI experiment. During this week of training, the experimenters followed up with participants to ensure that they understood how to practice meditation and to verify that they had been completing their practice daily. Compliance was followed up upon by a telephone interview, once in the middle of the week of training, during which participants were asked if they had questions. Before beginning their training period, participants were given the experimenters' contact information and were welcomed to ask any questions. Only one individual had two days of meditation practice prior to testing (due to scheduling restraints), but reported compensating accordingly by practicing additional time each day. In all other participants, 100% compliance was observed. All participants reported having successfully understood the mindfulness exercises. Participants were remunerated 50$ for their participation in this study. They all gave written informed consent and the study was approved by the ethics research committee of the CRIUGM.

Stimuli and Experimental Procedure

Before the start of the experiment, in order for participants to be comfortable to practice mindfulness within a scanner environment, participants were given some practice trials in a mock scanner, which simulated the physical environment. Participants were given approximately 20 practice trials in the Baseline condition, and 20 practice trials in the Mindful condition.

Blood oxygen level dependent (BOLD) signal changes were measured while participants viewed pictures in a 'normal' state (i.e., without attempting to modulate attention; this condition is referred to as the '*Baseline*' condition) and in a mindful state (during which they were instructed to mindfully attend to the stimuli; this condition is referred to as the '*Mindful*' condition). Two runs were acquired per condition. In order to prepare themselves for the runs in the Mindful Condition, participants were instructed to relax and focus on their breath (for approximately 1-2 min) until they felt they had attained a mindful state of awareness, and were instructed to maintain this state throughout the run. Before the start of the runs in the Baseline condition, participants were told that they were not required to meditate during the upcoming session. The Baseline and Mindful conditions alternated between runs, but the order in which the conditions were completed was counter-balanced across participants (Mindful, Baseline, Mindful, Baseline vs. Baseline, Mindful, Baseline, Mindful). The task design was based on a previous neuroimaging study of emotional self-regulation (Ochsner and Gross, 2005). Within each run, each trial consisted of the following events: a cue was first presented for 2 s in the centre of a screen (‘*Baseline’* or ‘*Mindful’* – depending on the condition), simply to serve as an indicator of the upcoming stimulus presentation. Next, a positive, negative or neutral picture was presented for 6 s, after which a rating scale appeared for participants to rate the strength of their emotional state induced by the stimuli (0 = no emotion, 4 = very strong emotion) using a five-button response box. Finally, there was a brief rest period until the beginning of the next trial during which the word ‘*Relax*’ appeared for a variable time (1 - 3 s) in the center of the screen. The duration of the rest period between stimuli was randomized throughout each scan, in order to prevent participants from anticipating the onset of subsequent stimuli. Each run lasted approximately 10 minutes. Participants were explicitly instructed to watch the screen at all times.

The stimuli consisted of a total of 216 pictures selected from the International Affective Picture System ([IAPS] Lang et al 1998). An event-related design was implemented. Each run consisted of 54 trials (18 positive pictures, valence = 7.20 ± 0.48, arousal = 5.01 ± 1.04; 18 negative pictures, valence = 3.01 ± 0.78, arousal = 5.74 ± 0.89, 18 neutral pictures, valence = 4.93 ± 0.27, arousal = 2.88 ± 0.47). Within each run and for each participant, the pictures were presented in a randomized manner. Valence and arousal ratings (Lang et al, 1998) for positive, negative, and neutral pictures were equated across conditions (negative pictures: valence = 2.97 ± 0.76, arousal = 5.78 ± 0.86 for the Baseline condition, valence = 3.00 ± 0.79, arousal = 5.79 ± 0.78 for the

Mindful condition; neutral pictures: valence = 4.94 ± 0.32, arousal = 2.90 ± 0.45 for the Baseline condition, valence = 4.89 ± 0.26, arousal = 2.86 ± 0.48 for the Mindful condition; positive pictures: valence = 7.20 ± 0.45, arousal = 4.96 ± 1.10 for the Baseline condition, valence = 7.21 ± 0.52, arousal = 5.06 ± 0.98 for the Mindful condition).

Stimulus presentation and response selection were controlled by the program E-Prime (version 1.0, Psychology Software Tools, Inc.) running on a separate portable computer. Stimuli were projected via a projector, through a lense onto a rear-projection screen that was attached in the magnet bore at the level of the neck. Participants viewed the stimuli on a slanted mirror placed inside the head coil.

To examine the effects of mindfulness on the magnitude of the subjective emotional responses experienced while viewing the stimuli, a Condition x Valence x Group mixed measures ANOVA was performed. The responses from two beginner participants were excluded, one because responses had been rated according to valence, and the other due to response box recording failure during scanning. Thus, a total *n* = 20 (12 experienced, 8 beginners) cases were included in these analyses. For each condition, the mean response for pictures in each emotional category was computed. The assumptions for conducting a mixed-measure ANOVA, such as homogeneity of variance between groups and linearity, were met. All variables were normally distributed, with skewness and kurtosis values ranging from -1.5 to 1.5. No univariate or multivariate outliers were detected. Due to response box failure on certain trials, some stimuli were missing emotional intensity ratings (with no more than 25% of participant ratings missing for any given stimulus), which were distributed at random across groups. These missing values were replaced with the group's corresponding mean value to avoid losing statistical power. The Greenhouse-Geisser correction was used to correct for sphericity of repeated measures. Statistical significance was set at an alpha level of .05. Self-report data were analyzed using the SPSS package (Version 17.0).

fMRI Data Acquisition and Analysis

MRI was performed using a whole-body 3.0 Tesla MRI system (Magnetom Trio, Siemens Electric, Erlangen, Germany) located at the Unité de Neuroimagerie Fonctionnelle (UNF) of the CRIUGM. Thirty-five contiguous slices (3.5 mm thick, voxel size = 3 mm x 3 mm x 3.5 mm) were acquired in an inclined axial plane. These T2* weighted functional pictures were acquired using a two-dimensional echo-planar-imaging pulse sequence (repetition time [TR] = 2500 ms, echo time [TE] = 40 ms, flip angle = 90^{o}, matrix size = 64 x 64 voxels). For each participant, a high resolution anatomical scan was also performed (three-dimensional, spoiled gradient echo sequence; 176 slices, slice thickness = 1 mm, TR = 19 ms, TE = 4.92 ms, flip angle = 25^{o}; matrix size = 256 x 256 voxels). The anatomical scan was acquired after the first two functional scans were completed.

fMRI data were analyzed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Two participants in each group only had data for two runs (one in each condition) due to testing constraints or excessive movement; however, the number of degrees of freedom was adjusted accordingly in the group analyses. The first three volumes of each run was excluded from the analyses to eliminate any T2*-equilibrium effects. For each participant, images were motion corrected and spatially normalized into an MRI stereotactic space (Talairach and Tournoux, 1988). Volumes deviating in translation by more than 3 mm, which only occurred at the very beginning or very end of a given session, were considered outliers and were excluded from the analyses. Images were spatially smoothed with a gaussian kernel of 8 mm at full-width half maximum to improve the signal-to-noise ratio, and to accommodate for residual variations in functional neuroanatomy that usually persist between participants after spatial normalization. For the statistical analyses, the time series of the images were convolved with a canonical hemodynamic response function, and effects at each voxel were estimated using the general linear model. For each run, the onsets for the three categories of pictures (negative, neutral, positive) were included into the model. In addition, the six motion parameters (*x, y, z,* pitch, roll, yaw) were entered as regressors of no interest in order to remove unspecific residual activation patterns related to movement (Friston, Holmes, Poline, Price, and Frith, 1996). For each participant, a fixed-effect model was used to compute specific contrast pictures. At the group-level, a random-effect full factorial Condition x Valence x Group ANOVA was performed by entering the contrast images for each condition and emotional category. Global normalization was carried out by including the global value (i.e. the average BOLD signal intensity for all within-brain voxels) from each participant as a nuisance variable. Unless otherwise specified, statistical parametric maps were first thresholded at $p < .001$ uncorrected for multiple comparisons. Then, an a priori search strategy was conducted to detect activation loci by performing small volume corrections in the regions of interest (ROIs). The ROIs encompassed the amygdala, insula (Brodmann area [BA] 13 and 14), putamen, caudate nucleus, hippocampus, dorsal (BA 24 and 32) and rostro-ventral (BA 24 and 25) ACC, MPFC (BA 9 and 10), LPFC (BA 9 and 10), and OFC (BA 11 and 47). These brain regions have been found to be activated on a more or less consistent basis in previous functional neuroimaging studies of emotional processing and self-regulation (Phan et al., 2002). For this a priori search, a cluster-level threshold of $p < 0.05$ corrected for multiple comparisons at the family-wise error rate (FWE) was used. Clusters exceeding a threshold of $p < 0.05$ FWE corrected at the whole –brain level are also reported. The predefined ROIs were located using masks created with the program MARINA (© Bertram Walter, 2002, Bender Institute of Neuroimaging, University of Glessen, Germany). A separate mask was created for each ROI, and small volume searches were performed for each region separately, within their own mask. Only clusters showing a spatial extent of at least 5 contiguous voxels were kept for image analysis. To aid in the clarity of the presentation of the results, "Mindfulness-Induced Activations" refer to increased activity observed in the Mindful relative to Baseline condition, and "Mindfulness-Induced Deactivations" refer to decreased activity observed in the Mindful compared to the Baseline condition. Cohen's *D* (*d*) effect sizes were examined for all significant loci of activation reported (by transforming *t*-maps into effect size maps using the Volumes toolbox implemented in SPM8).

Results

Self-Report Data

The ANOVA revealed a significant main effect of Valence (*F*(2, 18) = 122.39, $p < .001$, $\eta^2 = .87$). Negative pictures ($p < .0001$, $M = 2.08$; $SD = 0.65$) and positive pictures ($p < .001$, $M = 1.64$; $SD = 0.67$) were rated as more emotionally intense than neutral pictures ($M = 0.52$; $SD = 0.41$). A significant main effect of Condition (*F*(1, 18) = 7.23, $p < .05$, $\eta^2 = .29$) was also found. This effect was due to the fact that pictures viewed in the Mindful condition ($M = 1.29$; $SD = 0.57$) were rated as less emotionally intense than those viewed at Baseline ($M = 1.53$; $SD = 0.59$).

No significant effect of Group (*F*(1, 18) = 0.63, $p = .438$) was found. In addition, the Group x Condition (*F*(1, 18) = 0.72, $p = .382$), Group x Valence x Condition (*F*(1, 18) = 0.45, $p = .747$), or Valence x Condition (*F*(1, 18) = 1.94, $p = .17$, $\eta^2 = .170$) interactions were not significant. Nonetheless, to examine whether mindfulness had the same impact within each emotional category, simple effects of Condition (one-way repeated measures ANOVAs) were computed within each emotional picture category (collapsing across groups since no main effect or interactions with this factor were found). These analyses revealed a significant main effect of mindfulness on the processing of negative pictures (*F*(1, 18) = 6.23, $p = .022$, $\eta^2 = .25$), such that negative pictures viewed in a state of mindfulness were rated as less intense ($M = 2.16$, $SD = 0.71$) than negative pictures viewed in a normal state ($M = 1.93$, $SD = 0.65$). A similar effect was found for positive pictures (*F*(1, 18) = 6.23, $p = .015$, $\eta^2 = .25$; $M = 2.79$, $SD = 0.64$ for the Baseline condition; $M = 2.43$, $SD = 0.71$, for the Mindful condition). For neutral pictures, a significant effect of mindfulness was also found (*F*(1, 18) = 5.40, p = .031, η^2 = .22; *M* = 0.62, *SD* = 0.49 for the Baseline condition; *M* = 0.44, *SD* = 0.37, for the Mindful condition), but this result may have been due to a floor effect: indeed, as the lowest score on the scale was 0, and little variability was observed for neutral pictures, very small mean differences between conditions were significant. These results are shown in Figure 1.

At the end of the experiment, the Toronto Mindfulness Scale (TMS) (Lau et al., 2006) was administered to the participants to evaluate the level of mindfulness during the Mindful condition. Only scores on the Decentering factor of the scale were analyzed, since this dimension refers to a quality of detachment and distance from one's experiences and corresponds more closely to the emotional regulatory aspect of mindfulness (Curiosity, the other factor of the TMS, assesses a quality of openness and curiosity to one's experiences).

An independent samples *t*-test was conducted to examine between-group differences in scores on the Decentering component of the TMS. One participant in the group of beginner meditators was missing TMS questionnaire data, and his score was replaced with the corresponding group mean value. The *t*-test revealed no significant difference in decentering scores during the Mindful condition between experienced and beginner meditators (*t*(18) = .80, p = .434)."

