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The neurobiology of meditation for the control of pain

par
Joshua A. Grant

Département de Physiologie
Faculté de médicine

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présentée par:
Joshua A. Grant

a été évaluée par un jury composé des personnes suivantes:

Trevor Drew, président-rapporteur

Pierre Rainville, directeur de recherche

Adrianna Mendrek, membre du jury

Catherine Bushnell, examinateur externe

John Kalaska, représentant du doyen de la FES

Résumé

La douleur est une expérience multidimensionnelle comportant des aspects sensoriels, émotionnels et cognitifs. Il a été montré que cette expérience peut être modulée par des facteurs psychologiques ou des interventions cognitives comme l'attention, la distraction, l'hypnose ou les attentes. La tradition orientale suggère également que la pratique de la méditation pourrait avoir des effets analgésiques. D'un point de vue théorique, plusieurs mécanismes pourraient expliquer ces effets. Cependant, très peu d'études ont testé ces hypothèses. Les études présentées dans cette thèse avaient donc pour objectif d'examiner les mécanismes analgésiques de la méditation.

Dans un premier temps, une étude psychophysique a été réalisée afin de comparer les réponses à la douleur entre des adeptes de la méditation Zen et des sujets contrôles, dans différentes conditions attentionnelles. Durant la condition attentionnelle de type « mindful », les adeptes de la méditation ont présenté une plus faible sensibilité à la douleur, des réponses attentionnelles à la douleur atypiques et une diminution de la perception de la douleur associée à l'entraînement à la méditation. Une deuxième étude a été réalisée en imagerie par résonance magnétique fonctionnelle (IRMf) avec des groupes de participants similaires. Dans une condition sans méditation, les adeptes de la méditation ont présenté de plus fortes réponses nociceptives dans les régions primaires de la douleur. Les régions cérébrales associées aux processus d'évaluation, à la mémoire et aux émotions ont quant à elles montré une diminution d'activité. De plus, cette diminution était plus importante chez les adeptes de la méditation les plus expérimentés et elle était associée à des évaluations de douleur plus faibles. Par ailleurs, des changements de connectivité fonctionnelle entre le cortex préfrontal et une région primaires de la douleur étaient associés à la sensibilité à la douleur chez les adeptes de la méditation. Finalement, une étude d'imagerie cérébrale structurale (publiée comme deux études séparées) a été réalisée pour examiner les différences d'épaisseur corticale entre les groupes, pour des régions associées à la douleur. Les adeptes de la méditation ont présenté une épaisseur plus importante de matière grise dans plusieurs régions associées à la douleur et l'attention. De plus, ces différences étaient associées à une mesure expérientielle de l'attention, à la sensibilité à la douleur et à l'expérience de méditation. Dans l'ensemble, ces résultats suggèrent que la méditation pourrait influencer la perception de la douleur par des changements fonctionnels et physiques dans le cerveau. De plus, le patron d'activation et la modulation de l'expérience paraissent uniques en comparaison à ceux d'autres interventions, ce qui suggère qu'un état de détachement et un focus mental favorisent la dissociation entre les aspects désagréables et sensoriels d'un stimulus nociceptif.

Mots-clés: douleur, nociception, méditation, Zen, mindfulness, modulation de la douleur, IRMf, émotion, auto régulation, attention

Abstract

Pain is a multidimensional experience involving sensory, emotional and cognitive components. It is well known that mental factors or interventions such as attention, distraction, hypnosis or expectation can modulate painful experience. Traditional claims from the East suggest meditative practice may also have analgesic effects. Theoretically there are multiple avenues by which such practices could act, however little work has been done in this regard. The works presented in this dissertation were intended to address this paucity of research by contrasting pain perception in practicing meditators and non-meditating control participants.

A psychophysical pain study was first conducted with practitioners of Zen meditation contrasting their responses to pain with control subjects during different attention conditions. Meditators were found to have lower baseline pain sensitivity, atypical attention-related pain responses and training-related reductions of pain ratings during mindful attention. A second study, with similar groups of subjects, employed functional magnetic resonance imaging (fMRI) during the perception of pain. In a non-meditative state, meditators were found to have stronger nociceptive-related brain activity in primary pain regions while simultaneously exhibiting reductions of activation in brain areas associated with appraisal, memory and emotion. These later effects were largest in the most advanced practitioners and were associated with the lowest pain ratings. Importantly, changes in functional connectivity between prefrontal cortex and a primary pain region predicted baseline pain sensitivity in the meditation group. Finally, a structural imaging experiment (published as two separate reports) was conducted to examine whether grey matter thickness may differ, in pain-relevant ways, between the groups. Meditators were found to have thicker regional grey matter in several pain and attention-related regions which corresponded both with an experiential measure of attention, pain sensitivity and meditation experience. Taken together these results suggest meditation may influence pain perception through functional as well as physical effects on the brain. The pattern of brain activity and experience modulation appears to be unique, when contrasted with previously studied interventions, and suggests that adopting a non-elaborative but focused mental stance may allow one to dissociate the bothersome qualities from the sensory aspects of a noxious stimulus.

Key words: pain, nociception, meditation, Zen, mindfulness, pain modulation, fMRI, emotion, self regulation, attention

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Abbreviations

General:

ADHD: attention deficit hyperactive disorder, ANT: attention network task, ant: anterior, AWARE: awareness subscale of FFMQ, dor: dorsal, ECG: electrocardiogram, FFMQ: Five Factor Mindfulness Questionnaire, HF: high frequency, fMRI: functional magnetic resonance imaging, GLM: general linear model, HRV: heart rate variability, inf: inferior, L: left, lat: lateral, LF: low frequency, LF/HF: low to high frequency ratio, MBSR: Mindfulness Based Stress Reduction, med: medial, ML: midline, MNI: Montreal Neurological Institute, NJ: nonjudgmental subscale of FFMQ, NR: nonreactivity subscale of FFMQ, OBS: observe subscale of FFMQ, pos: posterior, R: right, ROI: region of interest, SD: standard deviation, sup: superior, TAS: Tellegen Absorption Scale, VAS: visual analogue scale

Anatomical:

ACC: anterior cingulate cortex, AMY: amygdala, BG: basal ganglia, CAUD: caudate, CB: cerebellum, CFP: cingulo-fronto-parietal, CS: central Sulcus, CLAU: claustrum, CUN: cuneus, DLPFC: dorsolateral prefrontal cortex, G.PAL: globus palidus, HF: hippocampal formation, HIP: hippocampus, IFG: inferior frontal gyrus, INS: insula, IPL: inferior parietal lobule, ITG: inferior temporal gyrus, MI: primary motor cortex, MFG: middle frontal gyrus, MTG: middle temporal gyrus, OFC: orbitofrontal cortex, PAG: periaqueductal grey, PAO: parietal operculum, PCC: posterior cingulate cortex, PFC: prefrontal cortex, PHG: parahippocampal gyrus, PoCG: post central gyrus, PreCUN(Cun): precuneus, PUT: putamen, rAI: right anterior insula, RtSpl: retrosplenial cortex, SI: primary somatosensory cortex, SII: secondary somatosensory cortex, SFG: superior frontal gyrus, SMG: supramarginal gyrus, SPL: superior parietal lobule, STS: superior temporal sulcus, T.Pole: temporal pole, THAL: thalamus

To my family

Whose love and support

Cannot be measured

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Forward

Considerable scientific and clinical attention has been devoted to meditation over the past few years. The broad rationale for this interest can be seen as two-fold. First, traditional accounts suggest that meditation may promote health, in various ways, and thus a substantial amount of clinical research has looked at potential applications of such practices. Second, training in meditation is said to bestow upon the practitioner skill levels related to mental processes such as attention and cognitive control which are beyond those typically attained in everyday life. Thus, it has been suggested that dedicated meditators could be viewed as the equivalent of elite athletes who may provide new insights into the potential of the human mind/brain. Over the course of the research presented in this dissertation I began to realize that Buddhist practices are akin to a behavioural modification system and further that these practices may have their influence through mechanisms related to neural plasticity. While the current work did not employ the necessary tools to establish this, if readers are at least willing to entertain such a claim I will consider it a success. The research spans both of the above mentioned motivations, dealing with the impact of previous meditation training on pain perception, informing our basic understanding of nociceptive processing, of the neural bases of meditation and of potential clinical applications of practice.

When this research began in 2005 very little had been done in terms of the influence of meditation on pain. In fact the literature contained but a single study, spaced over several years, looking at the effect of a secularized meditation program on the experience and quality of life of chronic pain patients. The picture is very different just five years later with a rapidly increasing number of published studies and research groups involved. This growth will be reflected in the dissertation presentation. The general introduction will describe pain experience and the involved neural systems. I will then introduce meditative practice and attempt to briefly situate it within cognitive neuroscience, ending with some hypotheses concerning the influence of meditative practice on pain perception. However, very little of the now existent literature on pain and meditation will be surveyed in the general introduction. This has been done intentionally to more accurately convey the state of knowledge at the time of our initial hypotheses. The main body of the dissertation will be composed of three research articles published between 2005 and 2011, and a fourth to be published in 2011. In each case I was the main contributor, designing the study, implementing it, analyzing the data and writing the manuscript, all under the guidance of my supervisor, Dr. Pierre Rainville. Finally, a general discussion will assimilate our findings with the results of others and those of the field of cognitive pain modulation. It should become clear that in five years, along with the work of others, significant headway has been made in demonstrating a positive impact of meditative practice on the suffering thought to be inescapably associated with pain.

GENERAL INTRODUCTION

General Introduction

The Neurobiology of Pain

Pain is defined, by the International Association for the Study of Pain, as: "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."*

The experience of pain is far from the simple burning or stabbing-like qualia it often seems to be when touching a hot stove or pinching one's finger. It is believed that the experience can be dissociated into several dimensions (Melzack and Casey, 1968). The sensory-discriminative dimension underlies the ability to locate the origin of the bodily stimulation and the perceived strength or intensity. The affective-motivational dimension of pain relates more to the way the offending stimulus makes one feel. That is, pain is nearly always associated with an affective or emotional response, likely reflecting the utility of the phenomenon in signalling danger and allowing the organism to adapt and ultimately survive. Lastly there are cognitive-evaluative aspects of pain perception which would seem to be less experiential in nature and more involved in shaping or modulating the experience. For example, anxiety of an upcoming painful stimulus is associated with certain brain activation patterns prior to receipt of the stimulus and is known to alter the subsequent experience and brain activity during noxious stimulation (Ploghaus et al., 2001).

It is important to differentiate between pain and nociception. As is evident in the definition above, pain is an experience. Nociception on the other hand refers to the processing of nociceptive or noxious stimulation in the periphery and central nervous system. The nociceptive processing that eventually leads to the experience of pain typically[1] begins in the periphery with stimulation of nociceptive-sensitive receptors. From the periphery the signal travels along A-delta and/or C fibres synapsing in the dorsal horn of the spinal cord and rising to the thalamus and brainstem via the spinothalamic and spinoreticular tracts (Willis and Westlund, 1997). From the thalamus, a recent study in monkeys (Dum et al., 2009) confirmed that nociceptive signals terminate contralaterally in the anterior cingulate cortex (ACC), posterior insula (pINS) and secondary somatosensory cortex (SII). In the brain, a large number of cortical and subcortical regions seem to underlie nociception and support the experience of pain. A meta-analysis of 68 brain imaging studies (Apkarian et al., 2005) reported the frequency with which a number of brain regions have been found to be activated during pain paradigms in healthy individuals. The thalamus (THAL), ACC and INS were the most commonly reported regions in over 80% of included studies. Primary and secondary somatosensory cortices (SI, SII) and prefrontal cortex (PFC) were also frequently reported, in approximately 70 – 80% of studies. Much is known about the functional significance of these regions for pain and nociception, however, the multidimensional nature of the phenomenon and dynamic interactions between regions has spurred much debate over the exact roles.

Generally, the sensory properties of painful stimuli are believed to be processed by SI, SII and THAL as positive correlations are often observed between the neural activation in these regions and participants' ratings of stimulus intensity

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[1] The word '*typically*' was used as there are cases such as certain chronic pain syndromes wherein a person will report the experience of pain with no known physical stimulus causing the sensation.

(Bushnell et al., 1999; Coghill et al., 1999; Hofbauer et al., 2001). The affective properties are thought to be processed in ACC and INS where ratings of pain unpleasantness are often found to correspond with brain activation levels (Rainville et al., 1997; Schreckenberger et al., 2005). However, this rather simplistic view is far from absolute with studies reporting correlations between intensity ratings in ACC and INS (Coghill et al., 1999; Villemure and Bushnell, 2009) and correlations between affective ratings and SI and SII (Villemure and Bushnell, 2009).

Several hurdles are apparent in taking this approach to delineating the contributions of brain regions to painful experience. First, the sensory and affective dimensions are likely to covary substantially with one another. As the objective stimulus strength increases both types of experience are likely to intensify as well, although this is not always the case as is demonstrated by research with hypnosis discussed below (Rainville et al., 1997). Second, pain is a salient, attention-grabbing stimulus with clear utility and has likely survived evolutionary pressure as a result. As such, distinguishing between brain activity reflecting saliency, as opposed to qualities specific to pain, is extremely challenging. Indeed several groups have found evidence that the activation of ACC and INS covaries with stimulus saliency even in other modalities such as vision or audition (Downar et al., 2000; Baumgartner et al., 2010; Legrain et al., 2010; Mouraux et al., 2010). This is not overly surprising as the ACC has a proposed role in attention, conflict monitoring and error detection (Bush et al., 2000) while the INS is thought to be involved in autonomic regulation (Cechetto and Saper, 1987) and interoception (Critchley et al., 2004; Craig, 2009). The point here is that these regions, and likely other pain-related regions, do more than simply process pain. Nonetheless, the presence of opioid receptors, an endogenous system promoting analgesia, in many pain-related regions (Zubieta et al., 2005), including ACC, INS and PFC, indicates that there is little doubt of their involvement in pain and nociception. The final brain region reported by Apkarian et al. (2005) to be commonly activated during noxious stimulation is the prefrontal cortex. The PFC is a vast expanse of grey matter generally dedicated to higher cognitive functions such as volition, attention, memory, planning and decision making (Miller and Cohen, 2001). In terms of pain perception the commonly activated dorsolateral PFC (DLPFC) is thought to underlie evaluation, appraisal or memory functions related to the stimulus (Coghill et al., 1999; Strigo et al., 2003). Taken together, a typical neural response to pain generally involves increased activity of SI, SII and thalamus, often reflecting the felt intensity, as well as ACC and INS reflecting felt unpleasantness (and possibly intensity) and finally PFC, thought to reflect memory or stimulus evaluation. Pain modulation, the topic of the next section, involves a different set of brain regions. Descending modulatory systems, thought to be triggered by various regions of PFC, may be inhibitory or facilitatory and originate in the midbrain and brainstem (i.e. periaqueductal grey (PAG) and the rostroventral medulla) (Fields, 2000; Bingel and Tracey, 2008). These regions project to the dorsal horn of the spinal cord to modulate afferent nociceptive signals and thereby reduce or increase the input to and activation of the cortical and subcortical pain regions discussed above.

Brain Imaging and Pain Modulation

Many factors, at the cognitive or emotional level, have been found to modulate nociceptive-related activation including, but not limited to, attention and distraction, hypnosis, expectation, placebo and emotion. Without fail each of these manipulations has been shown to involve numerous nociception-related brain regions, many of which are also believed to be involved in the experience of pain.

Seemingly, the most straightforward cognitive modulator of pain and nociception is attention. Attention has been studied far more extensively in other sensory domains, such as vision. It is generally believed that bottom-up stimulus driven attention competes with top-down cognitively driven attention in a flexible and adaptive manner to allow the pursuit of goals while still being receptive to saliency in the environment (Corbetta and Shulman, 2002). It is also widely held that attending to a percept magnifies the strength of the corresponding mental representation via increased neural activity (Corbetta and Shulman, 2002). This appears to be true of pain as behavioural studies have shown that attending to pain, or away from pain via distraction, increases and decreases pain ratings respectively (Quevedo and Coghill, 2007). Neuroimaging studies have shown that distraction reduces pain reports (both sensory and affective) and is associated with activity reductions in INS, ACC, THAL, SI and with increases in PFC and PAG (Bushnell et al., 1999; Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004). Involvement of the PFC and PAG suggests distraction may attenuate pain via inhibitory descending modulation of nociceptive inputs to the spinal cord, which in turn would reduce ascending input to and activity of ACC, INS, THAL and somatosensory cortex. However, in trying to disentangle attentional effects from possible confounds introduced by distraction tasks, Villemure and Bushnell (2009) reported that fewer areas were selectively modulated by attention than previously thought. More specifically they found that only the anterior insula (aINS) was selectively modulated by attention. This led to the recent suggestion that distraction studies may confound effects of attention with other factors like emotion (Villemure and Schweinhardt, 2010). Thus, the exact neurobiology underlying the effect of attention on pain is still unclear.

While attention has been shown to modulate both the sensory and affective dimensions of pain, hypnosis has been used to tease apart the underlying brain structures involved. Rainville et al. (1997) used hypnotic suggestions to selectively modulate the emotional aspect of pain perception and found altered unpleasantness reports to covary with activity in the dorsal ACC. Several years later the same group reported on a similar study, selectively modulating sensory aspects of pain with hypnosis (Hofbauer et al., 2001). Results showed that contralateral primary somatosensory cortex (SI) activation exclusively correlated with changes in intensity ratings. Taken together, these studies of pain modulation via hypnosis suggest a double dissociation between pain experience and the underlying brain structures instantiating the experiential qualities. While attention and hypnosis seem to operate through concurrent engagement with the stimulus, several modulatory effects begin in the period prior to the receipt of pain.

Koyama and colleagues (2005) employed a paradigm where participants learned that the length of a delay period, prior to stimulation, predicted the intensity of the subsequent stimulus. A short delay indicated that the coming stimulus would be mild, whereas intermediate and long delays indicated moderate and highly painful stimuli respectively. After establishing this mapping the researchers occasionally presented incongruent trials where an intermediate delay was coupled with a high pain stimulus or the reverse. FMRI scanning revealed that activation during the anticipation period (for congruent trials) closely resembled the actual pain maps, with graded activity for both pain and anticipation in regions such as ACC, PFC, INS, SI and THAL. Importantly, contrasting congruent and incongruent high pain trials revealed that the expectation of a moderate stimulus (via a shortened delay period) resulted in brain activation and ratings that seemed to reflect what was expected, rather than what was actually delivered. That is, given two identical stimuli, brain activation was reduced in INS, ACC, DLPFC, SI, SII and THAL, among others, when participants expected a lower intensity. The authors argued that perception is the product of a sensory stimulus merging with relevant information about past experiences and future predictions. Furthermore, the influence of an *'active mental representation of an impending event'* may occur in the same brain regions that actually process pain since both conditions activated largely the same network. The idea that expectations can influence pain perception is consistent with work on the placebo effect.

Research with placebos (innocuous or inert treatments) suggests that certain individuals (responders) have the ability to reduce their experienced pain, without the aid of a true external influence. In a basic placebo design the participant is led to believe, perhaps with the help of conditioning, that a particular manipulation has analgesic properties. Examples that have been employed are inert creams (Wager et al., 2004; Laverdure-Dupont et al., 2009) or sham acupuncture (Linde et al., 2010). The placebo response is typically measured as the difference, in the variable of interest, between the placebo and a control condition. One particularly illuminating study involved application of a cream to the forearm of participants that was suggested to have analgesic properties whereas the control condition involved a cream that was said to be non-analgesic (Wager et al., 2004). Participants were scanned with fMRI while being stimulated with noxious electric shocks, as well as thermal stimuli in a second experiment. Importantly, a cue indicating the upcoming stimulus strength was followed by a period where the participant presumably anticipated the upcoming stimulus. When contrasting the placebo and control conditions, brain activation was reduced in dorsal ACC, contralateral thalamus and INS, for both stimulus types. These reductions in brain activation were correlated with the placebo effect observed in participants' ratings. Interestingly, activation in bilateral DLPFC and orbitofrontal cortex (OFC) during the anticipation period (although not observed as main-effects) predicted subsequent placebo analgesia and correlated with activation of the PAG. This suggests that expectations of pain relief, generated and maintained in prefrontal cortex, trigger the descending inhibitory pathway (PAG) and further that placebo analgesia is opioid-meditated. The following year several of the suggestions made by Wager et al. (2004) were confirmed in a study by Zubieta et al. (2005). Using positron emission tomography (PET) the team imaged the availability of mu-opioid receptors in the brain during a placebo-pain challenge, verifying older claims (Amanzio and Benedetti, 1999) that placebo effects were opioid-meditated. Their results overlapped in many cases with those of Wager et al. (2004) suggesting that the reduced activation observed with fMRI during placebo (rostral ACC, THAL, INS) may in fact reflect inhibition from endogenous opioid release. Together these results strongly suggest that placebo involves the expectation of forthcoming pain relief, which seems to trigger opioid release via prefrontal cortex (OFC, DLFPC) projections to PAG.

Attention, distraction, hypnosis, placebo and expectation have been shown to influence the sensory as well as the affective dimension of pain but are not themselves always inherently emotional. Studies employing emotion-related paradigms have confirmed an influence of emotion induction exclusively on the affective dimension of pain. In a study by Villemure and Bushnell (2009) good and bad moods were induced through the application of odours during pain. They found that positive mood was associated with activation reductions in ACC, THAL, SI and SII. Furthermore, lateral OFC and PAG activity seemed to drive the effect of mood on pain-related regions suggesting that emotional modulation of pain may also involve descending modulatory pathways.

The studies presented in this section are but a fraction of reports demonstrating that cognitive and emotional factors can have substantial impact on the perception of pain. We move now to meditation and a brief description of what that entails. This will be followed by some discussion on scientific studies of meditation, and finally by predictions of how meditation may influence pain perception.

Introduction to Meditation

The term meditation, as used in this text, refers to a family of mental exercises aimed at enhancing the practitioner's ability to attain, and maintain, a target state, often attentional or affective in nature (e.g. sustained attention or a state of compassion) (Lutz et al., 2008b). There is no shortage of practices which may be classified as meditation and they likely span all known spiritual traditions. For the most part the research conducted and discussed here is secular or Buddhist in nature. This is not intended to suggest that one type of practice is better than another. The reason for the focus on Buddhism, as should become clear, is the very scientifically approachable mental training system it promotes, along with an extensive history of documenting the effects of various practices on the mind.

Traditionally, a serious practitioner of Buddhism is introduced over many years to a series of meditative practices, each with a slightly different aim or purpose. To understand the nature of the practices one must first understand the primary aim of Buddhism. Without belaboring the point, Buddhists generally believe that common perception is highly deluded and inaccurate (Gethin, 1998). They believe this stems from a combination of a lack of mental control and highly conditioned behaviors which perpetuate the delusion. The proposed solution lies in gaining control of the mind and a combination of de-conditioning and re-conditioning with wholesome states (Gethin, 1998; Bodhi and R., 2007). Typically, a beginner will practice techniques intended to stabilize the mind through the cultivation of sustained attention. These are often referred to as concentration techniques with an example being shamatha (calm abiding). As one becomes more adept they are taught to direct their stabilized attention toward the nature of mind, emotions or bodily sensations for example. These practices are often referred to as insight meditations with an example being vipashyana (seeing thoroughly). Finally, more abstract meditations may be introduced which aim to cultivate states such as compassion, perhaps the highest motivation of all of Buddhism. For a presentation of these and various other practices the interested reader is referred to an excellent book by Alan Wallace (2005).

Zen, the brand of meditation practiced by all of the participants examined in the research presented here, is Buddhist in nature and most prominent in Japan. Zen differs from many of the other schools of Buddhism in its minimalist approach. While doctrine is present, emphasis is heavily placed on meditation practice and looking deeply into the nature of things. There are two practices often taught in Zen centers. Zazen is sitting meditation wherein the meditator sits with legs crossed (possibly in lotus or half lotus position). The back is straight, chin slightly tucked and the eyes remain half open and loosely focused on the floor several meters in front of the person. The hands are positioned, one inside the other, in front of the navel. Typically practitioners are taught to begin the meditation by focusing non-elaboratively on the breath; attempting to simply observe the sensations around the nose or the movement of the abdomen. When one realizes that focus has been lost to other mental activity they are instructed to simply return to the breath. This is said to eventually calm the mind allowing one to drop the breath while retaining attentional stability in an ‘open’ state. Often, between sessions of Zazen, practitioners will engage in walking meditation called Kinhin. During Kinhin, practitioners walk in unison around the meditation hall. Hands are held as in Zazen. One foot is placed (often in very slow motion) in front of the other while trying to maintain mental focus on the ever changing point of contact between the front foot and the ground. A book by Austin (1999) is a great resource for Zen meditation in particular.

This brief introduction would not be replete without mention of a currently popular buzz word, that being ‘mindfulness’. Mindfulness is often used synonymously with vipashyana or insight meditation. In the West the term is often described using phrases such as moment to moment awareness, present moment awareness or observation which is accompanied by a non-elaborative, nonjudgmental, nonreactive or accepting stance toward one’s current experience. However, scholars have translated the term mindfulness from the Pali language (*sati*) as *‘not forgetting’*. When referred to in traditional texts the term seemed to imply that a practitioner would be mindful if they were aware of what they were doing while they were doing it. That is, not forgetting what one is doing, not zoning-out, day dreaming or acting on auto-pilot. It may be that in the West this present-centered notion was merged with a completely separate Buddhist principle, that of an accepting or nonjudgmental attitude. Nonetheless, the concept has been successfully applied, as will be discussed shortly, in clinics across North America and Europe to treat a range of disorders. Traditionally, mindfulness is applied to different spheres of attention to garner experiential insight into the nature of those phenomena, as mentioned briefly above.

While this extremely simplistic introduction to meditation does not do justice to the complexities of a rich 2500 year history, I hope it clarifies a common misconception that meditation is a single unitary practice or simply an attempt to ‘think of nothing’. At best it is hoped that the reader will come to understand that the primary aim of all of Buddhism is the cognitive, behavioural and emotional transformation of the practitioner through the application of an intricate arsenal of meditative practices.

Science and Meditation

Research with meditation is certainly not new. However, there has been an explosion of experiments over the past decade. These studies can be broken up roughly into experimental and clinical investigations. Clinical reports have largely employed secularized versions of mindfulness-based meditative practices often coupled with cognitive behavioural therapies. The clinical research to date lends support to a proposal that mindfulness practice has a positive impact on emotional processing via reductions in stress and reactivity. The most popular technique studied to date has been Mindfulness Based Stress Reduction (MBSR), an 8-10 week intervention involving the introduction of the concept of mindfulness and its application to real world situations.

The founder of MBSR, Jon-Kabat Zinn and colleagues (1992) found that the program was effective in reducing general anxiety and depression, findings which have been since replicated (Carlson and Garland, 2005; Carlson et al., 2007). Tacon et al. (2003) also found MBSR to be effective in reducing anxiety and in promoting positive emotions in hypertensive women. MBSR programs reportedly promote physical health outcomes (Grossman et al., 2004) such as relief from psoriasis (Kabat-Zinn et al., 1998). When taught to a cohort of factory workers the MBSR group exhibited enhanced immune functioning, evidenced by an increase in anti-body titres compared to a control group (Davidson et al., 2003). Similarly, MBSR also reportedly increases T-cell and overall cytokine production in cancer patients

(Carlson et al., 2003; Carlson et al., 2007). Overwhelmingly, researchers have suggested that the program teaches patients an alternative to reflexive tendencies for rumination and reactivity allowing a more controlled, relaxed and less stressful means of interacting with the world. Experimental studies with healthy participants have been fewer in number but are beginning to provide answers to the potential mechanisms driving the above mentioned clinical effects.

Studying high level Tibetan monks, Lutz et al. (2004) found that fast gamma oscillations, measured at frontoparietal scalp EEG electrodes, increase during a meditation technique involving the cultivation of compassion. Further, monks had a higher ratio of fast (gamma) to slow waves (alpha, theta) at baseline compared to controls which correlated with the experience level of the individual monks. The authors suggested the results may reflect a higher degree of neural synchrony in meditators which may correspond to increases in mental clarity reported to occur during the practice. In a subsequent study the monks were found to have more responsive limbic systems (INS, ACC) to emotional sounds during compassion meditation compared to their own baseline, to neutral sounds during meditation and to emotional sounds during meditation in controls (Lutz et al., 2008a). Furthermore, insular activation correlated with the self reported intensity of the meditative state in the monks. In yet another study the same group showed increases in positive affect after training naive subjects to meditate (Davidson et al., 2003). Positive relationships between the time spent meditating and changes in trait mindfulness, stress, psychological and medical symptoms and well-being have also been reported by others in a sample of 174 newly trained practitioners (Carmody and Baer, 2008). Farb et al. (2007) made the suggestion that meditation training may operate by altering communication between brain regions involved in emotion regulation. Their study demonstrated functional connectivity changes (decoupling) between medial prefrontal cortex (mPFC) and the insula (INS), following training with the MBSR program. Together these reports suggest meditation can have a positive impact on emotion processing and that effects are at least partly mediated by changes to neural systems. Another group of studies suggest meditation may also influence attention.

As mentioned above, meditation can be viewed as a family of techniques with the goal of transforming the practitioner in some manner, most commonly their attentional capacity. In support of this assertion, behavioural studies have shown superior performance by meditators on a variety of attention and executive function tasks such as the Attention Network Task (ANT), the Stroop Task, attentional blink, Symbol Digit Modalities Test, verbal fluency, and the n-back task (Tang et al., 2007; van Leeuwen et al., 2009; Prakash et al., 2010; Zeidan et al., 2010). Functional MRI studies have reported that high level monks, while meditating, activate attention-related cortices such as the ACC and frontoparietal networks (Brefczynski-Lewis et al., 2007; Manna et al., 2010). A large number of studies have also reported regional grey matter differences between individuals who meditate and those who do not (Lazar et al., 2005; Pagnoni and Cekic, 2007; Hölzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Holzel et al., 2010). In all cases meditators have been found to have greater levels of grey matter than non-meditators, regionally rather than globally, which has correlated with experience level. Several of these studies reported regions implicated in attention/executive processing (e.g. ACC, superior, middle and orbito-frontal regions (Lazar et al., 2005; Hölzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009). Importantly, there is now evidence from longitudinal training studies that both attention performance improvement (Tang et al., 2007; Lutz et al., 2009; Zeidan et al., 2010) and grey matter changes (Holzel et al., 2010) indeed relate to training, rather than reflecting pre-existing differences in distinct populations. As a whole these reports seem to validate traditional claims that meditation can enhance one's ability to attend (Austin, 1999). We turn now to the topic of pain and meditation and finally to our hypotheses concerning the potential influence of meditation on the perception of pain.

Meditation and Pain

It is clear that cognitive and emotional manipulations, such as attention, hypnosis, expectancy and placebo, can influence the experience of pain and the associated nociceptive brain activity. In 2005, when the present research began, evidence was beginning to emerge suggesting that meditation-related interventions may also be effective in modulating pain.

A series of articles, published over a 5 year span, reported on a group of chronic pain patients who had completed the MBSR program (Kabat-Zinn, 1982; Kabat-Zinn et al., 1985; Kabat-Zinn et al., 1987). The final paper included follow-up data (of up to 4 years post-training) from a heterogeneous group of chronic pain patients on measures of present moment pain, mood, medical symptoms, and psychiatric evaluation (Kabat-Zinn et al., 1987). Encouragingly, improvements were observed, even after 4 years post-training, on most measures. The exception however, was present moment pain. Despite high satisfaction and continued use of the program patients' pain ratings had reverted to pre-intervention levels. The authors suggested the results were indicative of the acquisition of an effective coping strategy, where the pain itself did not change but the relation or stance taken toward the pain was positively altered. This suggestion is consistent with the proposed influence of mindfulness on emotion regulation and reactivity, that is, general acceptance of experience and a shift in focus from an affective self-related perspective to a more objective and possibly sensory-related focus (Farb et al., 2010).

Hypotheses

Despite the scarcity of published works on meditation and pain in 2005 the proposed relationships between meditation, mindfulness, sustained attention and the cognitive-affective systems of the brain allowed several interesting hypotheses. Based on the reports of Kabat-Zinn et al. (Kabat-Zinn, 1982; Kabat-Zinn et al., 1985; Kabat-Zinn et al., 1987) and the clinical studies reviewed briefly above, one could hypothesize that the influence of meditation would be primarily on the emotional aspects of pain. As such, an experimental pain study with healthy practitioners of meditation (as we had planned) would be expected to reveal differences in the unpleasantness of the experience with little difference on more sensory aspects of pain such as intensity. Attenuated brain activity of ACC and INS and potentially increased activity in descending modulatory pathways would be predicted to accompany reductions in pain-related affect. Furthermore, practitioners with more extensive training would be expected to have larger effects. These served as our primary hypotheses for the studies described below. However studies of meditation and attention, coupled with findings in the pain and attention literature, provide another, albeit less clear, alternative.

Directing attention towards or away from a noxious stimulus has been shown to result in increased and decreased pain reports respectively (Quevedo and Coghill, 2007). Given that meditation is generally viewed as a family of attention-training protocols and that several reports now suggest practitioners have an enhanced capacity to deploy their resources, one could speculate that trained meditators would show different effects than non-meditators. The direction of this putative influence of meditation practice on pain perception is difficult to predict however. On the one hand, an increased capacity to direct attention toward a noxious stimulus, and retain the focus, might be expected to increase one's experience of pain intensity. On the other hand, such an ability could also be used to more successfully engage one's mind in a distracting task, thereby reducing the perceived intensity. Meditation itself might be viewed as the distracting task which could more effectively remove practitioners' attention from painful experience compared to untrained controls. Yet another possibility is introduced if in fact practitioners learn to sustain their attention in a more mindful or non-elaborative fashion as is suggested traditionally (Austin, 1999; Bodhi and R., 2007). In this scenario, although additional resources would be directed toward a noxious stimulus, reduced appraisal or evaluation of the offending stimulus may result in counterintuitive results, that is, strong stimulus-related activation accompanied by lower pain reports. Given the complete lack of studies examining meditation and pain, particularly in terms of brain imaging or attention, as well as the validity of the possible outcomes just listed, we considered this aspect of our work exploratory in nature.

