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Cognitive and neuronal mechanisms underlying the regulation of acute pain by mindfulness meditation: an investigation using experimental and experiential methods

Jelle Zorn

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Jelle Vincent ZORN

Cognitive and neuronal mechanisms underlying the regulation of acute pain by mindfulness meditation: an investigation using experimental and experiential methods

Devant le jury composée de:

SCHMIDT, Stefan, Professeur, Université de Fribourg (Allemagne), Rapporteur
VANHAUDENHUYSE, Audrey, PhD, Centre Hospitalier Universitaire de Liège (Belgique), Rapporteur
FROT, Maud, PhD, INSERM Lyon Intégration Central de la Douleur – Hopital Neurologique, Examinatrice
OLLGNIER-BELDAME, Magali, PhD, CRNS Lyon, Examinatrice
ROSSETTI, Yves, Professeur, Université Lyon 1, Président du Jury

LUTZ, Antoine, PhD, INSERM U1028 - CNRS UMR5292, Université de Lyon 1, Directeur de thèse

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Laboratoire

INSERM U1028 - CNRS UMR5292, Université de Lyon 1

Centre de Recherche en Neurosciences de Lyon (CRNL)

Équipe DYCOG (Directeur Olivier Bertrand)

Centre Hospitalier Le Vinatier (Bât. 452)

95, Bd Pinel

69500 Bron, France

Contact: Martine Theillère

Tél: +33 (0)4 72 13 89 00

Fax: +33 (0)4 72 13 89 01

Courriel: martine.theillere@inserm.fr

Résumé

La douleur ne reflète pas directement les stimulations de l'entrée sensorielle, mais est façonnée par plusieurs facteurs cognitifs et affectifs qui peuvent amplifier ou réduire l'expérience de la douleur. Un des principaux facteurs aggravants est la catastrophisation de la douleur, une disposition mentale délétère qui exagère et amplifie la douleur. Il a été proposé que la méditation de pleine conscience implique la cultivation d'une posture métacognitive centrée sur le moment-présent, appelée défusion cognitive, qui contrecarre les processus de pensée élaboratifs comme la catastrophisation de la douleur, tout en conservant l'ouverture à l'expérience sensorielle. Cette posture réduirait le désagrément de la douleur en induisant un découplage sensori-affectif de l'expérience de la douleur. Cette hypothèse n'a pas été explorée explicitement jusqu'à présent, ce qui a été le but du présent travail. Nous avons également exploré l'hypothèse selon laquelle la chronométrie de l'insula antérieure est un marqueur sensible du découplage sensori-affectif de l'expérience de la douleur pendant la méditation pleine conscience.

Nous avons appliqué une approche multidisciplinaire qui était informée par la phénoménologie des pratiques de pleine conscience et visait à répondre aux problématiques cliniques posées par la catastrophisation de la douleur. Cette approche combinait des méthodes expérientielles à des méthodes expérimentales dans le contexte d'un nouveau paradigme de douleur aiguë utilisant l'imagerie cérébrale fonctionnelle (IRMf). Ce paradigme a été conçu pour amplifier les aspects cognitifs-affectifs de l'expérience de la douleur, et a été utilisé chez des méditants novices et experts expérimentés. Nous avons constaté qu'un style de méditation de pleine conscience dit de Monitoring Ouvert réduisait le désagrément de la douleur mais pas l'intensité de la douleur par rapport à une condition de distraction attentionnelle chez les novices (effet d'état) et les méditants experts (effets d'état et de trait). La catastrophisation de la douleur prédisait ce découplage sensori-affectif (étude 1). De plus, la défusion cognitive a montré une relation inverse spécifique par rapport aux mesures de catastrophisation de la douleur (cette relation était encore présente une fois que la variance partagée avec d'autres échelles psychométriques cognitives-émotionnelles était enlevée). Les mesures de défusion cognitive et de catastrophisation prédisaient spécifiquement le désagrément de la douleur par opposition à l'intensité de la douleur, mais la défusion cognitive montrait une association plus forte avec ces variables de la douleur. Aucune dimension expérientielle n'a été identifiée comme médiateur de cette relation (étude 2). Enfin, les prédictions sur l'insula antérieure en tant que marqueur neuronal du découplage sensoriel-affectif de la douleur n'ont pu être que partiellement confirmées. Consistent avec nos hypothèses, les experts ont montré au cours de l'anticipation de la douleur une activation de l'insula antérieure inférieure à celle des novices dans un cluster qui prédisait négativement le découplage sensoriel-affectif rapporté par les participants pendant la douleur. Cette activité n'était pas corrélée avec les scores de catastrophisation de la douleur. Néanmoins, nous n'avons pas pu confirmer des hypothèses plus larges sur la fonction de l'insula antérieure pendant la douleur en raison de problèmes méthodologiques (étude 3).