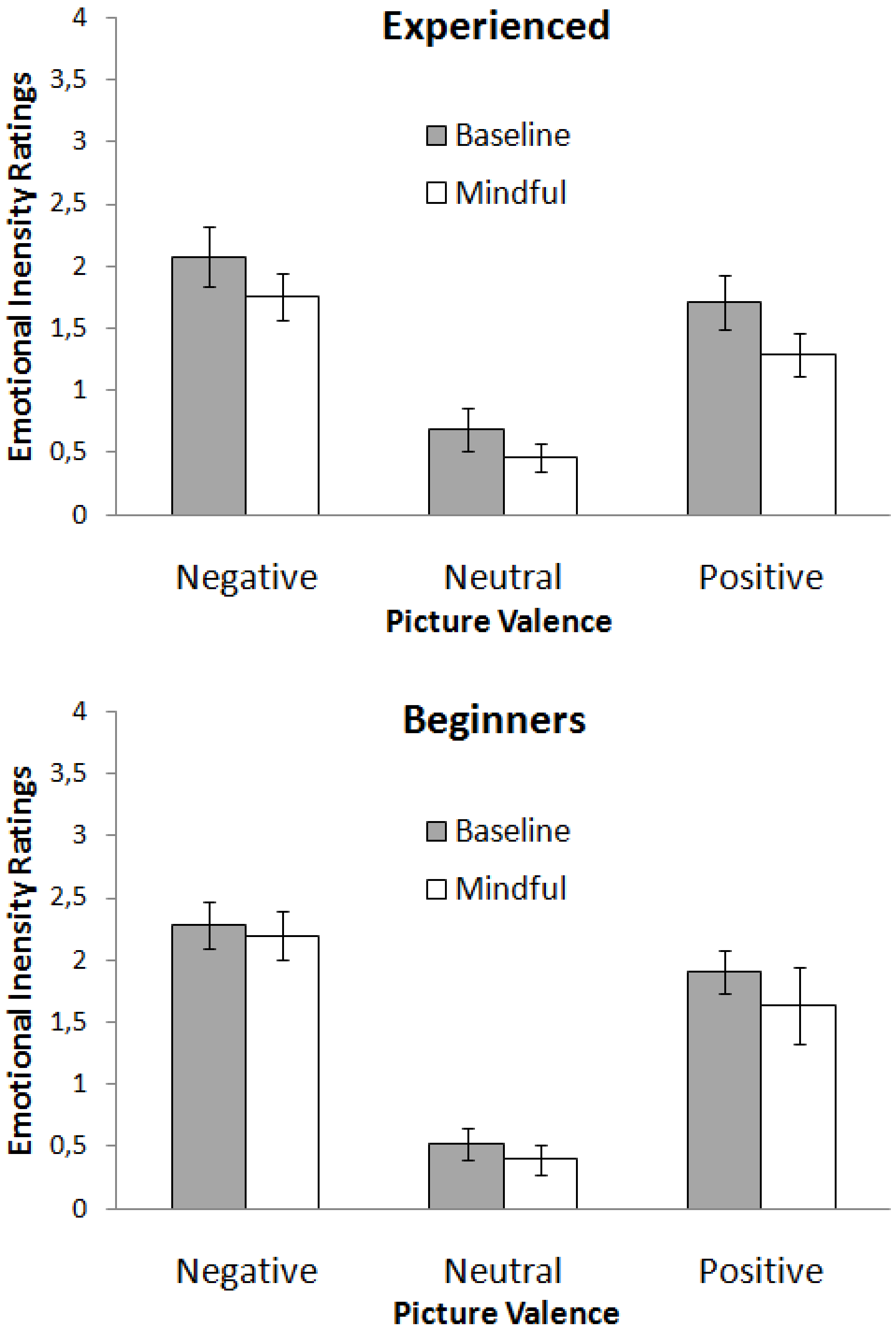

Figure1. Emotional intensity ratings (shown on the *y*-axis) by Group and Condition for each Valence category of pictures (*x*-axis). Emotional intensity was rated on a scale of 0 (no emotion experienced) to 4 (very intense emotion experienced). Mindfulness significantly reduced emotional intensity scores across Groups and Valence categories. No main effect of Group nor interactions were found. Means are shown with standard error bars.

fMRI Data

Emotional Processing at Baseline. When subtracting neutral from negative pictures in the Baseline condition, experienced meditators exhibited BOLD signal increases (two-sample *t*-test) in the LPFC (BA 9), MPFC (BA 9), OFC (BA 11 / 47), rostro-dorsal ACC (BA 32 / 24), anterior insula (BA 14), hippocampus, caudate nucleus, putamen, left amygdala and, though at a more liberal threshold ($p < .005$ uncorrected), right amygdala. Beginner meditators showed BOLD signal increases in the MPFC (BA 9), LPFC (BA 9), left rostro-dorsal ACC (BA 32), hippocampus, OFC (BA 47), anterior insula (BA 14), and, though at a more liberal threshold ($p < .007$), the amygdala. No between-group differences were observed for this contrast.

Additionally, when subtracting neutral from positive pictures in the Baseline condition, experienced meditators had BOLD signal increases (two-sample *t*-test) in the left LPFC (BA 9), MPFC (BA 9), left OFC (BA 47), hippocampus, left putamen, and left amygdala. Other loci of activation were found in the right rostro-dorsal ACC (BA 32), right caudate nucleus, and left anterior and posterior insula (BA 13 / 14). As for the beginner meditators, BOLD signal increases were noted in the rostro-dorsal ACC (BA 24 / 32), LPFC (BA 9), MPFC (BA 9), right anterior insula (BA 14), left anterior and posterior insula (BA 13 / 14), OFC (BA 47), PCC (BA 31), caudate nucleus, putamen, hippocampus, and amygdala. The only between-group difference for this contrast was a greater activation in the rostro-ventral ACC (BA 25) for beginner relative to experienced meditators.

Brain Activity Related to Mindfulness and Group

Condition x Valence x Group Interactions. Specific contrasts were computed with regard to the interactions for which we had a priori hypotheses, namely contrasts comparing between-group differences in Mindfulness vs. Baseline conditions. These were computed for negative emotional processing (by subtracting neutral from negative pictures), as well as for positive emotional processing (by subtracting neutral from positive pictures).

Negative Emotional Processing. During negative emotional processing, Mindfulness induced deactivations - for beginners relative to experienced meditators - in the left amygdala ($k = 16$, $t = 2.96$, $Z = 2.90$, $x = -27, y =-1, z = -18$, P(FWE) = .055, $d = 0.54$). No mindfulness-induced deactivations during negative emotional processing were observed when contrasting experienced vs. beginner meditators.

Mindfulness-induced activations and deactivations were also explored within each group, revealing mindfulness-induced deactivations (at a more liberal threshold of $p < 0.005$ uncorrected) in the left amygdala ($k = 22$, $t = 3.82$, $Z = 3.70$, $x = -27, y = -1, z = -18$, P (FWE) = .010, $d = 0.70$) and right amygdala ($k = 13$, $t = 3.52$, $Z = 3.43$, $x = 27, y = -1, z = -16$, P(FWE) = .012, $d = 0.65$) for beginners, but not for experienced meditators. For experienced meditators, mindfulness-induced deactivations during negative emotional processing were observed (at a more liberal threshold of $p < 0.005$) in the left LPFC (BA 9 / 46, $k = 33$, $t = 3.33$, $Z = 3.25$, $x = -36, y = 30, z = 15$, P(uncorr.) = .001, $d = 0.61$), though this was a sub-threshold trend. With respect to mindfulness-induced activations, no significant loci were observed within each group and between-groups

Positive Emotional Processing. During positive emotional processing, mindfulness induced deactivations (at a more liberal threashold of $p < 0.005$ uncorrected) in the left amygdala for beginners vs. experienced meditators (Table 1). No mindfulness-induced deactivations during positive emotional processing were noted when contrasting experienced vs. beginner meditators.

For beginners, but not for experienced meditators, mindfulness induced deactivations in the amygdala, right posterior insula (BA 13), putamen, left anterior insula (BA 13), caudate nucleus, left hippocampus, and right ACC (BA 24) (Table 1, Figure 2). No mindfulness-induced deactivations were observed for experienced meditators.

No mindfulness-induced activations between or within groups, were noted during positive emotional processing.

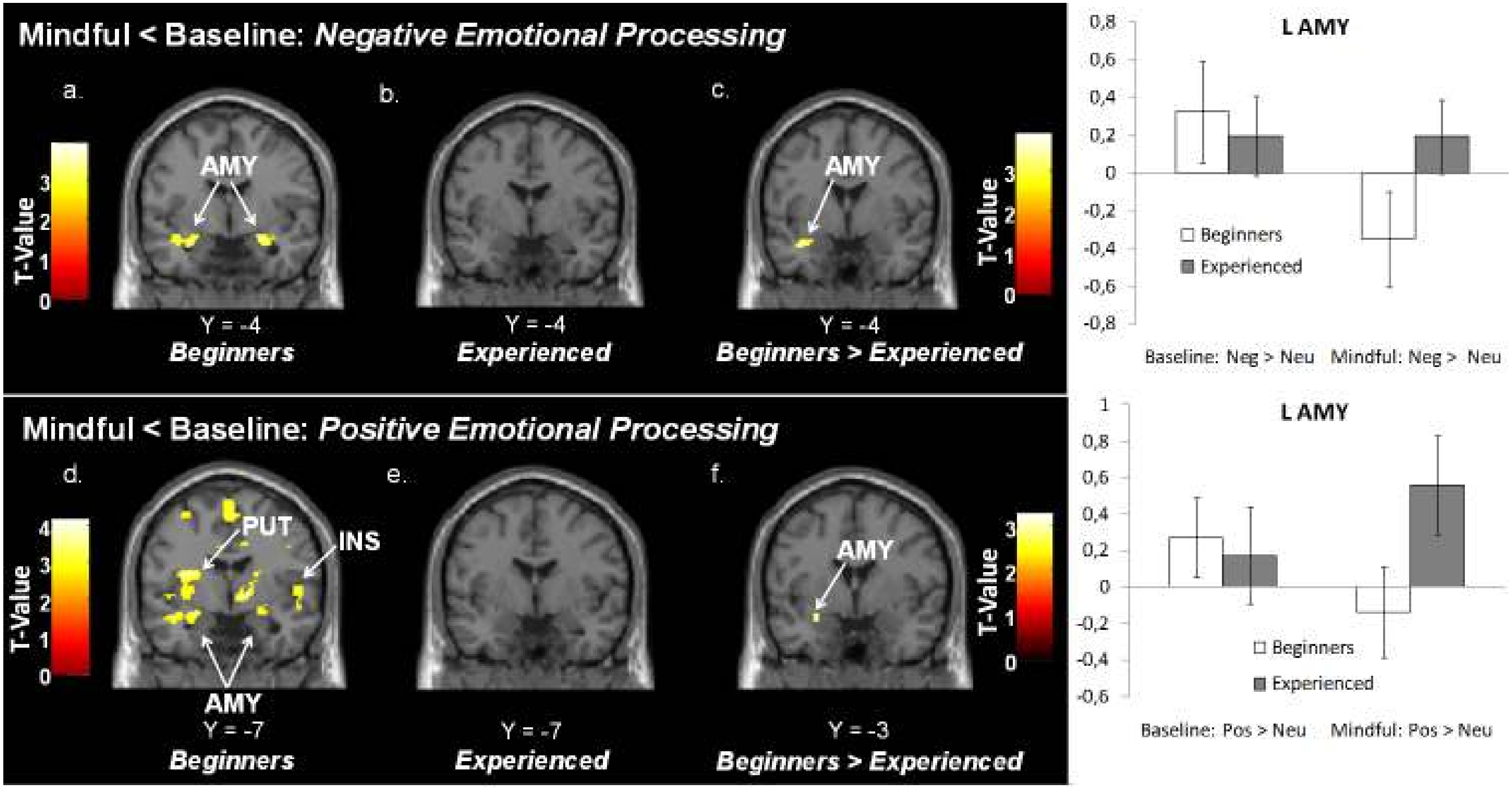

Figure 2. Statistical activation maps for the Mindfulness-Induced Deactivations. Mindfulness led to decreased activation in the left amygdala for beginners relative to experienced meditators (c) during negative emotional processing (by subtracting neutral from negative pictures) (f) and during positive emotional processing (by subtracting neutral from positive pictures). Activation maps for mindfulness-induced deactivations during negative and positive emotional processing are shown for each group separately (a-b and d-e). Contrast estimates (and 90% confidence interval) are shown for the indicated brain regions and peak voxels of activation. Activation maps are displayed on a single-subject T1-weighted template image included in the SPM8 software package. AMY,

Table 1

Mindfulness-Induced Deactivations: Positive vs. Neutral Pictures

Brain regions	**BA**	***#voxels***	***t*-value**	***Z*-value**	**Coordinates**			***p***	***d_c***
					x	**y**	**Z**		
Beginners									
R Posterior INS	13	579	4.26	4.02	29	-27	21	.004[a]	0.76
L Putamen		335	4.15	4.00	-20	3	-11	.035[a]	0.61
R Putamen/ AMY / Thalamus		395	4.08	3.94	18	6	-4	.020[a]	0.75
L Amygdala		31	4.07	3.93	-22	-1	-14	.009[b]	0.75
R Amygdala		5	3.43	3.34	24	-5	-11	.015[b]	0.63
L Putamen / Anterior INS	13	66	3.84	3.72	-29	-9	12	.023[b]	0.71
L Putamen / Caudate Nucleus		28	3.71	3.60	-13	6	5	.027[b]	0.70
R Caudate Nucleus		53	3.83	3.71	8	3	10	.017[b]	0.68
L Hippocampus		10	3.60	3.50	-33	-13	-15	.045[b]	0.66
R ACC	24	20	3.27	3.20	8	12	27	.046[b]	0.60
Experienced									
No mindfulness-induced deactivations were found for Experienced meditators									
Beginners > Experienced									
L AMY		14	3.03	2.97	-24	1	-14	.057[b]	0.56
Experienced > Beginners									
No mindfulness-induced deactivations were observed for Experienced vs. Beginner meditators									

Stereotaxic coordinates are derived from the human atlas of Talairach & Tournoux (1988) and refer to medial–lateral position (x) relative to midline (positive = right), anterior–posterior position (y) relative to the anterior commissure (positive=anterior), and superior–inferior position (z) relative to the commissural line (positive=superior). Designations of Brodmann areas for cortical areas are also based on this atlas. BA, Brodmann Area, AMY, amygdala; INS, insula; ACC, anterior cingulate cortex; L, left; R, right. [a]Corrected cluster-wise *p* value (FWE) at whole-brain level; [b]Corrected cluster-wise *p* value (FWE) within small volume correction. [c]Cohen's *D* measure of effect size.

Condition x Group Interaction

As mindfulness-induced activations or deactivations were not found for experienced meditators relative to beginners, between-group differences in other interactions were explored, such as the Condition x Group interaction. Thus, contrasts comparing between-group activations for the Mindful vs. Baseline conditions across all Valence categories were computed. Mindfulness-induced deactivations were found in the right MPFC (BA 10, $k = 51$, $t = 3.75$, $Z = 3.63$, $x = 11$, $y = 53$, $z = 11$, P (FWE) = .040, $d = 0.69$) and right PCC (BA 29, $k = 10$, $t = 3.34$, $Z = 3.26$, $x = 10$, $y = -48$, $z = 17$, P (FWE) = .023, $d = 0.61$) for experienced relative to beginners.