The aim of the work presented in this dissertation was to expand our knowledge of the effects of prior meditation experience on pain perception in healthy individuals. Toward this end practitioners of Zen meditation were sought out from the greater Montreal area and matched for age/gender with control participants. Over a three year span two experimental studies were conducted. First, a psychophysical pain study assessed baseline thermal pain sensitivity and sought to answer the question of whether meditators respond differently than non-meditators to pain (experientially), under different attention conditions. Second, magnetic resonance imaging (MRI) was employed (both structural and functional) to ask several additional questions. Are group differences in reported pain reflected in differential processing in the brains of meditators and controls? If so, which brain regions underlie these differences and could this suggest the possible mechanism? Additionally, might the structure of the brain (grey matter thickness) underlie the group differences in pain sensitivity and pain modulation? We move now to the first of three published articles that have provided nearly as many new questions as answers.

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ARTICLES

Article 1

Grant, J.A. and Rainville, P. (2009) Pain sensitivity and analgesic effects of mindful states in Zen meditators: A cross-sectional study. *Psychosomatic Medicine* 71: 106-114.

ABSTRACT

Objective: This study investigates pain perception and the potential analgesic effects of mindful states in experienced Zen meditators. **Methods:** Highly trained Zen meditators (N=13; >1000 hr of meditation) and age/gender-matched control volunteers (N=13) received thermal stimuli adjusted individually at pre-baseline to elicit moderate pain on the left calf. Conditions included: a) baseline-1: no task, b) concentration control: attend exclusively to the left calf, c) mindfulness: attend to the left calf and observe, moment to moment, in a non-judgmental manner, and d) baseline-2: no task. **Results:** Meditators required significantly higher temperatures at pre-baseline to elicit moderate pain (Meditators: 49.9 °C; Controls: 48.2 °C; p=0.01). While attending 'mindfully', meditators reported decreases in pain intensity while control subjects showed no change from baseline. In contrast, instructions to direct attention toward the stimulation (concentration condition) increased pain in controls but not in meditators. Changes in pain unpleasantness generally paralleled those found in pain intensity. In meditators, pain modulation was correlated with slowing of the breathing rate and with greater meditation experience. Covariance analyses further indicated that mindfulness-related changes could be explained at least partly by changes in respiration rates. Lastly, the meditators reported higher tendencies to observe and be non-reactive of their own experience as measured on the Five Factor Mindfulness Questionnaire (FFMQ), and these factors correlated with individual differences in respiration. **Conclusions:** These results indicate that Zen meditators have lower pain sensitivity and experience further analgesic effects during mindful states. Although the cross-sectional design of this study has some limitations, results are consistent with analgesic effects of mindfulness-based practice that may reflect cognitive/self-regulatory skills related to the concept of mindfulness and possibly mediated in part by changes in respiration. These results should motivate prospective studies using well-controlled quantitative sensory testing methods to investigate the effects of meditation training and respiration on pain regulation.

Six keywords: pain, meditation, Zen, mindfulness, respiration, psychophysics

Abbreviations: ECG: electrocardiogram; HF: high frequency; HRV: heart rate variability; LF: low frequency; LF/HF: low to high frequency ratio; FFMQ: Five Factor Mindfulness Questionnaire; MBSR: Mindfulness Based Stress Reduction; VAS: visual analogue scale

INTRODUCTION

Considerable scientific attention has been devoted recently to mindfulness (Bishop, 2002), a particular attentional stance with historic origins in Buddhist meditative traditions. Mindfulness can be described as an equanimous state of observation of one's own immediate and ongoing experience. Although much debate exists around the definition of mindfulness, both within spiritual traditions and between scientists, common ground can be found. Mindfulness can be considered a particular manner of attending which can be developed through practice. This attentional stance is not restricted to time spent in formal meditation and scales have been developed to measure mindfulness in both meditators and non-meditators (Baer et al., 2004; Baer et al., 2006; Lau et al., 2006). Mindfulness has been described as, "intentional self-regulation of attention from moment to moment… of a constantly changing field of objects… to include, ultimately, all physical and mental events…" (Kabat-Zinn, 1982). Furthermore, an attitude of acceptance toward any and all experience is stressed. Traditional accounts of mental and emotional transformation accompanying mindful practice (Thanissaro, 2000; Nyanaponika, 2003) are supported by scientific findings of psychological and biological effects on practitioners (Davidson et al., 2003; Lutz et al., 2004; Lazar et al., 2005) and patients (Kabat-Zinn, 1982; Kabat-Zinn et al., 1992; Miller et al., 1995; Teasdale et al., 2000; Schwartz and Begley, 2002; Ma and Teasdale, 2004). Here the potential of mindful attention to influence the perception of pain was investigated in highly trained meditators.

A growing body of research lends support to a proposed link between mindfulness practice and emotional processing. Mindfulness based therapies have reported success treating anxiety (Kabat-Zinn et al., 1992; Miller et al., 1995), obsessive compulsive disorder (Schwartz and Begley, 2002) and depression (Teasdale et al., 2000; Ma and Teasdale, 2004). Positive correlations between meditation experience of Buddhist monks and positive affect (Lutz et al., 2004) have been reported. Increases in positive affect have also been observed in a longitudinal study in which naïve subjects were trained to meditate (Davidson et al., 2003). Additionally, positive relationships have been found in a sample of 174 newly trained practitioners between the time spent meditating, changes in trait mindfulness, stress, psychological and medical symptoms and well being (Carmody and Baer, 2008). The proposed relationship between mindful attention and the affective systems of the body and brain raises interesting questions concerning the effect of mindfulness on emotionally salient experiences such as pain.

It is well known that cognitive manipulations such as hypnosis, attention, expectancy or placebo can influence the experience of pain and the associated neurophysiological activity (Apkarian et al., 2005; Koyama et al., 2005; Kupers et al., 2005). There is also mounting evidence that mindfulness may be effective in treating chronic pain. However, most of the available clinical studies suggest an effect primarily on emotional and functional aspects of pain conditions and little or no long-term effects on pain sensation. Over the course of 5 years, Kabat-Zinn reported on a group of chronic pain patients who had completed the Mindfulness Based Stress Reduction (MBSR) program (Kabat-Zinn, 1982; Kabat-Zinn et al., 1985; Kabat-Zinn et al., 1987). The final paper of the series included measures of present moment pain as well as symptom, mood and psychiatric evaluations before and after MBSR training in 225 patients, with follow-up data of up to 4 years (Kabat-Zinn et al., 1987). Significant positive improvements were found on all measures immediately following the 10 week training program. However, follow-up evaluation showed stable improvements on most measures with the exception of present moment pain. The authors interpreted the results as the acquisition of an effective coping strategy for pain where the pain itself did not change but the relation or stance taken toward the pain was positively altered. Improvements in pain acceptance were also obtained by Morone et al. in low back pain patients following an 8 week meditation program (Morone et al., 2007). Further, the MBSR program has been used effectively to treat female fibromyalgia patients, resulting in improvements in quality of life, pain coping, anxiety, depression, pain complaints as well as visual analog scales of pain severity, effects not observed in an active control group (Kaplan et al., 1993 ; Grossman et al., 2007). These positive effects remained stable at three years post-intervention. Similar conclusions were reached by McCracken et al. (McCracken et al., 2007) in a correlational study involving 105 chronic pain patients showing inverse associations between mindfulness and depression symptoms, pain related anxiety and disability, after controlling for other patient-related factors including pain intensity. However, this study further found a negative correlation between pain intensity and mindfulness evaluated using a questionnaire. Taken together, clinical studies suggest (a) significant benefits of mindfulness-based interventions on pain-related emotional and functional measures and (b) individual differences in pain sensory processing associated with mindfulness.

Little attention has been devoted to effects of mindfulness on pain using experimental methods in healthy subjects. Kingston et al. (Kingston et al., 2007) found increased tolerance to a cold pressor test and decreased reports of pain in a group of individuals trained in mindfulness compared to a group trained with visual imagery. However, changes in pain were completely independent from changes in mindfulness following training (i.e. correlation coefficients < 0.1). Those partly negative findings may be explained by the relatively limited amount of training provided to the subjects. The present study sought to clarify these effects in healthy individuals highly-trained in meditation.

The aim of the present study was to assess the effect of mindfulness and mindful states on pain perception in experienced meditators. Practitioners of Zen (a mindfulness based practice (Austin, 1999)) and age/gender-matched control subjects were recruited to participate in a psychophysical study involving thermal pain. The cross-sectional experimental design allowed us to examine potential differences in pain sensitivity between experienced meditators and individuals without meditation experience. Meditators were further expected to show greater reductions in pain than controls in a condition involving mindful attention. Secondarily, based on clinical studies showing benefits of mindfulness on stress and negative emotional states, effects were expected to be more pronounced on the affective-motivational aspect of pain (i.e. unpleasantness) as opposed to the sensory discriminative aspect (i.e. pain intensity). Furthermore, we examined associations between the amount of meditation experience, self-assessed mindfulness, the degree of pain modulation, and physiological activity. A cross-sectional design was used to take advantage of the extensive training of the meditation group, with the assumption that highly trained meditators would display more robust and stable effects. This approach was considered pre-required to future prospective randomized studies involving intensive training of naïve individuals and extensive quantitative psychophysical testing pre- and post-training.

MATERIALS AND METHODS

Participants

All participants provided written informed consent to participate in a study investigating the cognitive modulation of pain and received a monetary compensation. The recruitment process involved visits to meditation centers and posting ads in local newspapers and online classifieds. Exclusion criteria included current medication use, history of chronic pain, neurological or psychological illness, claustrophobia, and for control participants, previous experience with meditation or yoga. A list of possible meditators was first compiled (N=68). The list ranged greatly in experience level and spanned many meditative traditions. The largest possible sample controlling for homogeneity of training and meeting the arbitrary requirement of 1000 hr of experience consisted of 13 Zen practitioners. Meditators from other disciplines were not tested. Thirteen age- and gender-matched control subjects, with no previous experience with meditation or yoga, were recruited (Table 1). Experiments were conducted between May and December of 2006 at the Centre de recherché de l'Institut universtiaire de gériatrie de Montréal. All procedures were

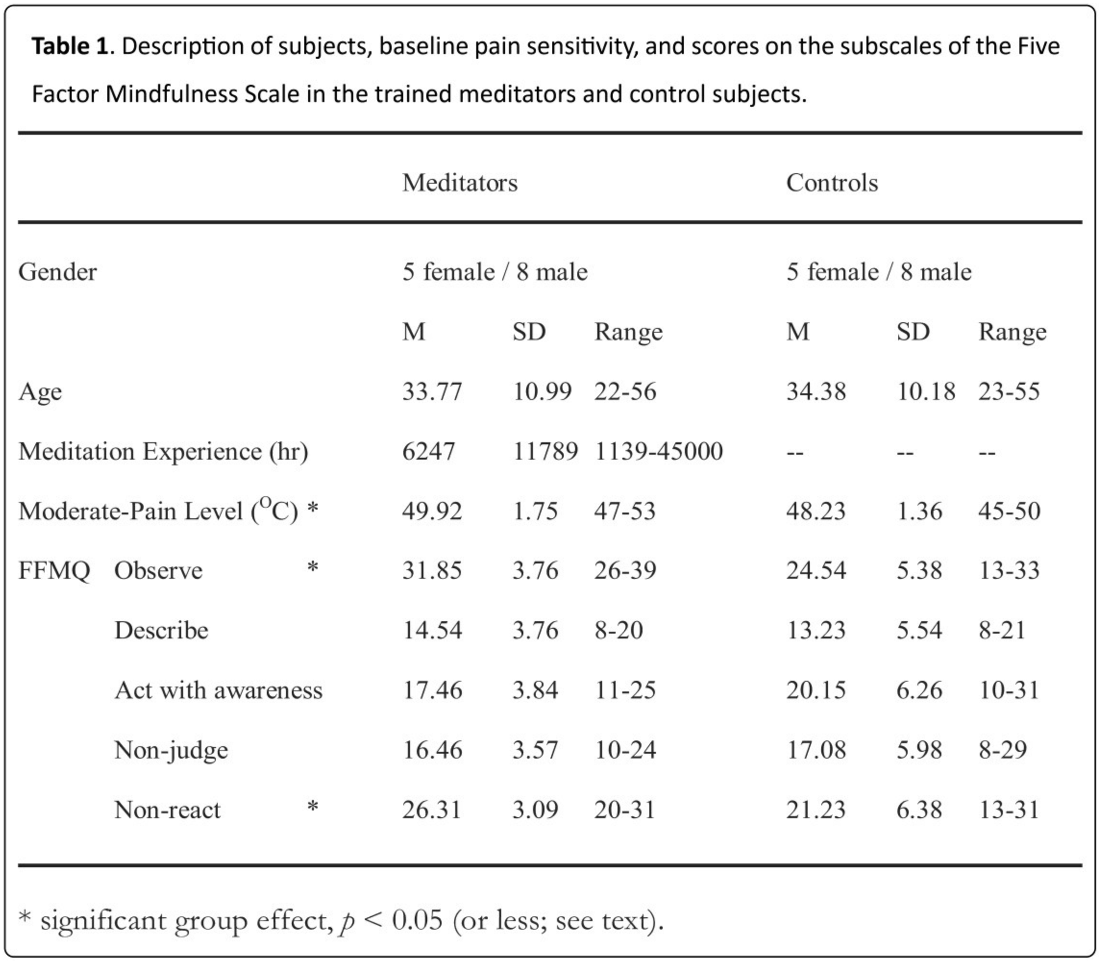


Table 1. Description of subjects, baseline pain sensitivity, and scores on the subscales of the Five Factor Mindfulness Scale in the trained meditators and control subjects.

	Meditators			Controls		
Gender	5 female / 8 male			5 female / 8 male		
	M	SD	Range	M	SD	Range
Age	33.77	10.99	22-56	34.38	10.18	23-55
Meditation Experience (hr)	6247	11789	1139-45000	--	--	--
Moderate-Pain Level (^{O}C) *	49.92	1.75	47-53	48.23	1.36	45-50
FFMQ Observe *	31.85	3.76	26-39	24.54	5.38	13-33
Describe	14.54	3.76	8-20	13.23	5.54	8-21
Act with awareness	17.46	3.84	11-25	20.15	6.26	10-31
Non-judge	16.46	3.57	10-24	17.08	5.98	8-29
Non-react *	26.31	3.09	20-31	21.23	6.38	13-31

* significant group effect, $p < 0.05$ (or less; see text).

approved by the local ethics committee (CMER-RNQ 05-06-020).

Thermal stimuli

Thermal stimulation was produced by a Medoc Thermode with a 9 cm^2 contact probe (TSA Neuro-sensory analyser, Medoc Ltd. Advanced Medical System, Israel). Each stimulation consisted in a 1s ascending ramp from 37 °C to the target temperature, a 4s plateau, and a 1s descending ramp back to 37 °C (Figure 1). In the experimental conditions the target temperature was always 43 °C for non-painful warm trials for all participants. The target temperature for painful hot trials was adjusted individually to produce moderate pain (up to a maximum of 53.0 °C), as described below. To minimize the likelihood of habituation or sensitization, the stimulation was applied in a pseudo-random order to 6 different locations of the lateral/posterior portion of the left calf, such that each position was stimulated twice at the painful and non-painful levels in each condition.

Experimental Protocol

First, a pre-baseline measure of the temperature required to elicit moderate pain was determined in each individual using the ascending method of limits. Beginning at 42°C and increasing in steps of 1°C, a series of thermal stimuli was applied to the inner surface of the left calf. The moderate-pain level was defined as the temperature required to elicit a pain intensity rating of 6-7 on a 10 point scale on which 0 corresponded to “no pain” and 10 to “extremely painful”. This was done to account for individual differences in pain sensitivity. Moderate pain was selected specifically to minimize the risk of ceiling or floor effects across the experimental conditions. The temperature required to produce moderate pain was evaluated again in a subset of 19 participants attending a separate experimental session. This allowed us to evaluate the test-retest reliability of this measure. Each subject’s moderate-pain level was subsequently used in all painful trials in each of the following experimental conditions.

Participants were in the supine position and received brief thermal stimuli in 4 experimental conditions, as depicted in Figure 1. Conditions were administered in the

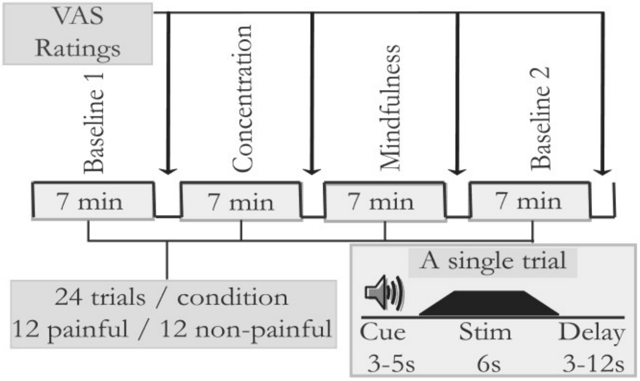


Figure 1. Experimental conditions. The experiment consisted in 4 blocks of 24 trials with each block lasting 7 min. Blocks differed in terms of the instructions given to subjects on how to attend to the stimulation (see Methods). Following each block, subjects rated the intensity and unpleasantness of the pain experienced using electronic visual analogue scales. A single trial began with an auditory cue that correctly identified the subsequent stimulus as either painful hot or non-painful warm. The inter-trial interval varied between 3 and 12 sec.

same order across all participants and differed only in the instructions given prior to the upcoming series of thermal stimuli. The first and fourth conditions were control conditions (baseline-1, baseline-2) in which instructions were given to: *Keep your eyes closed and try not to fall asleep*. The second condition was termed concentration and the instructions were: *Keep your eyes closed and focus your attention exclusively on the stimulation of your left leg*. This condition was designed to reflect the style of attending employed in various meditation techniques referred to as concentrative meditation (Austin, 1999) and was always performed immediately prior to mindfulness. In this type of meditation one attempts to focus solely on a single object considering everything else distraction with the goal of eventually becoming absorbed in the object. The concentration condition was used as an attentional control condition for mindfulness and allowed comparisons to be made with previous studies of pain and attention. The third condition was always mindfulness and the instructions were: *Keep your eyes closed and focus your attention on the stimulation of your left leg. Try not to judge the stimulation but simply observe the sensation, moment by moment*. The mindfulness condition involved attentional deployment patterned around that used during mindfulness meditation, of which Zen is one example (Austin, 1999).

Each condition was approximately 7 min in duration and contained 12 non-painful and 12 painful trials administered in a predetermined pseudo-random order. Each trial began with a 3-5s auditory cue (1 kHz or 100 Hz steady tones) which correctly indicated whether the subsequent stimulus was painful (hot) or non-painful (warm). Cues were used to help orient the subject, maximizing the efficacy of the attentional deployment during stimulation, and reducing potential effects of surprise or uncertainty regarding the occurrence of pain stimuli. A variable delay of 3-12s separated successive trials.

Dependent Measures

Subjects were asked to rate the pain induced by the painful stimuli immediately following each series of stimuli in each condition. Pain perception was assessed using electronic visual analogue scales (VAS) measuring pain intensity and pain unpleasantness. Scales ranged from 0-10 with verbal anchors at 0 (*not painful* or *not unpleasant*) and 10 (*extremely painful* or *extremely unpleasant*). Instructions to distinguish between the intensity and the unpleasantness of pain were based on those reported in previous studies (Price and Harkins, 1987; Rainville et al., 1992).

Cardiac and respiratory activity was monitored continuously to document possible modifications in ongoing physiological activity during all experimental conditions. Indices of heart rate variability (HRV) were computed according to the guidelines of the Task Force of The European Society of Cardiology and the North American Society for Pacing and Electrophysiology (1996). Respiration and heart rates were recorded with a Biopac MP150 system and analyzed using the Acknowledge software version 3.7.1. (Biopac Systems Inc.). Six min of continuous recording, beginning 30s after the initiation of each condition, to allow for acclimation, was analyzed. ECG was measured using a three electrode array and the peak of the R-wave was detected automatically to obtain a continuous R-R interval tachogram. The ECG was visually inspected offline to detect artefacts; the R-wave detection procedure was also verified and the tachogram was corrected accordingly. Respiration was measured with a strain-gage belt placed over the lower ribs.

Participants completed the Five Factor Mindfulness Questionnaire (FFMQ) (Baer et al., 2006), a 39 item questionnaire designed to measure five skills thought to be associated with mindfulness: observing, describing, acting with awareness, accepting without judgement and non-reactivity. A brief questionnaire was also developed to assess the meditative history of participants including: type of practice, number of years practicing, frequency and length of practice in days per week, length of individual sessions in hours, amount of time spent in retreat, and motivation for practicing.

Statistical Analysis

The temperature required to reach the moderate-pain level was compared between meditators and control subjects using an independent-sample t-test. For the experimental conditions, between-group differences in pain ratings and physiological measures were assessed via the interaction term of ANOVAs testing for the effects of Condition (baseline-1, concentration, mindfulness and baseline-2) as the within subject factor and Group (meditators and controls) as a between subject factor. Simple effects of conditions were also examined within each group using separate repeated-measure ANOVAs. To address *a priori* hypotheses on pain modulation during different attention conditions planned contrasts were also applied to examine specifically the difference between concentration and baseline and between mindfulness and baseline. Adding gender as an additional between-subject factor did not yield any significant interaction and this factor was not included in the present report. Relations between measures were assessed using Pearson and Spearman correlations. Pain modulation values used to correlate with other measures were calculated by subtracting the baseline-1 rating from the rating in the condition of interest. Covariance was further used to examine the pain modulation effects after accounting for changes in physiological activity. Percent pain modulation was calculated by dividing the pain modulation value by the baseline-1 value. Partial eta-squared (η_p^2) was used as the effect size for ANOVAs and Cohen's d (Cohen, 1988) was used for pair wise contrasts (adjusted for r and using Hedges' bias correction (Hedges and Olkin, 1985)). The threshold for significance was set to $p<0.05$, based on two-tailed tests, unless otherwise specified.

RESULTS

Pain Sensitivity

An individual-adjustment procedure was used in the pre-baseline phase of the study to insure that subjects felt moderate pain in the baseline condition. This procedure was found to be highly reliable (test-retest: R = 0.76, p < 0.001) and revealed important group differences. The moderate-pain level was significantly different between groups [*t*(24) = 2.75, *p* = .01, d = 1.04, Table 1; Figure 2a] with meditators requiring higher temperatures compared to controls (Mean ±SD = 49.9 ±1.75°C versus 48.2 ±1.36°C, respectively). Notably, two meditators reached the highest temperature allowed in this study (53.0°C). One of these subjects rated 53 °C as 6.5/10 whereas the other rated it as 5/10; i.e. lower than the target perceptual level. Thus, a ceiling effect prevented the full group difference from being captured.

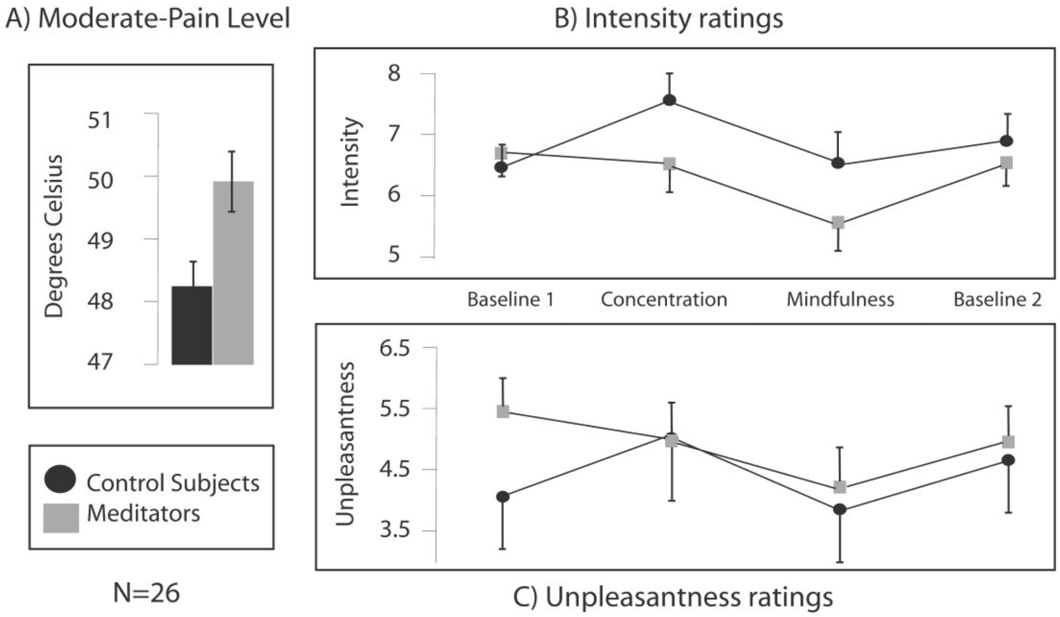


Figure 2. Perceptual results: a) Mean (±SEM) temperature required to produce a pain sensation of moderate intensity in the baseline condition. b) Mean (±SEM) intensity and c) unpleasantness ratings of each group in each condition.

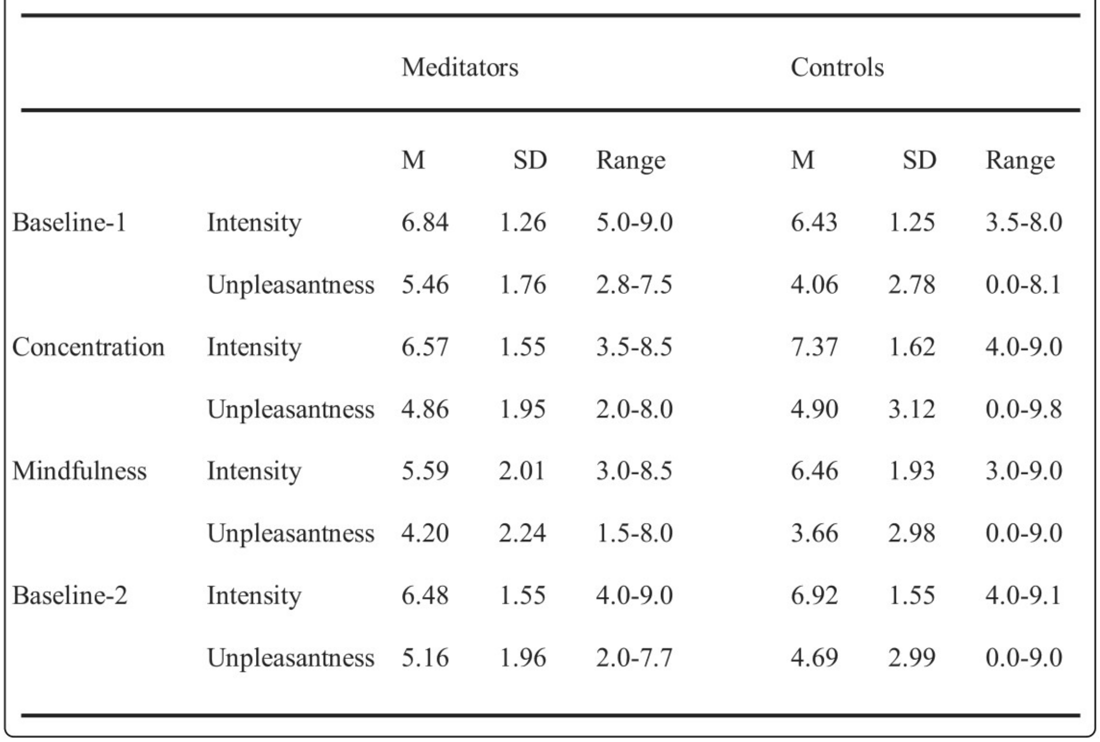
Nevertheless, the pain reported in the baseline-1 condition using those individually adjusted stimuli was comparable across groups [independent-sample t-tests; intensity: *t*(24) = -.92, *p* = .37, d = -.34; unpleasantness: *t*(24) = -1.70, *p* = .10, d = -.65]. This indicates that trained meditators had lower pain sensitivity which was adequately controlled in the baseline-1 condition, before testing the acute effects of concentration and mindfulness states.

Effects of Concentration and Mindfulness on Pain

Self-reported pain intensity and unpleasantness were acquired immediately following each experimental condition (Table 2). There was a significant Group x Condition interaction [$F(3, 72) = 2.76$, $p = .05$, $\eta_p^2 = .10$, Figure 2b] for intensity ratings indicating differing patterns between groups. The contrast analysis revealed that the overall interaction was accounted for by (1) an increase in pain during concentration (vs baseline-1) in controls while meditators showed a slight decrease [$F(1, 24) = 5.66$, $p = .02$, $\eta_p^2 = .19$] and (2) a decrease in pain during mindfulness (vs baseline-1) in meditators but not in control subjects [$F(1, 24) = 6.00$, $p = .03$, $\eta_p^2 = .20$]. Planned within-group contrasts revealed that the increase in intensity ratings during concentration was significant for controls (+14.6%) [$F(1, 12) = 17.50$, $p < .001$, d = 1.80] and that the decrease in intensity ratings during mindfulness was significant for meditators (-18.3%) [$F(1, 12) = 6.23$, $p = .02$, d = -.99]. Additionally, the meditators showed a significant reduction in pain (-15%) between the concentration and mindfulness conditions [$F(1, 12) = 4.8$, $p < .05$, d = -.86*;* this effect did not reach significance in control subjects: p=.09]. This confirms that concentration increased pain in controls and that mindfulness decreased pain in trained Zen meditators.

The overall Group x Condition interaction did not reach significance for unpleasantness ratings [$F(3, 72) = 1.92$, $p = .13$, $\eta_p^2 = .07$]. However, examination of

Table 2. Pain ratings in trained meditators and control subjects across experimental conditions.



		Meditators			Controls		
		M	SD	Range	M	SD	Range
Baseline-1	Intensity	6.84	1.26	5.0-9.0	6.43	1.25	3.5-8.0
	Unpleasantness	5.46	1.76	2.8-7.5	4.06	2.78	0.0-8.1
Concentration	Intensity	6.57	1.55	3.5-8.5	7.37	1.62	4.0-9.0
	Unpleasantness	4.86	1.95	2.0-8.0	4.90	3.12	0.0-9.8
Mindfulness	Intensity	5.59	2.01	3.0-8.5	6.46	1.93	3.0-9.0
	Unpleasantness	4.20	2.24	1.5-8.0	3.66	2.98	0.0-9.0
Baseline-2	Intensity	6.48	1.55	4.0-9.0	6.92	1.55	4.0-9.1
	Unpleasantness	5.16	1.96	2.0-7.7	4.69	2.99	0.0-9.0

the means (Figure 2c) and the planned contrasts suggested effects similar to those observed for pain intensity. A significant interaction was found between baseline-1 and concentration with controls showing increased unpleasantness ratings while meditators showed decreased ratings [$F(1, 24) = 4.27$, $p = .05$, $\eta_p^2 = .15$]. The Group x Condition interaction was not significant between baseline-1 and mindfulness [$F(1, 24) = 2.36$, $p = .14$, $\eta_p^2 = .09$]. However, the planned within-group contrasts revealed that the decrease in unpleasantness between baseline-1 and mindfulness for meditators (-23.1%) was significant [$F(1, 12) = 5.25$, $p = .04$, d = -.88]. The change in unpleasantness during mindfulness was significantly correlated with the corresponding changes in pain intensity across all subjects ($R = 0.76$, $p < .001$). Control subjects on the other hand showed a marginally significant increase (+20.7%)

in unpleasantness ratings [*F*(1, 12) = 4.54, *p* = .055, d = .85] between baseline and concentration. Additionally, the meditators showed a significant reduction in unpleasantness (-14%) between the concentration and mindfulness conditions [*F*(1, 12) = 6.2, *p* = .03, d = -.95]. Although the general ANOVA did not reach significance, these planned analyses and the correlation between change scores, suggest that, similar to pain intensity, pain unpleasantness is reduced during mindfulness for meditators and increased during concentration for control subjects.

Importantly, both pain intensity and unpleasantness ratings returned to the pre-test baseline (baseline-1) in the last condition (baseline-2). Direct statistical contrasts between the baseline values did not reach significance on pain intensity [control: paired t-test *t*(12) = -1.72, p = .11, d = .68; meditators: paired t-test *t*(12) = .97, p = .35, d = -.37] or pain unpleasantness [control: *t*(12) = -1.88, p = .08, d = -.73; meditators: *t*(12) = .54, p = .60, d = .21]. This indicates that subjects did not habituate or sensitize significantly to the stimuli over the repeated blocks of painful stimulation.