Ces résultats font progresser notre compréhension des mécanismes cognitifs et neuronaux qui sous-tendent la régulation de la douleur basée sur la méditation de pleine conscience et permettent de raffiner les futures investigations neuroscientifiques contemplatives ainsi que les stratégies psychothérapeutiques de traitement de la douleur chronique.

Mots Clés : Méditation de pleine conscience; Douleur thermique; Catastrophisme; Défusion cognitive; Intensité sensorielle; Affect de la douleur, IRMf.

Abstract

Pain is not a direct read-out of sensory input, rather it is shaped by cognitive-affective factors that can amplify or reduce pain experience. A key aggravating factor is pain catastrophizing, an exaggerated negative mental set. It has been proposed that mindfulness meditation involves the cultivation of a present-centered metacognitive stance, labeled cognitive defusion, that counteracts elaborative thought processes like pain catastrophizing, while retaining openness to sensory experience, thus inducing sensory-affective uncoupling of pain experience. This tentative hypothesis has not been explored so far, which was the aim of the present work. We additionally explored the hypothesis that the chronometry of the anterior insula is a sensitive marker of sensory-affective uncoupling of pain experience.

We applied a multidimensional approach that was informed by the phenomenology of mindfulness practices and aimed to address clinically relevant questions by combining experiential and experimental methods in the context of a novel fMRI-scanner acute pain paradigm devised to amplify the cognitive-affective aspects of pain experience in trained novice and expert meditators. We found that a style of mindfulness meditation labeled Open Monitoring reduced pain unpleasantness but not pain intensity compared to attentional distraction in novice (state effect) and expert meditators (state and trait effects). Trait pain catastrophizing predicted this sensory-affective uncoupling (Study 1). In addition, cognitive defusion showed a specific inverse relation to pain catastrophizing (that was robust to controlling for variance shared with other common cognitive-emotional constructs), and both constructs specifically predicted pain unpleasantness as opposed to pain intensity, with cognitive defusion showing the strongest associations. No experiential dimensions were identified that mediated this relationship (Study 2). Finally, predictions on the anterior insula as a neural marker of sensory-affective uncoupling of pain could only be partly confirmed. During pain anticipation, experts exhibited lower anterior insula activation in a cluster that negatively predicted self-reported sensory-affective uncoupling across participants but did not correlate with pain catastrophizing scores. We could not confirm predictions on pain periods due to methodological issues (Study 3).

These findings advance our understanding of the cognitive and neuronal mechanisms underlying mindfulness-based pain regulation and can be used to inform future contemplative neuroscientific investigations as well as treatment strategies for chronic pain.

Keywords : Mindfulness meditation; thermal pain; pain catastrophizing; cognitive defusion; sensory intensity; pain affect, fMRI.

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Contributions of the author

Chapter 5: Study 1. I designed the task with Dr. Antoine Lutz with help from Dr. Oussama Abdoun. I collected the data with help from Eléa Perraud and Liliانا Mondragon. I was primarily responsible for the data-analysis with help from Drs. Romain Bouet, Oussama Abdoun and Antoine Lutz. Dr. Oussama Abdoun kindly provided the supplementary analysis on practice metrics. I wrote the report with inputs from Drs. Antoine Lutz and Oussama Abdoun.