Mindfulness-induced activations and deactivations across Valence categories were also examined within each group separately. For experienced meditators, mindfulness induced a deactivation of the right MPFC (though this was a sub-threshold trend at a more liberal threshold of $p < .005$) (BA 10, $k = 36$, $t = 3.14$, $Z = 3.07$, $x = 13$, $y = 49$, $z = 9$, P(uncorr.) = .001, $d = 0.58$) in experienced, but not in beginner meditators. No mindfulness-induced activations were found for experienced meditators.

For beginners, but not experienced meditators, mindfulness induced increased activity in the right medial frontal gyrus (BA 8, $k = 486$, $t = 4.86$, $Z = 4.63$, $x = 29$, $y = 20$, $z = 40$, P(FWE) = .011, $d = 0.89$), the left medial frontal gyrus (BA 8, $k = 218$, $t = 3.98$, $Z = 3.85$, $x = -26$, $y = 22$, $z = 43$, P(FWE) = .007, $d = 0.85$), the right PCC (BA 31, $k = 84$, $t = 4.34$, $Z = 4.17$, $x = 11$, $y = -50$, $z = 22$, P(FWE) = .006, $d = 0.80$), the right inferior parietal lobule (IPL; BA 39, *k* = 460, *t* = 4.57, *Z* = 4.37, *x* = 38, *y* = -64, *z* =25, *P*(FWE corrected at whole-brain level) = .011, *d* = 0.84), and the left superior occipital gyrus (BA 19, *k* = 532, *t* = 4.27, *Z* = 4.11, *x* = -29, *y* = -69, *z* =26, *P*(FWE corrected at whole-brain level) = .006, *d* = 0.78). Mindfulness did not induce any deactivations in beginners across Valence categories (Figure 3).

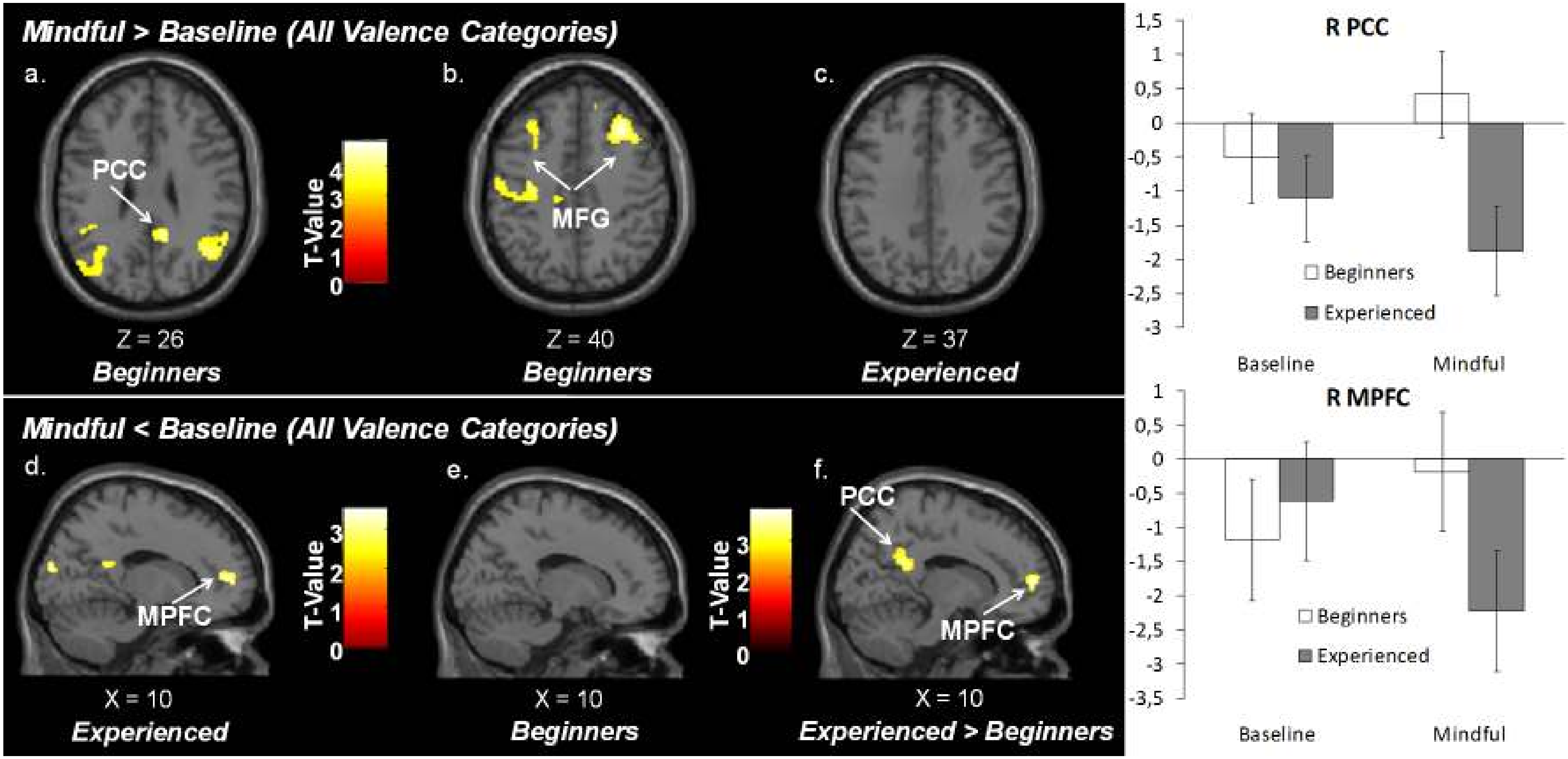

Figure 3. Statistical activation maps for the Mindfulness-Induced Deactivations. Mindfulness led to decreased activation in (f) the right medial prefrontal cortex and right posterior cingulate cortex for experienced meditators relative to beginners during the Mindful condition across all emotional categories. Activation maps for mindfulness-induced activations and deactivations are shown for each group separately (a-e). Contrast estimates (and 90% confidence interval) are shown for the indicated brain regions and peak voxels of activation. MPFC, Medial Prefrontal Cortex; PCC, Posterior Cingulate Cortex; MFG, Medial Frontal Gyrus.

Main effects

The main effects of interest and of relevance to this study, namely the main effect of Condition across Groups and Valence categories, as well as the main effect of Group across conditions and emotional categories, were also examined.

Condition. When collapsing across Groups and Valence categories, no mindfulness-induced deactivations were observed. However, mindfulness induced activations, at a threshold of $p < .005$ uncorrected, in the right MPFC / LPFC (BA 8, $k = 258$, $t = 3.83$, $z = 3.71$, $x = 31, y = 20, z = 38$, P (FWE) = .070, $d = 0.67$) and left MPFC / LPFC (BA8, $k = 231$, $t = 3.63$, $z = 3.53$, $x = -30, y = 18, z = 49$, P (FWE) = .055, $d = 0.70$). These activations seemed to be driven by the group of beginners, as they were situated in the same loci as those found within the group of beginners alone, and were not present in the group of experienced meditators alone.

Group. When examining group differences by collapsing across Conditions and Valence categories, beginners exhibited increased activity in the left lingual gyrus (BA 18/17), left fusiform gyrus (BA 37), left OFC (BA 47), right hippocampus, PCC (BA 29 / 31), and thalami (Table 2). Experienced meditators did not exhibit any increased activations relative to beginners for this contrast.

Table 2

Brain activations related to the Main Effect of Group

Brain regions	**BA**	**# *voxels***	***t*-value**	**Z-value**	**Coordinates**			***p***	***d*$_c$**
					x	**y**	**Z**		
Beginners > Experienced (across all Conditions and Valence Categories)									
L Lingual Gyrus	18/17	1172	6.75	6.20	-22	-79	-6	<.001[a]	1.24
L Fusiform Gyrus	37	322	5.47	5.16	-20	-40	-20	.040[a]	1.13
L OFC	47	13	3.97	3.84	-27	26	-8	.056[b]	1.01
L PCC	29	18	3.77	3.65	-12	-48	11	.016[b]	1.00
R PCC	31	6	3.51	3.41	12	-54	24	.017[b]	0.81
R Hippocampus		59	4.92	4.68	24	-31	-7	.016[b]	0.90
L Thalamus		59	3.50	3.41	-6	-23	4	.013[b]	0.64
R Thalamus		23	4.20	4.05	17	-30	4	.026[b]	0.77
R Thalamus		56	3.51	3.42	17	-23	11	.014[b]	0.62

Stereotaxic coordinates are based on the human atlas of Talairach and Tournoux (1988). These refer to th medial – lateral position (positive = right) relative to the midline (x), the anterior – posterior position (positive = anterior) relative to the anterior commissure (y), and the superior – inferior position (positive = superior) relative to the commissural line (z). For cortical areas, attributions of Brodmann areas are also derived from this atlas. BA, Brodmann Area; PCC, posterior cingulate cortex; OFC, orbital frontal cortex; L, left; R, right. [a]Corrected cluster-wise *p* value (FWE) within small volume corrections. [b]Corrected cluster-wise *p* value (FWE) at whole-brain level. [c]Cohen's *D* measure of effect size.

In sum, mindfulness induced deactivation of the amygdala during the processing of negative and positive emotional stimuli for beginners, but not for experienced meditators. Additionally, mindfulness induced opposite patterns of MPFC (BA 10) and PCC (BA 29) activity across all Valence categories in each group: for experienced meditators, mindfulness induced decreased activity in the MPFC and PCC, whereas for beginners, mindfulness induced increased activity in these regions.

Finally, for all activation loci reported, Cohen's *D* effect sizes (*d*) ranged from 0.54 – 1.24, which constitute medium to large effects according to established benchmarks (small: 0.20, medium: 0.50, large: 0.80; Cohen, 1992). Regression analyses with the number of hours of meditation practice on the contrasts reported above were also computed, but no significant activations for either group, nor between groups were found, perhaps due to the relatively small sample size and the heterogeneous range of meditation experience within the group of experienced meditators.

Discussion

The results of the present study can be summarized as follows. First, across the entire sample of participants, the pictures viewed in a mindful state were perceived as less emotionally intense than those viewed in a non-mindful state of awareness. Second, across all emotional categories, an opposite pattern of activity in the right MPFC and right PCC was observed. As such, mindfulness induced deactivations in these areas for experienced meditators relative to beginners. On the other hand, mindfulness induced increased activity in these regions for beginners relative to experienced meditators. Finally, during negative and positive emotional processing, mindfulness induced decreased activity in the left amygdala for beginners compared to experienced meditators.

Mindfulness and Subjective Emotional Intensity Elicited

The attenuating effects of mindfulness on subjective emotional intensity is consistent with the view that mindfulness promotes emotional stability and constitutes an efficient emotional self-regulation strategy (Arch et al., 2006; Broderick, 2005). Mindfulness may foster a more adaptive, relaxed, and objective manner of responding to emotional situations as opposed to habitual, automatic, and conditioned reaction patterns. Furthermore, our findings are in line with evidence that mindfulness is beneficial for individuals with anxiety-related clinical disorders and traits (Baer, 2003). As such, individuals with generalized anxiety disorder tend to respond to their experiences with greater emotional intensity relative to their control counterparts; they also tend to become overwhelmed by their emotions and understand them poorly (Mennin, Heimberg, Turk, and Fresco, 2005). Similarly, individuals high in neuroticism are more reactive (physiologically and subjectively) to emotional stimuli than individuals who are low on this trait (Norris, Larsen, and Cacioppo, 2007). It has been suggested that anxious people engage in maladaptive responses, such as avoidance, because the emotions they experience are too intense (Mennin et al., 2005). Thus, mindfulness may decrease the propensity to avoid processing emotions by attenuating emotional intensity, and constitute an adaptive alternative coping mechanism for populations with anxiety-related traits or psychopathology.

Nonetheless, the effect of mindfulness on subjective emotional intensity was observed across stimulus valence for both groups of participants. Surprisingly, the effect of mindfulness did not apply specifically to emotional pictures or to either group (no significant interactions were found between condition, valence, or group). This may indicate that mindfulness had a broader and more general effect on the processing of emotional and non-emotional stimuli. On the other hand, the fact that the attenuating effect of mindfulness applied to neutral pictures may have been due to the little variability observed for this category of pictures, and thus, very small mean differences may have attained significance. Moreover, the fact that group differences failed to reach statistical significance may imply that mindfulness constitutes an efficient emotional self-regulation strategy for both highly experienced meditators *and* individuals having practiced mindfulness meditation for a short period of time. Nevertheless, the ease at which the state of mindfulness is achieved, as well as the frequency at which it is called upon, is likely quite different for experienced meditators as opposed to beginners.

Since the ratings from two participants in the beginners' group were lost due to technical issues, an interaction between group and condition might have failed to attain statistical significance by virtue of reduced power. Consequently, these results should be interpreted with caution until being replicated in larger independent samples. However, although both experienced and beginner meditators showed effects of mindfulness on subjective emotional intensity, differences in brain response patterns suggest that the two groups were in fact processing the stimuli in distinct ways during the mindful condition.

Brain Patterns Associated with Mindfulness in Experienced and Beginner Meditators

In keeping with one of our hypotheses, mindfulness was associated, in experienced meditators, with decreased activation in the right MPFC (BA 10). This reduced activation in the right MPFC is consistent with findings from Baerensten and colleagues (2010), who reported deactivation of this cortical region during sustained meditation. The MPFC is densely connected to subcortical brain structures (amygdala, hypothalamus, peri-aqueductal gray) and is thought to play a critical role in the cognitive generation of emotion (Kober, Barrett, Joseph, Bliss-Moreau, Lindquist, and Wager, 2008). Thus, the fact that this region was less active in experienced relative to beginner meditators during the mindful state may reflect disengagement of attentional control over appraisal and thought-related processes. Such a process would be consistent with descriptions of mindfulness meditation as involving acceptance of sensations, emotions, and thoughts rather than attempting to control or change them (Bishop, 2004). The same interpretation, that is, reduced elaboration and appraisal, was recently put forth by Grant et al. (2011), who found a similar pattern of deactivation for meditators during pain perception, an inherently emotional experience. Finally, the MPFC deactivation noted here in experienced meditators during the mindful condition is also congruent with the results from Farb and colleagues (2007), who reported that mindfulness induced more pronounced deactivations in the MPFC for individuals having completed an 8-week MSBR training than in novices.