Changes in pain were further examined in relation to meditation training. The amount of meditation experience of individual practitioners predicted the degree of pain intensity modulation (i.e. Vs baseline) with more hours of experience leading to greater reductions in pain intensity during the mindfulness condition [*r*(9) = -.82, *p* < .01]. Hours of experience correlated to a lesser extent and not significantly with reductions in unpleasantness [*r*(9) = -.42, *p* = .20]. Two cases were classified as outliers based on Cook's Distance and Centered Leverage values and excluded from those correlation. One of these was a Zen monk, with ~45000 hr of experience versus the second highest at ~7000 hr. Both subjects were in the upper end of the analgesic effect. To include all 13 subjects non-parametric (Spearman) correlations were performed and reached significance on pain intensity [rho (11) = -.56, *p* = .04] but not unpleasantness [rho (11) = -.33, *p* = .28]. Notably, clinically significant analgesic effects (> 2/10 on the pain intensity VAS) were obtained only in meditators with more than 2000 hours of experience while the subjects with 1000-2000 hours of experience showed no changes or slight increases in pain.

Physiological Measures

Physiological activity was affected by the experimental conditions and this effect differed between groups as demonstrated by a significant Group x Condition interaction in respiration rate [*F*(3, 69) = 3.30, *p* = .04, η_p^2 = .13; also note a marginally significant main effect of Group: *F*(1, 23) = 3.85, *p* = .06, d = -.76]. The contrast analysis revealed that the overall interaction effect was accounted for by an interaction between baseline and mindfulness with controls having slightly increased breathing rates and meditators substantially decreased breathing rates [*F*(1, 23) = 4.25, *p* = .05, η_p^2 = .16; Figure 3]. The decrease in breathing rate observed in meditators did not reach significance in the follow-up pair wise contrast [*F*(1, 12) = 2.88, *p* = .11, d = .66]; however independent sample t-tests confirmed that meditators breathed at a slower rate than the controls in the concentration and mindfulness conditions [baseline-1, *t*(23) = 1.51, *p* = .07, d = -.58; concentration, *t*(23) = 2.03, *p* = .03, d = -.77; mindfulness, *t*(23) = 2.50, *p* = .01, d = -.95; baseline-2, *t*(23) = 1.61, *p* = .12, d = -.61]. Notably, pain modulation induced by mindfulness (relative to baseline-1) was correlated with the corresponding changes in respiration rate across all subjects [intensity: $r(23) = .37$, $p = .03$; unpleasantness: $r(23) = .42$, $p = .02$]. Furthermore, the significant decrease in pain intensity reported above in the meditators during the mindfulness condition relative to baseline-1 (see Figure 2) did not reach significance after including the changes in respiration as a covariate [$F(1,11) = 3.02$, $p = .11$]. In contrast, the significant increase in pain intensity reported by the control subjects in the concentration condition remained significant after accounting for changes in respiration rates [$F(1,11) = 20.94$, $p = .001$]. These effects suggest that the changes in pain induced by mindfulness, but not concentration, may be at least partly accounted for by changes in respiration.

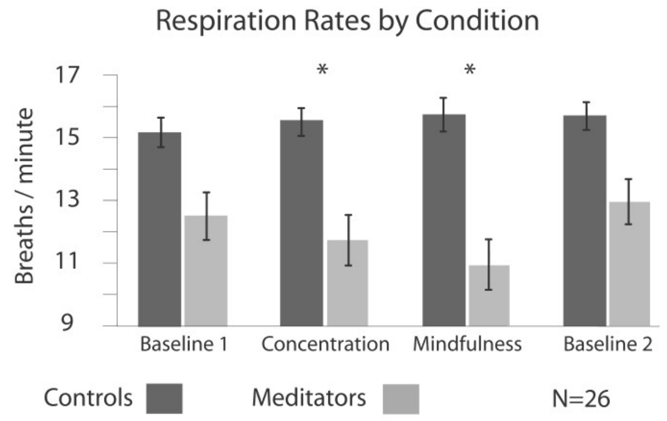


Figure 3. Respiratory rates across groups and conditions. Meditators breathed at a slower rate during each condition. The respiration pattern followed that of their pain ratings (Figure 2b-c). (* $p < .05$ for the independent sample t-test contrasting groups).

Heart rate, measured in beats per minute across each condition, differed over time but not between groups [main effect of condition, $F(3, 72) = 4.76$, $p = .04$, $\eta_p^2 = .17$; main effect of group, $F(1, 24) = .49$, $p = .49$, d = .27; Group x Condition interaction, $F(3, 72) = 1.97$, $p = .17$, $\eta_p^2 = .08$]. The significant effect consisted of a steady slowing of the heart rate for both groups from baseline-1 through to baseline-2. Spectral analyses of HRV revealed no significant main effects of condition or Group x Condition interactions for LF power, HF power or the ratio of LF to HF [LF main effect: *F*(3, 72) = 2.02, *p* = .17, $\eta_p^2 = .08$ and interaction: *F*(3, 72) = 1.11, *p* = .30, $\eta_p^2 = .05$; HF main effect: *F*(3, 72) = .65, *p* = .43, $\eta_p^2 = .03$ and interaction: *F*(3, 72) = 1.54, *p* = .23, $\eta_p^2 = .06$; LF/HF main effect: *F*(3, 72) = 2.79, *p* = .11, $\eta_p^2 = .10$ and interaction: *F*(3, 72) = 2.27, *p* = .15, $\eta_p^2 = .09$]. There was however a main effect of group for the LF/HF ratio [*F*(1, 24) = 7.13, *p* = .01, d = 1.01]. Independent sample t-tests revealed that meditators had a higher LF/HF ratio during baseline-1 [*t*(24) = -2.15, *p* = .05, d = .81], concentration [*t*(24) = -2.41, *p* = .03, d = .91] and mindfulness [*t*(24) = -2.10, *p* = .05, d = .78]. These differences are likely accounted for by the respiration rates (i.e. respiratory sinus arrhythmia) of six meditators that breathed in the low frequency range of heart rate variability (0.05-0.15Hz) as opposed to the more typical breathing rates found in the high frequency range (0.15-0.40Hz) that seven meditators and all 13 controls displayed. This difference in LF/HF may therefore be the result of either or both (a) an increased sympathetic activity in meditators or (b) a shift in respiratory sinus arrhythmia, mediated by the parasympathetic nervous system, into the LF range.

Five Factor Mindfulness Questionnaire

Groups also differed on psychological characteristics associated with mindfulness assessed using the FFMQ. There were significant group differences on the observe [*t*(24) = 4.01, *p* < .001, d = 1.53] and non-react [*t*(24) = 2.58, *p* = .02, d = .98] subscales (Figure 4) with meditators rating themselves as more observant and less reactive to their own experience than control subjects. Considering the entire sample, the correlation of the moderate-pain level reached significance with the observe subscale [*r*(24) = .43, *p* = .04] and approached significance with the non-react subscale [*r*(24) = .34, *p* = .08]. Lower reactivity (non-react subscale) was also associated with slower respiration rates in each condition [baseline-1: *r*(23) = .47, *p* = .02; concentration: *r*(23) = .40, *p* = .04; mindfulness: *r*(23) = .42, *p* = .04; baseline-2: *r*(23) = .41, *p* = .04].

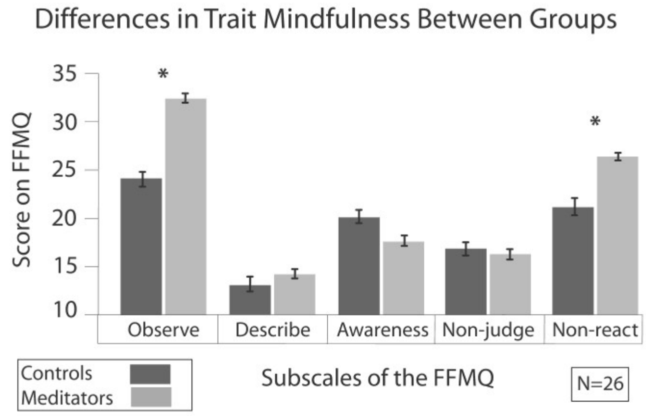


Figure 4. Mean (±SEM) scores on the subscales of the FFMQ. Scores on the observe and non-react subscales were different between groups with meditators rating themselves as more observant and less reactive than control subjects (* $p < 0.05$).

DISCUSSION

Thermal pain perception was investigated in a group of trained Zen meditators and compared to a group of untrained, age- and gender-matched, control subjects. The main findings are the following:

1) Meditators required hotter temperatures than controls to experience moderate pain.

2) As hypothesized, meditators experienced less pain while attending mindfully, whereas control subjects did not show such modulation.
3) Unexpectedly, analgesic effects of mindfulness were more clear on the sensory dimension of pain (i.e. perceived intensity) then the affective dimension of pain (i.e. pain unpleasantness), although effects were observed in the same direction.
4) The magnitude of the analgesic effect of mindfulness was predicted by the number of hours of meditation practice in meditators.
5) When attention was directed toward the stimulation, with no mention of attending mindfully, control subjects showed the expected increase in pain intensity and unpleasantness whereas meditators did not differ from baseline.
6) Physiologically, meditators had slower breathing rates than controls, consistent with their self-assessed reduced reactivity. Importantly, changes in respiration rate predicted the changes in felt pain and the analgesic effect of mindfulness states was no longer significant after accounting for changes in respiration rates (covariance).
7) On a mindfulness scale, meditators scored higher on the tendency to be observant and non-reactive. Higher scores on these dimensions of mindfulness were further associated with lower pain sensitivity and slower respiration rates.

Zen meditation was associated with lower pain sensitivity as demonstrated by the higher temperatures required to produce moderate pain. The observed difference (49.9°C Vs 48.2°C) should be considered large as it typically corresponds to an increase of about 50% on a ratio scale of pain perception or 20 to 25 points on a 0-100 numerical pain scale, based on similar psychophysical methods (Price et al., 1983; Price and Harkins, 1987). The procedure for acquiring the moderate-pain level did not involve explicit instructions in how to attend, was conducted before testing began and was intended to assess pain sensitivity while the subject was attending as naturally as possible. Zen practitioners are taught to generalize the skills learned in their formal mental training sessions to everyday life, to be mindful both in and out of meditation. Thus, one potential explanation for the group difference in pain sensitivity is the attentional stance generally taken toward any sensory event. This group difference was related parametrically to two facets of mindfulness. As subjects' scores increased on the observe and non-react subscales of the FFMQ the temperature required for moderate pain also rose. These correlations spanned all subjects with meditators concentrated at the high end of both scales and controls at the lower end of both scales. Whether this effect can be attributed to meditative training or pre-existing individual differences is discussed below.

Over and beyond the large pain sensitivity difference between groups, explicit instruction to attend mindfully had analgesic effects in meditators but not in control subjects. Furthermore and quite importantly, the magnitude of the analgesic effect was related to training. While attending mindfully, the Zen practitioners showed reductions of 18% pain intensity. Remarkably, individuals with more extensive training experienced greater reduction in pain. This finding is extremely important as it suggests that the observed pain reduction may not simply reflect a predisposition to meditation (individual differences) but may also involve experience-dependent changes associated with practice. This is in line with other studies linking meditation training with mindfulness, medical symptoms and well-being (Carmody and Baer, 2008); attention performance, anxiety, depression, anger, cortisol and immunoreactivity (Tang et al., 2007); an inverted U shaped function of attention related brain activity (Brefczynski-Lewis et al., 2007); electrophysiological markers of positive affect (Lutz et al., 2004); positive affect and stronger immune responses (Davidson et al., 2003); and cortical thickness and grey matter density (Lazar et al., 2005; Pagnoni and Cekic, 2007; Hölzel et al., 2008). Taken together these studies are consistent with the notion of meditation as a transformative practice evolving from the development of concentrative skills to more compassionate and mindful states associated with structural and functional changes in the brain leading to more positive emotional states, less pain and improved health.

Consistent with previous studies (Miron et al., 1989; Villemure et al., 2003), directing attention toward pain (i.e. the concentration condition) resulted in increased pain for control subjects. Pain intensity increased by 15% and pain unpleasantness increased by 21%. However the Zen meditators showed a slight non-significant reduction from baseline during this condition. In the meditators, a greater tendency to adopt a mindful stance may underlie the absence of the typical enhancing effect of attention on pain. This is consistent with the group differences observed on the FFMQ and in pain sensitivity. Having trained to be mindful in everyday life, it may be difficult for such individuals to not exercise this attentional stance.

The reduction in unpleasantness ratings for meditators while attending mindfully fits well with allegations that this type of meditation has an impact on affective processing. The efficacy of using mindfulness based therapies for affective disorders such as depression (Teasdale et al., 2000), anxiety (Kabat-Zinn et al., 1992;

Ma and Teasdale, 2004) and obsessive compulsive disorder (Schwartz and Begley, 2002) has already been demonstrated. However, the analgesic effect of mindful attention in Zen meditators was not restricted to the affective dimension of pain, as measured by unpleasantness, but it was equally potent and it reached significance primarily on pain intensity. Consistent with this effect, pain sensitivity was also predicted by trait mindfulness. Taken together these results suggest that mindfulness does not simply modify the emotional reaction to pain but may also interact with the sensory processing of the nociceptive input. Previous studies on the interaction of emotions and pain have generally found stronger effects of emotion on pain unpleasantness but significant effects have also been reported on pain sensation intensity (Rainville, 2004). The putative reduction in affective reactivity associated with meditative practice may thereby contribute to the reduction in both sensory and affective processing of the nociceptive input.

The analgesic effects of mindful attention may relate to the physiological state induced as suggested by the respiration data. Overall, the meditators breathed at a slower rate than control subjects in all conditions and their mean respiratory pattern followed that of their pain ratings. In contrast, respiration rate did not change noticeably across conditions in the control subjects. Slower breathing rates (typically meditators) were associated with less reactivity and with lower pain sensitivity. These relationships suggest that the meditators were in a more relaxed, non-reactive physiological state throughout the study which culminated in the mindfulness condition and which influenced the degree to which they experienced pain. In the mindfulness condition, the change in respiration (from baseline) further predicted the change in pain, with subjects who breathed more slowly also showing larger reductions in pain. The covariance analysis suggested that this analgesic effect could be mediated at least in part by the observed change in respiration. Previous studies have proposed a parasympathetic dominant, relaxed, physiological state of meditation (Jevning et al., 1992). However, there is also evidence suggesting that certain techniques are not simply physiologically relaxed states but can also involve high autonomic arousal (Corby et al., 1978). A relaxed yet alert state may be reflected by the tendencies seen here to be non-reactive yet highly observant. Interestingly heart rate did not differ between groups or conditions but meditators had a tendency to have more variable heart rates throughout the experiment. Taken together, the changes observed are consistent with effects of mindfulness on both respiration and pain, possibly reflecting an impact on at least partly common brain mechanisms underlying pain, emotion and self-regulatory/homeostatic function (Damasio, 1994, 1999; Saper, 2002; Craig, 2008).

A neuro-chemical model of meditation put forth by Newberg (Newberg and Iversen, 2003), offers a possible explanation for our results. Meditation practice, involving volitional regulation of attention appears to activate prefrontal cortex (Lazar et al., 2000; Newberg et al., 2001; Brefczynski-Lewis et al., 2007) and this has been observed during Zen practice (Ritskes et al., 2003). Increases in prefrontal activation can stimulate the production of b-endorphin (e.g. in the arcuate nucleus of the hypothalamus) (Newberg and Iversen, 2003). B-endorphin is an opiate associated with both analgesia and a reduction in respiration rate, as well as decreases in fear and increases in joy and euphoria (Newberg and Iversen, 2003). Interestingly, the direction of attention toward breathing and the volitional control of breathing rates is part of many meditative techniques; however, causation can obviously not be inferred from those observations. A study of meditation has also demonstrated changes in b-endorphin rhythms associated with practice (Infante et al., 1998). Another related possibility is that meditation leads to reductions in stress and stress-related chemicals such as cortisol which interact with the opiate system. A reduction of cortisol can greatly enhance the binding potential/efficacy of endogenous opioids (Austin, 1999), possibly contributing to a down-regulation of nociceptive responses. Studies have reported evidence of reduced cortisol responses in meditators (Sudsuang et al., 1991; Carlson et al., 2004; Tang et al., 2007). Taken together, a picture emerges of a highly efficacious endogenous opioid system in trained meditators. This could be readily tested by measuring cortisol at several times points during a pain study, examining the effect of the opioid antagonist naloxone, and using brain imaging techniques allowing for a quantification of the opioid binding potential (Zubieta et al., 2001; Petrovic et al., 2002; Zubieta et al., 2005). Although these possibilities should be considered hypothetical in the current state of knowledge, these observations offer promising avenues for future research.

Several limitations of the current study should be noted. The first is a confounding effect of keeping the order of the conditions constant across subjects. The concentration condition always preceded mindfulness to respect the normal sequence of attention that is said to lead to a successful mindful state. It is taught that the mind must first be calmed via concentrative meditation or restricted focus before moving into mindful meditation. Had the reverse order also been used, some carryover effects of mindfulness into concentration may have decreased the potential to separate the two states. Furthermore, the introduction of a second order as an additional between-subject variable would have required the testing of a larger sample, a goal difficult to achieve given the highly selective population. Two observations argue against an order effect. First, the analgesic effect of mindfulness was only observed in the meditators. Second, pain returned to baseline in both groups in the last condition. An effect of sensitization or habituation to repeated stimulation would be inconsistent with those observations.

Although a modest sample size may be viewed as a limitation, the multiple effects found in this study appear robust and consistent with one another. Again, given the highly selective population and the amount of training necessary to participate in the study (>1000 hours), a larger sample was simply not available and a cross-sectional design was necessary. This design admittedly limits the interpretation of a causal relation between meditation training and the observed effects. It is possible that pre-existing individual differences, beyond meditation training, underlie some of the observed results. Significant correlation with mindfulness scores may reflect such a priori individual differences at least partly independent from meditation training (consistent with effects reported in McCracken et al, 2007). However the significant correlation between meditation experience and analgesia is consistent with previous studies suggesting training-induced changes (Davidson et al., 2003; Lutz et al., 2004; Lazar et al., 2005; Brefczynski-Lewis et al., 2007; Pagnoni and Cekic, 2007; Carmody and Baer, 2008; Hölzel et al., 2008). While this study was not designed to tease apart all potential contributing factors in the relationship between pain perception and meditation, these issues could be dealt with effectively using a prospective design in which naïve subjects are trained (Davidson et al., 2003). This would also allow one to control for factors such as self-selection biases, self-efficacy and the effect of expectation, driven by prior experience of, or beliefs about, meditation-related hypoalgesia. However, the prospective design may not adequately capture the larger effects associated with more extensive meditation training as demonstrated by the correlation analyses in the present results.

Another potential limitation is the possible confounding effects of expectancy. In the present study, it is possible that the meditators expected mindful attention to diminish some aspects of their painful experience or responded in compliance with the perceived expectation of the experimenter. However, the more robust changes observed in pain intensity than unpleasantness did not confirm our hypothesis of a stronger effect on pain affect. Furthermore, Zen students are not taught that meditation reduces the perceived intensity of a stimulus but rather that it may reduce the suffering associated with aversive experiences. Such teaching promotes acceptance and a non-judgmental, non-reactive stance toward all experiences. Therefore, possible expectancy or compliance effects appear inconsistent with the more robust results observed on measures of pain intensity. Furthermore, the significant correlation relating experience levels with the analgesic effects of attending mindfully were such that advanced practitioners (>2000hrs) had large pain decreases while the most novice subjects had slight *increases* or no changes in pain. For these correlations to exist, individuals would need a priori knowledge of the experience level of other participants and of how that experience level interacts with pain; this seems rather unlikely. Finally, correlations between respiration and pain reduction are consistent with the notion that mindful states and/or meditation training are associated with central physiological change that modulate nociceptive processing and pain perception. Admittedly, this physiological effect and the proposed neural mechanisms discussed above are not inconsistent with a contribution of expectancy. Future investigation of pain-related brain responses may provide more direct evidence demonstrating how meditation affects central neurophysiological processes underlying pain and how much overlap there might be between expectancy- and meditation-related analgesia.

To conclude, the present study joins a growing body of work suggesting both state and trait properties of mindfulness-based meditative practice. The benefit of these practices, whether viewed scientifically, clinically or spiritually, could be of great importance for the health and wellbeing of practitioners and patients alike and should thus be considered an important avenue of research.

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Article 2

Grant, J.A., Courtemanche, J. and Rainville, P. (2011) A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain* 152: 150-156.

ABSTRACT

Concepts originating from ancient Eastern texts are now being explored scientifically, leading to new insights into mind/brain function. Meditative practice, often viewed as an emotion regulation strategy, has been associated with pain reduction, low pain sensitivity, chronic pain improvement, and thickness of pain-related cortices. Zen meditation is unlike previously studied emotion regulation techniques; more akin to 'no appraisal' than 'reappraisal'. This implies the cognitive evaluation of pain may be involved in the pain-related effects observed in meditators. Using functional magnetic resonance imaging and a thermal pain paradigm we show that practitioners of Zen, compared to controls, reduce activity in executive, evaluative and emotion areas during pain (prefrontal cortex, amygdala, hippocampus). Meditators with the most experience showed the largest activation reductions. Simultaneously, meditators more robustly activated primary pain processing regions (anterior cingulate cortex, thalamus, insula). Importantly, the lower pain sensitivity in meditators was strongly predicted by reductions in functional connectivity between executive and pain-related cortices. Results suggest a functional decoupling of the cognitive-evaluative and sensory-discriminative dimensions of pain, possibly allowing practitioners to view painful stimuli more neutrally. The activation pattern is remarkably consistent with the mindset described in Zen and the notion of mindfulness. Our findings contrast and challenge current concepts of pain and emotion regulation and cognitive control; commonly thought to manifest through increased activation of frontal executive areas. We suggest it is possible to self-regulate in a more 'passive' manner, by reducing higher-order evaluative processes, as demonstrated here by the disengagement of anterior brain systems in meditators.

Keywords: pain; meditation; fMRI; emotion; attention; mindfulness

INTRODUCTION

An ancient Eastern text describes two temporally distinct aspects of pain perception; the direct experience of the sensation and habitual, negative, mentation which follows (Bohdi, 2005). It was suggested that the so called 'second dart' of pain could be removed via meditative training, obliterating the suffering associated with noxious stimulation. Remarkably, the first claim parallels modern science which has demonstrated that cognitive and affective factors can greatly influence painful experience (Wiech et al., 2008). The present study examines the second claim; that meditative training alters how one experiences pain.

Pain is a complex experience involving sensory-discriminative, affective-motivational and cognitive-evaluative components; at least partially dissociable in terms of underlying brain networks (Apkarian et al., 2005). A typical neural response to pain involves increased activity of primary and/or secondary somatosensory cortices (SI, SII) and thalamus (THAL) often reflecting the felt intensity (Coghill et al., 1999) while anterior cingulate cortex (ACC) and insula (INS) can reflect both pain-related intensity and unpleasantness (Rainville et al., 1997; Coghill et al., 1999). Activation of prefrontal cortices, thought to reflect memory or evaluation (Coghill et al., 1999; Strigo et al., 2003), is also common (Apkarian et al., 2005). Several lines of evidence suggest that meditation training can influence pain perception (Grossman et al., 2007; Kingston et al., 2007; Morone et al., 2007; Grant and Rainville, 2009; Zeidan et al., 2010; Grant et al., 2010).

Consistent with traditional claims (Goleman, 2003), research suggests that meditation positively influences emotion as well as attention-related processes (Nielsen and Kaszniak, 2006; Brefczynski-Lewis et al., 2007; Tang et al., 2007; Zeidan et al., 2010). Studies suggest an affective-based mechanism for the effect of meditation on chronic pain (Grossman et al., 2007; Morone et al., 2007). However, a recent study (Grant and Rainville, 2009) found that healthy meditators had lower pain sensitivity at baseline and lacked typical attention-related increases in pain, as observed in controls. This suggests cognitive-evaluative factors are also involved and that the influence of meditation on pain outlives formal practice. Indeed, changes in grey matter have been reported in morphometric studies of meditators (Lazar et al., 2005; Pagnoni and Cekic, 2007; Hölzel et al., 2008; Vestergaard-Poulsen et al., 2009) including pain-related regions (Grant et al., 2010). In light of putative baseline differences we conducted a study examining nociceptive-related brain activity in meditators in a normal waking state. Advanced Zen meditators and non-meditators were recruited for a functional magnetic resonance imaging (fMRI) study involving brief (6s) thermal heat pain applied intermittently to the calf.

Zen meditation (Zazen) is not explicitly intended to be analgesic but rather to illuminate and extinguish deep-seated conditioned behaviors via acute monitoring of current experience while attempting to refrain from cognitive evaluation and elaboration (Austin, 1999). We reasoned that the tendency to adopt this stance in everyday life (as is encouraged) may underlie differences in pain perception and that differential processing of nociceptive signals should be apparent in the brain when compared to non-meditators. Further, a state of mind characterized by a shift away from cognitive evaluation and elaboration suggests the involvement of prefrontal cortices. Thus, it was hypothesized that during the experience of moderate pain, meditators would show reduced activation, in comparison to controls, in prefrontal regions implicated in appraisal (lat-PFC, med-PFC) (Rolls and Grabenhorst, 2008).

METHODS

Subjects

Thirteen healthy Zen meditators (9 male) and age/gender matched non-meditators (9 male) (mean age, 38.8 vs 37.6) participated in this study. All subjects gave written, informed consent, approved by the local Ethics Committee (CMER-RNQ 05-06-020).

Stimulation

A TSA thermal stimulator (Medoc, Israel) with a 9-cm^2 contact surface was used for pain induction. To minimize the likelihood of habituation or sensitization, stimulation was applied in a pseudorandom order to six locations of the lateral/posterior portion of the left calf. Each position was stimulated twice at painful and warm levels in each functional scan. Each stimulus consisted of a 2s rise/fall and a 6s plateau. Each participant's moderate-pain level (between 47 and 53°C) was used for pain while 43°C was used for warm for all subjects.

Experimental Paradigm

Upon arrival the moderate-pain level (MPL) was determined for each individual, using the ascending method of limits. Beginning at 42°C and increasing in 1°C steps, a series of thermal stimuli were applied to the inner surface of the left calf. The moderate-pain level was defined as the temperature required to elicit a pain intensity rating between 6-7 on an 11-point, visual analogue scale (VAS) (0 = no pain; 10 = extremely painful). Each participant's moderate-pain level was then used for all painful trials. Participants underwent fMRI scanning of 48 (24 painful/24 warm) trials, in pseudorandom order, spaced over 2 functional scans of roughly 9 min each. Each trial began with a 3s or 6s auditory cue (1 kHz or 100 Hz steady tones), which correctly indicated whether the subsequent stimulus was painful or warm. Cues were used to help orient the subject, maximizing the likelihood that participants were attending to the stimuli, while reducing potential effects of surprise or uncertainty. An analysis of the functional imaging results from the cue period revealed no statistically significant differences between groups and is discussed in the supplementary material. Cues were not analyzed further. A variable delay of 3s to 12s separated successive trials. Participants were instructed to attend to the stimuli as they normally would, with eyes closed. Meditators were specifically asked to not meditate. In the same session each participant also completed an anatomical scan and two functional scans where they were asked to meditate. Those results are not included in this report. Following each functional scan participants rated the intensity and unpleasantness of the painful stimuli (below).

Dependent Measures

Pain perception was assessed using electronic VAS measuring the intensity and unpleasantness of pain. Scales ranged from 0 to 10 with verbal anchors at 0 (not painful/not unpleasant) and 10 (extremely painful/extremely unpleasant). Standard BOLD-fMRI data collection was carried out on a 3-tesla Siemens Trio scanner with a

CP head coil and is described in more detail in the Supplementary Methods. A brief questionnaire was developed to assess the meditative history of participants including: number of years practicing, frequency and length of practice in days per week, length of individual sessions in hours and amount of time spent in retreat. Age was correlated with Years of meditation experience ($r=0.65$, $p=0.02$) and thus correlations with brain activation were also tested after controlling for Age (partial correlations).

Analyses

Imaging data were preprocessed and analyzed using Brain Voyager QX. For each participant, stimulus-related activity was identified with an event-related design with the entire duration of each event convolved with a canonical hemodynamic response function. A general linear model was then used to derive parameter estimates for the effects of interest for each individual. Random effects analyses, within and between groups, were then conducted using the individual subject contrast images. Correction for multiple comparisons for within and between group analyses involved a cluster-level threshold procedure based on Monte Carlo simulation and a cluster-level of $p < 0.01$. Pearson correlations between stimulus-related fMRI parameter estimates, pain ratings and meditation experience were performed in SPSS. A psychophysiological interaction analysis (Friston et al., 1997) allowing a comparison of task-related functional connectivity was implemented step-by-step within Brain Voyager. The PPI analysis was conducted to determine whether there was an interaction between a psychological variable (pain vs warm) and the functional coupling between two brain areas and whether this differed between groups. The time course of the dACC seed region (X=2, Y=6, Z=39, 1570 voxels) was extracted for each fMRI run and normalized. The normalized time course was then multiplied by a design matrix which specified pain as positive (a value of 1) and warm as negative (value of -1). The resulting 'interaction' term (a time course differentially reflecting task conditions) was then entered into a model. Single subject GLMs were then computed based on the fit of brain activation to the interaction term, while removing the variance associated with the seed time course and task. Statistical maps were set at a liberal threshold of $p < 0.01$ uncorrected due to the power loss from removing the variance associated with the main effects. The search area was restricted to regions showing group differences in pain-related activation (i.e. regions listed in Table S2). The resulting parameter estimates were used to assess group differences in functional connectivity.

RESULTS

Pain Assessment

Prior to the fMRI scans the temperature required to produce moderate pain was assessed in each participant. As a group, meditators required significantly higher stimulus intensities than non-meditators (49.9°C vs 47.9°C) (t (24) = 2.67, p= 0.01, d= 1.05), consistent with our previous reports (Grant and Rainville, 2009; Grant et al., 2010). These individually-determined temperatures were subsequently used in two functional MRI scans to examine potential group differences in brain activity underlying comparable perceptual levels of pain. An independent samples t-test confirmed that pain intensity and unpleasantness ratings were not different between groups during the fMRI scans (pain intensity: *t* (24)= -1.06, *p* = 0.30, d=-0.41; pain unpleasantness *t* (24) = -0.68, *p* = 0.50, d=-0.27).

Pain-related Brain Activity

Painful and warm stimuli were modeled and parameter estimates calculated for each participant using the GLM. Pain-related activation was first analyzed separately for each group with random effects analyses contrasting Painful and Warm stimuli, correcting for multiple comparisons using a spatial cluster criterion. Pain-related activation for meditators was robust with increases observed in bilateral SII, INS, THAL, dorsal ACC (dACC) and putamen (PUT)(Fig. S1). Activation decreases were also observed in bilateral dorsolateral-PFC (DLPFC), AMY, hippocampus (HIP) and an extensive region spanning med-PFC and orbitofrontal cortex (OFC). For control participants pain-related increases in activation were found in bilateral INS, right SII, DLPFC, inferior frontal gyrus (IFG) and dACC (Fig. S1). A complete list of regions with significant pain-related responses for each group can be found in Table S1.

Group Differences in Pain-related Brain Activity

Next, the pain-related activation maps of meditators and controls were contrasted (Meditators: Pain - Warm vs Controls: Pain - Warm). Significantly stronger pain-activation was found for meditators within dACC, THAL and INS. In contrast, controls showed stronger activation in bilateral DLPFC and AMY, left middle frontal gyrus (MFG) and right HIP and med-PFC/OFC. These results are presented in Table 1 and Figure 1 with a complete list in Table S2. In controlling for perceptual experience a limitation was encountered as meditators had higher objective input (stimulus intensity) than controls, which may have influenced the observed effects. In an attempt to control for stimulus intensity a covariance analysis was conducted to remove the influence of this variable from the observed pain-related group differences. Importantly, in most areas, group differences were not simply accounted for by the higher stimulus intensities required to elicit comparable ratings of pain in meditators (values reported in the far right column of Table 1). Left dorsal ACC, posterior insula, secondary somatosensory cortex and right thalamus were no longer significantly different between groups leaving right dACC, left thalamus, and insula stronger in meditators. Regions found to be more active for control subjects were, for the most part, unaffected by the covariance analysis.