Chapter 6: Study 2. I formulated the hypotheses for the study in collaboration with Drs. Oussama Abdoun and Antoine Lutz. Dr. Oussama Abdoun analyzed the data and provided the tables and figures. I wrote the majority of the report in collaboration with Dr. Antoine Lutz with inputs from Dr. Oussama Abdoun.

Chapter 7: Study 3. Antoine Lutz conceived the study design. I designed the task with Dr. Antoine Lutz with help from Dr. Oussama Abdoun. I performed the preprocessing with Dr. David Meunier. I analyzed the data and wrote the report.

Annex I: ERC method manual. I contributed to the design, planning and management of the ERC project, as well as in the conception and writing of the report.

Annex II: Protocol study. I contributed to the design, planning and management of the training program. Data collection and analysis for the MEG data presented in the report were performed by Dr. Oussama Abdoun. I contributed to the conception and writing of the report.

Annex III: Qualitative interview. I collected the experimental data for this study. Dr. Stefano Poletti conducted the qualitative interviews. Dr. Oussama Abdoun performed the statistical analyses. Dr. Stefano Poletti wrote the report. I provided inputs together with Drs. Antoine Lutz and Oussama Abdoun.

List of abbreviations

Brain areas

ACC: Anterior Cingulate Cortex

aINS: Anterior Insula

aMCC: Anterior Midcingulate Cortex

dACC: Dorsal Anterior Cingulate Cortex

dIPFC: Dorsolateral Prefrontal Cortex

IFG: Inferior Frontal Gyrus

Ig area: Insula Granular Cortex

Ig area: Insula Granular Cortex

FPC: Frontopolar Cortex

OFC: Orbitofrontal Cortex

OP4: Parietal Operculum 4

PAG: Periaqueductal Gray

pINS: Posterior Insula

PPC: Posterior Parietal Cortex

rACC: Rostral Anterior Cingulate Cortex

S1: Primary Somatomotor Cortex

S2: Secondary Somatomotor Cortex

vmPFC: Ventromedial Prefrontal Cortex

Nociception

CL: Centrolateral Nucleus

MDvc: Ventrocaudal Part Medial Dorsal Nucleus

NS: Nociceptive-specific

Pf; Parafascicular Nucleus

PN: Parabrachial Nucleus

STT: Spinothalamic Tract

VMpo: Posterior Part Ventromedial Nucleus

VPI: Ventral Posterior Inferior Nucleus

VPM: Ventral Posterior Medial Nucleus

VPL: Ventral Posterior Lateral Nucleus

WDR: Wide Dynamic Range (neuron)