Regarding the mindfulness-induced deactivation in the PCC for experienced relative to beginner meditators, our results are consistent with evidence that this cortical area plays a role in emotional processing (Kober et al., 2008; Maddock, Garrett, and Buonocore, 2003). The PCC, together with the MPFC, is a core structure of the so-called default mode network (DMN) (Buckner et al., 2008). The DMN consists of a set of spatially remote regions with coherent temporal dynamics, and is thought to reflect internally generated thought processes in the absence of explicit goal-directed tasks (Buckner et al., 2008). Thus, the greater deactivation observed in these two DMN regions in experienced meditators (relative to beginners) is consistent with the findings from a previous study (Brefczynski-Lewis et al., 2007). In long-term practitioners of meditation, Brefczynski-Lewis and colleagues (2007) found that during a state of concentration meditation (compared to a baseline state of rest), there was a negative correlation between the number of hours of meditation experience and activation in

DMN regions (MPFC and PCC) in response to emotional and non-emotional sounds. Additionally, a recent brain imaging study found that depressed individuals failed to deactivate several DMN structures during the re-appraisal and passive viewing of negative emotional pictures (Sheline et al., 2009). This finding was interpreted as reflecting increased interference from internally generated thoughts and rumination processes. In line with this, mindfulness meditation has been shown to reduce the occurrence of ruminative thoughts in remitted depressed patients (Ramel, Goldin, Carmona, and McQuaid, 2004). Thus, the greater mindfulness-induced deactivation of the MPFC and PCC in experienced meditators measured in our study may reflect an adaptive process through which information in the environment is processed without any interference from internally-generated thoughts.

In contrast with what we found in experienced meditators during the mindful condition across Valence categories, mindfulness induced increased activity in a superior portion of the medial frontal gyrus (BA 8) in beginners, but not in experienced meditators, which was reflected in the main effect of condition collapsed across groups. This result is compatible with the greater recruitment of a similar prefrontal cortical region previously reported in unexperienced meditators (compared with long-term practitioners of meditation) during a state of concentration meditation while listening to emotional and non-emotional sounds (Brefczynski-Lewis et al., 2007). This finding may reflect an increased need for beginner meditators to sustain attention on the task, and an attempt to reduce interference from the emotional stimuli. In agreement with this interpretation, it is plausible that the decreased activation in DMN regions found here indicates that experienced meditators had diminished need for effortful concentration, and experienced less interference from the stimuli. Thus, given their extensive experience, mindfulness may have been generated in a more automatic way, decreasing the need for recruitment of higher-order prefrontal cortical areas. It is also plausible that the PFC deactivations measured in experienced meditators reflect a state of acceptance as an absence of regulation *per se*. Future studies specifically examining the cognitive processes underlying prefrontal deactivations during meditation are needed to corroborate these hypotheses.

Brain Patterns Associated with Mindfulness and Emotional Processing in Experienced and Beginner Meditators

We had hypothesized that mindfulness would lead to greater deactivations of the amygdala during emotional processing for experienced meditators. In contrast to this hypothesis, our results indicated amygdala deactivations for beginners – and not experienced meditators - during the processing of emotional information in the mindful condition. With respect to experienced meditators, they may have had some degree of amygdala reactivity to emotional stimuli in the mindful state, but mindfulness may have altered what happened *after* their initial response (cognitive elaboration, judgements, etc.). From this perspective, mindfulness may constitute an emotion regulatory strategy that targets cognitive processes related to the interpretation or evaluation of emotional responses. Thus, for individuals with brief training in meditation, mindfulness may decrease emotional intensity by targeting bottom-up appraisal systems and brain regions involved in emotional reactivity, such as the amygdala (Gross, 2007). However, with extensive training, mindfulness may preserve bottom-up system responses and attenuate subjective emotional intensity by targeting higher-order cortical systems, or top-down appraisal cerebral structures implicated in attributing emotional significance to stimuli (Gross, 2007).

Particularly, the amygdala is widely known for its detection of threatening information in the environment (Whalen, Rauch, Etcoff, McInerney, Lee, and Jenike, 1998; Gross, 2007). Stein and colleagues (2007) also found that measures of anxiety were positively related to predominantly left-sided amygdala activation during emotional (positive and negative) processing. Therefore, our observed mindfulness-induced deactivations of the left amygdala during emotional processing - in beginners relative to experienced meditators - may reflect adaptive consequences of mindfulness on the processing of emotional stimuli for individuals with brief experience in meditation.

Interestingly, the mindfulness-induced amygdala deactivation observed in beginners was not specific to negative pictures, but was also observed during positive emotional processing. In line with this finding, a number of brain imaging studies having found activation of the amygdala in healthy individuals in response to aversive stimuli (see, for instance, Ochsner et al., 2002; Ochsner et al., 2004), but also to positive emotional stimuli (Beauregard et al., 2001; Sergerie, Chochol, and Armony, 2008), indicating that the amygdala may not be specific to the detection of aversive information but to generally relevant motivational information. Additionally, during the processing of positive emotional stimuli, mindfulness induced deactivation in brain areas involved in addiction, awareness of interoceptive states of urges and pleasure, and reactivity to positive stimuli (amygdala, hippocampus, insula, basal ganglia; Craig, 2004; Everitt, Parkinson, Olmstead, Arroyo, Robledo, and Robbins, 1999; Haruno, Kuroda, Doya, Toyama, Kimura, Samejima, Imamizu, and Kawato, 2004; Naqvi and Bechara, 2010; Phillips and Ledoux, 1992; Prado-Alcala and Wise, 1984) in beginners, but not experienced meditators. This may reflect the fact that mindfulness is based on generating an endogenous state of well-being, thereby diminishing the necessity for external rewards to provide happiness (Wallace and Shapiro 2006).

Limitations and Future Directions

Some limitations of this study have to be acknowledged. First, there may have been differences between the two groups of participants other than meditation training (e.g., lifestyle, temperamental predispositions). However, our main objective was to study the effect of long-term meditation experience, and studying the effects of more than 1000 hours of meditation practice would have been unrealistic or very challenging using a longitudinal design. Nonetheless, future longitudinal studies explicitly examining the impact of mindfulness on emotional processing should be conducted in order to corroborate the findings from this study. Second, due to technical constraints, we were unable to acquire other measures of emotional reactivity, such as galvanic skin response. Ideally, future studies of the impact of mindfulness on emotional processes should include such objective measures.

Conclusions

These results indicate that extensive mindfulness practice can significantly reduce the activity of a number of brain regions implicated in the neural responses to emotional stimuli. Our results also demonstrate that for individuals with long-term practice of meditation, mindfulness leads to decreased activity in cortical areas involved in top-down appraisal and the default mode network. Another important finding of this study is that after only one week of mindfulness training, mindfulness led to a down-regulation of subcortical brain regions implicated in emotional reactivity in individuals with no prior experience with this form of meditation. This last finding suggests that the early beneficial effects of mindfulness practice on mood and anxiety disorders, as well as addiction-related disorders, may occur in part by decreasing activity in areas associated with low-level emotional processing. With more extensive experience, mindfulness may promote a state of mental calmness by deactivating higher order prefrontal and posterior cingulate cortical areas involved in the default mode network.

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Article 2

Title

Impact of Mindfulness Training on the Default Mode Network during a Restful State: A Functional Connectivity Study

Authors

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Author Contributions

V.T. wrote the manuscript and conducted all of the statistical analyses included in this article. V.D. coordinated and conducted all of the data collection for this research project, with the assistance of G.S. for the second half of participants. J.G. provided feedback on the experimental design, interpretations and rationale included in this manuscript. E.S and S. R.-V. largely contributed to the design of the experiment. J.C. contributed to the experimental design and participant recruitment. A.S.L. aided in part of the data collection. G.M. and H.B designed the statistical analysis tools used in this article, and provided feedback on the manuscript M.B. edited and revised the manuscript into its final form.

Impact of Mindfulness Training on the Default Mode Network during a Restful State: A Functional Connectivity Study

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Abstract

Mindfulness meditation has been shown to promote emotional stability. In addition, meditation is associated with reduced activity in the medial prefrontal cortex (MPFC), a central component of the default mode network (DMN). It remains unclear whether mindfulness practice influences functional connectivity between DMN regions and, if so, whether such impact persists beyond a state of meditation *per se*. In this context, the present study examined the effect of extensive mindfulness training on functional connectivity within the DMN during a restful state. Resting-state data (two functional 6-minute runs) were collected from 13 experienced meditators (with over 1000 hours of training) and 11 beginner meditators (with no prior experience, trained for 1 week before the study) using functional magnetic resonance imaging (fMRI). Pairwise correlations and partial correlations were computed between the time-course of DMN seed regions, and were compared between the two groups utilizing a Bayesian sampling scheme. Relative to beginners, experienced meditators had weaker functional connectivity between DMN regions involved in self-referential processing, emotional appraisal, and autobiographical emotional memory retrieval. In addition, experienced meditators exhibited increased connectivity between certain DMN regions (e.g., dorsomedial PFC and right inferior parietal lobule), compared to beginner meditators. These findings suggest that mindfulness training leads to considerable changes in functional connectivity between core regions in the DMN, which are perhaps related to the long-term beneficial effects of mindfulness on emotional stability.

Originating from Ancient Eastern traditions, meditation has become increasingly studied using brain mapping methods. Particularly, there is evidence that mindfulness meditation is beneficial for the treatment of psychological disorders involving emotional dysregulation, such as major depressive disorder (MDD) and anxiety disorders (Baer, 2003). Mindfulness promotes an objective manner of interpreting thoughts, events and emotions, without elaborating or ‘ruminating’ on their potential implications for the self (Bishop, 2004).

Mindfulness has been shown to diminish activity in the medial prefrontal cortex (MPFC; Farb et al., 2007), a cortical area playing a pivotal role in self-referential processing and the ‘default mode network’ (DMN) (Gusnard, Akbudak, Shulman, and Raichle, 2001). Indeed, Farb and colleagues (2007) showed that an experiential focus condition, involving the mindful monitoring of present-moment circumstances, was associated with decreased MPFC function (dorso-medial PFC [DMPFC], ventro-medial PFC [VMPFC]), compared with a narrative focus condition (i.e. monitoring self-descriptive traits). These researchers also found that the MPFC deactivations associated with experiential focus were more pronounced in participants having received an 8-week mindfulness-based stress-reduction (MBSR) program, relative to a control group.

There is also evidence supporting the view that mindfulness training leads to MPFC deactivations during the processing of aversive stimuli, such as painful stimulations (Grant et al., 2011) and negative emotional pictures (Taylor, Grant, Daneault, Breton, Roffe-Vidal, Scavone, Courtemanche, Beauregard, submitted). Moreover, individuals with MDD fail to deactivate the MPFC (and other cerebral structures in the DMN) while passively looking at negative pictures or trying to reappraise them (Sheline et al., 2009). These findings may reflect a failure to down-regulate DMN regions involved in self-referential processing, rumination, and the monitoring of internal emotional states.

Other core regions in the DMN - which are consistently deactivated during goal-directed tasks and activated during a restful state - include the inferior parietal lobule (IPL), the precuneus (PC), the posterior cingulate cortex (PCC), as well as the inferolateral temporal cortex (ITC) (Gusnard et al., 2001; Greicius, Krasnow, Reiss, and Menon, 2003; Buckner et al., 2008; Raichle, MacLeod, Snyder, Powers, Gusnard, and Shulman, 2001). Together, regions of the DMN are thought to operate as a coherent network, as they exhibit synchronized low-frequency blood-oxygen-level-dependent (BOLD) signal fluctuations during 'resting states', i.e. when participants are scanned for several minutes and are instructed to rest without engaging in any specific mental activity or task (Fransson and Marrelec, 2008; Biswal, Yetkin, Haughton, and Hyde, 1995; Damoiseaux, Rombouts, Barkhof, Scheltens, Stam, Smith, and Beckmann, 2006; De Luca, Beckmann, De Stefano, Matthews, and Smith, 2006; Beckmann and Smith 2004). DMN activity has been proposed to be associated with cognitive processes such as envisioning future scenarios, theory of mind, autobiographical memory, moral decision making, and self-referential processing (Buckner et al, 2008; Gusnard et al., 2001; Northoff, Heinzel, de Greck, Bermpohl, Dobrowolny, and Panksepp, 2006). It therefore appears that this network may underlie adaptive planning and reflection mechanisms when not engaged in any external activity (Buckner et al., 2008).

It currently remains unknown whether mindfulness training influences functional connectivity within DMN regions during a state of rest. Examining the relationship between mindfulness training and functional connectivity within the DMN during rest is important to determine whether the effects of such training extend beyond a meditative state. In this context, the aim of this functional magnetic resonance imaging (fMRI) study was to investigate the impact of extensive mindfulness training on functional connectivity between regions of the DMN during a restful state. Spatial independent component analysis was used at the group level to identify DMN seed regions, and pair-wise correlations and partial correlations were computed between DMN regions. The various correlations between all pairs of nodes were then compared between individuals highly experienced in meditation (with over 1000 hours of experience in mindfulness-based meditation) relative to beginner meditators (with no prior exposure to mindfulness meditation, trained for one week before the completion of the study). Predicated on evidence that mindfulness is associated with deactivation of MPFC during self-referential processing (Farb et al., 2007), it was hypothesized that functional connectivity between medial prefrontal cortical areas and other DMN regions would be weaker in experienced relative to beginner meditators.

Materials and Methods

Participants

The sample consisted of two groups. The first group was composed of 13 (6 males) experienced meditators (age: *M* = 46 years, *SD* = 11) with over 1000 hours of meditation experience (*M* = 6519, *SD* = 14 445). They were recruited from Zen meditation centres in the Montreal metropolitan area.