Effect of Meditation Training

To investigate whether pain-related activation, or differential pain-related activation between groups, was related to meditation experience, correlation analyses were performed between the parameter estimates extracted from the pain-activation maps and the number of years and hours of practice. More years of meditation experience was associated with lower pain-activation in bilateral INS (right: r =-0.60, $p<0.05$; left: r =-0.65, $p<0.05$) and dACC (r =-0.69, $p<0.01$) while more hours of experience predicted lower pain-activation in dACC (r =-0.63, $p<0.05$) and larger decreases in pain-activation in left DLPFC (r =-0.59, $p<0.05$). In regions differing in pain-related activity between groups (Table 1), more years of experience was again associated with lower pain-activation in dACC (r =-0.69, $p<0.01$) and left INS (r =-0.66, $p<0.05$) as well as larger pain-related decreases in bilateral DLPFC (right: r =-0.63, $p<0.05$; left: r =-0.80, $p<0.001$) (Figure 2) and right med-PFC/OFC (r =-0.64,

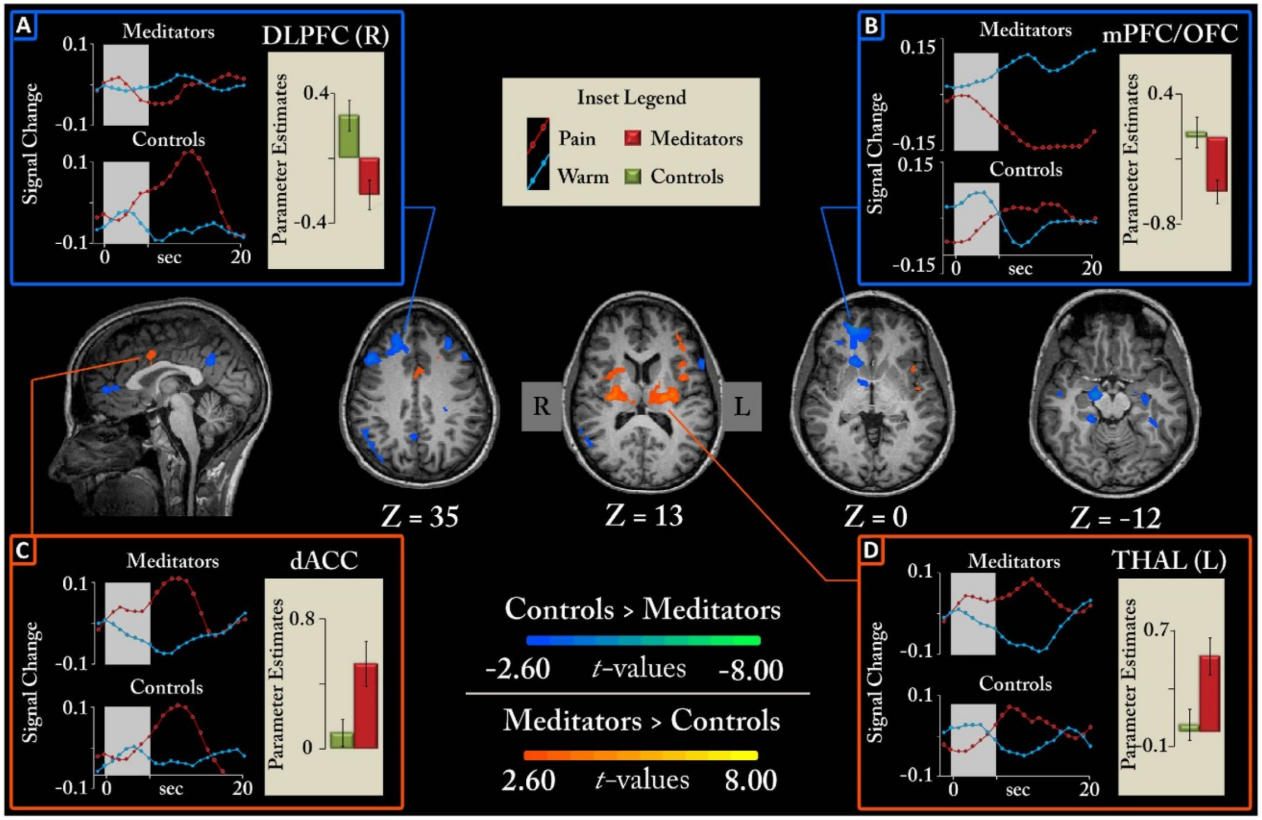

Figure 1. Group differences in pain-related activation. Central MRI images illustrate brain regions with statistically significant group differences in pain-related responses (orange-yellow: meditators > controls)(blue-green: controls > meditators). Corner insets show mean pain-related parameter estimates for each group (right side of each box) (error bars = SEM) as well as the time courses of activation (left side) for pain (red) and warm (blue) for each group separately. Grey bars represent stimulus presentation. Top left corner: right DLPFC, top right corner: right med-PFC/OFC, bottom right: left THAL, bottom left corner: dACC spanning the midline. X,Y,Z are in Talairach space. R = right, L = left. N=26.

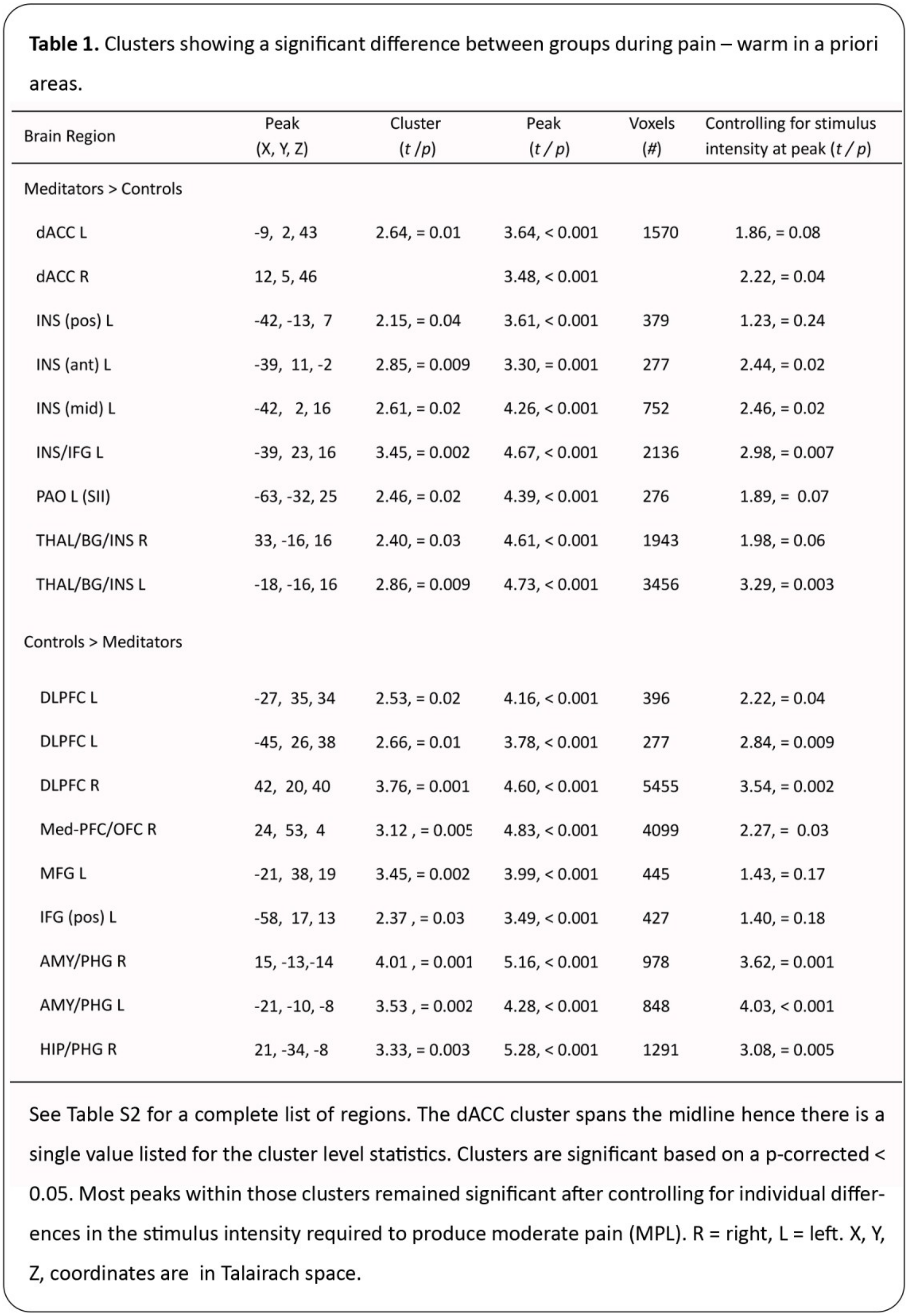

Table 1. Clusters showing a significant difference between groups during pain – warm in a priori areas.

Brain Region	Peak (X, Y, Z)	Cluster (*t* /*p*)	Peak (*t* / *p*)	Voxels (#)	Controlling for stimulus intensity at peak (*t* / *p*)
Meditators > Controls					
dACC L	-9, 2, 43	2.64, = 0.01	3.64, < 0.001	1570	1.86, = 0.08
dACC R	12, 5, 46		3.48, < 0.001		2.22, = 0.04
INS (pos) L	-42, -13, 7	2.15, = 0.04	3.61, < 0.001	379	1.23, = 0.24
INS (ant) L	-39, 11, -2	2.85, = 0.009	3.30, = 0.001	277	2.44, = 0.02
INS (mid) L	-42, 2, 16	2.61, = 0.02	4.26, < 0.001	752	2.46, = 0.02
INS/IFG L	-39, 23, 16	3.45, = 0.002	4.67, < 0.001	2136	2.98, = 0.007
PAO L (SII)	-63, -32, 25	2.46, = 0.02	4.39, < 0.001	276	1.89, = 0.07
THAL/BG/INS R	33, -16, 16	2.40, = 0.03	4.61, < 0.001	1943	1.98, = 0.06
THAL/BG/INS L	-18, -16, 16	2.86, = 0.009	4.73, < 0.001	3456	3.29, = 0.003
Controls > Meditators					
DLPFC L	-27, 35, 34	2.53, = 0.02	4.16, < 0.001	396	2.22, = 0.04
DLPFC L	-45, 26, 38	2.66, = 0.01	3.78, < 0.001	277	2.84, = 0.009
DLPFC R	42, 20, 40	3.76, = 0.001	4.60, < 0.001	5455	3.54, = 0.002
Med-PFC/OFC R	24, 53, 4	3.12 , = 0.005	4.83, < 0.001	4099	2.27, = 0.03
MFG L	-21, 38, 19	3.45, = 0.002	3.99, < 0.001	445	1.43, = 0.17
IFG (pos) L	-58, 17, 13	2.37 , = 0.03	3.49, < 0.001	427	1.40, = 0.18
AMY/PHG R	15, -13,-14	4.01 , = 0.001	5.16, < 0.001	978	3.62, = 0.001
AMY/PHG L	-21, -10, -8	3.53 , = 0.002	4.28, < 0.001	848	4.03, < 0.001
HIP/PHG R	21, -34, -8	3.33, = 0.003	5.28, < 0.001	1291	3.08, = 0.005

See Table S2 for a complete list of regions. The dACC cluster spans the midline hence there is a single value listed for the cluster level statistics. Clusters are significant based on a p-corrected < 0.05. Most peaks within those clusters remained significant after controlling for individual differences in the stimulus intensity required to produce moderate pain (MPL). R = right, L = left. X, Y, Z, coordinates are in Talairach space.

p<0.05). Hours of experience predicted lower pain-activation in bilateral dACC (*r* =-0.65, p<0.05), THAL (right: *r* =-0.56, p<0.05; left: *r* =-0.59, p<0.05), left INS (*r* =-0.62, p<0.05) and larger pain-related decreases in left DLPFC (*r* =-0.84, p<0.001). In all cases, the most experienced practitioners showed lower responses in pain-related areas (i.e. dACC, THAL and INS) while displaying the greatest pain-related decreases in prefrontal regions (i.e. DLPFC and med-PFC/OFC).

There were no significant correlations between either measure of meditation experience and stimulus intensity (pain sensitivity) or pain ratings during the functional scans. Age did not correlate with any of the brain activation results reported and the results reported above remained significant after controlling for Age.

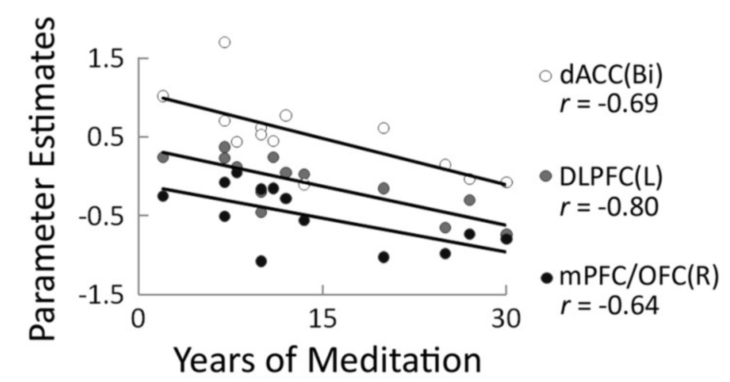

Figure 2. Correlation between pain-related activation and meditation experience. More years of meditation experience was associated with smaller increases, or larger decreases, in BOLD in left DLPFC, right med-PFC/OFC and dACC spanning the midline. N=13.Results remained significant after accounting for Age.

Pain Experience - Brain Activation Correlations

After successfully balancing subjects in terms of perceptual experience and using a constant subject-wise pain provoking stimulus, there was still variability across scans in pain intensity and unpleasantness ratings. A post-hoc analysis was conducted to examine possible relationships between the varying experiences of pain and brain activity. Parameter estimates from pain-related regions identified for each group (Table S1) and for regions found to differ between groups (Table 1) were extracted and correlation analyses were run with pain intensity and unpleasantness ratings. For the meditation group left DLPFC (R=0.61, $p < 0.05$) and right MTG (R=0.58, $p < 0.05$) predicted pain intensity ratings such that greater activity reduction was associated with lower intensity ratings. No regions were found that predicted pain unpleasantness in meditators. For controls increased activation predicted pain unpleasantness such that more activation was associated with higher pain ratings in right DLPFC (R=0.59, $p < 0.05$), left INS (R=0.64, $p < 0.05$), and right posterior IFG (R=0.62, $p < 0.05$). Dorsal ACC also correlated positively with pain unpleasantness (R=0.50, $p < 0.05$) at 1-tailed level of significance. In regions differentially activated during pain, a single region, left DLPFC, predicted pain intensity ($r = 0.39$, $p < 0.05$) as well as unpleasantness ratings ($r = 0.47$, $p < 0.05$) across all subjects. The correlation was such that more intense and/or unpleasant experience was associated with higher activation of DLPFC. This left DLPFC cluster was more anterior to, and did not overlap with, the left DLPFC region found to predict pain ratings in meditators alone. An examination of the groups separately revealed that this effect was accounted for primarily by controls (Meditators: INT (R=0.28, p=0.35 ns); UNP (R=0.06, p=0.84, ns); Controls: INT (R=0.43, p=0.14, ns); Unpleasantness: (R=0.81, p<0.001)).

Psychophysiological Interaction Analysis

The dACC figures prominently in the present report as well as our previous morphometric study demonstrating differences in cortical thickness associated with pain sensitivity and meditation experience (Grant et al., 2010). This region has recognized roles in pain perception (Apkarian et al., 2005) but also in cognitive monitoring (Bush et al., 2000); a role which could be considered a hallmark of meditation. To probe the area further a post-hoc psychophysiological interaction (PPI) analysis was performed. The PPI analysis, using the dACC as a seed region, allowed us to test differences in functional connectivity (correlation between regions) as a function of condition (pain vs warm). Restricting the test to areas showing group differences in pain-related responses (Table 1), it was revealed that during pain, meditators and controls displayed significantly different connectivity patterns between dACC and bilateral PUT ($t(24)$ L = 3.56, $p < 0.01$, d= 1.45; R = 2.86, $p < 0.01$, d=1.17), left mid-INS ($t(24) = 3.25$, $p < 0.01$, d=1.33) and INS/IFG ($t(24) = 3.01$, $p < 0.01$, d=1.23). In these areas meditators had stronger connectivity than controls during pain compared to warm. In sharp contrast, controls displayed stronger connectivity between dACC and right DLPFC ($t(24) = 3.02$, $p < 0.01$, d=1.23) with meditators having negative connectivity values. Importantly, the degree of pain-related connectivity between dACC and right DLPFC, strongly predicted baseline pain sensitivity in meditators ($r= -0.71$, $p<0.01$) but not in controls ($r= -0.20$, $p=0.52$) (Figure3). That is, the meditators displaying the lowest pain sensitivity (requiring high temperatures for pain) had the weakest correlations between dACC and DLPFC. This suggests that a decoupling of these regions may underlie the lower pain sensitivity observed in meditators

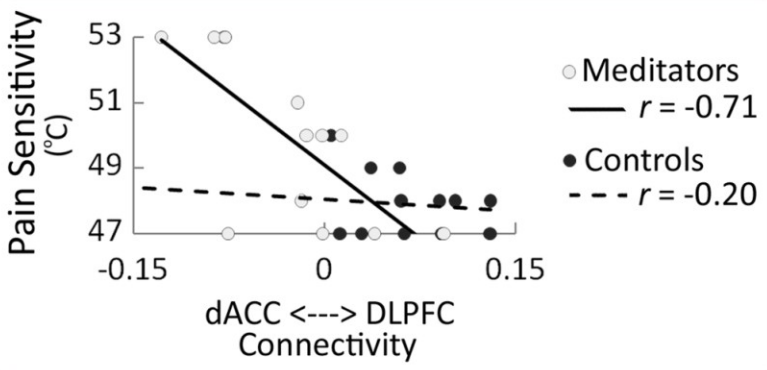

Figure 3. Functional connectivity predicts pain sensitivity. The degree of functional connectivity during pain of dACC and right DLPFC predicts baseline pain sensitivity in meditators but not controls. Meditators with more pronounced decoupling (i.e. larger reduction in connectivity) are less sensitive to pain. N=26.

DISCUSSION

The present report follows-up a psychophysical study (Grant and Rainville, 2009) which found that Zen meditators: a) had lower baseline pain sensitivity, b) did not report typical attention-related pain increases and c) reported training-related, sensory and affective pain decreases during mindful attention. We hypothesized that these effects could be due to ongoing modulation of noxious input by processes related to the mindset learned through Zen practice (Austin, 1999). The following novel results were found:

1) During pain, meditators had stronger activity in regions typically associated with sensory and affective pain processing.
2) Large activity decreases were observed in brain regions implicated in appraisal, memory and emotion where the most advanced meditators had the largest effects and which were accompanied by the lowest pain ratings.

3) Meditators had reduced functional connectivity between DLPFC and dACC where the degree of connectivity strongly predicted baseline pain sensitivity, an effect not found in controls.

The pattern of brain activity observed in meditators offers a convincing explanation for the lower pain sensitivity observed in this group. We argue that the results are consistent with a mental stance described in Zazen; involving acute monitoring of one's present moment experience with an emphasis on being nonjudgmental and free of cognitive evaluation and elaboration (Austin, 1999). However, it should be noted that without corroborating behavioural data, inferences of functional-anatomical relationships remain speculative.

As reported previously (Grant et al., 2010) meditators were less sensitive to thermal stimulation requiring on average ~50°C for moderate pain versus ~48°C for control participants. With perceptually adjusted stimuli the groups reported equivalent levels of pain in a non-meditative, eyes closed, state. Despite equal ratings, meditators had stronger pain-related activation of target regions of the spinothalamic nociceptive tract (Dum et al., 2009) (i.e. INS, THAL and dACC); areas often suggested to reflect the sensory-discriminative and affective-motivational aspects of pain (Apkarian et al., 2005). Effects in these early receiving areas were weakened after controlling for stimulus intensity with covariance, suggesting that these group differences were at least partially, but not fully, explained by the hotter stimulation for meditators. Activation within these regions is found in a variety of contexts and may relate to more general functions relevant, but not specific, to pain.

One possibility is that ACC and INS code stimulus saliency (Mouraux and Iannetti, 2009), whether perceived as painful or not. Indeed, both structures activate in response to change in visual, auditory and tactile stimuli (Downar et al., 2000) and may be conceived as the primary nodes of a 'saliency network' (Seeley et al., 2007). In a related vein, the dACC has a known role in cognitive monitoring (Bush et al., 2000) while the insula has been argued to work with the ACC to instantiate subjective awareness of internal body states (Craig, 2009). Meditation, a task which purportedly trains practitioners to monitor their experience, would presumably recruit both regions robustly; effects which have been observed (Brefczynski-Lewis et al., 2007; Hölzel et al., 2007). Structural MRI studies, including our own with an overlapping sample, have also reported thicker grey matter for meditators in dACC and INS (Lazar et al., 2005; Hölzel et al., 2008; Grant et al., 2010). This suggests that greater activity of INS and dACC may partially reflect the 'task' or learned mindset of meditation. An enhanced tendency to monitor everyday experience, as is encouraged in the Zen, would in turn increase stimulus saliency and strengthen the corresponding neural representation of the attended input.

However, paradoxically, within the meditation group, dACC activation was the strongest in the most inexperienced meditators. A similar result; stronger dACC activation during meditation for intermediate compared to advanced Tibetan practitioners (Brefczynski-Lewis et al., 2007), was interpreted as reflecting the effort required to sustain attention. While this interpretation may apply here, the lack of a measure of attention, warrants caution. It should also be noted that the functional MRI scans reported here were part of a larger study and were interspersed with (but separate from) active meditation scans. Thus, carryover effects, potentially stronger in more advanced practitioners, have likely influenced what is interpreted here as baseline effects. Nevertheless, the notion of a heightened state of attentiveness is consistent with our earlier finding that meditators are more mindful and do not show typical attention-related increases in pain, compared to their own baseline (Grant and Rainville, 2009). Furthermore, longitudinal studies now support a causal link between meditation training and enhancements of executive processing (Tang et al., 2007; Zeidan et al., 2010), providing support for activation differences in dACC and INS reflecting an augmented capacity/tendency to attend or monitor.

While Zen practitioners had stronger activation of dACC, THAL and INS, control subjects had stronger activation, not sensitive to stimulation intensity, in med-PFC/OFC, DLPFC, AMY and HIP, among others. In several cases effects were driven by reductions of the fMRI signal (BOLD) below baseline in meditators, rather than or in addition to, increases in controls. The most commonly observed of these, in pain studies, is DLPFC (Apkarian et al., 2005); here decreased in meditators and increased in controls. Activity is typically increased in DLPFC during pain and thought to reflect higher cognitive processes such as working memory and stimulus evaluation (Coghill et al., 1999; Strigo et al., 2003). Also reduced, the OFC receives output from sensory 'what' pathways, transforming the information into reward-related representations involving emotional and affective value (Rolls and Grabenhorst, 2008) required for decision making (Bechara et al., 2003). The HIP and AMY, which work in conjunction with PFC and OFC in memory and emotion (Buchanan, 2007) also had lower activation in meditators. We suggest that a reduction or absence of activity within brain networks subserving working memory and evaluative processing may be a physiological correlate of aspects of Zen and/or mindfulness. That is, attending to the present moment (potentially reflected by dACC activation) precludes the possibility of thinking about the past or future (memory-related reductions), and without such reference, judgment or appraisal would presumably be diminished (evaluative reductions). Further, the largest reductions in DLPFC were associated with the lowest pain ratings and more advanced meditators had larger activity decreases in bilateral DLPFC and right med-PFC/OFC, supporting the notion of learned state. As a whole, this pattern of reduced activation exclusively found in meditators and associated with experience, suggests a reduction of cognitive-emotional and evaluative processing during aversive stimulation and maps on well to the psychological construct of mindfulness (i.e. present moment, non-judgmental awareness).

There are several relevant relationships between the increased and decreased activations observed for meditators during pain. The first involves the notion of intrinsic brain networks. The med-PFC, part of the 'default network' (Gusnard et al., 2001; Raichle et al., 2001), is suggested to underlie self-reflective processing; active during rest and becoming 'de-activated' during cognitive tasks. It is thought that the shift of neural resources away from self-related processes involves activation of central executive and salience networks (Seeley et al., 2007) which includes dACC, INS and THAL; areas found to be highly active and functionally cohesive in meditators. Together, these results are consistent with the notion of meditators engaging in a task (monitoring) involving less self-focus during pain perception. The

PCC, also involved in self-related appraisal and the default network (Raichle et al., 2001), was also reduced in activation for meditators during pain. Previous meditation studies have reported med-PFC decreases (Farb et al., 2007) as well as dACC and INS increases (Brefczynski-Lewis et al., 2007; Hölzel et al., 2007). Further, Zen practitioners reportedly have temporal reductions of conceptual-related processing in default-mode regions (Pagnoni et al., 2008). Importantly, stimulus intensity (meditators > controls) could only partially account for activation increases, and not at all for activity decreases.

A second relationship between activation increases and decreases in meditators revolves around goal-directed behavior. It is thought that engagement and regulation of executive function and goal-directed behavior is achieved through reciprocal connections between frontal and cingulate cortices (Miller and Cohen, 2001). Reduced activity of PFC and subcortical memory structures in the present study might indicate an absence or attenuation of higher-order processing of the noxious stimuli. Using functional connectivity we tested whether communication between frontal and cingulate cortices may underlie meditators' responses to noxious inputs. Crucially, the connectivity of DLPFC and dACC was reduced during pain in meditators possibly suggesting a disruption of communication between these regions. Remarkably, the degree of connectivity between dACC and DLPFC strongly predicted baseline pain sensitivity, exclusively in meditators. Practitioners requiring the highest temperatures to report pain (low sensitivity) had the weakest connection (correlation) between dACC and DLPFC during pain. Thus, a functional decoupling of regions typically involved in higher-order cognitive processes seems to underlie the lower pain sensitivity observed in meditators. This raises the possibility that highly-salient noxious stimuli are labeled as painful via interactions between prefrontal areas and cortical targets of the spinothalamocortical pathways. A disruption of such a pathway could conceivably reduce the suffering associated with noxious stimuli, rendering it more 'neutral' or less threatening.

CONCLUSION

To conclude, our results suggest that Zen meditators may have a training-related ability to disengage higher-order brain processes while remaining focused on a painful stimulus. Such an ability could have widespread and profound implications for pain and emotion regulation as well as cognitive control; theories of which postulate, is achieved though frontal activation (Gross, 2002; Wiech et al., 2008; Mansouri et al., 2009), rather than disengagement as suggested here. A functional decoupling between DLPFC and dACC, perhaps stemming from a lack of prefrontal output, seems to underlie the low pain sensitivity observed in this group. The activation pattern is consistent with the mindset described in Zen and with the notion of mindfulness, possibly reflecting claims made about meditative practice in classical texts (Bohdi, 2005).

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ABBREVIATIONS

General: ant = anterior, dor = dorsal, inf = inferior, L = left, lat = lateral, med = medial, ML = midline, pos = posterior, R = right, sup = superior

Anatomy: ACC = Anterior cingulate cortex, AMY = Amygdala, BG = Basal ganglia, CAUD = Caudate, CB = Cerebellum, CS = Central Sulcus, CLAU = Claustrum, CUN = Cuneus, DLPFC = Dorsolateral prefrontal cortex, G.PAL = Globus palidus, HIP = Hippocampus, IFG = Inferior frontal gyrus, INS = Insula, IPL = Inferior parietal lobule, ITG = Inferior temporal gyrus, MI = Primary motor cortex, MFG = Middle frontal gyrus, MTG = Middle temporal gyrus, OFC = Orbitofrontal cortex, PAO = Parietal Operculum, PCC = Posterior cingulate cortex, PFC = Prefrontal cortex, PHG = Parahippocampal gyrus, PoCG = Post central gyrus, PreCUN = precuneus, PUT = Putamen, RtSpl = Retrosplenial cortex, SI = Primary somatosensory cortex, SII = Secondary somatosensory cortex, SPL = Superior parietal lobule, STS = Superior temporal sulcus, T.Pole = Temporal pole, THAL = Thalamus

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Participant Recruitment

The recruitment process involved visiting meditation centers throughout Montreal as well as posting advertisements in local newspapers and online classifieds. Participants were invited to a study investigating the cognitive modulation of pain. We first compiled a list of possible meditators (N=68), consisting of individuals from many meditative traditions. The largest possible sample controlling for homogeneity of training and meeting the arbitrary requirement of 1000 hr of experience consisted of 13 Zen practitioners. Zen is considered to be a meditative tradition emphasizing mindfulness. Thirteen control subjects matched precisely for age and gender, with no previous experience with meditation or yoga, were subsequently recruited. All participants were Caucasian with the exception of one control subject of Asian decent. Experiments were conducted between Sept. of 2006 and Oct. 2007 at the Centre de recherché de l'Institut universtiaire de gériatrie de Montréal. All procedures were approved by the local ethics committee (CMER-RNQ 05-06-020). All participants provided written informed consent and received a monetary compensation.

fMRI acquisition and processing.

Full-brain imaging data were acquired at Unité de Neuroimagerie Fonctionnelle of the Centre de recherché de l'Institut de gériatrie de Montréal on a 3-Tesla Siemens Trio scanner (Munich, Germany) using a CP head coil. Participants' heads were stabilized using a vacuum bag. They were instructed to refrain from moving, wore earplugs and were fitted with MR-compatible headphones. The functional scans were collected using a blood oxygen level-dependent (BOLD), T2* weighted, gradient echo-planar imaging sequence (TR: 3000ms; TE: 30ms; flip angle: 90°; 64 x 64 matrix; voxel size: 3.4mm^3, 180 volume acquisitions). Each participant underwent a high-resolution T1 weighted structural MRI scan (3D MP-RAGE; TR: 2300 ms, TE: 2.94ms, flip angle: 9°, 256 x 240 matrix, voxel size: 1 x 1 x 1.2 mm. Following data collection images were preprocessed and analyzed using Brain Voyager QX version 1.10.4. Pre-processing included slice-time correction (cubic spline), 3-D motion correction (trilinear/sinc interpolation), 3-D spatial smoothing with a Gausian filter with a FWHM of 6mm^3 and temporal filtering with a frequency-based, high-pass, filter with a cu t-off of 0.0078Hz. Anatomical and functional images were then spatially normalized to Talairach space (Talairach and Tournoux, 1988) and aligned.

Data analysis.

Imaging data were analyzed using Brain Voyager QX version 1.10.4. To assess brain regions which were sensitive to pain we used an event-related design with painful stimulation, warm stimulation, pain cues and warm cues as variables of interest. A fifth nuisance variable, the white matter time course of each run of each subject, was included to remove non-spatially specific variance (Fox et al., 2005). For each participant, stimulus-related activity was identified with an event-related design by convolving stimuli (painful hot and warm) with a canonical hemodynamic response function. A general linear model was used to model the effects of interest. Second level (random effects) analyses, within and between groups, were then conducted using the individual subject contrast images (Painful - Warm). A cluster-level, multiple comparisons correction was used based on the procedure of Forman et al. (Forman et al., 1995) and implemented by Goebel et al. (Goebel et al., 2006). In brief, the spatial cluster criterion for multiple comparison correction works as follows. The statistical map to be corrected (i.e. individual group pain-related activity or group differences) is first set to a voxel-level threshold ($p < 0.001$ uncorrected in the present study). An automated Monte Carlo simulation procedure of 1000 iterations is run, constrained by the volume, voxel size, degree of spatial smoothing and number of activated voxels within the map. This produces a cluster-size frequency table of the 1000 randomly generated noise images. A false positive value (α) is automatically assigned to each cluster size. The user then selects the accepted cluster-level false positive rate, $\alpha = 1\%$ or $p < 0.01$ in the present study. Any clusters falling below the cluster size threshold, in the original statistical map, are subsequently removed. Thus, there is a 1% chance or lower that clusters reported in the current study are due to spurious activation.

A psychophysiological interaction (PPI) analysis (Friston et al., 1997) was conducted to determine whether there is an interaction between a psychological variable (in the current context pain, versus warm) and the functional coupling between two brain areas. This analysis assesses whether the functional connectivity between areas differ during pain compared to warm. The interested reader is directed to the following website for an informative discussion of PPI analyses (http://www.fmrib.ox.ac.uk/Members/joreilly/what-is-ppi). Here, the PPI analysis was implemented in Brain Voyager as follows. The time course of the dACC seed region (X=2, Y=6, Z=39, 1570 voxels) was extracted for each fMRI run and normalized. The normalized seed region time course was then multiplied by a design matrix which specified pain as positive (a value of 1) and warm as negative (value of -1). The resulting 'interaction' term (a time course differentially reflecting task conditions) was then entered into a model. Single subject GLMs are then computed based on the fit of brain activation to the interaction term, while removing the variance associated with the seed time course and task. The resulting parameter estimates are used to assess group differences in functional connectivity. The areas of interest for this PPI analysis were restricted to regions showing groups differences in pain-related activation. Statistical maps were set at a liberal threshold of $p < 0.01$ uncorrected.