Networks

CEN: Central Executive Network

DMN: Default Mode Network

SN: Salience Network

Neuroimaging

BOLD: Blood Oxygen Level-Dependent

EEG: Electroencephalography

fMRI: Functional Magnetic Resonance Imaging

FWE: Family-Wise Error

FWHM: Full Width at Half Maximum

GLM: General Linear Model

LMM: Linear Mixed Model

PET: Positron Emission Tomography

SMS: Simultaneous Multislice

SVC: Small-Volume Correction

TR: Repetition Time

Questionnaires

BDI: Beck Depression Inventory

BIDR: Beck Depression Inventory

CFQ: Cognitive Fusion Questionnaire

DDS: Drexel Defusion Scale

FFMQ: Five Facet Mindfulness Questionnaire

STAI: State Trait Anxiety Inventory

PCS: Pain Catastrophizing Scale

PSWQ: Penn State Worry Questionnaire

MAIA: Multidimensional Assessment Interoceptive Awareness

Behavioral interventions

ACT: Acceptance and Commitment Therapy

CT: Cognitive Therapy

MBCT: Mindfulness Based Cognitive Therapy

MBIs: Mindfulness Based Interventions

MBSR: Mindfulness Based Stress Reduction

Task conditions – Stimuli - Ratings

DIS: Distraction

Dist: Distraction

FA: Focused Attention

OM: Open Monitoring

OP: Open Presence

SH: Short Hot

LH: Long Hot

LW: Long Warm

Int: Intensity

Unp: Unpleasantness

Miscellaneous

ERC: European Research Council

IASP: International Association Study of Pain

SMD: Standardized Mean Difference

Preamble

“When touched with a feeling of pain, the uninstructed run-of-the-mill person sorrows, grieves and laments, beats his breast, becomes distraught. He feels two pains, physical and mental. Just as if they were to shoot a man with an arrow and right afterward, were to shoot him with another one, so that he would feel the pains of two arrows. Now, the well-instructed disciple of the noble one, when touched with a feeling of pain, he does not sorrow, grieve, or lament, does not beat his breast or become distraught. So he feels one pain: physical, but not mental. Just as if they were to shoot a man with an arrow, and right afterward did not shoot him with another one, so that he would feel the pain of only one arrow.”

- Sallatha Sutta – The arrow

The basic premise laid out in the short parable above -derived from an Ancient Buddhist text, is that although negative mentation often habitually follows awareness of unpleasant physical stimuli, this need not be necessarily so, as for individuals trained in mindfulness meditation, it is possible to uncouple sensory and affective pain dimensions, such that the physical component can be fully experienced without concomitant emotional distress (Bodhi, 2005). It is based on such contemplative notions that, in 1982, Kabat-Zinn introduced a secular mindfulness-based intervention for chronic pain management (Kabat-Zinn, 1982). The basic assertion underlying this program was that repeated mindfulness practice could help patients learn to assume an intentional attitude of detached observation towards intense sensations, and to observe with similar detachment affective and evaluative thought processes that lead to the labeling of a sensation as painful. It was argued that this could help patients perceive catastrophic thoughts as simply events in the mind, which could help them realize that thoughts are not necessarily accurate reflections of reality; a process nowadays known as cognitive defusion (Hayes et al., 1999). This in turn, could lead to thoughts losing their otherwise powerful influence: in effect leading to ‘an uncoupling of the sensory component of pain from the affective and cognitive dimensions (alarm reaction)’ (Kabat-Zinn, 1982).

In his pioneering study, Kabat-Zinn reported promising outcomes on pain symptoms, mood disturbance, anxiety and depression that were found to be relatively stable at follow-up in a sample of chronic pain patients for whom traditional treatments had been unsuccessful (Kabat-Zinn, 1982). Ever since, mindfulness-based interventions (MBIs) for chronic pain management, including mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) have ballooned, and their efficacy has now been supported for a wide range of clinical pain disorders including but not limited to fibromyalgia (Kozasa et al., 2012), back pain (Anheyer et al., 2017) and migraine (Gu et al., 2018). A recent systematic review and meta-analysis on mindfulness-based interventions for chronic pain found that, collectively, evidence is strongest in favor of an effect on the affective dimension of pain, including

on pain-related depression and quality of life, as compared to on the physical dimension, for which only weak evidence was found (Hilton et al., 2017).

In parallel to clinical studies investigating the efficacy of mindfulness-based interventions for chronic pain, experimental studies have started to explore the neural underpinnings of mindfulness-based pain regulation. The relatively few experimental studies available, have mostly but not exclusively compared novice to long-term meditation practitioners in various meditation traditions, and indicate that mindfulness meditation primarily impacts pain unpleasantness as opposed to pain intensity in line with clinical findings (as reviewed by Zeidan et al., 2019). The available neuroimaging studies also indicate that mindfulness-meditation impacts neural representations of pain anticipation and experience. Interestingly, several of the studies found that -in contrast to other well known pain-regulation strategies such as placebo and distraction- a mindfulness state or expertise increased, rather than decreased, brain activity in primary pain processing regions, while decreasing brain activity in prefrontal areas commonly considered to be involved in pain regulation and evaluation (Grant et al., 2011; Gard et al., 2012; Lutz et al., 2013): thus providing plausible neuronal substrates for sensory-affective uncoupling. Nevertheless, in spite of considerable advances, the field is still young and findings thus still need to be consolidated.