One participant deviated from the group in terms of the number of hours of meditation (45 000 hours of practice), and hence constituted an outlier from the rest of the group. Without the inclusion of this participant, the group of experienced meditators had on average 1709 hours of meditation practice (*SD* = 694). Consequently, the analyses reported in the present study were also conducted with the exclusion of this participant. Since the results remained essentially unchanged, this participant was kept in the analyses to avoid losing any statistical power by decreasing the sample size.

The second group was composed of 11 beginner meditators (7 males), with an average of 37 years of age (*SD* = 13) recruited with the use of advertisement posters placed at the Université de Montréal and the Centre de Recherche de l'Institut Gériatrique de Montréal (CRIUGM). These individuals had no prior exposure to meditation (or other practices such as yoga) and were trained for one week before the completion of the study. Implemented by the experimenters, the mindfulness training was documented from several sources (Kabat-Zinn, 1994; Ricard, 2008; Thich Nhat Hanh, 1994) and consisted of a guided meditation session recorded on a compact disc (a written record was also provided). Participants were instructed to meditate for 20 minutes each day for seven days. The experimenters followed-up throughout the training week to ensure that participants completed their practice, and they all confirmed to have understood and successfully completed their training (except for one participant who had two days of training due to scheduling constraints, but confirmed having practiced the compensating number of hours). There were no significant differences in the male-to-female ratio or age between the group of experienced meditators and the group of beginners.

Before being selected to participate in the study, all participants underwent telephone screening, and were excluded if they had a current or past mental health illness, took any psychotropic drugs, were suffering from major physical health problems, or were not eligible to undergo an MRI exam (pregnancy, metal parts in body, pacemaker, etc.). After the completion of the study, participants were compensated 50$ for their time. This research project was approved by the Ethics Research Committee of the CRIUGM.

fMRI Data Acquisition

T2*-weighted functional images were acquired using a two-dimensional echo-planar imaging pulse sequence (TR = 2500 ms, TE = 40 ms, voxel size = 3 x 3 x 3.5 mm, 35 contiguous axial slices, matrix size = 64 x 64, flip angle = 90^{o}). A high-resolution T1-weighted anatomical scan was also acquired for each subject (three-dimensional, spoiled gradient echo sequence, TR = 19 ms, TE = 4.92 ms, flip angle =

25^{o}, matrix size = 256 x 256 voxels voxel size = 1 x 1 x 1 mm, 176 contiguous axial slices).

Experimental Protocol

Participants first gave informed consent and underwent screening and questionnaires related to MRI safety and eligibility. Then, each participant completed two functional 6-minute runs (144 volumes) in a state of rest (except for two participants from each group who completed only one run, due to time or testing constraints). Throughout these runs, participants observed a cross fixated centrally on the screen inside the scanner, and were instructed to rest, without engaging in any specific task or mental activity. In between these two sessions, participants also completed sessions consisting of different experimental paradigms; these data are not reported here. At the end of the experiment, participants were compensated for their time.

Data Analysis

The fMRI data were pre-processed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). For each subject, functional images were slice-time corrected, realigned, and spatially smoothed using a Gaussian kernel (8 mm at full-width at half-maximum). Next, functional connectivity analyses were conducted using the NetBrainWork software (Laboratoire d’Imagerie Fonctionnelle, Paris, France). To identify functional network maps across participants, the NEDICA (for Network Detection using Independent Component Analysis; Perlbarg, Marrelec, Doyon, Pélégrini-Issac, Lehéricy, and Benali, 2008) approach was employed. First, as previously validated (Esposito, Scarabino, Hyvarinen, Himberg, Formisano, Comani, Tedeschi, Goebel, Seifritz, and Di Salle, 2005) the data for each run were reduced to 40 temporal dimensions using principal component analysis (PCA). Next, 40 spatially independent components were extracted from each run using the infomax algorithm (Bell and Sejnowski, 1995). Independent component (IC) maps were then converted into *Z*-maps and normalised into MNI standard stereotaxic space.

After the ICs were extracted at the individual level, ICs with similar spatial distributions were indentified across participants, and between-subject ICs were aggregated into clusters or 'classes' based on their spatial similarity. Using a hierarchical grouping algorithm (Esposito et al., 2005), a class was identified as a set of ICs from different subjects minimally distant from each other (the distance was calculated with a formula based on the spatial correlation between ICs; Perlbarg et al., 2008) beyond a certain threshold. In a step-wise manner, ICs from other subjects were included into a given class by gradually lowering the distance threshold at each step. The number of classes was calculated automatically by NetBrainWork, as a way to determine those which were most representative of the population. In order to best generalize to the population, each class should ideally have been composed of only one IC from each run (Perlbarg et al., 2008). Thus, for each class, NetBrainWork calculated the degree of representativity (DR; number of runs contributing to the class divided by the total number of runs) and the degree of Unicity (DU; number of runs contributing to class with only one IC, divided by the total number of runs). As these scores should ideally be equal to 1, only classes with DR > 0.5 and DU > 0.75 were retained (Perlbarg et al., 2008).

Then, fixed effect analyses were conducted to compute *t*-maps for each class: at each voxel, the mean value of each IC contributing to the class was divided by the variance of each IC contributing to the class. The resulting *t*-maps were thresholded at $P < 0.05$ corrected at the False Discovery Rate. Finally, a bootstrap procedure was conducted to assess the confidence interval of each class retained. To do this, NEDICA was reapplied on half of the runs (randomly selected), yielding new group maps. The spatial correlation between each initial group map and new group map was calculated. The initial map with the highest correlation coefficient with its new bootstrap map was retained (except if the correlation value was below 0.30). As a result of this bootstrap procedure, which was repeated 100 times, a number of *t*-maps for the classes of interest were retained. The remaining classes represented functionally coherent brain networks across the entire sample.

Next, each network map was manually inspected. Based on previous reports (Buckner et al., 2008; Perlbarg et al., 2008), the map which best corresponded to the DMN was selected for the functional connectivity analyses. Regions of interest (ROI) were selected based on the peak voxels identified in the DMN *t*-map. Each region selected was composed of 10 voxels, delimited by a region-growing algorithm (Bellec, Perlbarg, Jbabdi, Pelegrini-Issac, Anton, Doyon, and Benali, 2006) from the given peak, and was located at least 30 mm apart from another ROI. Similarly to previous studies

(Fransson et al, 2008; Marrelec, Krainik, Duffau, Pelegrini-Issac, Lehericy, Doyon, and Benali, 2006), the network comprised nine nodes: the PC / PCC, the VMPFC, the DMPFC, the left and right IPL, the left and right ITC, and the left and right parahippocampal gyrus (PHG). Regions of the DMN selected for the analyses are shown in Figure 1, and the coordinates are shown in Table 1.

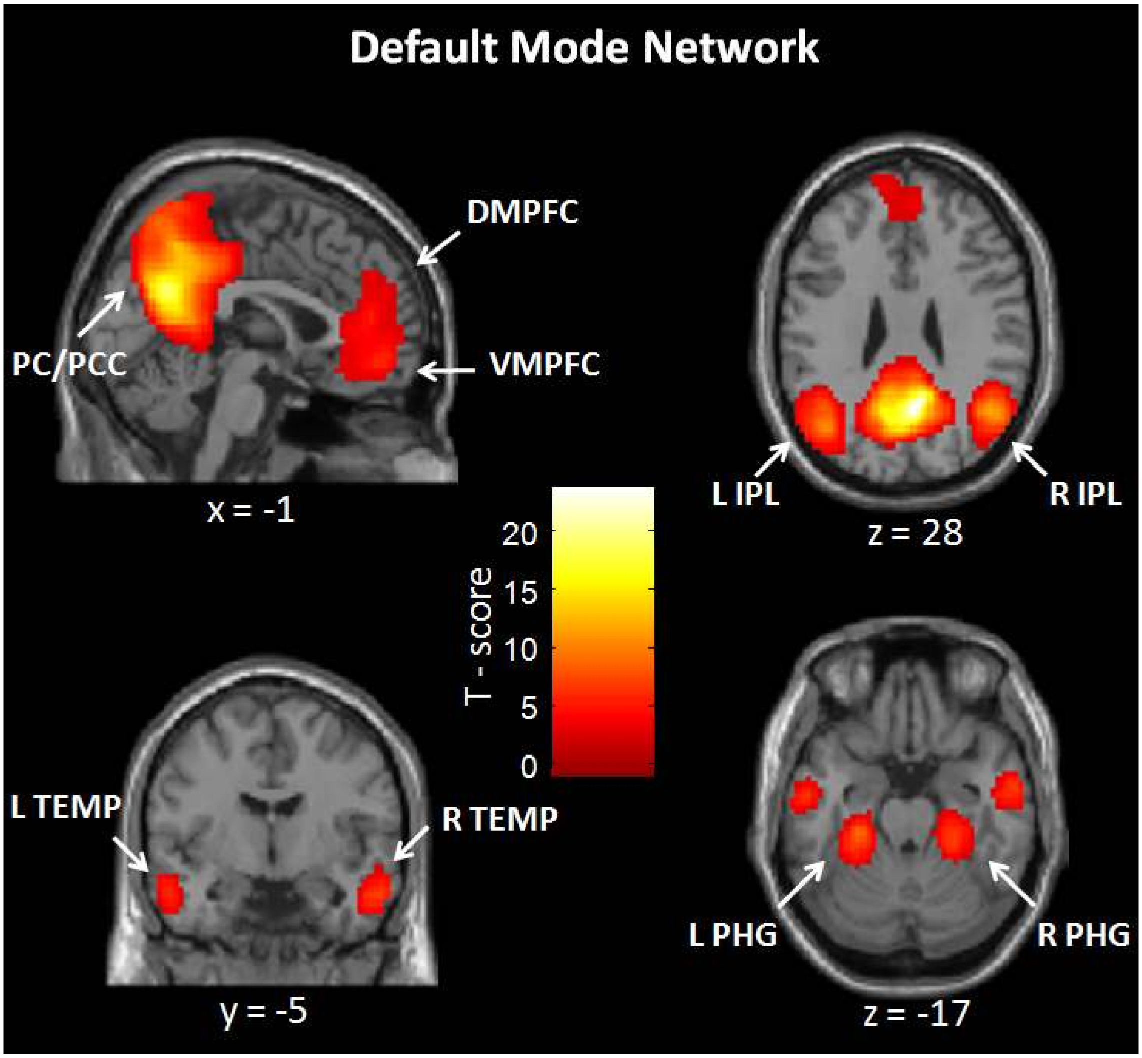

Figure 1. Default mode network *t*-map identified at the group level using NEDICA across all participants. Peaks revealed in the *t*-map were chosen as seed regions for the functional connectivity analyses, to compare connectivity between regions of the network for experienced relative to beginner meditators. Abbreviations: Precuneus (PC), Posterior Cingulate Cortex (PCC), Dorso-Medial Prefrontal Cortex (DMPFC), Ventro-Medial Prefrontal Cortex (VMPFC), Inferior Parietal Lobule (IPL), Inferolateral Temporal Cortex (ITC), Parahippocampal gyrus (PHG); R: Right; L; Left.

Table 1 *Coordinates for Seed Regions within the Default Mode Network*

Region	BA	x	y	z
PC / PCC	**31**	8	-53	27
DMPFC	**10**	-10	57	19
VMPFC	**10**	-2	47	-10
R IPL	**39**	48	-56	27
L IPL	**39**	-40	-67	34
R ITC	**21**	56	-4	-22
L ITC	**21**	-56	-10	-17
R PHG	**36**	26	-32	-15
L PHG	**36**	-26	-29	-18

Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988), referring to the medial–lateral position (x) relative to the midline (positive = right), and anterior–posterior position (z) relative to the commissural line (positive=superior). Designations of Brodmann position (y) relative to the anterior commissure (positive=anterior), and superior–inferior areas for cortical areas are also based on this atlas.

Abbreviations: BA (Brodmann Area), Posterior Cingulate Cortex (PCC), Precuneus (PC), Dorso-Medial Prefrontal Cortex (DMPFC), Ventro-Medial Prefrontal Cortex (VMPFC), Inferior Parietal Lobule (IPL), Inferolateral Temporal Cortex (ITC), Parahippocampal gyrus (PHG); R: Right; L; Left.

Group maps identified using NEDICA were also computed within each group, and the peak locations of all seed regions were very similarly located. As participants were all healthy individuals and did not significantly differ with respect to age, it seemed more appropriate to identify DMN regions based on the group map computed across the entire sample (for both experienced and beginner meditators). This approach was also considered best suited for the present study given that our main interest was to examine functional connectivity between seed regions of the DMN.

After DMN seed regions were identified, Corrrection of Structured noise using spatial Independent Component Analysis (CORSICA; Perlbarg, Bellec, Anton, Pelegrini-Issac, Doyon, and Benali, 2007) was applied to remove components related to physiological noise. Then, pairwise correlations between the time-course of each seed regions were calculated within the group of experienced meditators, and within the group of beginner meditators, using the correlation coefficient *cc* (Biswal et al., 1995). Significant correlations between groups were evaluated based on a Bayesian sampling scheme (Marrelec, Krainik, Duffau, Pelegrini-Issac, Lehericy, Doyon, and Benali, 2006; Marrelec, Bellec, Krainik, Duffau, Pelegrini-Issac, Lehericy, Benali, and Doyon, 2008) thereby reducing the risk of Type I errors by accounting for multiple comparisons with a significance level set at $P < 0.05$. In addition, the total correlation (average of all pairwise correlations) within each network was calculated and compared across groups.

Finally, in the same manner, partial correlations were also computed, using the partial coefficient denoted by Π, as previously described (Marrelec et al., 2006). Partial correlations have the advantage of reflecting the unique covariation between two regions after accounting for variance explained by any other seed region. In this sense, the relationship between two regions cannot be explained by the contribution of a third seed region.