SUPPLEMENTARY RESULTS

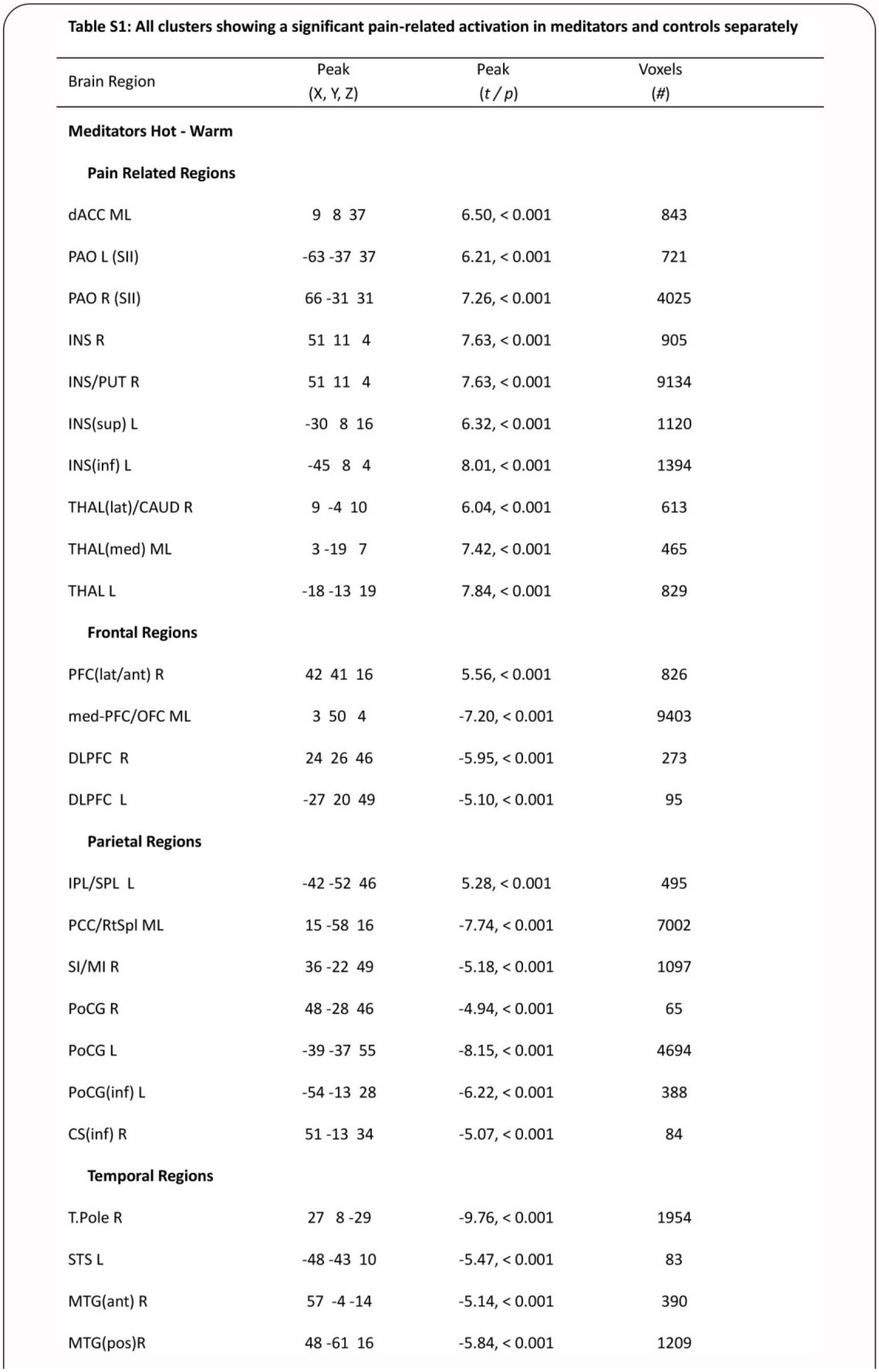
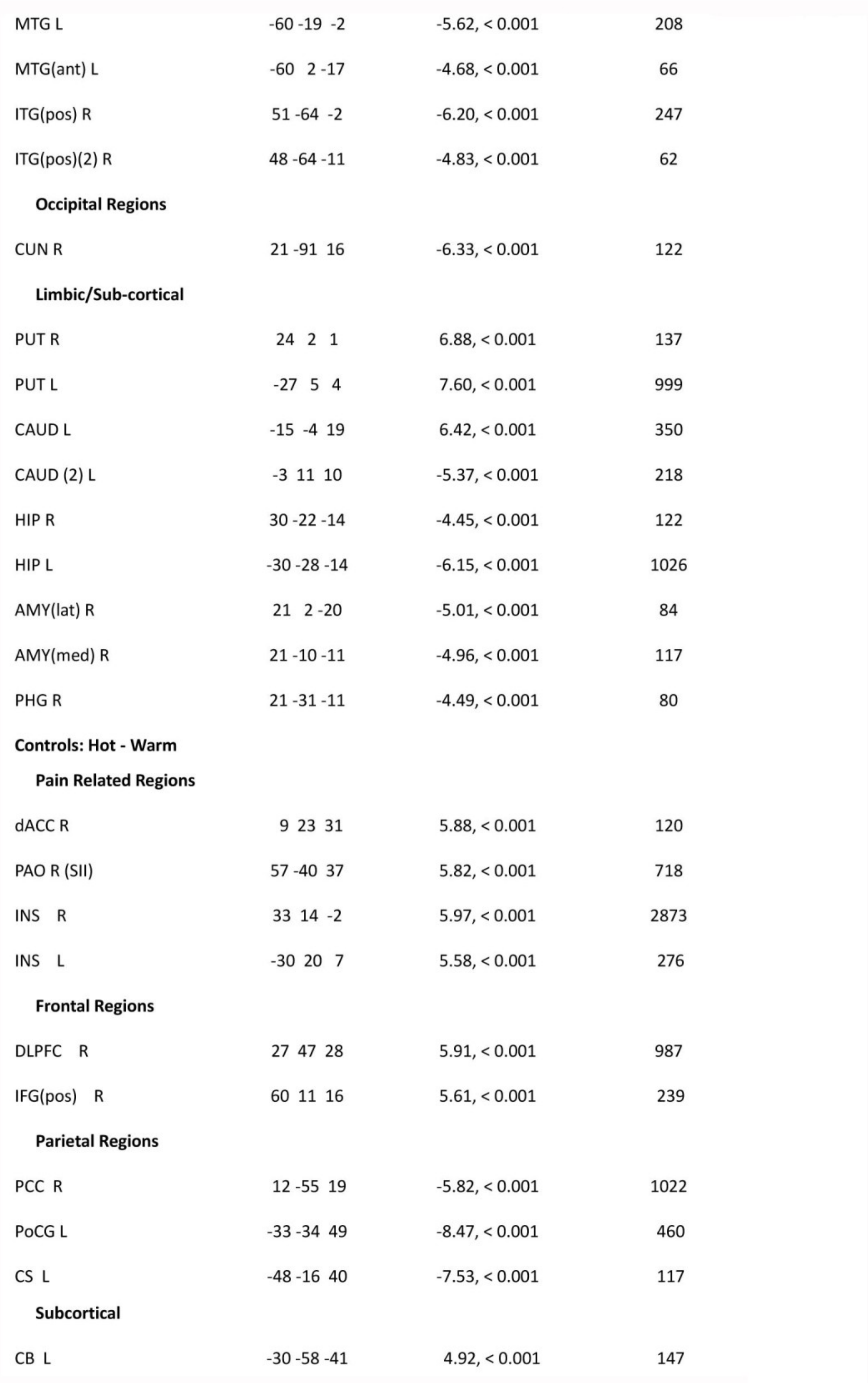


Table S1: All clusters showing a significant pain-related activation in meditators and controls separately

Brain Region	Peak (X, Y, Z)	Peak (*t* / *p*)	Voxels (*#*)
Meditators Hot - Warm			
Pain Related Regions			
dACC ML	9 8 37	6.50, < 0.001	843
PAO L (SII)	-63 -37 37	6.21, < 0.001	721
PAO R (SII)	66 -31 31	7.26, < 0.001	4025
INS R	51 11 4	7.63, < 0.001	905
INS/PUT R	51 11 4	7.63, < 0.001	9134
INS(sup) L	-30 8 16	6.32, < 0.001	1120
INS(inf) L	-45 8 4	8.01, < 0.001	1394
THAL(lat)/CAUD R	9 -4 10	6.04, < 0.001	613
THAL(med) ML	3 -19 7	7.42, < 0.001	465
THAL L	-18 -13 19	7.84, < 0.001	829
Frontal Regions			
PFC(lat/ant) R	42 41 16	5.56, < 0.001	826
med-PFC/OFC ML	3 50 4	-7.20, < 0.001	9403
DLPFC R	24 26 46	-5.95, < 0.001	273
DLPFC L	-27 20 49	-5.10, < 0.001	95
Parietal Regions			
IPL/SPL L	-42 -52 46	5.28, < 0.001	495
PCC/RtSpl ML	15 -58 16	-7.74, < 0.001	7002
SI/MI R	36 -22 49	-5.18, < 0.001	1097
PoCG R	48 -28 46	-4.94, < 0.001	65
PoCG L	-39 -37 55	-8.15, < 0.001	4694
PoCG(inf) L	-54 -13 28	-6.22, < 0.001	388
CS(inf) R	51 -13 34	-5.07, < 0.001	84
Temporal Regions			
T.Pole R	27 8 -29	-9.76, < 0.001	1954
STS L	-48 -43 10	-5.47, < 0.001	83
MTG(ant) R	57 -4 -14	-5.14, < 0.001	390
MTG(pos)R	48 -61 16	-5.84, < 0.001	1209



MTG L	-60 -19 -2	-5.62, < 0.001	208
MTG(ant) L	-60 2 -17	-4.68, < 0.001	66
ITG(pos) R	51 -64 -2	-6.20, < 0.001	247
ITG(pos)(2) R	48 -64 -11	-4.83, < 0.001	62
Occipital Regions			
CUN R	21 -91 16	-6.33, < 0.001	122
Limbic/Sub-cortical			
PUT R	24 2 1	6.88, < 0.001	137
PUT L	-27 5 4	7.60, < 0.001	999
CAUD L	-15 -4 19	6.42, < 0.001	350
CAUD (2) L	-3 11 10	-5.37, < 0.001	218
HIP R	30 -22 -14	-4.45, < 0.001	122
HIP L	-30 -28 -14	-6.15, < 0.001	1026
AMY(lat) R	21 2 -20	-5.01, < 0.001	84
AMY(med) R	21 -10 -11	-4.96, < 0.001	117
PHG R	21 -31 -11	-4.49, < 0.001	80
Controls: Hot - Warm			
Pain Related Regions			
dACC R	9 23 31	5.88, < 0.001	120
PAO R (SII)	57 -40 37	5.82, < 0.001	718
INS R	33 14 -2	5.97, < 0.001	2873
INS L	-30 20 7	5.58, < 0.001	276
Frontal Regions			
DLPFC R	27 47 28	5.91, < 0.001	987
IFG(pos) R	60 11 16	5.61, < 0.001	239
Parietal Regions			
PCC R	12 -55 19	-5.82, < 0.001	1022
PoCG L	-33 -34 49	-8.47, < 0.001	460
CS L	-48 -16 40	-7.53, < 0.001	117
Subcortical			
CB L	-30 -58 -41	4.92, < 0.001	147

Table S1: Negative indicates the effect was a reduction in activation compared to warm. R = right, L = left. X, Y, Z, coordinates are in Talairach space.

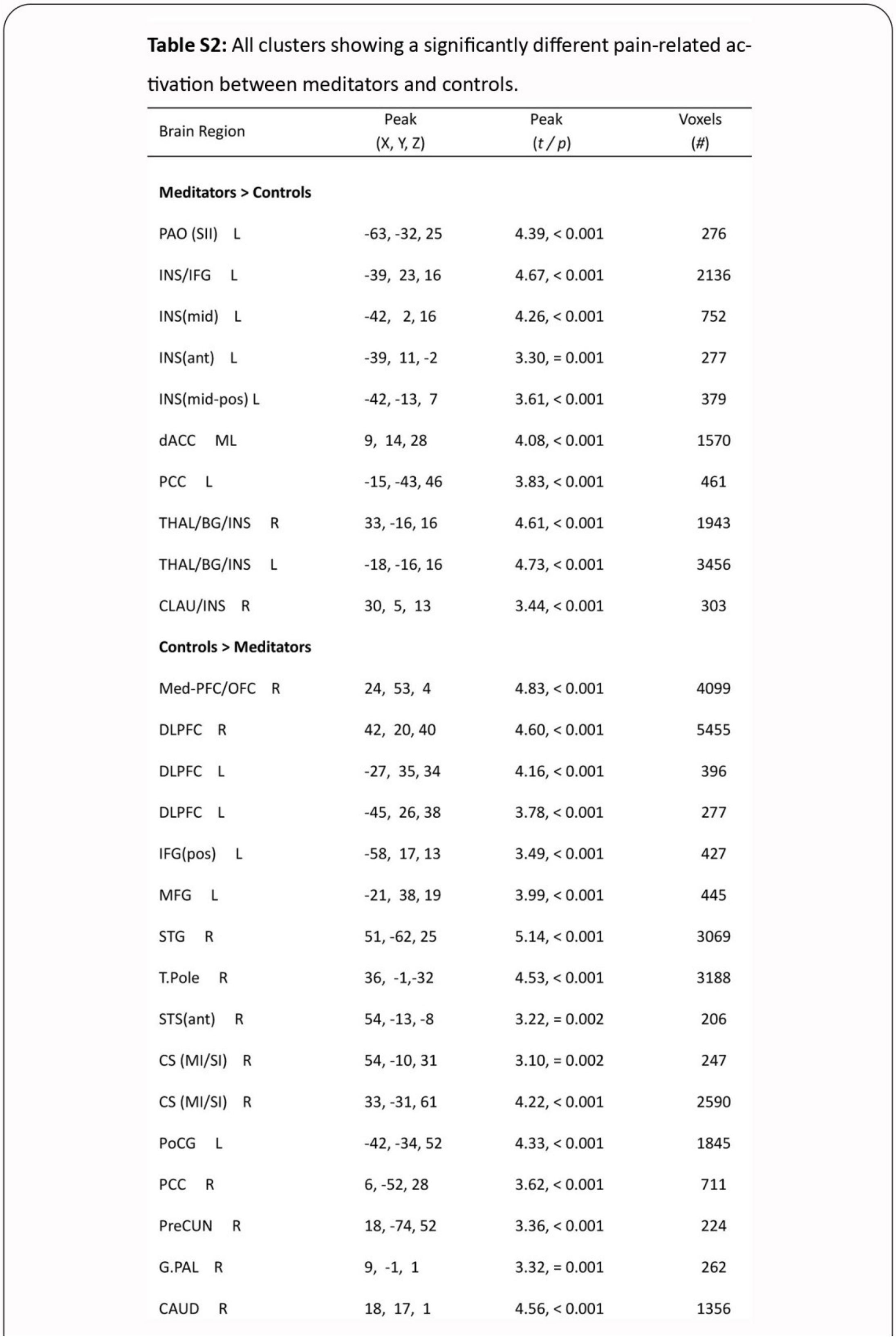
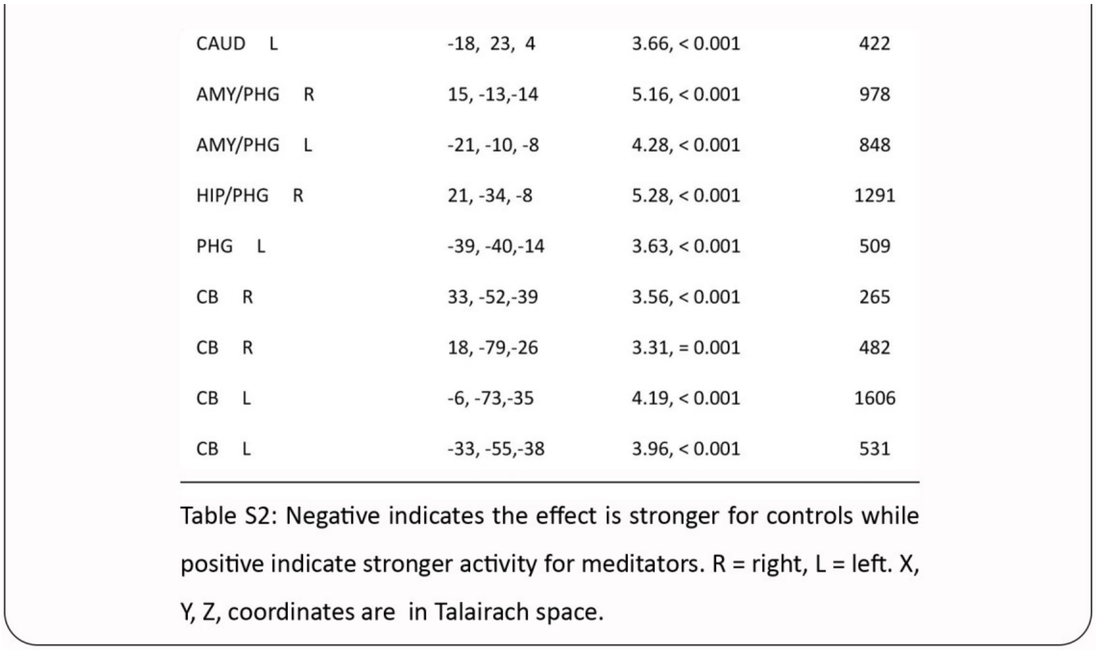


Table S2: All clusters showing a significantly different pain-related activation between meditators and controls.

Brain Region	Peak (X, Y, Z)	Peak (*t* / *p*)	Voxels (#)
Meditators > Controls			
PAO (SII) L	-63, -32, 25	4.39, < 0.001	276
INS/IFG L	-39, 23, 16	4.67, < 0.001	2136
INS(mid) L	-42, 2, 16	4.26, < 0.001	752
INS(ant) L	-39, 11, -2	3.30, = 0.001	277
INS(mid-pos) L	-42, -13, 7	3.61, < 0.001	379
dACC ML	9, 14, 28	4.08, < 0.001	1570
PCC L	-15, -43, 46	3.83, < 0.001	461
THAL/BG/INS R	33, -16, 16	4.61, < 0.001	1943
THAL/BG/INS L	-18, -16, 16	4.73, < 0.001	3456
CLAU/INS R	30, 5, 13	3.44, < 0.001	303
Controls > Meditators			
Med-PFC/OFC R	24, 53, 4	4.83, < 0.001	4099
DLPFC R	42, 20, 40	4.60, < 0.001	5455
DLPFC L	-27, 35, 34	4.16, < 0.001	396
DLPFC L	-45, 26, 38	3.78, < 0.001	277
IFG(pos) L	-58, 17, 13	3.49, < 0.001	427
MFG L	-21, 38, 19	3.99, < 0.001	445
STG R	51, -62, 25	5.14, < 0.001	3069
T.Pole R	36, -1,-32	4.53, < 0.001	3188
STS(ant) R	54, -13, -8	3.22, = 0.002	206
CS (MI/SI) R	54, -10, 31	3.10, = 0.002	247
CS (MI/SI) R	33, -31, 61	4.22, < 0.001	2590
PoCG L	-42, -34, 52	4.33, < 0.001	1845
PCC R	6, -52, 28	3.62, < 0.001	711
PreCUN R	18, -74, 52	3.36, < 0.001	224
G.PAL R	9, -1, 1	3.32, = 0.001	262
CAUD R	18, 17, 1	4.56, < 0.001	1356



CAUD L	-18, 23, 4	3.66, < 0.001	422
AMY/PHG R	15, -13,-14	5.16, < 0.001	978
AMY/PHG L	-21, -10, -8	4.28, < 0.001	848
HIP/PHG R	21, -34, -8	5.28, < 0.001	1291
PHG L	-39, -40,-14	3.63, < 0.001	509
CB R	33, -52,-39	3.56, < 0.001	265
CB R	18, -79,-26	3.31, = 0.001	482
CB L	-6, -73,-35	4.19, < 0.001	1606
CB L	-33, -55,-38	3.96, < 0.001	531

Table S2: Negative indicates the effect is stronger for controls while positive indicate stronger activity for meditators. R = right, L = left. X, Y, Z, coordinates are in Talairach space.

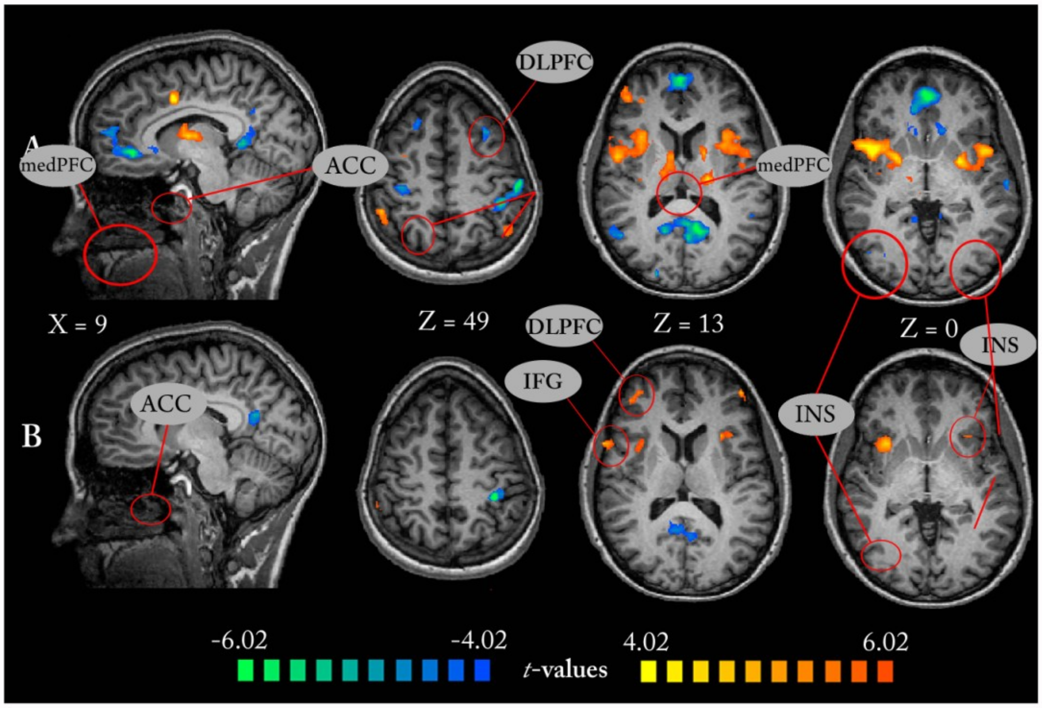


Figure S1. Within group pain-related activation (painful VS non-painful stimuli) for A) meditators (top row: N=13) and B) controls (bottom row: N=13). Color maps represent group t-statistics overlaid on a single subject's anatomical MRI and X,Y,Z coordinates are in Talaraich space (1) and corresponding peaks are listed in Table S1 (below). Orange represents areas where stronger activation was found for Painful stimuli and blue represents areas with lower activation for Painful stimuli (compared to Non-painful warm). There are many more areas active for meditators. All maps are cluster-level corrected for multiple comparisons at $p < 0.05$.

SUPPLEMENTARY DISCUSSION

Cue Period

No group differences were observed during the cue period which may seem at odds with the interpretation of baseline appraisal differences in meditators. One potential explanation for this is that in a non-meditative state the meditators process the cues similar to the control subjects but use them as an indicator of when to adopt a meditative stance. Indeed the primary reason for the inclusion of cues was to ensure engagement with the stimulation, as this interpretation would indicate. However, this would suggest that results reported here may reflect the ability to readily adopt a meditative stance (at baseline) rather than outright baseline differences. Such a possibility could be explored in future reports.

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Article 3

Grant, J.A., Courtemanche, J., Duerden, E.G., Duncan, G.H. and Rainville, P. (2010) Cortical thickness and pain sensitivity in Zen meditators. *Emotion* 10: 43-53.

ABSTRACT

Zen meditation has been associated with low sensitivity on both the affective and the sensory dimension of pain. Given reports of grey matter differences in meditators as well as between chronic pain patients and controls, the present study investigated whether differences in brain morphometry are associated with the low pain sensitivity observed in Zen practitioners. Structural magnetic resonance imaging scans were performed, and the temperature required to produce moderate pain was assessed, in 17 meditators and 18 controls. Meditators had significantly lower pain sensitivity than controls. Assessed across all subjects, lower pain sensitivity was associated with thicker cortex in affective, pain-related brain regions including the anterior cingulate cortex and bilateral parahippocampal gyrus and anterior insula. Comparing groups, meditators were found to have thicker cortex in the dorsal anterior cingulate and bilaterally in secondary somatosensory cortex. More years of meditation experience was associated with thicker grey matter in the anterior cingulate while hours of experience predicted more grey matter bilaterally in the lower leg area of the primary somatosensory cortex as well as the hand area in the right hemisphere. Results generally suggest that pain sensitivity is related to cortical thickness in pain-related brain regions and that the lower sensitivity observed in meditators may be the product of alterations to brain morphometry from long-term practice.

Keywords: pain; meditation; Zen; mindfulness; cortical thickness

INTRODUCTION

Research on meditation and meditation related techniques often emphasize the positive influence of such practices on affective processing (Nielsen and Kaszniak, 2006; Creswell et al., 2007). The cultivation of a state of equanimity toward one's experience, the goal of many meditative practices, is traditionally viewed as vitally important to a healthy mind (Thanissaro, 2000). This Buddhist concept, more generally referred to as 'mindfulness', has been shown to influence a great number of indices including those measuring depression (Ma and Teasdale, 2004), anxiety (Kabat-Zinn et al., 1992), immune function (Davidson et al., 2003) and pain (Kabat-Zinn, 1982; Kabat-Zinn et al., 1985; Kabat-Zinn et al., 1987; Grossman et al., 2007; McCracken et al., 2007; Grant and Rainville, 2009).

Consistent with an influence on affective processing, meditation has been found to have a positive impact on chronic pain patients (Kabat-Zinn, 1982; Kabat-Zinn et al., 1985; Kabat-Zinn et al., 1987; Grossman et al., 2007; McCracken et al., 2007). Over the course of five years, Kabat-Zinn reported on a group of 225 chronic pain patients who had completed the Mindfulness Based Stress Reduction (MBSR) program (Kabat-Zinn, 1982; Kabat-Zinn et al., 1985; Kabat-Zinn et al., 1987). Follow-up evaluation at four years showed stable improvement on most measures with the exception of pain intensity. This led the authors to conclude that MBSR teaches an effective coping strategy for pain, whereby the physical sensation of pain remains unchanged, but the patients' emotional reaction toward, or even acceptance of the pain is positively altered. The MBSR program has since been used effectively to treat many different chronic pain conditions (Grossman et al., 2007; McCracken et al., 2007) and also appears to increase tolerance to the cold pressor test in healthy subjects (Kingston et al., 2007). In addition, improvements specifically in pain acceptance have been reported in low back pain patients following an eight week meditation program (Morone et al., 2007).

More recently, one study has challenged the view that meditation solely influences the affective dimension of pain. Studying healthy individuals with previous training in Zen meditation, we found comparable effects of practice on the affective and sensory aspects of pain (Grant and Rainville, 2009). During exposure to moderate pain, meditators were found to modulate both the unpleasantness and intensity of the stimulation more than controls during a mindful attention condition, and this effect was positively correlated to their experience. Furthermore, the practitioners had significantly lower baseline heat-pain sensitivity than non-meditating control subjects. Higher trait mindfulness in meditators, coupled with slower respiratory rates that predicted meditative analgesia, suggested that training-related cognitive, affective or autonomic self-regulation may underlie the observed effects. An additional possibility, stemming from previous work (Lazar et al., 2005; Pagnoni and Cekic, 2007; Hölzel et al., 2008; Vestergaard-Poulsen et al., 2009) is that meditation practice influences the structural organisation of the brain in pain-related pathways.

The neural networks underlying the affective and sensory-discriminative aspects of pain are dissociable (Rainville et al., 1997; Hofbauer et al., 2001). Whereas the lateral thalamus and primary somatosensory cortex (SI) are associated with sensory aspects of noxious processing, the anterior cingulate and insular cortices have been repeatedly associated with the emotional response to pain (Apkarian et al., 2005). Furthermore, the hippocampus has been proposed to mediate emotional and avoidance responses to noxious stimuli (Melzack and Casey, 1967), a suggestion supported by functional magnetic resonance imaging (fMRI) studies, which have shown differential hippocampal activation dependant on the anticipated level of pain intensity (Ploghaus et al., 2001). Over the past few years it has also become evident that a substantial amount of plasticity can occur within the nociceptive pathways. For example many chronic pain conditions have now been associated with more or less grey matter in pain-related regions (May, 2008). This is consistent with the notion that long-term changes in pain are associated with specific modifications in grey matter reflecting altered neural processing of nociceptive signals. A similar observation has recently been made in healthy individuals.

In a longitudinal study examining the effect of repeated noxious stimulation on pain sensitivity and grey matter density, Teutsch et al., (2008) found rather surprising results. Receiving 20 minutes of painful thermal stimulation per day, healthy subjects exhibited reduced pain sensitivity over the course of 8 days. Pain intensity ratings were decreased and pain thresholds increased. This is consistent with a previous study from our lab (Gallez et al., 2005) demonstrating spatially-specific, reduced pain sensitivity following repeated nociceptive stimulation. In a comparison of grey matter between baseline and day 8, Teutsch et al., (2008) found increased density in pain processing regions including those with sensory-discriminative functions such as SI and those involved in pain affect including the mid-anterior cingulate cortex. Importantly, the location of grey matter increase within SI corresponded precisely to the somatotopic region representing the stimulated forearm. This implies that people who repeatedly engage in activities in daily life that involve pain may also have increases in grey matter in somatotopically relevant areas. Considering the fact that meditation is often a pain-provoking exercise due to the cross-legged posture, it is possible that a similar phenomenon underlies the lower pain sensitivity previously observed in Zen meditators (Grant and Rainville, 2009). Indeed morphometric studies have reported training-related differences in grey matter in meditators, compared to non-meditating control subjects, in regions implicated in pain processing such as the right anterior insula and SI in the vicinity of the leg (Lazar et al., 2005; Hölzel et al., 2008).

In the current study we sought to determine whether structural differences in the brains of meditators underlie previously observed pain sensitivity differences (Grant and Rainville, 2009). Since meditation is commonly viewed as an emotionally transformative practice (Nielsen and Kaszniak, 2006; Creswell et al., 2007), which has been proposed to underlie the benefit that mindfulness training bestows upon chronic pain patients (Kabat-Zinn et al., 1985), one possible outcome of this study is grey matter differences between groups in emotion related brain regions, which are also known to be involved in pain processing. However, our previous work has shown comparable and even stronger effects of Zen meditation on sensory aspects of pain (Grant and Rainville, 2009). Given that the posture adopted during prolonged meditative practice can be painful and that repeated exposure to noxious stimuli leads to lower pain sensitivity and somatotopically organized grey matter increases

(Teutsch et al., 2008), we also explored whether low pain sensitivity in Zen meditators might be associated with grey matter differences in sensory-discriminative cortical regions. To address these possibilities, high-resolution structural MRI scans were acquired from a group of Zen meditators and age and gender matched control subjects. Thermal pain sensitivity was assessed and regressed against the thickness of the grey matter across the cortical mantel. Based on our previous work and an overlapping sample, it was expected that Zen practitioners would exhibit lower pain sensitivity. Here, we hypothesized that such lower pain sensitivity would be associated with thicker cortex in sensory and affective pain processing regions. Lastly we explored the possibility that differences observed between groups may be related to meditation training by testing the correlation between cortical thickness and time spent meditating. However, note that although training-related effects would be expected to produce significant correlations, such a finding in the present cross-sectional study would not be sufficient to infer causality or rule out the possibility that effects may reflect pre-existing individual differences associated with the propensity for meditation.

METHODS

Participants

The recruitment process involved visits to meditation centers as well as advertisements in local newspapers and online classifieds inviting participants to a study investigating the cognitive modulation of pain. Exclusion criteria included current medication use, history of chronic pain, neurological or psychological illness, claustrophobia, and for control participants, previous experience with meditation and/or yoga. A list of possible meditators was first compiled (N=68), consisting of individuals who spanned a large range of experience and meditative traditions. The largest possible sample controlling for homogeneity of training and meeting the arbitrary requirement of 1000 hr of experience consisted of 19 Zen practitioners (15 male) (Table 1). Zen is considered to be a meditative tradition emphasizing mindfulness (Deikman, 1982; Goleman, 1997). Meditators from other disciplines were not tested. Twenty control subjects (15 male), matched precisely for age and gender, with no previous experience with meditation or yoga, were subsequently recruited. Two meditators and two controls did not undergo thermal pain sensitivity testing bringing the N for that analysis to 35 (17 meditators/18 controls). Experiments were conducted between Sept. of 2006 and Oct. 2007 at the Centre de recherché de l'Institut universitaire de gériatrie de Montréal. All procedures were approved by the local ethics committee (CMER-RNQ 05-06-020). All participants provided written

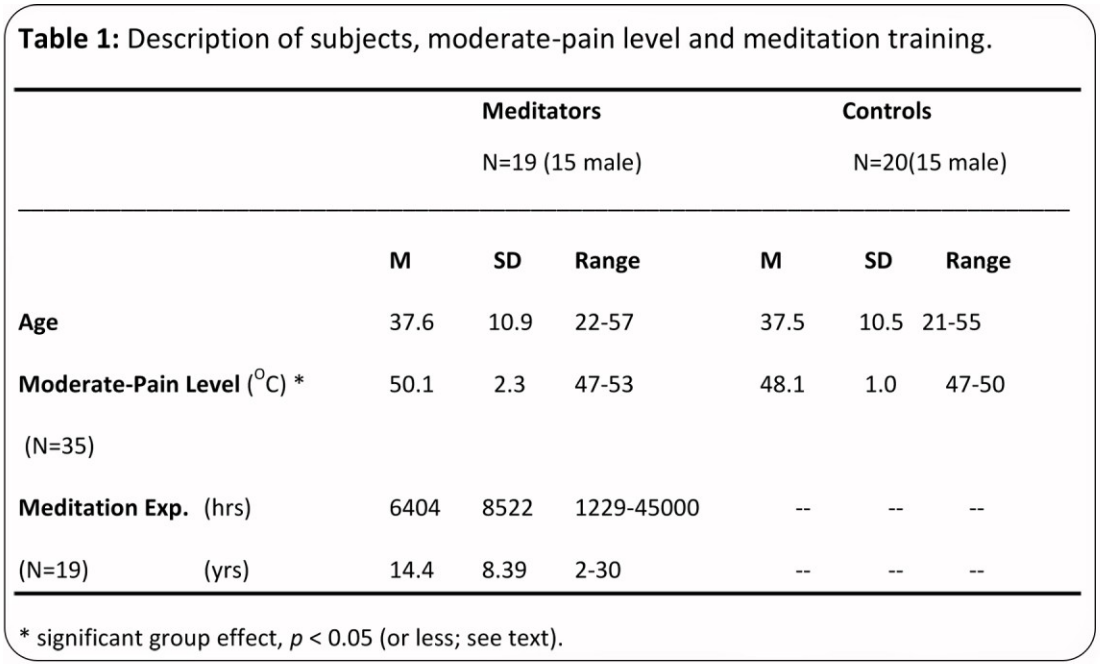


Table 1: Description of subjects, moderate-pain level and meditation training.