Furthermore, several studies have examined interrelations between mindfulness-related constructs and pain catastrophizing and reported inverse relations between the constructs (Day et al., 2015, Turner et al., 2016; Schutze et al., 2010; Elvery et al., 2016). However, interrelations between mindfulness and pain catastrophizing in an acute pain context as well as the role of cognitive defusion in mindfulness-based pain regulation remain virtually unexplored. Clarification of these outstanding research questions could help improve the implementation of mindfulness-based pain regulation in clinical settings.

The general aim of the present thesis was to study the cognitive and neuronal mechanisms underlying the pain-regulatory qualities of mindfulness meditation. Our core hypothesis was that the specific meta-cognitive stance, labeled cognitive defusion (which includes the subprocesses of meta-awareness and dereification important for monitoring and control of the mind), underlies sensory-affective uncoupling of pain in meditation. We also explored how this pain regulation strategy was modulated by meditation state and expertise, as well as psychometrics scales of pain catastrophizing and meditation and investigated putative neural markers. For the purpose of examining these questions, we designed a novel fMRI-scanner acute pain paradigm specifically devised to amplify the cognitive-affective aspects of pain experience. Participants were novice trained in the practice mindfulness meditation and expert meditators in the Kagyu or Nyingma schools of Tibetan Buddhism with at least 10,000 hours meditation experience in life. We used a first-person methodology to refine the description of the participants' pain experience. The overall structure of the thesis will be outlined below.

Overview

Chapter 1: provides an introduction on mindfulness-based sensory-affective uncoupling of pain and its proposed underlying cognitive mechanisms.

Chapter 2: provides an introduction on the current knowledge of the neuronal mechanism underlying mindfulness-based sensory-affective uncoupling of pain.

Chapter 3: outlines the general hypotheses for the studies presented in this work

Chapter 4: outlines the general methods of this work

Chapter 5: provides a detailed investigation of the effect of meditation state and expertise on sensory and affective pain experience. It also examines interrelations between meditation expertise, trait pain catastrophizing and sensory-affective uncoupling of pain.

Chapter 6: provides an investigation of interrelations between trait cognitive defusion and pain catastrophizing, while controlling for variance shared with other more general mindfulness-related and cognitive-emotional constructs. It also examines the respective relation of trait cognitive defusion and pain catastrophizing to sensory and affective pain self-reports.

Chapter 7: provides a neuroscientific investigation on the effect of mindfulness state and expertise on the chronometry of the anterior insula as a putative marker of present-centeredness vs top-down conceptual processing during pain anticipation and early and late pain. We additionally explored the relationship of anterior insula chronometry to sensory-affective uncoupling of pain and pain catastrophizing.

Chapter 8: provides a general discussion and conclusion of this work

THEORETICAL FRAMEWORK

Chapter 1: Cognitive mechanism underlying sensory-affective uncoupling of pain during mindfulness meditation

This chapter starts with a brief introduction on mindfulness meditation. I then discuss how common conceptualizations of mindfulness in the literature are only of limited use to the empirical investigation of mindfulness meditation as they are either too broad or fail to take into account its lived, multidimensional and transformative character. I then introduce the phenomenological matrix of mindfulness meditation, a heuristic framework that aims to facilitate the neuroscientific study of mindfulness meditation, and does so by identifying phenomenally and behaviorally relevant cognitive processes that are provisionally mapped onto different meditation styles and levels of expertise, hence providing verifiable predictions. From this framework, I highlight meta-awareness and dereification as two core cognitive processes deemed particularly salient to mindfulness-based emotion regulation and detail their presumed developmental trajectory. I then discuss how, in the literature, these closely related but distinct cognitive processes are commonly subsumed under the single construct of cognitive defusion, and detail hypothesized relationships between the metacognitive perspective enabled by cognitive defusion, pain catastrophizing and sensory-affective uncoupling of pain experience. I conclude by reviewing clinical and experimental studies assessing the current state of evidence on these theoretical claims, on the basis of which I detail some of the aims and scope of the present work.