Finally, in order to maximise statistical power, it was optimal to acquire two resting state runs per participant. Nonetheless, to avoid inducing fatigue or boredom effects before the beginning of the experimental paradigm, these runs were acquired at the very beginning and at the end of the experimental paradigm. However, given that the default mode network is consistently detected across sessions and time for older and young populations (Beason-Held, Kraut, and Resnick, 2009; Meindl, Teipel, Elmouden, Mueller, Koch, Dietrich, Coates, Reiser, and Glaser, 2010), as well as within different experimental paradigms regardless of the type of task or modality in which these were conducted (Buckner et al., 2008), acquiring resting state runs before and after the experimental paradigm was chosen in order to provide a more representative pattern DMN connectivity across time. To exclude the possibility of potential session effects, the partial correlation analyses reported below were conducted within each group comparing the two sessions: no differences in between-region partial correlations were observed within the group of experienced meditators, and only one partial correlation difference (between the VMPFC and L PHG) was observed within the group of beginners. In addition, all of the between-group partial correlations (except for the one between the VMPFC and R ITC) reported by conducting the analyses across both sessions were also observed when only examining differences across the first session alone. Thus, given the stability and reproducibility of the DMN across tasks, experiments, and participants (Beason-Held et al., 2009; Meindl et al., 2010; Buckner et al., 2008), as well as the absence of major session effects observed in the present study, the analyses reported below were conducted across both sessions to obtain a reliable and representative DMN connectivity pattern for each group across time as well as to maximise statistical power.

Results

Group Differences in Correlations between DMN Regions

The results of the analyses revealed that correlations between nodes of the DMN were significantly decreased ($P < 0.05$) for experienced meditators, relative to beginners, between the DMPFC (BA 10) and the following regions: left IPL (BA 39; *cc* = 0.29, SD = 0.03 for experienced; *cc* = 0.41, *SD* = 0.03 for beginners), right ITC (BA 21; *cc* = 0.18, SD = 0.03 for experienced; *cc* = 0.26, *SD* = 0.03 for beginners), and left PHG (BA 36; *cc* = -0.01, *SD* = 0.04 for experienced, *cc* = 0.07, SD = 0.04, for beginners). Weaker correlations were also found, for experienced compared to beginner meditators, between the VMPFC (BA 10) and the following regions: DMPFC (BA 10; *cc* = 0.40, SD = 0.03 for experienced, *cc* = 0.53, *SD* = 0.03, for beginners), right ITC (BA 21; *cc* = 0.27, SD = 0.03 for experienced, *cc* = 0.39, *SD* = 0.03, for beginners), and left PHG (BA 36; *cc* = 0.01, *SD* = 0.04 for experienced, *cc* = 0.11, *SD* = 0..04, for beginners). Finally, other weaker correlations for experienced vs. beginners were measured between the left IPL and the following regions: PC / PCC (BA 39; *cc* = 0.47, *SD* = 0.03 for experienced; *cc* = 0.54, *SD* = 0.03 for beginners), right PHG (BA 36 ; *cc* = 0.13, *SD* = 0.04 for experienced, *cc* = 0.24, *SD* = 0.04, for beginners), left ITC (BA 21; *cc* = 0.17, *SD* = 0.04 for experienced, *cc* = 0.24, *SD* = 0.04, for beginners), and left PHG (BA 36; *cc* = 0.16, *SD* = 0.04 for experienced, *cc* = 0.24, *SD* = 0.04, for beginners).

The analyses also revealed stronger correlations for experienced meditators, relative to beginners, between the right IPL and the following regions: PC / PCC (BA 31; *cc* =

0.65, *SD* = 0.02 for experienced, *cc* = 0.53, *SD* = 0.3, for beginners), DMPFC (BA 10; *cc* = 0.34, *SD* = 0.03 for experienced, *cc* = 0.25, *SD* = 0.03, for beginners), and left IPL (BA 39; *cc* = 0.53, *SD* = 0.03 for experienced, *cc* = 0.44, *SD* = 0.03, for beginners) (Figures 2 and 3).

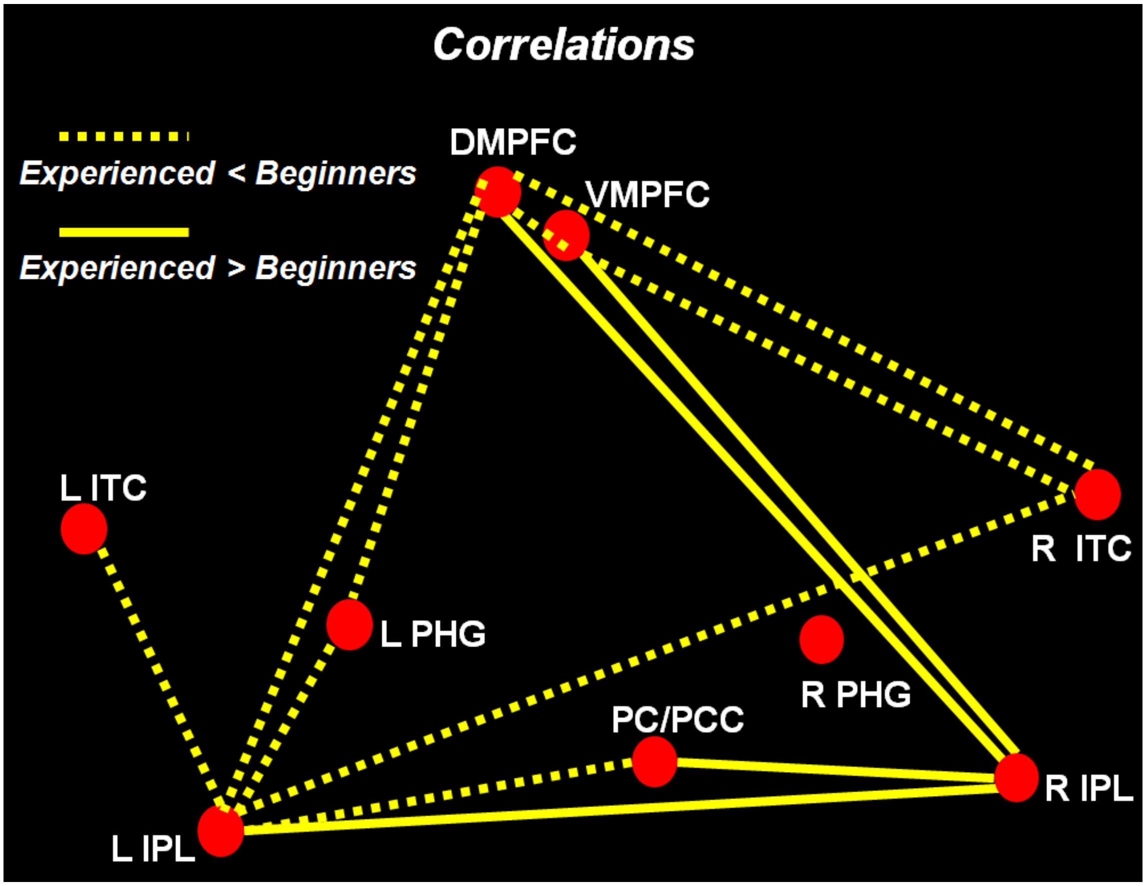

Figure 2. Diagram illustrating significant group differences ($P < .05$) in correlations (*cc*) between regions of the default mode network. Dotted lines represent significantly weaker correlations for experienced relative to beginner meditators, whereas full lines represent significantly stronger correlations for experienced meditators compared to beginners. Abbreviations: Precuneus (PC), Posterior Cingulate Cortex (PCC), Dorso-Medial Prefrontal Cortex (DMPFC), Ventro-Medial Prefrontal Cortex (VMPFC), Inferior Parietal Lobule (IPL), Inferolateral Temporal Cortex (ITC), Parahippocampal gyrus (PHG); R: Right; L; Left.

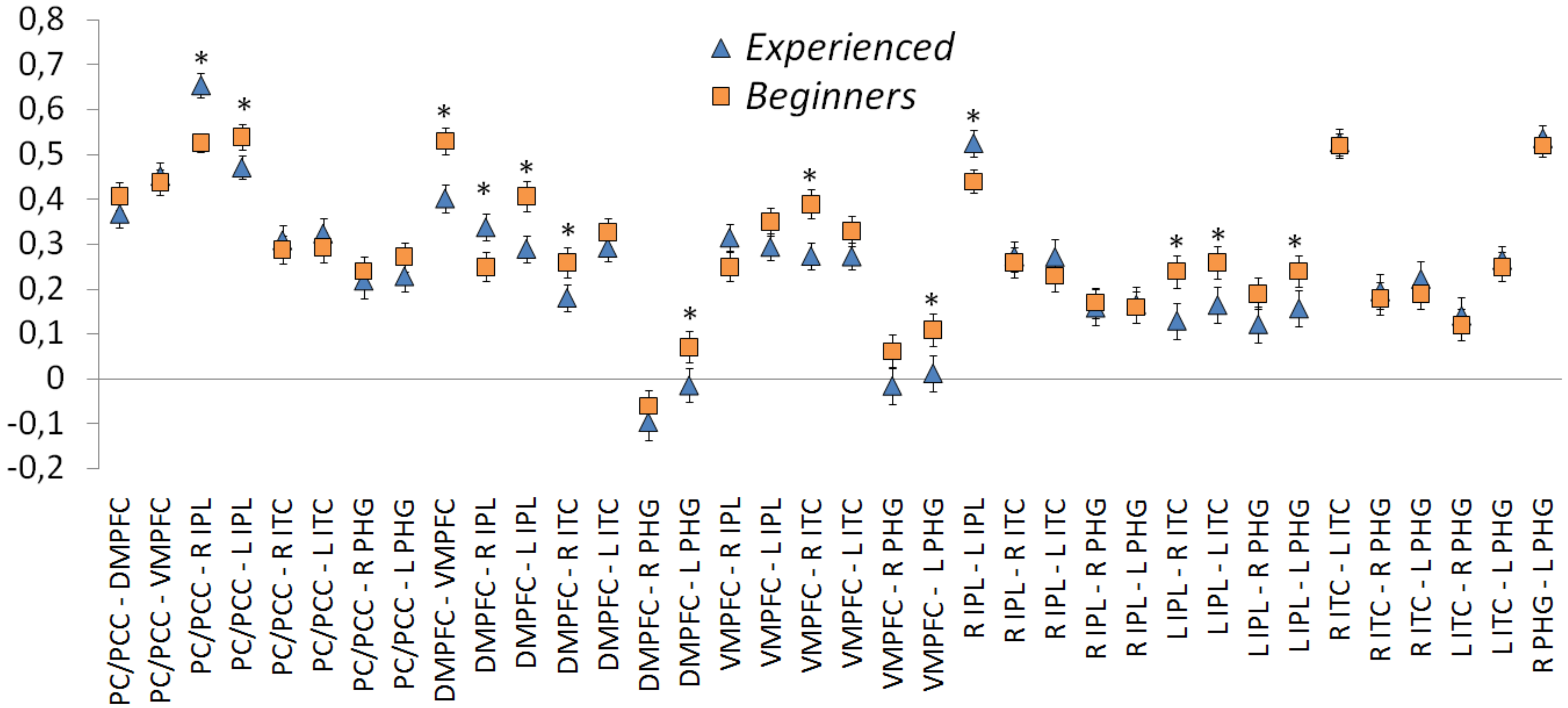

Figure 3. Correlation values (*cc*; y-axis) for all pairwise relationships between default network regions (x-axis). Error Bars represent SD values. Blue triangles represent values for experienced meditators, and orange squares represent values for beginner meditators. Abbreviations: Precuneus (PC), Posterior Cingulate Cortex (PCC), Dorso-Medial Prefrontal Cortex (DMPFC), Ventro-Medial Prefrontal Cortex (VMPFC), Inferior Parietal Lobule (IPL), Inferolateral Temporal Cortex (ITC), Parahippocampal gyrus (PHG); R: Right; L; Left.

*Significant group differences ($P < 0.05$).

Group Differences in Partial Correlations Between DMN Regions

The weaker relationships between DMN regions observed in experienced vs. beginners meditators which remained significant ($P < 0.05$) using the partial correlations measure were found for the following pairs of regions: PC / PCC (BA 31) and left IPL (BA 39, $\Pi = 0.14$, $SD = 0.04$ for experienced, $\Pi = 0.27$, $SD = 0.03$, for beginners), DMPFC (BA 10) and left IPL (BA 39, $\Pi = 0.09$, $SD = 0.04$ for experienced, $\Pi = 0.21$, $SD = 0.04$, for beginners), DMPFC (BA 10) and VMPFC (BA 10, $\Pi = 0.28$, $SD = 0.03$ for experienced, $\Pi = 0.36$, $SD = 0.03$, for beginners), as well as VMPFC (BA 10) and right ITC (BA 21, $\Pi = 0.13$, $SD = 0.04$ for experienced, $\Pi = 0.22$, $SD = 0.04$, for beginners).

In addition, all of the *stronger* correlations for experienced meditators relative to beginners, which involved the right IPL (BA 39), remained significant using the partial correlation measure ($P < 0.05$). The following partial correlation coefficients between the right IPL (BA 39) and these regions were found: PC / PCC (BA 31, $\Pi = 0.47$, $SD = 0.03$ for experienced, $\Pi = 0.35$, $SD = 0.03$, for beginners), DMPFC (BA 10, $\Pi = 0.09$, $SD = 0.04$ for experienced, $\Pi = -0.001$, $SD = 0.04$, for beginners), and PC / PCC (BA 31, $\Pi = 0.32$, $SD = 0.03$ for experienced, $\Pi = 0.20$, $SD = 0.04$, for beginners) (Figures 4 and 5).