	Meditators N=19 (15 male)			**Controls** N=20(15 male)		
	M	**SD**	**Range**	**M**	**SD**	**Range**
Age	37.6	10.9	22-57	37.5	10.5	21-55
Moderate-Pain Level (^{O}C) * (N=35)	50.1	2.3	47-53	48.1	1.0	47-50
Meditation Exp. (hrs)	6404	8522	1229-45000	--	--	--
(N=19) (yrs)	14.4	8.39	2-30	--	--	--

* significant group effect, *p* < 0.05 (or less; see text).

informed consent and received a monetary compensation.

Meditation experience questionnaire

Participants completed a questionnaire designed to assess various aspects of their meditative history including: type of practice, number of years practicing, frequency and length of practice in days per week, length of individual sessions in hours, amount of time spent in retreat, and motivation for practicing. Using Cook's Distance and Central Leverage values a single subject was classified as an outlier in terms of hours of experience with ~45000 hr, compared to the next closest at ~10000 hr and removed from correlations involving hours of lifetime practice. Control subjects had previously been screened for meditation and/or yoga experience and thus did not complete this questionnaire. The Five Factor Mindfulness Questionnaire (Baer et al., 2008) was also completed by all participants but effects related to the five dimensions assessed in this scale will be described in a follow-up report.

Thermal pain sensitivity

Thermal stimulation was produced by a computer-controlled Peltier thermode with a 9 cm^2 contact probe (TSA Neuro-sensory analyser, Medoc Ltd. Advanced Medical System, Israel). The temperature required to elicit moderate pain was determined in each individual using the ascending method of limits. Each stimulation consisted of a 2s ascending ramp from 34°C, a 4s plateau at the target temperature, followed by a 2s descending ramp back to 34°C. Discrete trials began at a target temperature of 42°C and increased in 1°C increments to a maximum of 53.0°C if tolerated. All stimuli were applied to the inner surface of the left calf. The moderate-pain level was defined as the temperature required to elicit a pain rating of 6-7 on a

10 point scale on which 0 corresponded to “no pain” and 10 to “extremely painful”. These subject-specific temperatures provided the pain sensitivity index used in the morphometric analyses.

MRI and cortical thickness measurements

Brain images were acquired on a 3 Tesla (T) Siemens Trio (Siemens, Erlangen, Germany). Each participant underwent a high-resolution T-1 weighted structural MRI scan (3D MP-RAGE; TR=2300 ms, TE=2.94 ms, flip angle=9°, FOV=256 x 240 mm, in plane resolution=1x1 mm, measurement = 1). Cortical thickness processing and measurements were carried out using an automated analyses pipeline developed at the Montreal Neurological Institute (MNI) (Lerch and Evans, 2005). Anatomical MRIs were linearly registered and transformed into a common stereotactic space and were corrected for non-uniformity artefacts (Collins et al., 1994; Sled et al., 1998). The processed MRIs were then segmented according to their physiological classification (grey matter, white matter, cerebrospinal fluid) (Zijdenbos et al., 2002). In order to produce the surfaces of grey and white matter the constrained Laplacian anatomic segmentation using proximities (CLASP) method was applied (Kim et al., 2005). The white matter surfaces were expanded out to the grey matter/cerebrospinal fluid surface boundary using a surface deformation algorithm (MacDonald et al., 2000). This procedure is ideal for comparison of the two surfaces in that it permits close matching of grey and white matter boundaries. In turn cortical thickness can be calculated based on the distance between the surfaces. Lastly, individual cortical thickness data were smoothed following surface curvature using a blurring kernel of 20 mm. This technique allows for the identification of cortical thickness changes amongst the population.

Statistical Analysis

Group differences for the moderate-pain level were assessed with an independent-sample t-test using the SPSS software. About half of the participants of the present study had also participated in our previous psychophysical study (Grant and Rainville, 2009). This between-subject factor (New Vs Returning participants) was included in a two-way ANOVA to verify the stability of the meditation-related effect. The test-retest reliability of the individual moderate-pain level was also tested in the returning participants using Pearson correlation. Statistical analysis of cortical thickness was performed using SurfStat (Worsley et al., 2009) at individual points on the cortical surface (vertices) using a general linear model (GLM) controlling for age. Main effects of group (meditators versus non-meditators) and pain sensitivity (regression of moderate-pain level with cortical thickness in the entire sample) were computed as well as the interaction between group and pain sensitivity. Lastly, cortical thickness was regressed against hours and years of meditation experience in Zen practitioners. These effects are reported as partial Pearson correlations (i.e. the contribution of the variable after removing the effect of age).

Stemming from our *a priori* hypotheses we performed a directed search within pain-related regions-of-interest (ROIs). Pain-related ROIs were created from a probabilistic meta-analysis of 122 functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies (Duerden et al., 2008) developed using the activation likelihood estimate (ALE) method (Laird et al., 2005). Studies included in the meta-analysis involved the application of a variety of experimental painful stimulus applied to the skin, muscle or viscera. Brain activation coordinates were converted into standardized stereotaxic space and ALE maps were created using a blurring kernel of 8mm. Regions with the highest probabilistic values across all pain conditions were used as ROIs including: bilateral insular cortices, the primary (SI) and secondary (SII) somatosensory cortices, the dorsal anterior cingulate cortex (dACC), and the prefrontal cortex including right Brodmann Area (BA) 10/46, and left BA 10. Given the hypothesis that reduced emotional reactivity may underlie the pain sensitivity differences previously observed in Zen practitioners, an additional ROI was included based on the coordinates of the peak activation previously associated with pain-related anxiety in the hippocampal formation (HF) (Ploghaus et al., 2001). Finally, an ROI (10mm radius) was created manually, centered over the lower leg representation of SI (i.e. posterior part of the paracentral lobule). The rationale for testing this ROI was that the posture assumed during Zen meditation involves sitting cross-legged. This posture can create considerable pain and numbness with extended periods of practice which may lead to structural changes in the brain.

A two stage process was used to analyze the cortical thickness data testing our *a priori* hypotheses. First, significance was tested using small volume correction based on the number of vertices across all defined ROIs. The second approach involved averaging the thickness values at each vertex within each ROI separately and regressing that value against the variables of interest (i.e. pain sensitivity and meditation experience). All statistical analyses controlled for the age of the subjects. Lastly, a whole brain analysis was conducted for each assessment, cluster corrected for multiple comparisons using random field theory and thresholded at p<0.05 (Worsley et al., 1996).

RESULTS

Pain sensitivity

A significant group difference was found for thermal pain sensitivity ($t = 3.34$, $p = .002$). To experience moderate pain, meditators required on average 50.1° C and control subjects 48.1° C. It should be noted that approximately half of these participants (49%) also participated in our previous study (Grant and Rainville, 2009), and thus this result should not be considered a completely independent replication of our previous results. A two-way ANOVA comparing *New and Returning* participants as well as *Groups* (meditators Vs controls) confirmed that new subjects did not differ from the returning subjects (main effect New or Returning: F=0.001, p=0.978; main effect Group: F=10.82, p=0.003, interaction; F=0.85, p=0.36). Furthermore, in the 17 subjects to return (9 meditators/8 controls), the test - retest analysis showed that moderate pain levels were consistent across time (test-retest: $R = .76$, $p < .001$). Pain sensitivity, as measured by the moderate pain level, was not associated with meditation experience (Years: $R = -.24$, $p = .35$, Hours: $R = -.24$, $p = .36$).

Group differences in cortical thickness

The ROI analysis revealed that meditators had thicker grey matter than control subjects in several regions known to be involved in pain processing (Table 2a, Figure 1). Regions included the right dorsal ACC (BA24) and SII bilaterally. The

Table 2. Significant effects of cortical thickness

Brain Region / BA	**Side**	**X Y Z MNI-space**	***Vertex-wise t /p-corrected***	***Average thickness t /p-uncorrected***
a) Group difference				
Anterior Cingulate (24)	R	4, 16, 29	4.14, < 0.01 *	1.99, < 0.05
	L	-8, 0, 42	1.90 ns	0.59 ns
Operculum SII (40/43)	R	57, -25, 25	3.79, < 0.05	2.58, < 0.01
	L	-52, -27, 19	2.20 ns	1.93, < 0.05
Insula (13/14)	R	39, 6, -9	1.93 ns	1.01 ns
	L	-37, 12, -6	2.55 ns	0.54 ns
Parahippocampal Gyrus (28)	R	20, -20, -8	2.42 ns	0.17 ns **
	L	-21, -37, -12	1.54 ns	
Primary Somatosensory (1-3)	R	30, -26, 62	1.36 ns	0.10 ns **
	L	-33, -26, 61	0.60 ns	
Frontal (10/46)	R	47, 42, 0	2.31 ns	1.40 ns
	L	-31, 54, 12	0.88 ns	-0.08 ns
b) Pain sensitivity				
Anterior Cingulate (24)	R	4, 12, 27	3.53, < 0.05	1.51 ns
	L	-3, 2, 37	1.33 ns	0.42 ns
Operculum (52)	R	51, -27, 25	3.37, < 0.05	2.93, < 0.01
	L	-40, -24, 20	1.85 ns	1.39 ns
Insula (13/14)	R	51, 2, 6	3.57, < 0.05	2.49, < 0.01
	L	-37, 12, -7	2.53 ns	0.48 ns
Parahippocampal Gyrus (28)	R	20, -3, -11	4.94, < 0.001 *	2.60, < 0.01 **
	L	-21, -36, -13	2.93 ns	
Primary Somatosensory (1-3)	R	20, -36, 71	1.54 ns	0.07 ns **
	L	-39, -34, 46	0.37 ns	
Frontal (10/46)	R	44, 45, 0	1.95 ns	0.87 ns
	L	-31, 54, 12	0.83 ns	-0.23 ns

***** indicates the result was significant at the whole brain level, ****** indicates that, for the average thickness analysis, the ROI was a single unit spanning both hemispheres, BA = Brodmann area, R = right, L = left, ns = non-significant

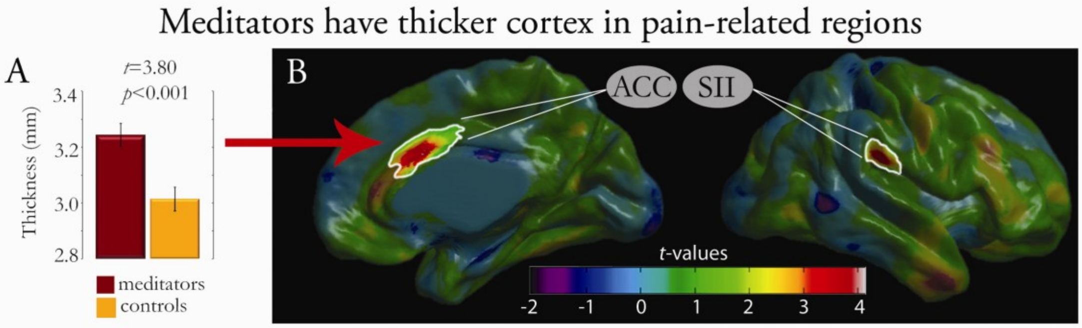
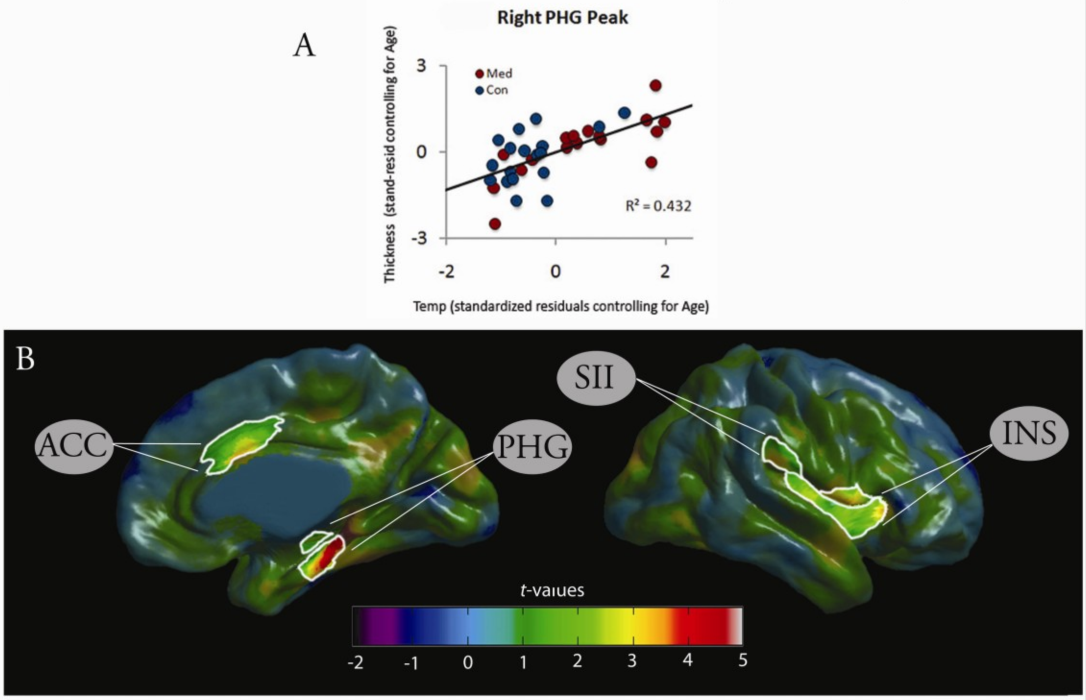


Figure 1. A) Thickness values at the peak of the anterior cingulate ROI. **B)** Medial and lateral views of the right hemisphere with t-statistic maps projected onto an averaged brain revealing areas of statistically different cortical thickness between meditators and non-meditators. ROIs are traced in white and appear brighter for illustrative purposes. Peak coordinates and statistical values are reported in Table 2a. All effects are adjusted for age.

dorsal ACC was also significant in the whole brain search but no additional regions were found outside the pain mask. No areas exhibited greater grey matter thickness in control subjects.

Pain sensitivity correlations with cortical thickness

The temperature required for each subject to report moderate pain was first regressed against cortical thickness for the entire sample. Several pain-related areas showed thicker cortex associated with lower pain sensitivity, that is, a higher moderate-pain level (Table 2b, Figure 2). These areas included the right dorsal ACC, HF, SII and insular cortices. No regions were found where thicker cortex was associated with higher pain sensitivity. At the global search level (whole brain) no additional areas were found but the HF survived this more strict statistical criterion. The interaction with Group revealed that the relationship between cortical thickness and pain sensitivity (i.e. the direction and magnitude of the slope) did not differ between groups even though the meditators had significantly thicker cortex than controls in some areas (ACC and SII). This suggests there is a general relationship between cortical thickness and pain sensitivity with meditators and controls at opposite ends of the distribution.



Thicker cortex is associated with lower pain sensitivity

Figure 2. A) Positive correlation between cortical thickness, at the peak of the parahippocampal gyrus ROI, and the moderate-pain level (pain sensitivity) in degrees Celsius. **B)** Medial and lateral views of the right hemisphere revealing areas where cortical thickness significantly relates to pain sensitivity (thicker cortex = lower pain sensitivity). ROIs are traced in white and appear brighter for illustrative purposes. Peak coordinates and statistical values are reported in Table 2b. All effects are adjusted for age.

Correlation between meditation experience and cortical thickness

A correlation between the hours of meditation practice and cortical thickness was seen in the lower leg representation of SI bilaterally (Table 3a; Figure 3a,b), such that more hours of experience was associated with thicker cortex. A similar analysis, using years of meditative experience, revealed that bilateral dorsal ACC was also related to cortical thickness in Zen meditators (Table 3b; Figure 3c,d). In each case more hours of experience was associated with thicker cortex. The same relationship was found in the right hemisphere SI ROI, derived from the pain mask, near the hand representation. This later SI effect was also significant at the global search level but no other regions, outside the pain mask, were found.

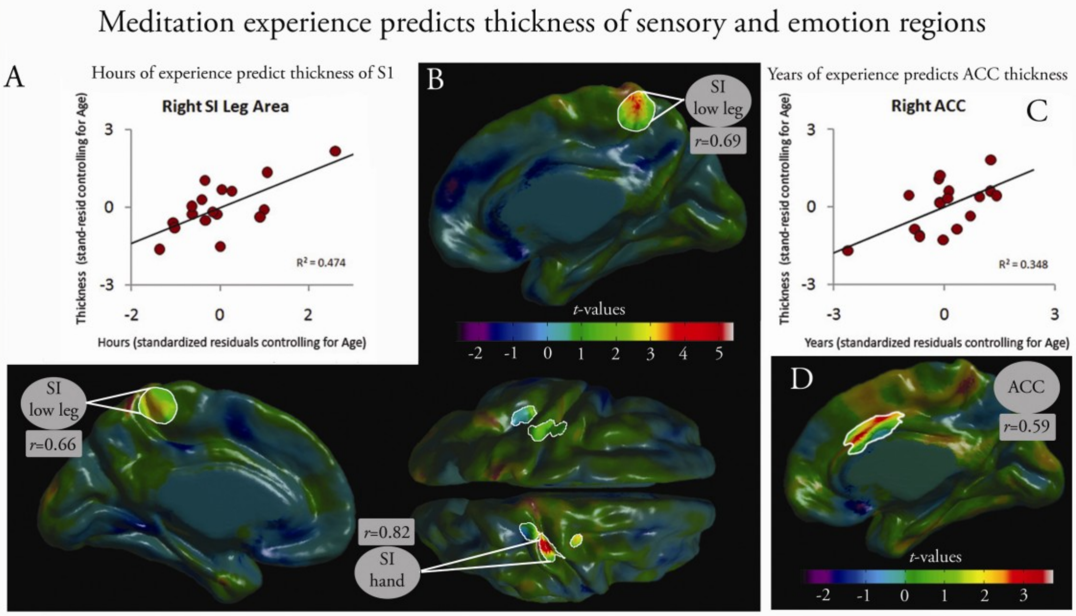


Figure 3 A) A positive correlation between hours of life time meditation practice and cortical thickness in the right SI leg area. **B)** Medial and overhead views illustrating areas where cortical thickness significantly relates to meditation experience in hours (more hours = thicker cortex). **C)** A positive correlation between years of practice and cortical thickness in the right ACC. **D)** Medial view of right hemisphere illustrating the area of ACC where more meditation experience in years is associated with thicker cortex. Peak coordinates and statistical values are reported in Table 3. All effects are adjusted for age including Pearson R's (i.e. partial correlation).

DISCUSSION

Pain sensitivity

The potential influence of Zen meditative practice on cortical thickness was investigated to probe the mechanisms underlying the low pain sensitivity previously observed in these individuals (Grant and Rainville, 2009). With an increased sample size it was again found that Zen practitioners were less sensitive to thermal pain than controls subjects, requiring on average 50°C versus 48°C to report moderate pain. This difference is an underestimate as 5/17 meditators that were tested for moderate pain reached the maximum temperature (53°C) permitted for stimulation. In contrast, only 2/18 control subjects surpassed 50°C. Thus, a ceiling effect prevented the true extent of the difference from being measured. Nonetheless, this difference corresponds to an increase of ~50% on a ratio scale of pain perception or 20-25 points on a 0-100 numerical pain scale (Price et al., 1983; Price and Harkins, 1987) and should be considered large.

Emotion-related effects

The first hypothesis was that the cortical thickness of brain areas involved in emotion processing, as well as the affective dimension of pain, would be related to pain sensitivity. Overall, considering the entire sample, sensitivity was inversely related to cortical thickness in the right dorsal ACC (BA24), right anterior insula (rAI) and bilateral HF. In each case thicker cortex was associated with lower pain sensitivity (i.e. higher moderate-pain level). Each of these regions will be discussed in turn.

In terms of emotion in general, the region of dorsal anterior cingulate cortex reported in the present study is also activated during emotion induction using film excerpts as well as recall of emotional events, possibly reflecting enhanced focal attention to conscious emotional experience (Lane et al., 1998). Greater cortical thickness in this region may thus enhance one's ability to attend to, or be consciously aware of, emotional states including pain. This same dACC region is among the most commonly activated areas in functional imaging studies of nociception (Apkarian et al., 2005) and has been specifically linked to meditating the affective dimension of pain (Rainville et al., 1997). If indeed the dACC is a mediator of affective responses to nociceptive input, which is not inconsistent with a role in promoting attention toward conscious emotional states, then more grey matter in this region may be indicative of greater control or efficacy of this mediation, thereby reducing pain sensitivity. In support of this, meditators, whose practice is often considered an emotion regulation technique (Wallace, 2000; Goleman, 2003), had thicker cortex in this region of the ACC than control subjects. Furthermore, there was a significant positive correlation observed between years of meditation experience and thickness in the dACC such that the most experienced meditators had the most grey matter. Lastly, the dorsal ACC has been observed as more active during meditation than during control tasks ((Baerentsen et al., 2001; Lazar et al., 2003) reviewed in Cahn & Polich, (2006)). Taken together the present results and previous studies suggest that the dACC may be a cortical site that is engaged in, and altered by meditative practice. Changes to this region may lead to enhanced awareness and control of emotional experience, including pain.

Thicker grey matter in right anterior insula (rAI) was also associated with lower pain sensitivity in the present study. This region has known roles in interoception (Critchley et al., 2004) and perception of body states underlying emotion (Craig, 2008), and it is almost always activated in functional brain imaging studies of acute pain (Apkarian et al., 2005). Consistent with the proposed role of the dACC above, greater cortical thickness of the rAI may represent heightened awareness of the representation of internal body states. Indeed, Craig (2008) suggests the rAI and ACC together form the neural basis for conscious emotional awareness. However, unlike the ACC there was no group difference in grey matter in rAI as reported previously in Vipassana and Buddhist Insight meditators (Lazar et al., 2005; Hölzel et al., 2008) nor was the correlation with meditation experience significant as it was in those studies. It should be noted however that previous morphometric studies of meditation (Lazar et al., 2005; Pagnoni and Cekic, 2007; Hölzel et al., 2008; Vestergaard-Poulsen et al., 2009) all have substantial methodological differences. Although a recent study comparing cortical thickness and grey matter volume/density/concentration has reported a fairly high correspondence between these measures (Hutton et al., 2009) varying meditative traditions, scanner strengths (Han et al., 2006) and statistical methods limit the expected similarities. Nonetheless, the interpretation of both Hölzel et al. (2008) and Lazar et al (2005) was that meditation trains one to be highly aware of internal experience and thus engages, and increases grey matter in, interoceptive cortex. However, contrary to predictions, a recent study of Kundalini and Tibetan meditators failed to find any difference in interoceptive acuity, as measured by heart-rate detection, between subjects trained in meditation and non-meditators, (Khalsa et al., 2008). Thus, the nature of the involvement of the anterior insula in meditation is unclear and appears to differ across meditative traditions.

The final emotion-related area where cortical thickness predicted pain sensitivity was the hippocampal formation (HF). The HF has been shown to mediate the emotional response to aversive painful stimulation such that greater activation accompanies anxiously awaited stimuli compared to identical stimuli without anxiety. This structure has also been found more active, concomitantly with the rAI. Seminowicz et al. (2006) reported increased activity in the HF, as well as the rAI, in association with higher pain catastrophizing in healthy individuals. Similar to the rAI there was no group difference between meditators and controls and no correlation with meditation experience in the HF. Interestingly, the study by Hölzel et al. (2008) that reported group differences in rAI between meditators and controls also reported differences in grey matter concentration in the hippocampus, very near to the peak found in the current study. Similarly, they also found no correlation with meditation experience. Thus the rAI and HF may play a different and more general role in pain sensitivity than the ACC, perhaps related to trait-like emotional reactivity such as catastrophizing or anxiety that might be more consistent across meditative traditions.

Taken together the results in emotion-related brain regions, particularly the dACC, are consistent with the possibility that meditation may lead to reduced pain sensitivity, although we cannot strictly exclude pre-existing physiological differences. However Zazen is not practiced to relieve pain but to promote mental clarity and emotional stability (Austin, 1999) and so the relationship of cortical thickness and pain sensitivity may relate more generally to heightened control, awareness and/or acceptance of one's emotional state. These may be viewed as skills, and part of the concept of mindfulness (Baer et al., 2006), which are allegedly learned through meditation. Just as physical skills are learned and result in grey matter alterations (Draganski and May, 2008) mental skills acquired through meditation may do the same, although a physiological explanation of these effects is still lacking (see below). There is however an alternative interpretation for the relationship between these brain regions and pain sensitivity.

Pain regulation in the ACC

The dorsal ACC is putatively involved in pain inhibition (Rainville et al., 1999; Zubieta et al., 2001). In this view thicker cortex in the dACC may influence the potential for inhibitory regulation, with more grey matter allowing greater attenuation, thereby resulting in lower pain sensitivity. Support for this interpretation comes from a recent longitudinal pain study of healthy individuals (Teutsch et al., 2008). Over the course of 8 days subjects' thermal pain thresholds and tolerance rose, in response to repeated noxious stimulation, with a concomitant increase in grey matter density in ACC (BA24). Chronic pain patients, who often exhibit hyperalgesia and allodynia, have also been shown to have less grey matter in BA24 (May, 2008). This loss may influence self-regulatory processes, associated with cognitive and emotional function, thought to modulate lower-level nociceptive responses through descending pathways affecting brain stem and spinal activity. These findings are consistent with the notion that long-term changes in pain are associated with specific modifications in brain morphometry reflecting altered neural processing of nociceptive signals. Interestingly, the rAI also has a role in pain modulation. Jasmin et al. (2003) showed that increasing or decreasing GABA transmission in the rAI leads to analgesia and hyperalgesia respectively. It should be noted that these two alternatives; thicker ACC enhancing attentional control and awareness of emotional states and thicker ACC leading to more pain inhibition are not necessarily mutually exclusive.

Sensory effects

The second hypothesis of the study was that cortical thickness in brain regions involved in the sensory aspect of nociceptive processing would correlate with pain sensitivity. A single region, right secondary somatosensory cortex (SII), was inversely correlated with sensitivity such that thicker cortex was associated with a higher moderate pain level. Group differences were also observed, bilaterally in SII, with meditators having thicker cortex than controls. Although neither region of SII correlated with meditation experience a rather striking relationship was found in the Zen practitioners bilaterally in primary somatosensory cortex, in the regions receiving input from the lower legs. The thickness of the grey matter in these regions was strongly correlated with the amount of lifetime hours that the individuals had spent meditating, such that more hours were associated with thicker cortex. This remarkable result offers an interesting comparison with the study mentioned above by Teutsch et al. (2008) in which healthy participants were given 20 min of painful forearm stimulation for 8 consecutive days. In that study contra-lateral SI, in the vicinity of the forearm representation, was shown to increase in grey matter density, along with subjects' pain thresholds, over the 8 days. This is consistent with findings in a previous study of healthy subjects, in whom we described a spatially specific decrease in pain sensitivity, associated with extended exposure to nociceptive stimuli within the context of psychophysical training over a period of several days (Gallez et al., 2005). At first blush, the relation to meditation may not be apparent until one considers that the practice is notoriously associated with pain in the knees and ankles (Austin, 1999). The observation of thicker grey matter in the lower leg areas of SI in meditators may be due to a phenomenon similar to that observed in the above studies (Gallez et al., 2005; Teutsch et al., 2008). Namely, the brains of meditators may be physically altered due to the sensory input associated with the cross-legged posture. Although an intriguing possibility, this interpretation appears incomplete for two reasons. First, unlike Teutsch et al. (2008) thermal pain sensitivity did not correlate specifically with cortical thickness in SI in our study. This implies that if cortical thickness is associated with the painful posture, the effect of this repeated exposure to pain from deep tissue may not be sufficient to explain the reduced sensitivity in cutaneous thermal pain perception. Second, an additional area of the right SI cortex, the sensory hand region, also demonstrated a significant increase in thickness that was correlated with hours of meditation experience; however, the hand is not typically subjected to uncomfortable or painful stimulation during meditation.

A complementary explanation for these results lies once again in the processing of somatosensory signals associated with Zen practice; however, pain may not be the necessary component. An aspect of Zen practice that is not often discussed is walking meditation. Zen practice typically involves sitting meditation (Zazen) interspersed with walking meditations (Kinhin) (Austin, 1999). During Kinhin, practitioners turn complete attention to the soles of their feet contacting the ground as they walk in unison around the meditation hall. During Zazen, the hands are held in front of the abdomen and serve as a focal point during the sitting meditation. Thus, an alternative explanation for our results in SI is that the increased awareness of the hands and feet, during meditation practice, may lead to an increase in cortical thickness within the corresponding somatotopic area. Consistent with previous studies showing morphometric changes associated with sensori-motor training (Gaser and Schlaug, 2003; Driemeyer et al., 2008; Ilg et al., 2008), changes in SI may be driven by the voluntary and repeated attentional allocation to the incoming somatosensory signals rather then, or in addition to, the painfulness of the sensory experience associated with the meditative posture. In support of this, Lazar et al. (2005) found thicker cortex in SI also in the vicinity of the leg area, as well as in auditory cortex, in Buddhist Insight meditators. This suggests that the focused attentional processes involved in meditation may promote morphological changes in the cerebral networks underlying the attended representation.

Physiological considerations

The specific physiological mechanisms underlying changes in cortical thickness are not well understood and could involve a host of phenomena such as an increase in cell size, neuro-, glio-, angio- or synapto-genesis, or changes in interstitial fluids (Draganski and May, 2008). Based on the short time frame of induced grey matter changes observed in several studies (May et al., 2007; Driemeyer et al., 2008; Teutsch et al., 2008) ranging from 5 to 8 days, it is likely that several of these possibilities can be ruled out. Alterations in axonal architecture have been suggested to underlie transient grey matter increases observed during skill acquisition (Ilg et al., 2008). The present finding of a correlation between the hours spent in meditation and thickness in SI suggests that thickness changes may be retained and continue to increase, at least as practice is sustained in time. This is consistent with studies in musicians (Gaser and Schlaug, 2003) where grey matter density in the SI hand representation was shown to correlate with experience level. Clearly the brain cannot expand indefinitely, and it should be noted that thickening is likely a very subtle effect. Indeed in the present study, the meditators as a group had thicker cortex in the leg area than controls, but not significantly. The effect was specifically observed in the correlation with meditative experience. It is not yet clear whether these long-term effects reflect the same underlying mechanisms as the short-term changes.

Limitations

Several limitations of the present study should be raised. First, the cross-sectional nature of the design implies that strong causal claims concerning the effect of meditative training on pain sensitivity or cortical thickness cannot be made. For example, we can not fully exclude the possibility that confounding factors such as expectancy may contribute to the reduced pain sensitivity in meditators (see the discussion of this possibility in Grant & Rainville, (2009)). A recent report further suggests that individual differences in expectation-induced analgesia (placebo) relates at least partly to differences in grey matter density within cortical and sub-cortical structures also associated dopamine-related personality traits (Schweinhardt et al., 2009). However, with only one possible exception (insula/parietal operculum), the cortical areas found to be associated with these variables did not overlap with those related to meditation or reduced pain sensitivity in the present study (e.g. ACC; HF and SI; see Tables 2 and 3). Although we can not exclude all possible confounds, differences in pain sensitivity and cortical thickness reported here do not match those related to expectation-related factors.

Second, as in our previous study (Grant and Rainville, 2009), stimuli were always applied to the subjects' calves, that is, within the site of somatotopic change in cortical thickness. Consistent with the spatially specific analgesia previously reported following daily exposure to pain (Gallez et al., 2005), it is altogether possible that the lower pain sensitivity observed in Zen practitioners is restricted to regions of the legs from the knees down, reflecting a secondary effect of the posture adopted during Zazen. Future studies will need to address this issue by testing pain sensitivity in meditators in an area not influenced directly by the posture or the attentional focus during meditation. Lastly, although we relied on well accepted statistical methods to control for type I error, several effects reported here may be considered relatively small, particularly in the ROI average thickness analysis. This may be due to insufficient power or to the statistical approach which involved averaging vertices within an ROI. Although this was performed because it is more sensitive to weaker but spatially diffuse patterns, possibly due to individual anatomo-functional variability, averaging larger ROIs (i.e. containing more vertices) also has a greater chance of washing out more localized effects.

Conclusion

The goal of the current study was to attempt to dissociate between an affective transformative explanation for reduced pain sensitivity in Zen meditators and sensory habituation stemming from the often painful posture associated with meditative practice. There is evidence that the posture adopted during Zen meditation may result in cortical thickening in brain regions involved in sensation; however the involvement of nociceptive input is debatable. Increased attention to the feet and hands, focal points of the meditation technique, may be a more parsimonious explanation. However, regions involved in emotion induction, pain affect and pain modulation were also significantly thicker in meditators compared to non-meditators, possibly reflecting increased attentional control or decreased emotional reactivity learned through training. This study suggests that the perceptual and emotional changes often attributed to meditation training – observed here in psychophysical measures of pain sensitivity – are associated with structural brain changes in pain-related cortical areas. This provides evidence in support of the notion that meditation strengthens brain processes involved in emotion as well as pain regulation. Future prospective studies should further clarify how much of those differences can be attributed to meditative training.

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Article 4

Associations between cortical thickness, attentional absorption and prior mental training : possible implications for disorders of attention.

Running head: CORTICAL THICKNESS AND PRIOR ATTENTION TRAINING

Title: Associations between cortical thickness, attentional absorption and prior mental training: possible implications for disorders of attention

Authors: Joshua A. Grant[1,2,3], Emma G. Duerden[1,2,3], Jérôme Courtemanche[3,4], Gary H. Duncan[2,5,6] and Pierre Rainville[2,3,5]

Correspondence concerning this article should be addressed to: Joshua Grant

ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is associated with behavioral deficits, under-activation of attention/executive-related brain regions and cortical thinning in overlapping networks. The complete opposite appears to be true, behaviorally, functionally and structurally of a family of concentration training techniques which are now associated with substantial mental and physical health benefits. The purpose of this study was to assess the relationships between prior training in meditation, the capacity for attentional absorption and cortical thickness in brain regions implicated in attention and executive functioning which have been reported as thinner in ADHD populations.