1.1 Mindfulness meditation: definition, basic concepts and historical perspective

The term meditation has been used to describe a broad range of practices and mental states in a variety of spiritual, religious and secular contexts (Van Dam et al., 2017; Davidson & Kaszniak, 2015; Lutz et al., 2006; Goleman, 1988). Such generic use of the term meditation greatly complicates the formulation of verifiable hypotheses in neuroscientific contexts. As a solution, it has been suggested to more closely attend to the individual practices under study (Lutz et al., 2006). As mentioned above, the type of meditation most frequently implemented and investigated in contemporary settings is Buddhist meditation (often in neuroscientific contexts) and its secular derivatives (in clinical settings) (Van Dam et al., 2017). This is not incidental. Buddhist practices envision specific changes in cognitive and emotional states as part of a soteriological path aimed at the cessation of personal suffering (Thera, 1962; Silananda, 1990), which presents a clear parallel to modern clinical psychology aimed at reducing emotional distress and targeting maladaptive behavior (Bishop et al., 2004). In addition, traditional Buddhist accounts have offered detailed, methodological descriptions of meditative practices in a manner that lends itself well to scientific scrutiny (Lutz et al., 2006). As a result, these practices have been readily adopted in Western

secular settings, where meditation has been conceptualized as “a family of complex emotional and attentional regulatory strategies developed for various ends, including the cultivation of well-being and emotional balance” (Lutz et al., 2008). Of the different families of meditation (See Dahl et al., 2015), so-called mindfulness practices in particular have seen widespread implementation in contemporary settings and will be further discussed below.

Mindfulness has been described as moment-to-moment awareness, cultivated by paying attention in a specific way, in the present moment, as non-reactively, non-judgmentally, and open-heartedly as possible (Kabat-Zinn, 1990; Kabat-Zinn, 2011). It is important to note that this is a widely accepted definition tailored to Western clinical audiences (Van Dam et al., 2017), while the exact meaning of the word mindfulness still is and has traditionally been subject to considerable controversy (Van Dam et al., 2017). Nonetheless, in both clinical and traditional contexts, the capacity to sustain a heightened awareness of thoughts, emotions and sensations is considered central to mindfulness meditation (Dahl et al., 2015). Below I will take a closer look at difficulties surrounding the meanings of mindfulness and its empirical investigation, before detailing the scientific approach adopted in the present work.

1.2 Difficulties surrounding the meanings of mindfulness

According to Lutz and colleagues (Lutz et al., 2015), in experimental and clinical psychology, the construct of mindfulness is generally used with three different meanings to refer to: 1) a mental trait or dispositional inclination (e.g. the Five Facet Mindfulness Questionnaire; Baer et al. 2006), 2) a soteriological or spiritual path conceived in therapeutic and health-promotion terms (e.g. the Mindfulness Based Stress Reduction program; Kabat-Zinn, 1982), and 3) a single cognitive process that may be cultivated with meditation practice (e.g. a present-centered and non-judgmental awareness; Bishop et al., 2004). While these various meanings remain useful in many contexts, they are also problematic for empirical research. Specifically, Lutz and colleagues noted that approaching mindfulness as a trait (meaning 1) is too unspecific (i.e. learning that participant’s scores increase after training does not advance our understanding of which cognitive, affective and social processes might be altered via training), and leads to contradictory findings (trait mindfulness instruments suffer from a variety of issues including doubts about construct validity and relation to actual behavior and sensitivity to mindfulness rhetoric following training; see Grossman, 2011). In addition, it does not account for the possibility to cultivate mindfulness as a state. Furthermore, interpreting mindfulness as a soteriological process (meaning 2) is often too broad to guide empirical research, and up to this point, discussion of mindfulness as a cognitive process (meaning 3) makes it difficult to account for differences in practice styles and level of expertise, while also lacking sufficient specificity for formulating mechanistic hypotheses.