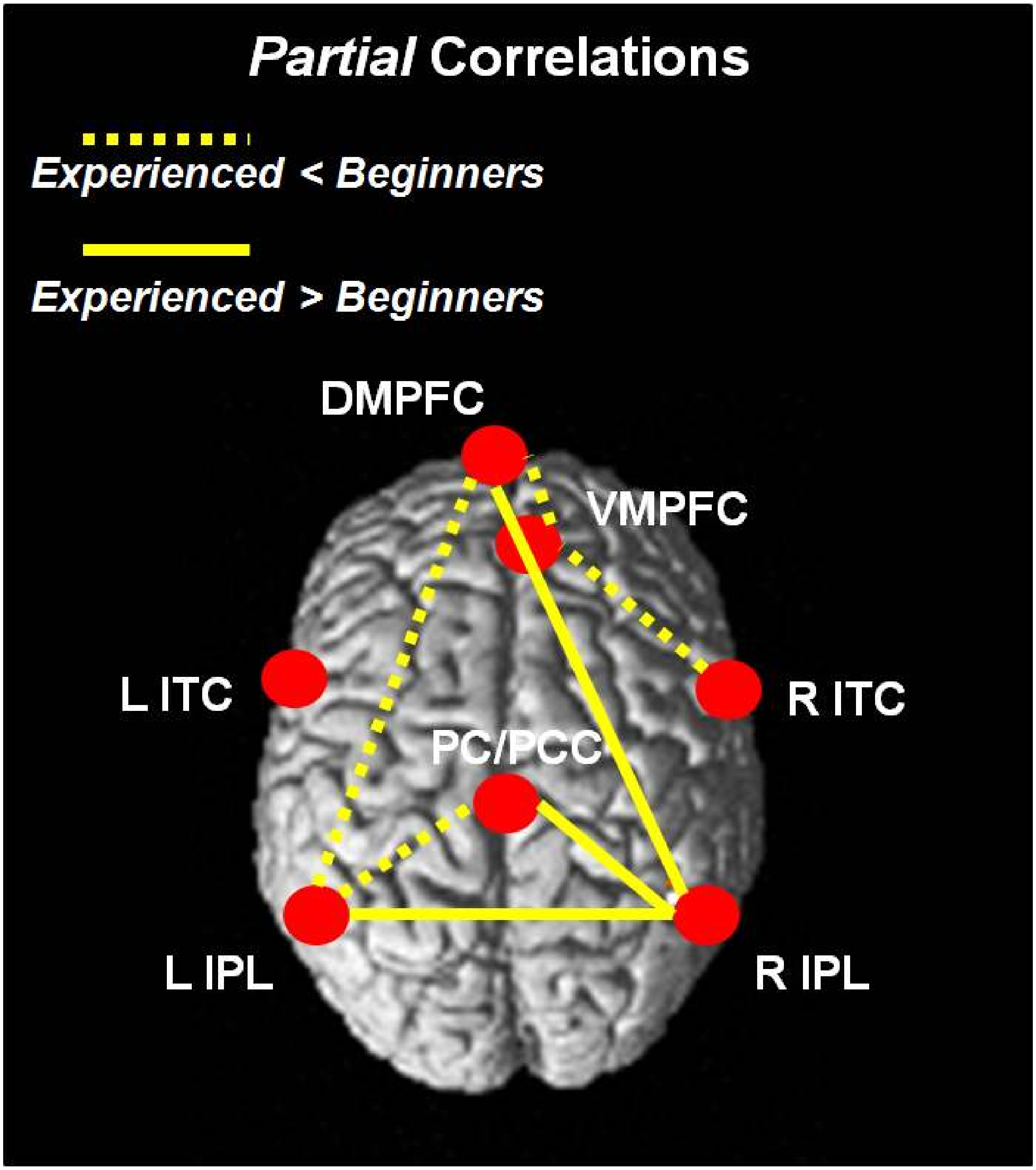

Figure 4. Diagram illustrating significant (*P* < .05) group differences in partial correlations (Π) between default mode network regions. Dotted lines represent significantly weaker partial correlation coefficients for experienced compared to beginner meditators, and full lines represent significantly stronger partial correlation values for experienced meditators relative to beginners.
Abbreviations: Precuneus (PC), Posterior Cingulate Cortex (PCC), Dorso-Medial Prefrontal Cortex (DMPFC), Ventro-Medial Prefrontal Cortex (VMPFC), Inferior Parietal Lobule (IPL), Inferolateral Temporal Cortex (ITC), Parahippocampal gyrus (PHG); R: Right; L: Left.

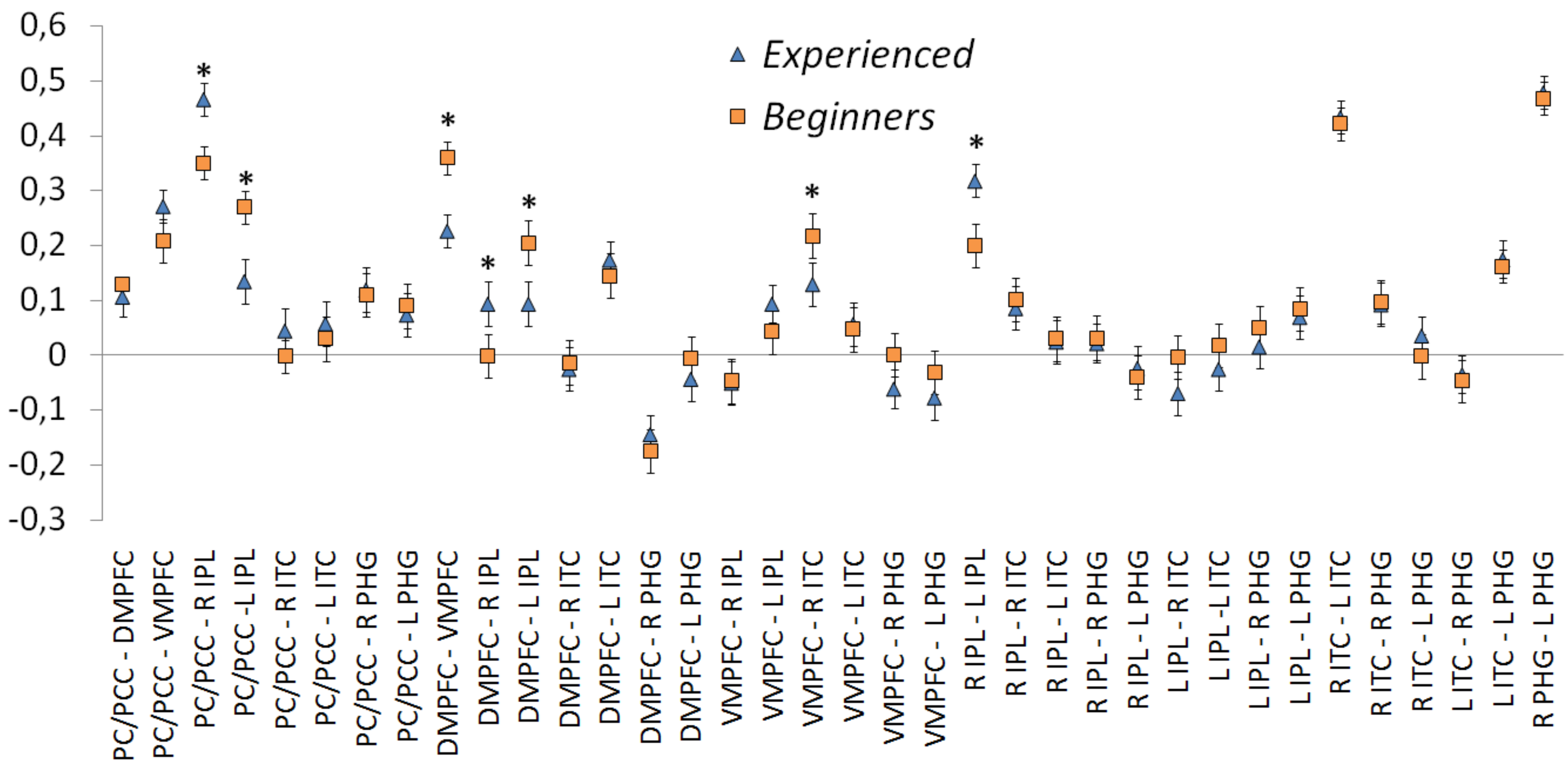

Figure 5. Partial correlation coefficients (Π; y-axis) for all pairwise relationships between default mode network regions (x-axis). Error bars represent SD values. Triangles represent the group of experienced meditators, and squares represent the group of beginner meditators. Abbreviations: Precuneus (PC), Posterior Cingulate Cortex (PCC), Dorso-Medial Prefrontal Cortex (DMPFC), Ventro-Medial Prefrontal Cortex (VMPFC), Inferior Parietal Lobule (IPL), Inferolateral Temporal Cortex (ITC), Parahippocampal gyrus (PHG); R: Right; L: Left.
*Significant group differences ($P < 0.05$).

Discussion

The results of this study can be summarized as follows. First, the DMN was successfully identified using the NEDICA approach at the group level. Second, experienced meditators exhibited stronger functional connectivity between the right IPL (BA 39) and three other DMN regions (DMPFC [BA 10], left IPL [BA 39], and PC / PCC [BA 31), relative to beginners. Third, as hypothesized, functional connectivity between regions of the medial prefrontal cortex and other DMN nodes was weaker for the group of experienced meditators compared with beginners (such as the relationship between the DMPFC (BA 10) and three other DMN regions (left IPL [BA 39], VMPFC [BA 10]), as well as the relationship between the VMPFC (BA 10) and the right ITC [BA 21]). Weaker functional connectivity for experienced meditators was also found between the left IPL (BA 39) and PC/PCC (BA 31). These group differences in the connectivity between DMN regions for experienced meditators, relative to beginners, were significant when assessed using both correlation *and* partial correlation coefficients. This finding indicates that these functional coupling differences were not mediated by any other DMN nodes.

Identification of the Default Mode Network using NEDICA

The NEDICA approach successfully identified the DMN at the group level, across the entire sample. This is consistent with the extensive literature demonstrating that specific prefrontal, temporal, temporolimbic, and parietal brain regions have correlated time-courses during a restful state (Buckner et al., 2008; Damoiseaux, et al., 2006; De Luca et al., 2006; Fransson et al., 2008; Greicius, et al., 2003; Perlbarg et al, 2008).

However, our seed for the DMPFC (BA 10) was slightly lateralised to the left, and the seed for the right IPL (BA 39) was slightly inferior compared with those used in other studies (Fransson et al., 2008). Currently, it remains unclear as to the optimal method for identifying seed regions in functional connectivity analyses, which can be determined using foci obtained from univariate analyses of task-related paradigms, anatomical landmarks, or seed regions previously reported in the literature. Nonetheless, for the purpose of the present study, we selected seed regions based on the peaks revealed in the DMN group map, to reflect more ecological validity with respect to the particular DMN function of our sample.

Increased Connectivity for Experienced Meditators compared to Beginners

The stronger functional connectivity between the right IPL (BA 39) and DMPFC (BA 10) in experienced meditators, relative to beginners, is consistent with previous studies (Fell, Axmacher, and Haupt, 2010; Lutz, Greischar, Rawlings, Ricard, and Davidson, 2004). For instance, it has been reported that, compared to control subjects with no meditative experience, Buddhist meditators (with 10 000 to 40 000 years of meditation experience) exhibit greater gamma synchrony between prefrontal and parietal areas during a resting state (Lutz et al., 2004). Interestingly, increased gamma wave synchrony between frontal and parietal lobes has been interpreted as reflecting enhanced conscious awareness of the present moment (Engel, Fries, Konig, Brecht, and Singer, 1999; Tononi and Edelman, 1998), a central characteristic of the mindful state.

The strengthened correlation between the right IPL (BA 39) and the DMPFC (BA 10) for experienced meditators (relative to beginner meditators) might reflect adaptive consequences of mindfulness training, as this connection has been shown to be hypofunctional in individuals with high basal cortisol levels (Schutter, Van Honk, Koppeschaar, and Kahn 2002). Indeed, it has been found that elevated baseline levels of the steroid hormone cortisol, previously associated with depression (Holsboer, 2000), are correlated with reduced functional connectivity between the left PFC and right parietal cortex. These findings are consistent with evidence showing that transcranial magnetic stimulation (TMS) applied locally to the left prefrontal or to the right parietal cortex (to increase activity in these regions) reduces depressive symptoms (George, Lisanby, Avery, McDonald, Durkalski, Pavlicova, Anderson, Nahas, Bulow, Zarkowski, Holtzheimer, Schwartz, and Sackeim, 2010; George, Wassermann, Williams, Callahan, Ketter, Basser, Hallett, and Post, 1995; George, Wassermann, Williams, Steppel, Pascual-Leone, Basser, Hallett, and Post, 1996; van Honk, Schutter, Putman, de Haan, and d'Alfonso, 2003). Given this, the increased connectivity between the DMPFC and the right IPL found here in experienced meditators may reflect a beneficial impact of mindfulness training in terms of emotional resources and conscious awareness of the present moment. This hypothesis is consistent with evidence that mindfulness is accompanied by increased mood and well-being, enhanced attention and cognitive performance, as well as reduced stress, depressive symptoms, anger and cortisol levels (Baer, 2003; Jung, Kang, Jang, Park, Byun, Kwon, Jang, Lee, An, and Kwon, 2010; Tang, Ma, Wang, Fan, Feng, Lu, Yu, Sui, Rothbart, Fan, and Posner, 2007).

Increased connectivity was also noted for experienced meditators, compared to beginners, between right IPL (BA 39) and two other DMN nodes (PC/PCC [BA 31] and left IPL [BA 39]). The heightened connectivity between the right IPL and the PC/PCC is in accordance with a recent study (van Buuren, Gladwin, Zandbelt, Kahn, and Vink, 2010), which demonstrated that self-referential processing is associated with reduced coupling between the right parietal cortex and the precuneus. This finding supports the view that mindfulness training induces brain function changes that are accompanied by a reduction of self-referential thoughts during rest. Alternatively, as the parietal cortex is involved in working memory and visuo-spatial attention (Culham and Kanwisher, 2001), this finding may reflect greater global attention and moment-to-moment awareness in experienced meditators during a restful state.

Individuals with MDD and a concomitant anxiety disorder display greater right vs. left parietal alpha activity (Bruder, Fong, Tenke, Leite, Towey, Stewart, McGrath, and Quitkin, 1997). In contrast, depressed individuals without a comorbid anxiety disorder exhibit greater left vs. right alpha activity over parietal areas. Consequently, the increased connectivity between the left and right parietal regions measured in experienced meditators, relative to beginners, may reflect the greater emotional stability that results from long-term practice of mindfulness (Taylor et al., submitted).