Methods: We analyzed magnetic resonance images from a sample of 38 meditators and controls, who had also completed a measure of attentional absorption (Tellegen Absorption Scale). Grey matter thickness across the cortical mantle was regressed against absorption across all subjects, compared between groups and regressed against meditation experience within the group of meditators. The physical distance was then calculated between effects observed in the present study and a prior ADHD study by Shaw et al. (2006).

Results: The cortical thickness of a distributed network of regions previously identified as comprising the cingulo-fronto-parietal attention networks was found to be related to subjects' reports of how absorbed they become in their experiences. Within this network the meditation subjects were found to have greater cortical thickness which was positively related to the amount of training they had previously acquired. Several of these effects were in close proximity to cortically thinner regions in ADHD, particularly those associated with worse outcome.

Conclusions: We found that mental absorption is positively associated with grey matter thickness in attention-relevant cortical regions and that meditation experience is associated with thicker grey matter in these areas. These regions overlap substantially with cortical areas found to be underactive and thinner in ADHD. Given the previous suggestions and evidence that meditation may ameliorate symptoms of ADHD we propose that this form of mental training may operate by targeting and bolstering vulnerable brain regions underlying the functional deficits.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, impulsiveness and hyperactivity. Functional MRI studies of ADHD have repeatedly shown hypoactivation of the anterior cingulate, dorsolateral and inferior prefrontal cortices as well as the basal ganglia, thalamus, and parietal cortices (Dickstein et al., 2006). Morphometric brain imaging studies have likewise found structural differences such as cortical thinning, in many of these same areas, in populations of both adults and children with ADHD (Shaw and Rabin, 2009). Furthermore, poor clinical outcome has been linked with these structural differences (Shaw et al., 2006). While ADHD and cortical thickness, are highly heritable (Durston et al., 2004; Faraone and Mick, 2010; Rimol et al., 2010), morphometric longitudinal studies suggest grey matter may also vary as a function of training and performance (Draganski and May, 2008). One particularly notable study found that training naïve participants to juggle resulted in grey matter density increases, concomitant with performance gains, in brain regions previously implicated in processing visual motion (Draganski et al., 2004). Together these findings suggest that, despite the high likelihood of a genetic predisposition, it may be possible to combat the functional deficits of ADHD by targeting the vulnerable cortices with a suitable training intervention.

One potential candidate to bolster grey matter thickness and attentional function is meditative practice. Although often viewed as spiritual, many such techniques are, for the most part, completely secular and are gaining recognition as clinically relevant

(Chiesa and Serretti).The term meditation refers to a family of mental exercises aimed at enhancing the practitioner's ability to attain, and maintain, a target state, often attentional or affective in nature (e.g. sustained attention or a state of compassion) (Lutz et al., 2008). Fittingly, functional imaging studies have reported that meditating in an MRI scanner activates attention-related cortices such as the anterior cingulate cortex (ACC) and frontoparietal networks (Brefczynski-Lewis et al., 2007; Manna et al., 2010). A fair number of studies have also reported regional grey matter differences between individuals who meditate and those who do not (Lazar et al., 2005; Pagnoni and Cekic, 2007; Holzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Grant et al., 2010; Holzel et al., 2010). In all cases meditators have been found to have more grey matter than non-meditators. Several of these studies reported regions implicated in attention/executive processing (e.g. ACC, superior, middle and orbito-frontal regions (Lazar et al., 2005; Holzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Grant et al., 2010)). Behaviourally, practitioners of meditation have been shown to perform significantly better on attention and executive function tasks such as the Attention Network Task (ANT), the Stroop Task, attentional blink, Symbol Digit Modalities Test, verbal fluency, and the n-back task (Zeidan et al.2010; Tang et al., 2007; van Leeuwen et al., 2009; Prakash et al., 2010). Further, there is now evidence from longitudinal studies that both attention performance improvement (Zeidan et al.2010; Tang et al., 2007; Lutz et al., 2009) and grey matter changes (Holzel et al., 2010) relate to training, rather than reflecting only pre-existing differences in distinct populations. Finally, preliminary evidence indeed suggests that meditative training may be an effective adjunctive treatment for patients with ADHD. After an 8 week meditation program improvements were observed on the ANT, the Stroop Task and the Trail Making Test (Zylowska et al., 2008).

The present study took advantage of an existing structural MRI data set and a self-report measure of attentional engagement (absorption), in a sample of meditators and healthy controls, to test the following hypotheses: (a) Regional grey matter thickness will exhibit a positive relationship with an experiential-based measure of attention in functionally relevant brain regions (ACC, frontoparietal attention networks) and (b) Within these regions meditators will have greater cortical thickness than non-meditators which will positively correlate with measures of meditation experience.

METHODS AND MATERIALS

Participants

Nineteen Zen meditators (15 males) with a minimum of 1000 hr of lifetime practice (mean = 6406, SD = 1955, min = 1229, max = 45000) and nineteen age and gender matched control subjects (15 males) provided informed written consent and participated in the study. Meditators were recruited from centers around the Montréal area. With the exception of two monks, all participants were lay practitioners. Control subjects had no previous experience with meditation or yoga.

Self Report Measures

The Tellegen Absorption Scale (TAS) is a 39-item subscale of the Multidimensional Personality Scale (Tellegen and Atkinson, 1974) measuring one's tendency for "episodes of 'total' attention that fully engage one's representational (i.e. perceptual, enactive, imaginative and ideational) resources" (Tellegen and Atkinson, 1974). Two previous studies have reported higher absorption scores for meditators (Davidson et al., 1976; Holzel and Ott, 2006), the later also finding correlations between absorption and meditation depth and mindfulness. To further examine this connection we also administered the Five Factor Mindfulness Questionnaire (FFMQ) (Baer et al., 2008). The FFMQ measures skills associated with the construct of mindfulness, namely, the tendencies to be observant (OBS), nonjudgmental (NJ) and nonreactive (NR) toward one's experiences as well as aware in the present moment (AWARE). A meditation experience questionnaire was administered sampling years, hours and number of days per week of lifetime practice.

MRI Acquisition and Cortical Thickness Measurement

A single high-resolution (voxel size = 1mm^3) T-1 weighted structural MRI image (MP-RAGE) was acquired for each participant on a 3 Tesla Siemens Trio MR scanner (Siemens, Erlangen, Germany). An automated cortical thickness analysis pipeline was employed (Montréal Neurological Institute (MNI) (Lerch and Evans, 2005). Images were linearly registered, transformed into MNI space and corrected for non-uniformity artifacts (Collins et al., 1994; Sled et al., 1998). Images were then segmented into grey and white matter and cerebrospinal fluid (Zijdenbos et al., 2002). Grey and white matter surfaces were produced using constrained Laplacian anatomic segmentation using proximities (Kim et al., 2005). A surface deformation algorithm (MacDonald et al., 2000) then expanded the white matter surfaces to the surface boundary between grey matter and cerebrospinal fluid, allowing the calculation of cortical thickness. Thickness data were smoothed following surface curvature using a blurring kernel of 20 mm allowing identification of differences among the population.

Statistical Analyses

Questionnaires and hemispheric grey matter volume were analyzed with correlation and independent samples t-tests in SPSS. Cortical thickness data were analyzed with the general linear model (GLM), controlling for age and gender, in SurfStat (www.stat.uchicago.edu/~worsley/surfstat) and with multiple linear regression in SPSS. First, we regressed cortical thickness at 81924 locations (vertices) across the cortical mantle, on attentional absorption scores across the entire sample (N=36/38). Absorption scores were not available for two subjects so they were not included in the analysis. The threshold for significance was set to $p<0.05$, Bonferroni-corrected for multiple comparisons using the random-field theory (Worsley et al., 1996) to strictly control Type I error. This allowed verification of whether the measure of attentional engagement bore any significant relationship with grey matter thickness across the whole brain, including in attention-related regions. Regions meeting this strict criterion (i.e. showing a relation between absorption and cortical thickness) were then defined as regions of interest (ROIs) of the TAS-related network. Mean thickness within each ROI was subsequently computed and: a) compared across groups, b) regressed on measures of meditation experience and c) regressed on scores of the FFMQ. Lastly, we performed full brain exploratory searches for each of the FFMQ subscales. The main effects of group and meditation experience, at the full brain level, have been reported as part of the original study from which this data was acquired, investigating the structural correlates of pain sensitivity (Grant et al., 2010). Given our unidirectional hypotheses 1-tailed tests were used for all analyses.

RESULTS

Self Report Measures

Scores for all questionnaires were normally distributed. Meditators scored slightly, but significantly, higher on the TAS (t (34) = 1.71, $p<0.05$, d = 0.56) indicating a tendency to be more absorbed in their experience. Meditators also scored higher on three of the subscales of the FFMQ (OBS: t (34) = 3.30, $p < 0.01$, d = 1.09, NR: t (34) = 3.64, $p < 0.001$, d = 1.20 and AWARE: t (34) = 2.03, $p < 0.05$, d = 0.67) indicating a greater tendency to be mindful. Across the entire sample TAS scores were positively correlated with OBS scores (r (34) = 0.39, $p < 0.01$) and NR scores (r (34) = 0.32, $p < 0.05$) suggesting that absorption and mindfulness may have shared experiential dimensions. Absorption scores in the meditation group were predicted by the number of days of practice per week (r (16) = 0.41, $p < 0.05$) while years of practice predicted NR scores (r (16) = 0.47, $p < 0.05$) with more experience being associated with less reactivity.

Cortical Thickness Measures

Across the entire sample, higher absorption was associated with thicker grey matter in the cingulo-fronto-parietal (CFP) attention network (Fig. 1, Table 1). A large and highly significant cluster was found in the left superior frontal gyrus expanding substantially into supra-callosal parts of the medial frontal and cingulate gyri. Additional significant clusters were found in the middle frontal gyri and superior

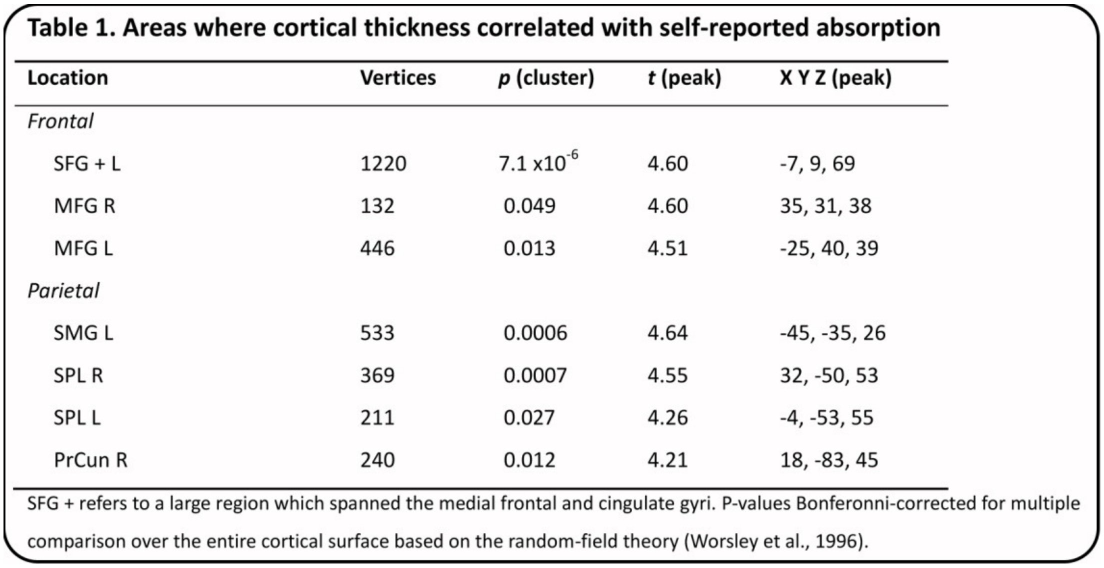

Table 1. Areas where cortical thickness correlated with self-reported absorption

Location	Vertices	*p* (cluster)	*t* (peak)	X Y Z (peak)
Frontal				
SFG + L	1220	7.1 x10^{-6}	4.60	-7, 9, 69
MFG R	132	0.049	4.60	35, 31, 38
MFG L	446	0.013	4.51	-25, 40, 39
Parietal				
SMG L	533	0.0006	4.64	-45, -35, 26
SPL R	369	0.0007	4.55	32, -50, 53
SPL L	211	0.027	4.26	-4, -53, 55
PrCun R	240	0.012	4.21	18, -83, 45

SFG + refers to a large region which spanned the medial frontal and cingulate gyri. P-values Bonferonni-corrected for multiple comparison over the entire cortical surface based on the random-field theory (Worsley et al., 1996).

parietal lobule bilaterally, the left supramarginal gyrus as well as the right precuneus. No negative correlations between TAS scores and thickness were observed. There were no group differences in grey matter volume of the left or right hemispheres reinforcing the focal nature of the effects. For the subsequent analyses the large cluster spanning left SFG, medial frontal and cingulate gyri was split, based on clearly visible borders, into three components (SFG, ACC and PCC). Within the TAS-network, meditators had significantly greater cortical thickness than controls in left SFG (t (33) = 1.90, $p < 0.05$), SMG (t (33) = 2.37 $p < 0.05$) and SPL (t (33) = 1.85, $p<0.05$) (Fig. 2, Table 2). Within the meditation group, years of training (after accounting for Age) was positively associated with thickness of the left SFG (r (15) = 0.42, $p < 0.05$), ACC (r (15) = 0.49, $p < 0.05$), SPL (r (15) = 0.44, $p < 0.05$) and MFG bilaterally (left: r (15) = 0.53, $p < 0.05$; right: r (15) = 0.43, $p < 0.05$) (Fig. 2, Table 2). Hours of experience was associated with thickness of the right precuneus (r (15) = 0.50, $p < 0.05$).

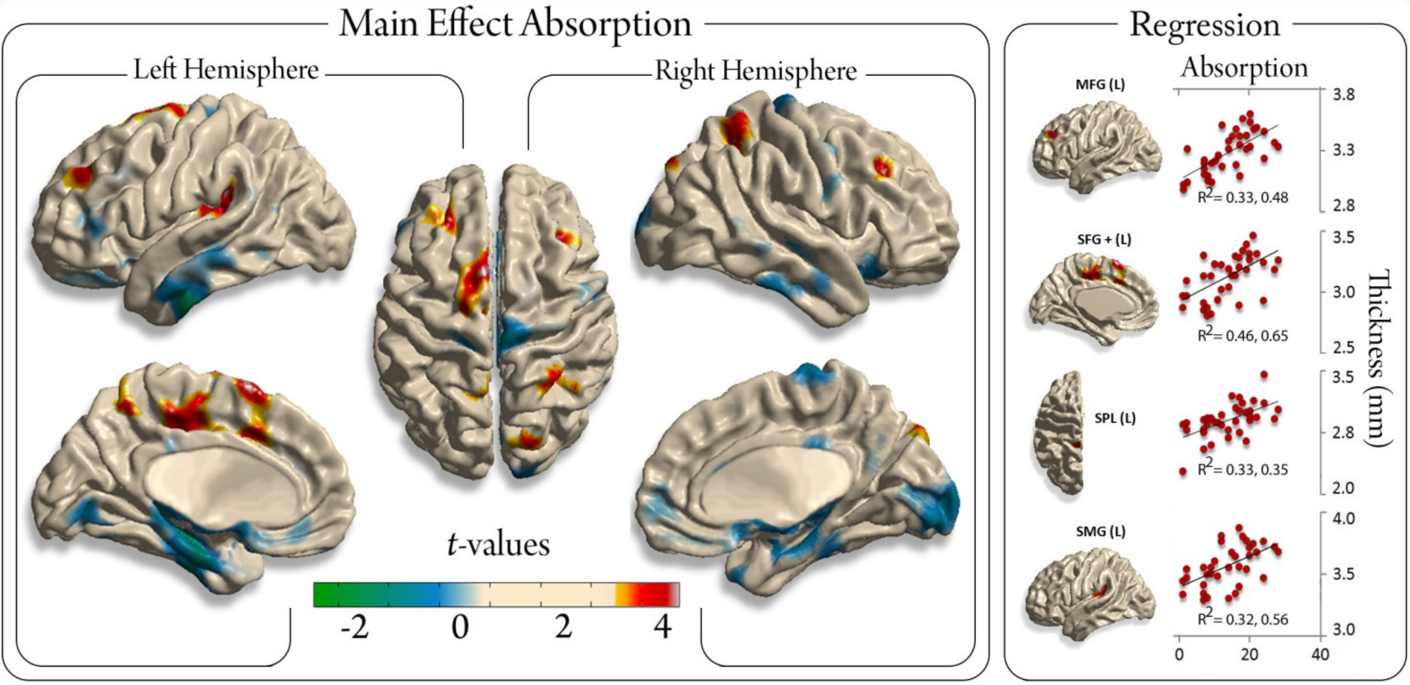

Figure 1. Cortical thickness correlations with self-reported absorption are shown in orange-red (threshold at t=3.6). P-values Bonferonni-corrected for multiple comparison over the entire cortical surface and based on the random-field theory. No regions were found were thinner gray matter was associated with absorption (blue-green clusters). Right: relationship between thickness and absorption within 1, 2 and 3. R2 values correspond with the actual line (upper value) and after controlling for Age and Gender.

Table 2: Group differences and effects of meditation and mindfulness in TAS network ROIs

	Group Dif.	**Med. Training**		**FFMQ**	
ROI	(t/p)	YRS (*r*/*p*)	HRS (*r*/*p*)	OBS (*r*/*p*)	NR (*r*/*p*)
SFG L	1.95, < .05	0.42, < .05	ns	0.46, < .01*	0.37, < .05
ACC L	ns	0.49, < .05	ns	ns	ns
PCC L	ns	ns	ns	ns	ns
MFG R	ns	0.43, < .05	ns	ns	ns
MFG L	ns	0.53, < .05	ns	0.34, < .05	0.31, < .05
SMG L	2.35, < .05	ns	ns	0.37, < .05	ns
SPL R	ns	ns	ns	ns	ns
SPL L	1.95, < .05	0.44, < .05	ns	0.48, < .01*	0.34, < .05
PrCun R	ns	ns	0.50, < .05	ns	ns

The large ROI spanning SFG, ACC and PCC was divided into three regions. Reported *r*-values are partial correlation coefficients, that is, representing unique variance after accounting for age and gender in the regression model. * indicates corrected for multiple comparisons across the number of tests (i.e. ROIs).

To examine possible relations between absorption and mindfulness, mean cortical thickness of the TAS network ROIs was regressed on the FFMQ revealing positive associations between OBS scores and left SFG ($r (33) = 0.46$, $p < 0.01$), MFG ($r (33) = 0.34$, $p < 0.05$), SPL ($r (33) = 0.48$, $p < 0.01$) and SMG ($r (33) = 0.37$, $p < 0.05$). NR scores were associated with mean thickness in the same regions with the exception of the SMG ($r (33) = 0.37$, $p < 0.05$; $r (33) = 0.31$, $p < 0.05$; $r (33) = 0.34$, $p < 0.05$ for left SFG, MFG and SPL, respectively). In each of these cases, greater thickness was associated with higher self-reported mindfulness. The AWARE and NJ subscales were not associated with mean thickness in any of the TAS network ROIs. Subsequent full brain searches revealed a correlation between NR scores and cortical thickness in the right fusiform gyrus but no additional regions were found for OBS, NJ and AWARE scores. As reported in Grant et al. (Grant et al., 2010) a global

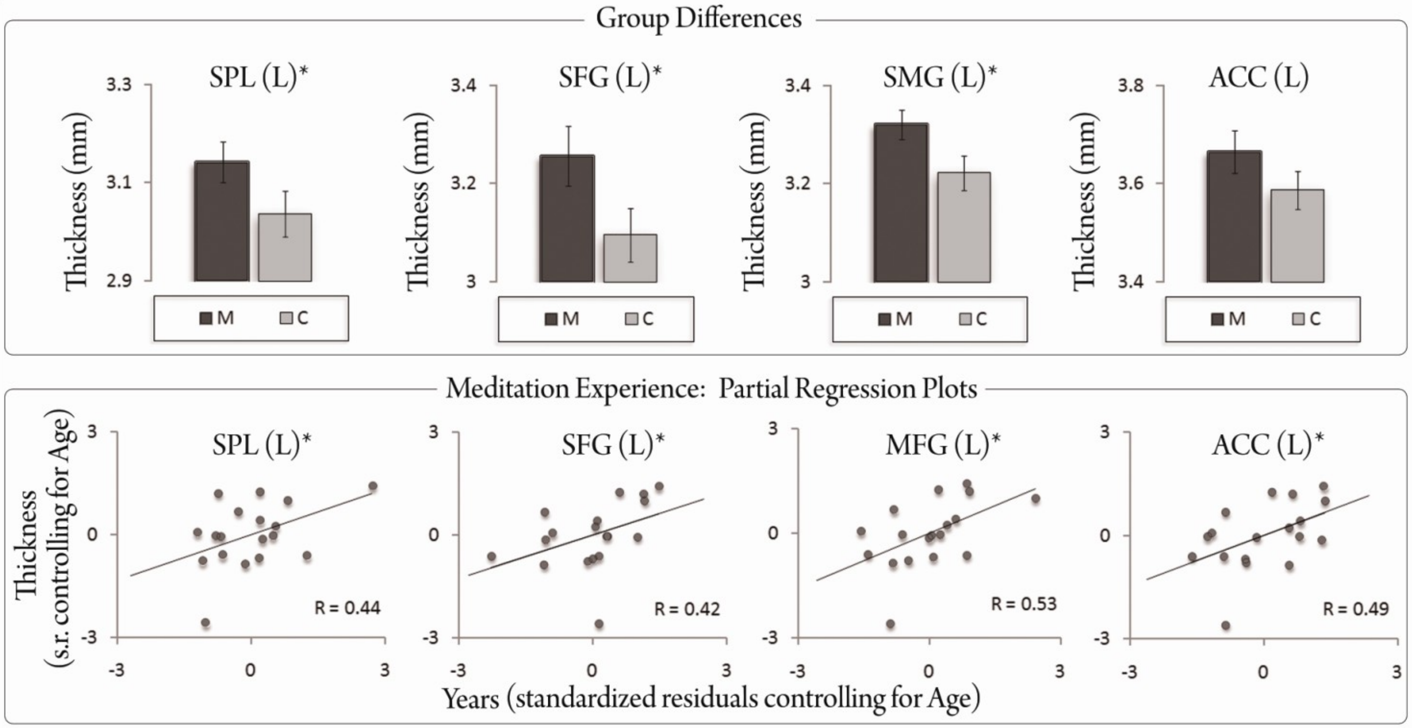

Figure 2. Group differences and meditation experience correlations within the TAS-network. Upper panels: meditators had significantly thicker gray matter in SFG, SPL and SMG all of the left side. M = meditators, C = controls. Lower panels: partial regression plots show the standardized residuals (s.r.) of cortical thickness and years of practice after accounting for age, separately for each variable. The R-value is the partial coefficient and the best fit line maintains the true relationship between the variables. More years of experience was associated with greater thickness of left SFG, SPL, ACC and MFG. For additional regions see Table 2.

search contrasting meditators and controls revealed that the right dorsal ACC was significantly thicker in meditators and a single region on the right precentral gyrus was found to be related to hours of meditation experience.

DISCUSSION

Absorption, a measure of the degree of attentional engagement, was found to correlate with grey matter thickness, robustly, across a sample of meditators and controls. This was true for practically all nodes of the cingulo-fronto-parietal (CFP) attention networks. Practitioners of Zen meditation were found to score higher on absorption and to have thicker cortex in several of these regions, with both effects predicted by the extent of training. Based on previous behavioral, functional and structural evidence, we suggest that meditative practice may prove to be a useful adjunct treatment for ADHD by bolstering grey matter thickness in highly susceptible regions.

Attentional absorption has been described as one’s tendency for “episodes of ‘total’ attention that fully engage one’s representational resources” (Tellegen and Atkinson,1974). Most pertinent to the present report is perhaps the notion of absorption as reflecting sustained attention or imperviousness to distraction (Stavrinou et al., 2007), as distraction is what many meditation techniques help one to overcome. Consistent with previous reports (Davidson et al., 1976; Holzel and Ott, 2006), meditators were found to have higher absorption, compared to controls, which correlated with the frequency of practice, suggesting the trait may be malleable and sensitive to training. This is in line with behavioral studies, both longitudinal and cross-sectional, which have shown that meditative training can enhance performance on tests such the ANT, Stroop, attentional blink, a cued-response task, the Symbol Digit Modalities Test, verbal fluency, and the n-back task (Hodgins and Adair, 2010; Zeidan et al.2010; Tang et al., 2007; van Leeuwen et al., 2009; Prakash et al., 2010). Given the well known deficits in populations with ADHD (Faraone and Biederman, 1998) one could speculate that meditation may be a beneficial intervention for such disorders. This is certainly not a novel idea. Preliminary results already indicate that an 8 week meditation program can improve scores on the ANT, Stroop and the Trail Making Test in adults and adolescents with ADHD (Zylowska et al., 2008). Our results further suggest one potential mechanism by which this intervention may operate.

Individuals' propensity for attentional absorption was strongly related to the grey matter thickness of left ACC, SFG, SMG and bilateral MFG and SPL. Each of these regions has been implicated in CFP attention networks which include dorsolateral and ventrolateral PFC, frontal eye fields, dorsal ACC, SPL and IPL and which can be broken down into functional sub-networks (Bush et al., 2000; Cabeza and Nyberg, 2000; Corbetta and Shulman, 2002). Within all of these regions, compared to controls, meditators had thicker grey matter in the left SFG, SMG and SPL. Furthermore, the number of years of practice of individual meditators, after controlling for age, predicted the thickness of left SFG, ACC and SPL as well as bilateral MFG. Although cross sectional in nature, these results suggest that engaging in meditative practice may increase grey matter thickness in brain regions important for the control and maintenance of attention. Longitudinal and cross-sectional support for this claim comes from the behavioral studies discussed above (Hodgins and Adair, 2010; Zeidan et al., 2010; Tang et al., 2007; van Leeuwen et al., 2009; Prakash et al., 2010) as well as structural imaging studies discussed next (Lazar et al., 2005; Holzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Grant et al., 2010).

The idea that training results in structural changes in the brain is not new (Buonomano and Merzenich, 1998). It has only been in the past decade however, that MRI analyses have been able to show, in living humans, that skills such as juggling (Draganski et al., 2004), mirror reading (Ilg et al., 2008) or playing a musical instrument (Gaser and Schlaug, 2003) can influence the amount of grey matter in functionally relevant brain regions. In a similar manner, learning the skills associated with meditation, such as being mindful or sustaining focus, may increase grey matter thickness in regions implicated in attention. Our results support this notion and are consistent with previous meditation studies reporting thicker or denser grey matter in attention/executive regions such as ACC, superior, middle and orbito-frontal regions (Lazar et al., 2005; Holzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Grant et al., 2010). Functional MRI studies of meditation offer additional support for the engagement of attention networks during practice (Lutz et al., 2008). More specifically, Brefczynski-Lewis et al. (2007) found greater activation of left MFG, DLPFC, SMG, right SFG and SPL bilaterally during sustained attention in advanced Tibetan meditators compared to novices. Similarly, Manna et al. (Manna et al., 2010) reported stronger cingulate and medial PFC activation during meditation for Theravadin monks compared to controls. Interestingly, a brain imaging study of attentional absorption, stemming from hypnotic induction, reported absorption specific increases in regional cerebral blood flow in the ACC as well as bilaterally in the SFG, MFG, IFG and IPL (Rainville et al., 2002). Importantly, it is within these same networks that the majority of structural and functional abnormalities have been observed in children, adolescents and adults with ADHD and which are the probable origins of the associated behavioral deficits (Bush, 2010). Furthermore, there is evidence that stimulant treatment for ADHD acts partly by staving off cortical thinning (Shaw et al., 2009) suggesting it may be the ability to engage certain brain regions which prevents grey matter loss.

A meta-analysis of 16 functional imaging studies of ADHD reported a high prevalence of hypoactivity of anterior cingulate, dorsolateral and inferior prefrontal cortices as well as basal ganglia, thalamus, and the parietal cortex in suffers of the disorder (Dickstein et al., 2006). The picture is remarkably similar for structural studies which have reported thinner or less dense grey matter in cingulate, prefrontal and parietal cortices (for review see (Shaw and Rabin, 2009)). This is in stark contrast to the meditation studies discussed above showing stronger activation (Brefczynski-Lewis et al., 2007; Manna et al., 2010) and thicker of more dense grey matter in overlapping networks (Lazar et al., 2005; Holzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Grant et al., 2010). Our results suggest that this may indeed be the case. Of particular note, cortical thinning of the cingulate cortex, measured longitudinally, was found to be related to worse outcome in patients (Shaw et al., 2006). This region directly overlaps with the main effect of absorption in the present study where meditators had thicker cortex as well as positive relationship with training. Another study (Makris et al., 2007) has reported cortical thinning in adults with ADHD in ACC, DLFPC and inferior parietal lobule, again, regions found to be related to absorption and exhibiting experience-related effects in meditators in the present study.

Thus far we have argued that our results point to meditation as the causal agent, positively influencing cortical thickness and potentially behavior in turn. However, such causality cannot be determined from a cross sectional study and indeed a case can be made for alternative interpretations. For example, it may be, and is perhaps even likely, that there is a substantial genetic contribution to one's tendency for absorption (Ott et al., 2005) as there is for regional cortical thickness (Rimol et al., 2010) and ADHD (Durston et al., 2004; Faraone and Mick, 2010). It may be that, due to such factors, a phenotype characterized by high absorption is attracted to, and persevere in, the practice of meditation. Indeed, Holzel and Ott (Holzel and Ott, 2006) suggest it may be one's propensity for absorption that influences the depth of their meditative state. Nonetheless, rarely are contributions to a complex mental phenomenon purely genetic or environmental and the existent longitudinal evidence suggests a significant contribution of meditative training to changes in grey matter over time (Holzel et al., 2010). Given the preliminary evidence of the effectiveness of meditation as an adjunct treatment for ADHD, there seems to be adequate justification for larger longitudinal studies combining cognitive measures of attention processes and morphometry. Additionally, the substantial financial burden that this disorder places on health care systems (Guevara et al., 2001), makes a complementary treatment option socially and economically quite attractive.

A further limit to the present study is the lack of a measure of attentional performance. This stems from the fact that this data was collected for a study designed to assess the structural correlates of pain perception (Grant et al., 2010). Such a measure would have certainly been helpful although the strong correlation between absorption and the CFP networks also suggests that the scale did indeed tap attention processes. While a construct like absorption may not be diagnostically useful for ADHD it is certainly of relevance. After all, one certainly must feel or experience their inattentiveness or hyperactivity, particularly in the face of putative improvements in mental function following treatment.

Although not the primary measure of the study we also found correlations between absorption and mindfulness, namely, the tendencies to be observant and nonreactive toward one's experience. This was true both experientially and structurally. Mindfulness refers to a mental stance involving present centered awareness with a de-emphasis on cognitive appraisal or elaboration. Holzel and Ott (Holzel and Ott, 2006) have reported influences of both meditation depth and trait absorption on mindfulness however they could not determine the direction of influence. We previously provided evidence that the non-react scale corresponds to physiological relaxation (Grant and Rainville, 2009). Thus, it seems plausible to suggest that a state of mental calmness may accompany, or even be required for, deep absorption.

To conclude the current study provides evidence that grey matter thickness, in regions of the brain susceptible to thinning in ADHD, are associated with an individual’s capacity to become engaged in their experience. Furthermore, individuals who practice meditation had thicker cortex in several of these regions which was also related to the extent of their training. Given the evidence that meditation can aid the deficits of ADHD we suggest that meditation may be a practical, adjunctive treatment which operates via alterations of cortical thickness.

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GENERAL DISCUSSION

General Discussion

The aim of the research presented in this dissertation was to expand what is known about the influence of previous meditation experience on the perception of pain. The research began with a fairly simple question. Do meditators experience pain differently than non-meditators when attention is deployed in specific ways? Clearly the answer to that question is yes. However, many details remain to be elucidated and new questions have been raised in the process of investigation. The remainder of the text will provide an interpretation of these findings, taking into consideration the results of others and current theories of pain perception and modulation.

Summary of Our Results

The first experiment we conducted with practitioners of Zen meditation was a psychophysical study (Study #1)(Grant and Rainville, 2009). In that report meditators were found to have lower baseline pain sensitivity, atypical attention-related pain responses (no difference from their own baseline) as well as training-related reductions of sensory and affective pain ratings during mindful attention. In the follow up functional imaging study (Study #2)(Grant et al., 2011) those effects were built upon by showing that, in a non-meditative state, meditators had stronger nociceptive-related brain activity in regions typically activated during pain (INS, dorsal ACC (dACC), THAL). Simultaneously, activation reductions were found for meditators in brain regions implicated in appraisal, memory and emotion (DLPFC, OFC, AMY, HIP), with the most advanced meditators showing the largest reductions; effects which were themselves associated with the lowest pain ratings.