As a solution to the above problem, Lutz and colleagues have argued against the use of a single, universally applicable consensus definition of mindfulness and have instead proposed to reconceive

mindfulness through a family resemblance approach whereby mindfulness can be conceptualized as “a variety of cognitive processes embedded in a complex postural, aspirational, and motivational context that contribute to states that resemble one another along well-defined phenomenological dimensions” (Lutz et al., 2015). This approach and its practical implication will be detailed in the next section.

1.3 The phenomenology of mindfulness meditation

In order to facilitate the neurophenomenological investigation of mindfulness meditation, Lutz and colleagues have proposed a heuristic model that decomposes mindfulness into different dimensions that can be used to map multiple practice styles and levels of expertise (see Figure 1). The model is based on the phenomenology of mindfulness practice (i.e. what observable, manipulable features of experience are modified by mindfulness training) and is grounded on both clinical and classical Buddhist sources (Lutz et al., 2015). The model proposes a number of core cognitive processes (dimensions) that are taken to maximally distinguish between different meditation styles and are deemed crucial to mindfulness-based emotion regulation; while also providing testable predictions about how these dimensions vary as a function of mindfulness practices and levels of expertise. Thus, the model assumes that the proposed dimensions are dynamic and manipulable in that they are affected -directly or indirectly- by the instruction set and/or level of expertise. The three primary orthogonal dimensions are: Object Orientation, Dereification, and Meta-awareness; orthogonal means that the dimensions can vary independently from each other. It is proposed that certain identifiable phenomenological states emerge in participants due to the interaction of the dimensions subsumed within the model: each state occupying a given position in a multidimensional phenomenological space. The model also leaves open the possibility that individuals reliably differ in their typical location in the phenomenological space to account for the notion of trait. The three primary functional dimensions and their relevance to the present work will be further detailed below.

1.3.1 Object Orientation

This dimension is modulated by many styles of meditation practice and refers to ‘the phenomenological sense that an experience or mental state is directed to an object or class of objects’. The relevant feature of this dimension is the sense that the state is strongly or weakly oriented toward an object, rather than the actual selection of the object itself. This construct resembles the orienting of endogenous attention in psychology. An example of a state with high object selection is so called focused attention (FA) meditation (see the description of mindfulness practices in the next section), that involves a continuous sustaining of a highly selective focus on a single object (hence the positioning of FA practices on the right side of the cube in Figure 1; indicating high object orientation). Conversely, another broad class of meditation practice is so called Open Monitoring (OM) meditation (see the next section for a description) that involves a deliberate reduction of any intentional stance towards objects (hence the positioning of

OM practices on the left side of the cube in Figure 1; indicating low object orientation). For the remainder of this thesis this dimension will remain mostly implicit, but of relevance to the meditation practices and instructions in the here specified manner.

1.3.2 Meta-awareness

This dimension involves the monitoring of experience. It has been defined as the mental state that arises when attention is directed toward explicitly noting the current contents of experience (Smallwood & Schooler, 2015). It involves a heightened awareness of the processes of consciousness, including the processes of thinking, feeling, and perceiving (corresponding to a higher position in the cube in Figure 1). When meta-awareness is absent, we become experientially 'fused' with experience (corresponding to a lower position in the cube in Figure 1). We may be aware of the contents of experience, but remain unaware of the processes of thinking, feeling and perceiving themselves (Dahl et al., 2015). Importantly, a variety of clinical disorders such as depression, anxiety and chronic pain are marked by states of high experiential fusion with negative thoughts and feelings (Lo et al., 2015; Hoge et al., 2014, McCracken et al., 2014). Furthermore, the ability to step back from being entangled in thoughts and feelings through the cultivation of meta-awareness is considered an important predecessor to mental health in the clinical domain (Hayes 2004; Segal et al., 2014; Kabat-Zinn 2013). Meta-awareness enables a change in perspective from being immersed within experience onto that experience. While meta-awareness can occur spontaneously, such as for instance in the moment of becoming aware of mind wandering, mindfulness practices aim to deliberately cultivate this capacity (to some degree in FA, but mostly in OM). With sufficient expertise in meditation, meta-awareness can be sustained for extended periods of time without explicit focus (see the description of OM in the next section). Thus, meta-awareness as conceptualized here can be understood as a sustained and graded process that is deliberate, embodied and intentional (Lutz et al., 2013, Dunne et al., 2019).