Decreased Connectivity for Experienced Meditators relative to Beginners

Greater coherence in the theta range between the PFC and the left parietal cortex has been measured during working memory tasks involving verbally-related content, whereas theta coherence enhancement between the PFC and the right parietal cortex has been observed in working memory tasks implicating spatial features (Sarnthein, Petsche, Rappelsberger, Shaw, and von Stein, 1998). Therefore, the decreased connectivity between the DMPFC (BA 10) and the left IPL (BA 39) in experienced meditators, compared to beginners, may be related to a diminution of analytic self-referent processes (Northoff et al., 2006).

For experienced meditators relative to beginners, reduced connectivity was also measured between the VMPFC (BA 10) and DMPFC (BA 10). Since these medial prefrontal areas are adjacent to each other, it is difficult to tease apart their distinct contributions to DMN functioning. Both areas play a role in self-relatedness (Schneider, Bermpohl, Heinzel, Rotte, Walter, Tempelmann, Wiebking, Dobrowolny, Heinze, and Northoff, 2008), self-referential processing (van Buuren, Gladwin, Zandbelt, Kahn, and Vink, 2010), emotional judgements (Northoff, Heinzel, Bermpohl, Niese, Pfennig, Pascual-Leone, and Schlaug, 2004), and in the appraisal of stimuli relative to the self (Ochsner, Knierim, Ludlow, Hanelin, Ramachandran, Glover, and Mackey, 2004; Ochsner and Gross, 2005). The VMPFC (BA 10), which has dense projections to the amygdala (Amaral et al., 1992), is also thought to be implicated in the extinction of conditioned fear, as well as the down-regulation of emotional responses (Davidson, 2002; LaBar, Gatenby, Gore, LeDoux, and Phelps, 1998; Phelps, Delgado, Nearing, and LeDoux, 2004). It thus appears plausible that the decreased coupling between the DMPFC (BA 10) and the VMPFC (BA 10) noted in experienced meditators may reflect a reduction in emotional appraisal during self-referent processes, consistent with the view that mindfulness is intended to promote acceptance of thoughts, perceptions, and feelings (Bishop, 2004).

Correlations and Partial Correlations between DMN Regions

Distinct patterns of functional connectivity within the DMN regions were revealed, in experienced vs. beginner meditators, by both correlations *and* partial correlations. Several correlations, however, involving the VMPFC (BA 10), the right IPL (BA 39), the PHG (BA 36), and the left ITC (BA 21) were no longer different, between the two groups, when analyzed using partial correlations. This finding is consistent with the notion that the DMN is segregated into functional subsystems (Buckner et al., 2008; Fransson, 2005), and that the power of low-frequency BOLD fluctuations in different regions of the DMN is rank-ordered, with the ITC exhibiting the lowest power, and the PC/PCC the highest power, followed by the VMPFC and the DMPFC (Jiao, Lu, Zhang, Zhong, Wang, Guo, Li, Ding, and Liu, 2011).

Limitations and Future Directions

This study is nonetheless limited in some respects. First, the two groups of participants may have differed in other aspects (personality traits, lifestyle, etc.). Second, the partial correlation method used in this study does not allow for *causal* inferences to be made about the relationships between different regions. Thus, further studies using effective connectivity methods, such as dynamic causal modelling, are needed in order to investigate causal relationship between DMN regions as a result of meditation training. Furthermore, although the groups did not significantly differ with respect to age or male/female ratio (*p*s > 0.05), more homogeneous groups with respect to these factors may have been optimal for the present study. Given that it was not possible to add any covariates into the independent component analyses as well as correlational analyses between DMN nodes, the results of the present study should be interpreted with caution until further replication in larger samples with participants precisely matched for age and sex. It is also possible that between the two groups, the state of rest may have qualitatively differed. Thus, future studies examining resting state network connectivity should acquire qualitative descriptions of resting state periods to aid in interpreting brain imaging results. In addition, due to technical constraints in the scanner environment, it was not possible to acquire autonomic measures of emotional arousal, such as the galvanic skin response, which would have aided in the interpretation of functional connectivity results. Thus, future studies examining the relationship between meditation training and brain function should optimally acquire such physiological objective measures. Furthermore, given that the main objective of this study was to examine differences in correlations between pairs of regions within the DMN, the software NetBrainWorks was chosen to conduct the analyses. This software does not allow, however, to explicitly compare spatial maps for the default mode network between the two groups. Thus, future studies using other functional connectivity tools allowing direct comparisons between spatial patterns associated with the default mode network are needed to address this question. Finally, a third group completely naive to meditation was not tested in the present study, and this would have aided in interpreting functional connectivity results. Thus, future studies examining the relationship between DMN functional connectivity within the DMN and meditation training should include a baseline control group, having never had any exposure to the practice of meditation.

Conclusions

To our knowledge, this is the first study to demonstrate that individuals with extensive mindfulness training exhibit significant differences in functional connectivity between regions of the DMN. Our findings suggest that mindfulness training leads to changes in the functional dynamics of the DMN that extend beyond a state of meditation *per se*.

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General Discussion

The main findings of this research project can be summarized as follows. First, in Study #1, mindfulness attenuated the subjective impact of emotional intensity for all categories of pictures in both groups of participants (though the effect for neutral pictures may more likely be due to the minimal variability in scores for this category of pictures). Second, mindfulness led to a down-regulation of amygdala activity during emotional processing in beginner meditators but not in experienced meditators. Third, across all categories of pictures, mindfulness led to an opposite pattern of results in brain areas involved in the DMN, self-referential processing, and responsiveness to emotional stimuli (MPFC [BA 10] and PCC [BA 31]). Specifically, mindfulness led to a deactivation of these areas in experienced meditators, whereas for beginners, mindfulness induced increased activity in these brain regions.

In Study #2, experienced meditators exhibited different functional connectivity between regions of the DMN compared to beginners. Specifically, experienced meditators, displayed decreased connectivity between the DMPFC [BA 10] and two other DMN regions (left IPL [BA 39] and VMPFC [BA 10]), as well as between the left IPL [BA 39] and PC/PCC [BA 31], and between the VMPFC [BA 10] and the right ITC [BA 21]. Experienced meditators also exhibited increased functional connectivity between the right IPL [BA 39] and three other DMN regions (DMPFC [BA 10], PC/PCC [BA 31], left IPL [BA 39]). All of these connections were significant when assessed using the correlations and partial correlations measures, indicating that they were not mediated by any other DMN nodes.

Mindfulness and Emotional Processing

As hypothesized, mindfulness had a down-regulating impact on amygdala activity during the processing of emotional pictures. Based on previous reports demonstrating that mindfulness leads to decreased amygdala activity during negative aversive stimuli in experienced relative to beginners (Brefczynski-Lewis et al., 2007), we had predicted that down-regulation of amygdala response to emotional stimuli would be more pronounced in experienced meditators. In contrast, during negative and positive emotional processing, mindfulness did not influence experienced meditators' amygdala response, while mindfulness let to *decreased amygdala* activity in beginners. Since mindfulness attenuated the subjective emotional intensity responses for both groups of participants, the neural mechanisms through which this was achieved likely differed for each group of participants.

Thus, at an initial level of meditation training, mindfulness may have attenuated emotional intensity by down-regulating low-level appraisal neural systems, consistent with the view that mindfulness promotes emotional stability and decreases reactivity to emotional stimuli (Arche et al., 2006). However, at an advanced stage of meditation training, a state of mindfulness may have preserved low-level responsivity to emotional stimuli, consistent with the idea that emotions are accepted during meditation and not suppressed (Bishop, 2004). In addition, *greater deactivations* of the MPFC [BA 10], a brain region associated with appraisal and evaluation of stimuli relevant to the self (Ochsner et al., 2004), were observed in experienced meditators during mindfulness across all emotional stimuli. This may indicate that for experienced meditators, the appraisal process occurring *following* the initial emotional response may have been lessened during a state of mindfulness. This may have, in turn, led to greater distancing from emotional stimuli, and attenuated the subjective emotional intensity perceived.

The greater MPFC [BA 10] and PCC [BA 31] deactivations observed during the mindful condition in experienced meditators across all valence categories may suggest that a mindful state of awareness is associated with increased ability to deactivate key regions of the DMN. As such, failure to deactivate regions of the DMN (including the VMPFC [BA10], the IPL [BA 39], and the lateral temporal cortex [BA 21]) has been observed in depressed patients during the passive viewing and re-appraisal of negative images (Sheline et al., 2009). This finding was interpreted as greater interference from internal emotional states. Thus, the mindfulness-induced deactivations in the MPFC [BA 10] and PCC [BA 31] for experienced meditators may reflect greater self-distancing from emotional and non-emotional stimuli, which would allow emotional information to be processed in a more objective manner.

Mindfulness and the Default Mode Network

The attenuating effects of mindfulness on subjective emotional intensity measured in Study #1 may be related to the different relationship between DMN regions found in experienced meditators in Study #2. Indeed, the connections differing between experienced and beginner meditators observed in Study #2 may be related to the attenuating effect of mindfulness on emotional intensity found in Study #1. Particularly, the connection between the right IPL and left DMPFC has been shown to be *decreased* in individuals with high cortisol levels, a characteristic associated with major depression and chronic stress (Holsboer, 2000). Consequently, the increased connectivity between the DMPFC [BA 10] (which is somewhat left-lateralized) and the right IPL observed in experienced vs. beginner meditators during a state of rest may reflect an adaptive consequence of meditation training. Also consistent with this view, the connection between the right temporal cortex and the VMPFC [BA 10] is associated with increased autobiographical memory retrieval (Dolan, Lane, Chua, and Fletcher, 2000). Thus, the weaker connectivity between the right ITC [BA 21] and the VMPFC [BA 10] observed in experienced vs. beginner meditators during a restful state may indicate that long-term mindfulness meditation practice reduces emotion-related thought processes at rest, promoting a calmer and more objective state when one is not engaged with any explicit task.

Of interest, the right IPL [BA 39] has been shown to be more active during a state of compassion meditation in experienced Buddhist meditators (Lutz et al., 2008). This cortical area is involved in understanding others' intentions (theory of mind). Thus, the fact that all of the stronger connections measured for experienced vs. beginner meditators implicated the right IPL may suggest that this parietal region also plays a crucial role in mindfulness. In addition, increased gamma wave synchrony measured using electroencephalography (EEG) is thought to reflect increased present-moment awareness (Engel et al., 1999; Tononi et al., 1998). Thus, the increased connection observed between the DMPFC (BA 10) and the right IPL (BA 39) is consistent with increased gamma wave synchrony observed in Buddhist meditators during a state of meditation (Lutz et al., 2004).

The decreased connectivity between the DMPFC (BA 10) and the VMPFC (BA 10) for experienced vs. beginner meditators noted during a restful state is in line with the study by Farb and colleagues (2007), who demonstrated that an experiential self condition (compared with a narrative self condition) is associated with decreased MPFC activity in individuals having completed an eight-week mindfulness meditation training. Though less is known about the connectivity between these adjacent regions, the dorsal portion of the MPFC has been described as being a part of a description-based emotional appraisal system, whereas the ventral portion of the MPFC is densely connected to the amygdala and is thought to be involved in an outcome-based appraisal processes based on the learning of stimuli-contingency associations (Gross, 2007). It is therefore plausible that the reduced connectivity observed between the dorsal and ventral portions of the MPFC (BA 10) - in experienced meditators during a restful state - reflects a greater dissociation between automatic reactivity to emotional stimuli and the cognitive assessment of the emotional responses. This may therefore promote an objective manner of responding to emotional events. Future studies explicitly examining connectivity between the dorsal and ventral MPFC (BA 10) and emotional reactivity are needed to test this speculation.

Farb and colleagues (2007) also found that the experiential self condition was associated with increased activity in regions of the the right hemisphere, including the

IPL. This finding is consistent with the stronger DMPFC (BA 10) – right IPL (BA 39) connection and weaker DMPFC (BA 10) – left IPL (BA 39) observed in experienced meditators vs. beginners. Thus, since mindfulness meditation promotes monitoring the self in the present moment, this state of awareness is perhaps more associated with spatial as opposed to verbal processing, consistent with increased connectivity found between the PFC-right parietal cortex during working memory for spatial material, and increased connectivity between the PFC-left parietal cortex during working memory for verbal material (Sarnthein et al., 1998).

Limitations and Future Directions

This research project is limited in some respects. First, it is possible that experienced meditators differed from beginners in other aspects (temperamental predispositions, lifestyle, etc.). However, our main objective was to study the effect of long-term meditation experience, and studying the effects of more than 1000 hours of meditation practice would have been unrealistic or very challenging using a longitudinal design. Nonetheless, to date, the best compromise for research investigating meditation-related processes remains the convergence of findings from studies using corss-sectional and longitudinal designs. Thus, the findings obtained from this research project should be interpreted with caution until replicated in future studies using larger samples and longitudinal designs, by testing the same individuals before and after having completed a mindfulness training intervention. Third, we had not included independent measures of emotional arousal, such as the galvanic skin response, due to technical constraints during testing. Therefore, future studies should include such independent measures in order to understand the impact of mindfulness on emotional processing at a physiological level. Fourth, in Study #2, the state of rest in experienced and beginner meditators may have differed qualitatively. Thus, future studies investigating the relationship between brain function, resting states and mindfulness meditation should include qualitative measures of the mental processes unfolding during rest. Finally, the results obtained in Study #2 reflected functional connectivity between regions, but causal relationships could not be inferred. Thus, future studies should investigate the relationship between mindfulness and DMN functioning using approaches permitting to analyze effective connectivity.

Conclusions

In conclusion, the findings of this research project contribute to the understanding of the relationship between mindfulness meditation, emotional processing, and brain function. These results imply that mindfulness attenuate the impact of emotional information, possibly by deactivating structures involved in self-referential processing, the DMN, and appraisal of emotional stimuli in individuals with long-term meditation experience. On the other hand, the present findings suggest that individuals with initial experience in meditation may also benefit from this practice, as mindfulness induced a down-regulation of amydgala activity during emotional processing in the group of beginners. Finally, our findings indicate that the effects of mindfulness training extend beyond a state of meditation *per se*, and influence functional connectivity between regions of the DMN during a state of rest.

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