Crucially, reduced functional connectivity between prefrontal cortex (DLPFC) and a primary pain region (dACC), exclusively observed in meditators, predicted baseline pain sensitivity in the group. Lastly, in the structural imaging experiments (Study #3)(Grant et al., 2010), (Study #4)(Grant et al., in prep) meditators were found to have thicker grey matter in several pain and attention-related regions, including the dACC. Thickness of this region corresponded both with absorption, pain sensitivity and meditation experience with more grey matter being associated with greater absorption, more meditation experience and lower pain sensitivity. Taken together these results suggest practicing Zen meditation may influence pain perception through functional as well as physical effects on the brain. Furthermore, the pattern of brain activity observed in Study #2, coupled with structural differences in Study #3 and #4, map on well to the mental state purportedly cultivated during Zazen. More specifically, meditators are said to train themselves to non-elaboratively and non-judgmentally monitor their momentary experiences (Austin, 1999) suggesting a novel mechanism for the pain modulatory effects observed in this population. These results are consistent with our initial hypotheses that meditation training would have an influence on the affective dimension of pain. They further suggest that meditation can influence the sensory aspects of pain and that both effects may be instantiated through alterations to cognitive systems in the brain.

Attention

In Study #1 and Study #2 thermal stimuli were perceptually adjusted for each individual resulting in equivalent levels of reported pain for meditators and controls in a baseline non-meditative state. The functional imaging results revealed that, despite equal ratings, meditators had stronger pain-related activation of the INS, THAL and dACC. These are the three most commonly reported regions in pain imaging studies with an incidence rate of over 80% (Apkarian et al., 2005). Each of the three regions receives input from the spinothalamic nociceptive tract (Dum et al., 2009) and the functional activation often reflects the felt sensory-discriminative (intensity) (Bushnell et al., 1999; Coghill et al., 1999; Hofbauer et al., 2001) and affective-motivational (unpleasantness) (Rainville et al., 1997; Schreckenberger et al., 2005) aspects of pain. Consistent with these previous works activation of INS and dACC positively correlated with unpleasantness ratings in control participants, however, no such correlations were observed for meditators. Along with further evidence discussed below we suggest the activation of INS, dACC and THAL in meditators may reflect more general functions relevant, but not specific, to pain.

It has been shown that directing attention toward pain results in increased sensory and affective ratings (Quevedo and Coghill, 2007). This was true of the control participants in Study 1 who showed 15% and 21% increases in pain intensity and unpleasantness respectively, from their baseline. Meditators on the other hand showed no difference at all from their baseline. One potential explanation for this is that meditators have trained themselves to be highly attentive toward their ongoing experiences. As a result, it may be that during the baseline condition practitioners were already highly attentive to the noxious stimulation and thus little difference was observed when attention was explicitly directed toward the stimulus. Previous work has suggested that distraction from pain is associated with activation decreases in INS, ACC, THAL and SI (Bushnell et al., 1999; Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004). Conversely, greater pain-related activation observed for meditators in these same areas in Study #2, compared to controls, may reflect enhanced processing of the stimulus due to higher attentional engagement. There are several lines of evidence suggesting this may be the case.

Being attentive to one's ongoing experience is one aspect of mindfulness and often the goal of meditation (Bishop et al., 2004). Zen practitioners indeed scored higher on a measure of their tendency to be observant of their experience. Previous work, including several longitudinal studies, have provided solid evidence that meditative training results in superior performance on a variety of attention and executive function tasks such as the Attention Network Task (ANT), the Stroop Task, attentional blink, Symbol Digit Modalities Test, verbal fluency, and the n-back task (Tang et al., 2007; Lutz et al., 2009; van Leeuwen et al., 2009; Prakash et al., 2010; Zeidan et al., 2010). Functional MRI studies have also reported that high level monks, while meditating, activate attention-related cortices such as the ACC and frontoparietal networks (Brefczynski-Lewis et al., 2007; Manna et al., 2010). However, Brefczynski-Lewis et al. (2007) found the strongest activation of dACC, INS, THAL and inferior parietal cortices for intermediate level practitioners, compared to both advanced Tibetan monks and controls. The results resembled an inverted u-shaped function and were interpreted as reflecting the effort required to sustain attention in the intermediate practitioners. This pattern fits with our own results in dACC and INS where the most experienced meditators had less activation than more novice meditators (although these meditators still had substantial training). While the present studies lacked a formal measure of attention, meditators did score higher on an experiential measure of absorption, in Study #4, which was strongly associated with the cortical thickness of several attention-related cortices. Further, the experience level of the meditators predicted the thickness of the cortex in these regions. A fair number of structural imaging studies with meditators, including two of our own (Studies #3, #4), have now reported thicker grey matter, related to training, in regions implicated in attention/executive processing (Lazar et al., 2005; Hölzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Grant et al., 2010). In study #3 Zen practitioners had thicker grey matter than controls in dACC and INS; effects which correlated with pain sensitivity and meditation experience (Grant et al., 2010). This may indicate that the training effects of meditation occur through physical changes to the brain; reinforced by a recent longitudinal study showing grey matter increases after meditation training (Holzel et al., 2010). Together, the above mentioned works clearly make a case for the possibility that meditative practice is associated with enhanced attention processing. Such an enhancement could certainly influence the perception of pain by allowing more resources to be devoted to the sensation. This would presumably be associated with strong activation of brain regions underlying the experiential aspects of nociception such as dACC, INS, THAL, SI, SII. However, an increase in attention devoted to a noxious stimulus would not explain why the meditators failed to show the often observed correlation between pain ratings and INS/dACC activation (Rainville et al., 1997; Bushnell et al., 1999; Coghill et al., 1999; Hofbauer et al., 2001; Schreckenberger et al., 2005)? One possibility, which is consistent with traditional claims, is that additional skills are learned during meditation which may interact with attention effects. The widespread brain activation reductions observed exclusively for meditators during pain certainly suggests a difference between the groups in more than just attention-related brain regions.

Mindfulness

The concept of mindfulness is multidimensional (Bishop et al., 2004). It is claimed that to be mindful, in a meditative fashion, one tries to simply observe their ongoing experience, with minimal cognitive elaboration or appraisal. An accepting attitude is recommended as one attempts to sustain this mental stance. Getting lost in thought, zoning out or operating on autopilot is the antithesis of a mindful state. The result of this non-elaborative and non-judgmental mental stance is said to be a distancing of oneself from rumination and thought patterns which perpetuate negative emotion (Bishop et al., 2004). Skills related to mindfulness have been shown longitudinally to be learned through meditation practice (Carmody and Baer, 2008). In the present studies meditators indeed scored higher on several aspects of a mindfulness questionnaire, specifically on the tendencies to be presently aware, observant of and nonreactive toward their experience. Furthermore, greater mindfulness was associated with lower pain sensitivity in meditators. While much has been done to validate the clinical effectiveness of mindfulness-based programs (e.g. for anxiety and depression (Grossman et al., 2004)) little work has been done on elucidating the brain regions which may underlie this mental state. Based on the above description of mindfulness one could postulate that prefrontal cortex would be involved due to its proposed roles in executive function, volition, appraisal, planning and memory (Miller and Cohen, 2001). The purported reduction in emotional reactivity further suggests the involvement of emotion centers. The brain activation pattern observed in Study #2, particularly the activity reductions exclusively observed in meditators, seems to support this idea.

Simultaneously with the stronger activation of dACC, THAL and INS, meditators had less activation of med-PFC/OFC, DLPFC, AMY, HIP as well as several other regions. Rather than being driven by activity increases for control subjects these effects were generally caused by signal reductions below baseline in meditators. In pain studies, the most commonly observed of these areas is DLPFC (Apkarian et al., 2005). Activity is typically increased in DLPFC during pain and thought to reflect higher cognitive processes such as working memory and evaluation of the stimulus (Coghill et al., 1999; Strigo et al., 2003). The OFC was also reduced selectively in meditators during the receipt of a noxious stimulus. This region receives output from all sensory pathways and is thought to transform the information into reward-related representations, that is, to determine emotional and affective value of the attended stimulus (Rolls and Grabenhorst, 2008). This information is crucial for decision making and goal directed behavior (Bechara et al., 2003). Two further regions showing activity reductions for meditators were the HIP and AMY. These areas are thought to work in conjunction with PFC and OFC in memory and emotional memory (Buchanan, 2007). Taken as a whole this pattern of activity, or lack of activity, could potentially represent a mindful mental state. More specifically, the proposed functional roles for these regions (DLPFC - evaluation, memory; OFC – appraisal of affective/reward value; AMY – emotion/memory; HIP – memory) are precisely the mental processes said to be reduced during mindful attending. Attenuated brain activity may indeed reflect a reduction in the mental processes attributed to these areas, however, the present studies lacked behavioural measures which could corroborate these claims. Nonetheless, the claim is supported by the fact the most advanced meditators had the largest activity decreases in both bilateral DLPFC and right med-PFC/OFC and further, that the largest activation reductions in DLPFC were associated with the lowest pain ratings.

As a whole our imaging results seem to be of two types: meditators compared to controls had a) stronger activation of primary pain regions and b) weaker activation of affective and cognitive regions. Farb et al. (2010) have suggested that a mindful state may involve a shift from self-dominant focus to a more sensory-dominant focus. In this formulation mindfulness could, in a sense, be viewed as a form of distraction where attention is focused in a sustained manner on particular attributes of a stimulus or experience, at the expense of higher level appraisal and elaboration. This fits nicely with meditation practitioners activating primary pain regions such as the dACC, INS and THAL more robustly than control subjects, and importantly, without correlative pain reports. Thus, these activations may reflect the present-centered observational aspect of mindfulness. Interestingly, if sustained, this may preclude the possibility of memory, appraisal and even emotion-related processing, which may drive down activation in relevant cortices. Unfortunately the fMRI design employed is not temporally sensitive enough to determine whether memory-related activity reductions may occur prior to appraisal or elaborative-related reductions or vice versa. Answering this may shed considerable light on the mechanisms of mindfulness. For example, it may be that learning to sustain one’s attention, in a particular manner, on present moment experience, reduces memory-related processing and negates the possibility of cognitive appraisal, which presumably requires comparison of current and past experiences. Conversely, it may be that one needs to learn to reduce cognitive elaboration or appraisal in order to sustain their attention on the present experience. At the very least our functional connectivity results (discussed next) suggest there are two separable aspects of the adopted mental stance underlying the lower pain sensitivity observed in meditators.

The first result that was observed in our investigations resulted from the attempt to ensure that all participants felt a comparable level of pain. We measured individual thresholds and determined the temperature required for each individual to report moderate pain. This revealed a group difference in pain sensitivity. Meditators were less sensitive, that is, required much hotter stimuli to report moderate pain (50 °C vs 48 °C). Remarkably, it was revealed in Study #2 that pain sensitivity of individual meditators was predicted by the degree of connectivity between DPLFC and dACC. More specifically, during pain, meditators reduced the functional connectivity between these two regions which are normally thought to communicate to guide goal directed behaviour (Miller and Cohen, 2001). Greater decoupling of DLPFC and dACC was associated with higher stimulation required for the individual to report moderate pain at baseline. That is, the least sensitive participants (meditators only) had the largest connectivity reductions. This raises the intriguing possibility that highly-salient noxious stimuli are given the label of ‘painful’ via interactions between prefrontal cortex and target regions of the spinothalamocortical pathways. A disruption of such a pathway could conceivably reduce the suffering associated with noxious stimuli, rendering it more 'neutral' or less threatening. Results also suggest that while baseline pain sensitivity may often be thought of as a trait, evidence from the meditation group suggests it can be meditated by ongoing modulation of brain regions involved in the interpretation of noxious stimuli.

Meditation and Pain

At the outset of the current work a single study existed that had examined pain and meditation. Kabat-Zinn and colleagues (Kabat-Zinn, 1982; Kabat-Zinn et al., 1985; Kabat-Zinn et al., 1987) found that pain ratings did not ultimately change after training chronic pain patients to meditate. However, patients had positive improvements on many mood and symptom measures and seemed to value and continue to use the technique. This led to the suggestion that the meditative-based program was a valued coping strategy. In the past five years several other clinical studies have come forth. Morone et al. (2007) studying elderly low back pain patients found improvements in pain acceptance following an 8 week meditation program. The MBSR program has also been used effectively to treat fibromyalgia patients, resulting in improvements in quality of life, pain coping, anxiety, depression, pain complaints as well as visual analog scales of pain severity, effects not observed in an active control group (Kaplan et al., 1993 ; Grossman et al., 2007). These positive, affective-based results remained stable three years post-intervention. McCracken et al. (2007) found similar results in a correlational study involving 105 chronic pain patients showing inverse associations between trait mindfulness and depression symptoms, pain related anxiety and disability, after controlling for other patient-related factors including pain intensity. Interestingly, this study also found a negative correlation between pain intensity and mindfulness evaluated using a questionnaire.

This may suggest that the increased attention to or observation of noxious feelings can, if one is not sufficiently trained, lead to increases in pain. This is consistent with the current results of Study #1 where the more inexperienced practitioners had increases in reported pain during the mindful attention condition as opposed to reductions for the more experienced practitioners. Taken together, these clinical studies suggest that mindfulness interventions with patients operate primarily on the affective aspects of pain. Combined with our results, and consistent with the suggestion of Farb et al. (2010), it could be postulated that this is accomplished by learning how to attend to sensory aspects of the experience at the expense of affective, self-related aspects. Furthermore, this may be accomplished by altered functional connectivity of higher cognitive and pain-related regions, as observed in Study #2. Functional connectivity changes between PFC and pain-related regions (INS) have also been shown after training participants to meditate (Farb et al., 2007).

Several studies have also investigated the effects of meditative practice on pain perception in healthy individuals. Similar to the results of Study #1 and #2, Kingston et al. (2007) showed that training participants to meditate increased tolerance time on the cold pressor task. Another short longitudinal study (Zeidan et al., 2010) found that as little as 3 days of meditative training is required to reduce sensitivity to electrical stimulation. That group also observed relationships between reduced pain and reductions in anxiety, supporting the idea that the effect of meditation may be more general, influencing pain perception through changes in emotional or cognitive processes. However, lower pain sensitivity was not observed in a study of extremely advanced practitioners (Perlman et al., 2010). Perlman et al.

(2010) did not find baseline pain sensitivity differences between high level Tibetan monks and novices. However, in accord with our results, reductions of pain unpleasantness were observed, exclusively for the meditators, in an open monitoring condition similar to the mindful attention condition of the current Study #1. The functional imaging results accompanying their behavioural results have yet to be published but it will be interesting to see if this sample also has functional connectivity differences while receiving pain. Using EEG, Brown and Jones (2010) recently reported that after matching subjects for perceived intensity (of noxious laser stimulation) more experienced meditators found the stimulation as less unpleasant. Also in that report, lower electrical activity was observed for meditators during an anticipation period, localized to the dorsal cingulate gyrus and inferior parietal cortex, which correlated with pain unpleasantness and meditation experience. This was suggested to reflect higher trait mindfulness in meditators. This result is quite different from our own results with Zen practitioners. Study #2 also involved an anticipation period and similar to Brown and Jones (2010) meditators were not asked to formally meditate. However, in the current study we found no differences in anticipatory activation. It may not be overly surprising that these two studies differed given the variability in methodologies, stimuli, paradigms and meditation techniques. Importantly, whereas Brown and Jones used a heterogeneous group of meditators (i.e. from various traditions who practiced different techniques) our research involved a very homogeneous group of practitioners who all train with the same technique. Future studies will be required to definitively determine the reason for these discrepancies.

Despite the high degree of variability of the existing studies, in terms of methodologies, stimuli, paradigms and perhaps most importantly, meditation techniques, consensus seems to support three major points. First, meditation seems to promote lower baseline pain sensitivity and second, meditation seems to attenuate the affective dimension more so than the sensory discriminative dimension. Lastly, the proposed mechanisms for these effects have ubiquitously been increased mindfulness, including less judgment and reactivity toward the painful stimuli. Given that several of these effects have been observed outside of a formal meditative state, the effects of meditation on pain may be long lasting and potentially related to physical changes in the brain, as has been observed in several studies (Lazar et al., 2005; Hölzel et al., 2008; Luders et al., 2009; Vestergaard-Poulsen et al., 2009; Grant et al., 2010). However, the lower pain sensitivity in our sample seemed to be predicted by ongoing modulation of the connectivity between brain regions and there was also sensory pain modulation in Study #1 when meditators actively engaged in mindful attention. Thus, the effects of meditation on pain seem to be dynamic, consistent with earlier claims that these types of practice teach practitioners a strategy which needs to be implemented.

The Bigger Picture

The analgesic properties of meditation appear to be unique among the known modulators of pain. It seems unlikely that attention or distraction can fully account for the findings of the studies that have been conducted to date. Our own study revealed that deliberately attending to a noxious stimulus did not result in pain increases as it did for controls. If, as we suggest above, this is a result of heightened attention in all conditions it still cannot explain why pain ratings are dissociated from activation levels in meditators. Furthermore, the only study to date employing distraction with meditators (Perlman et al., 2010) found no difference between high level practitioners and controls. Meditative analgesia could conceivably be related to placebo however the exact opposite pattern of results have been observed in imaging studies of placebo. That is, reduced brain activity in primary pain regions (dACC, INS, THAL) accompanied reduced pain ratings and increased anticipatory-activity of frontal cortices (DLPFC, OFC) and PAG. This suggests meditative analgesia may not operate via the commonly discussed frontal-PAG descending inhibitory pathway (Bingel and Tracey, 2008). Granted, while the present reports did not observe any effects within the PAG this does not prove the region was not involved. As discussed next, perhaps the closest correspondence that can be observed between meditative analgesia and other modulatory effects is with the concepts of pain acceptance, and conversely, fear of pain.

As suggested above the effect of meditation training on pain perception may be secondary to more general changes in emotional reactivity, stress or anxiety. Consistent with this, Brown and Jones reported less anticipatory activation during pain, which was related to the extent of meditation training. While we did not find group differences in the anticipation period of Study #2, meditators did exhibit slower respiratory rates in Study #1, which, when controlled for with covariance, removed the analgesic effects of mindful attention. Furthermore, respiratory rates were related to non-reactivity as measured on a mindfulness scale with less reactive individuals breathing slower. These results suggest that pain may be associated with a diminished autonomic or emotional response in meditators compared to controls. Such a reduction may signify greater acceptance of the painful experience, as several studies with pain patients have reported occurs following meditation training (McCracken et al., 2007; Morone et al., 2008). In terms of brain imaging it has been reported that right OFC and med-PFC activation correlates with subjects' fear of pain and anxiety sensitivity scores respectively (Ochsner et al., 2006). Importantly, the regression of fear and anxiety sensitivity scores on pain-related brain activity revealed that individuals with lower scores had activation that fell below zero, that is, 'deactivations'. These regions were in close proximity to those found in the present Study #2 where activity was reduced for meditators, below baseline, with the most advanced practitioners having the largest reductions and lowest pain ratings. Thus, an additional interpretation, not inconsistent with our proposal that meditators engage in less evaluation and elaboration, is that practitioners experience less fear or concern for anxiety symptoms when faced with a noxious stimulus. These hypotheses are indeed compatible as reducing the tendency to cognitively evaluate or elaborate would likely prevent fear from arising. As a final point, an anecdotal report from a participant debriefing may help the interpretation. When asked to describe the sensation he experienced, a soft spoken meditation subject, who rated the highest possible stimulation level (53 ^{o}C) at ~5/10, calmly said, "It feels a bit like a needle is being repeatedly stuck into your calf." He then smiled and added, "But it's not like it was going to last forever."

Conclusion

The present research conducted over the past 5 years, combined with the work of others, has substantially advanced our knowledge of the influence of meditation on pain. Although a great deal of work lies ahead the results to date have certainly validated traditional claims that meditative practice can reduce the suffering that is thought to be inherent to noxious stimulation. Rather, results suggest meditation may provide an effective coping mechanism, not involving distraction away from pain, rather by teaching patients a novel way of attending to the sensation.

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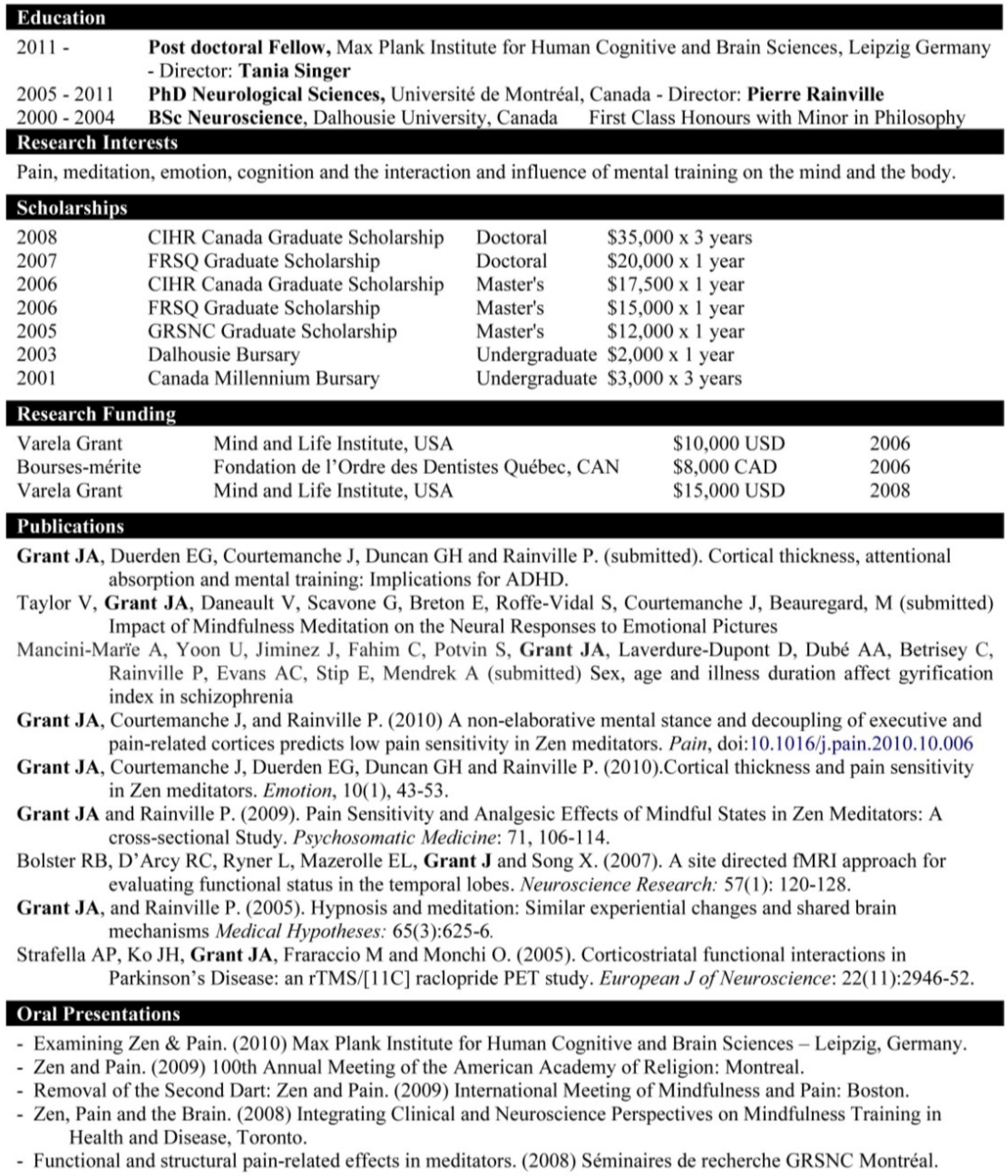
CURRICULUM VITAE

Curriculum Vitae



Education

2011 -	**Post doctoral Fellow,** Max Plank Institute for Human Cognitive and Brain Sciences, Leipzig Germany - Director: **Tania Singer**
2005 - 2011	**PhD Neurological Sciences,** Université de Montréal, Canada - Director: **Pierre Rainville**
2000 - 2004	**BSc Neuroscience**, Dalhousie University, Canada First Class Honours with Minor in Philosophy

Research Interests

Pain, meditation, emotion, cognition and the interaction and influence of mental training on the mind and the body.

Scholarships

2008	CIHR Canada Graduate Scholarship	Doctoral	$35,000 x 3 years
2007	FRSQ Graduate Scholarship	Doctoral	$20,000 x 1 year
2006	CIHR Canada Graduate Scholarship	Master's	$17,500 x 1 year
2006	FRSQ Graduate Scholarship	Master's	$15,000 x 1 year
2005	GRSNC Graduate Scholarship	Master's	$12,000 x 1 year
2003	Dalhousie Bursary	Undergraduate	$2,000 x 1 year
2001	Canada Millennium Bursary	Undergraduate	$3,000 x 3 years

Research Funding

Varela Grant	Mind and Life Institute, USA	$10,000 USD	2006
Bourses-mérite	Fondation de l'Ordre des Dentistes Québec, CAN	$8,000 CAD	2006
Varela Grant	Mind and Life Institute, USA	$15,000 USD	2008

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Taylor V, **Grant JA**, Daneault V, Scavone G, Breton E, Roffe-Vidal S, Courtemanche J, Beauregard, M (submitted) Impact of Mindfulness Meditation on the Neural Responses to Emotional Pictures

Mancini-Marïe A, Yoon U, Jiminez J, Fahim C, Potvin S, **Grant JA**, Laverdure-Dupont D, Dubé AA, Betrisey C, Rainville P, Evans AC, Stip E, Mendrek A (submitted) Sex, age and illness duration affect gyrification index in schizophrenia

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- Zen and Pain. (2009) 100th Annual Meeting of the American Academy of Religion: Montreal.
- Removal of the Second Dart: Zen and Pain. (2009) International Meeting of Mindfulness and Pain: Boston.
- Zen, Pain and the Brain. (2008) Integrating Clinical and Neuroscience Perspectives on Mindfulness Training in Health and Disease, Toronto.
- Functional and structural pain-related effects in meditators. (2008) Séminaires de recherche GRSNC Montréal.

- Cortical thickness and pain perception in Zen meditators (2008) 17th Meeting of CERNEC: St. Sauveur.
- Functional imaging of pain perception in Zen meditators (2008) Unité Neuroimagerie Fonctional: Montréal.
- The neurobiology of meditation for the control of pain. (2007) Retraite du GRSNC: Val Morin.
- The neurobiology of meditation for the control of pain. (2007) Mind/Life Summer Research Institute: New York.
- Meditative analgesia and Zen meditation. (2006) Mind/Life Summer Research Institute: New York.
- Zen meditation and the control of pain. (2007) Placebo NET: Mont Tremblant.
- The neurobiology of meditation for the control of pain. (2007) Douglas Hospital: Montréal.
- Can we study the neural mechanisms of meditation with fMRI. (2005) University of Zurich.
- Functional MRI and the assessment of temporal lobe epilepsy. (2004) University of Zurich.

Poster Presentations/Published Abstract (*)

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Grant, JA, Courtemanche J and Rainville, P (2010) *On Zen, Pain and the Brain*. 18th Annual Meeting of CERNEC: St. Sauveur.

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*Grant, JA, Duerden, EG, Duncan, GH and Rainville, P (2008) *Cortical thickness, Absorption and Mindfulness in advanced Zen meditators*. Neuroscience: Washington.

*Grant, JA, Duerden, EG, Duncan, GH and Rainville, P (2008) *Cortical thickness and pain sensitivity in advanced Zen meditators*. 12th World Congress on Pain (IASP): Glasgow.

Grant, JA and Rainville, P. (2008) *Experienced Zen Meditators Exhibit Attenuation and High Moderate-Pain Threshold...* Journée Scientifique de la Faculté de Médecine Dentaire: Montréal.

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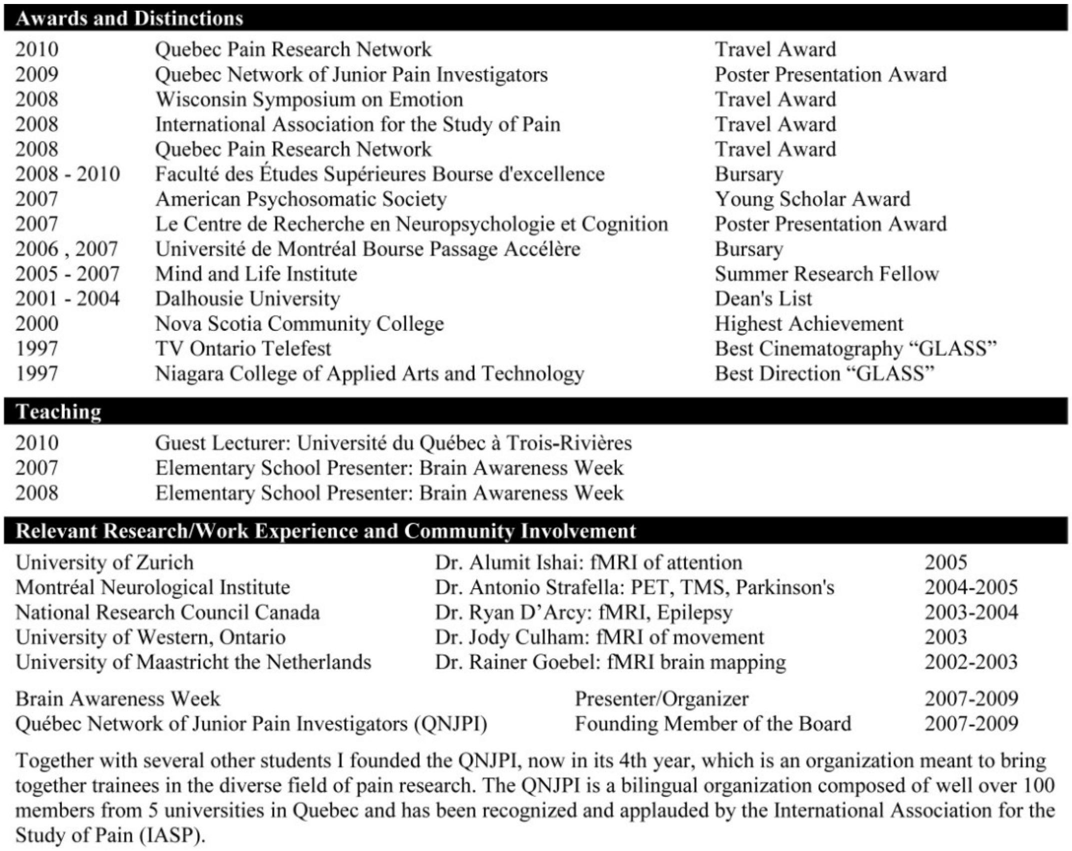
Selected Media Coverage

In press	**Sports Illustrated**:
Sept. 2010	**La Code Chastenay** : Episode 58 - Douleur et Méditation (television documentary)
Mar. 2010	**Corriere Della Sera** (Italy): Lo zen modifica il cervello e fa sopportare il dolore
	Science (AAAS): Saying 'Om' Instead of 'Ow' (Vol: 327, Pg - 1183)
Feb.2010	**Bloomberg Business Week**: Zen May Thicken Brain, Thwart Pain
	The Daily Telegraph (UK): Zen meditation raises pain threshold - fact
June 2009	**Reader's Digest and Discovery Channel Magazine**: Zen Medication
Feb. 2009	**Science Daily**: Zen Meditation Alleviates Pain, Study Finds
	United Press International: Zen's slower breathing may lower pain
	CBC Evening News: Scientists explore how Zen meditation reduces pain perception (interview)
	Times of India: Meditate your pain away
	UdeM Nouvelles: La méditation zen peut alléger la douleur (youtube.com/watch?v=SNAtLpwgey8)
Jan. 2009	**Washington Post**: The Zen Way to Pain Relief
	USA Today: The Zen Way to Pain Relief



Awards and Distinctions

2010	Quebec Pain Research Network	Travel Award
2009	Quebec Network of Junior Pain Investigators	Poster Presentation Award
2008	Wisconsin Symposium on Emotion	Travel Award
2008	International Association for the Study of Pain	Travel Award
2008	Quebec Pain Research Network	Travel Award
2008 - 2010	Faculté des Études Supérieures Bourse d'excellence	Bursary
2007	American Psychosomatic Society	Young Scholar Award
2007	Le Centre de Recherche en Neuropsychologie et Cognition	Poster Presentation Award
2006 , 2007	Université de Montréal Bourse Passage Accélère	Bursary
2005 - 2007	Mind and Life Institute	Summer Research Fellow
2001 - 2004	Dalhousie University	Dean's List
2000	Nova Scotia Community College	Highest Achievement
1997	TV Ontario Telefest	Best Cinematography “GLASS”
1997	Niagara College of Applied Arts and Technology	Best Direction “GLASS”

Teaching

2010	Guest Lecturer: Université du Québec à Trois-Rivières
2007	Elementary School Presenter: Brain Awareness Week
2008	Elementary School Presenter: Brain Awareness Week

Relevant Research/Work Experience and Community Involvement

University of Zurich	Dr. Alumit Ishai: fMRI of attention	2005
Montréal Neurological Institute	Dr. Antonio Strafella: PET, TMS, Parkinson's	2004-2005
National Research Council Canada	Dr. Ryan D’Arcy: fMRI, Epilepsy	2003-2004
University of Western, Ontario	Dr. Jody Culham: fMRI of movement	2003
University of Maastricht the Netherlands	Dr. Rainer Goebel: fMRI brain mapping	2002-2003

Brain Awareness Week	Presenter/Organizer	2007-2009
Québec Network of Junior Pain Investigators (QNJPI)	Founding Member of the Board	2007-2009

Together with several other students I founded the QNJPI, now in its 4th year, which is an organization meant to bring together trainees in the diverse field of pain research. The QNJPI is a bilingual organization composed of well over 100 members from 5 universities in Quebec and has been recognized and applauded by the International Association for the Study of Pain (IASP).