1.3.3 Dereification

This dimension reflects the degree to which thoughts, feelings, and perceptions are phenomenally interpreted as mental processes rather than as accurate depictions of reality (Lutz et al., 2015). For example, a typical pain-related catastrophizing thought is "It's terrible and it's never going to get better" (Sullivan et al., 1995). When this thought occurs and appears as a realistic it may induce anxiety and pain amplification. This is an instance of high reification in that the thought presents itself as if the situation it represents is real (corresponding to a more anterior position in the cube in Figure 1, indicating low dereification). Dereification then refers to the process of thoughts losing their representational integrity and being experienced simply as mental events (corresponding to a more posterior position in the cube in Figure 1, indicating high dereification). As for meta-awareness, the capacity for dereification can occur

without explicit training, such as for instance in the moment of becoming aware of daydreaming. However, what characterizes mindfulness meditation is that this capacity is trained deliberately. At the beginning stages of mindfulness practice dereification might be accomplished through the use of cognitive reappraisals such as “This is just a thought” (this strategy might for instance be employed in FA to deal with distracters; see the description in the next section). However, at more advanced levels of mindfulness practice dereification may be spontaneously maintained by just sustaining a monitoring state (see the description of OM in the next section) (Lutz et al., 2015). In the latter case, dereification is fostered by the shift in perspective brought about by the cultivation of meta-awareness. This change in perspective enables a meta-cognitive awareness that allows thoughts to be experienced as mere mental events, situated within a field of sensory, proprioceptive, affective and somatic feeling tones. It is to promote awareness of this embodied field that mindfulness practices emphasize deliberate attention to bodily sensations.

Before continuing, it should be mentioned that, in addition to the here presented primary functional dimensions, the model also identifies several secondary features of mindfulness practices (Aperture: broadness of the scope of attention; Clarity: degree of vividness of experience; Stability: degree to which experience presents itself as enduring over time; Effort: impression that one’s mental state is easy or difficult to sustain; see Figure 1). Although these are all considered necessary elements of mindfulness practice, they have been less explicitly mentioned as they are less relevant to distinguishing different styles of practice. Furthermore, the model also identifies several contextual features of mindfulness practices including, among others, the need to cultivate a positive or at least non-aversive affective attitude (Lutz et al., 2015). Practically, this involves maintaining an accepting and friendly attitude towards thoughts and feelings as they arise during mindfulness meditation (Bishop et al., 2004; Shapiro et al., 2006). Although the role of acceptance is not explicitly investigated in the present work, some lead authors in the field have operationalized mindfulness in very terms of acceptance (Bishop et al., 2004; Dahl et al., 2015), and acceptance as a construct is likely integral to enabling the shift in perspective brought about by meta-awareness (Hayes et al., 2006; Chambers et al., 2009; McCracken et al., 2014); i.e. one can only step back from being entangled in the contents of experience if one first cultivates a non-judgmental, open and accepting stance towards that experience (see also Grossman 2011, for a detailed explanation of the importance of cultivating certain mind qualities like kindness, patience, tolerance, gentleness, empathy, non-striving and openness in strengthening the ability to maintain concentration). Therefore, although little mentioned or investigated here, acceptance is considered integral to mindfulness meditation and meta-awareness in the present work.

To summarize, meta-awareness and dereification are two cognitive processes that are closely related, yet distinct. Meta-awareness involves the monitoring of experience, and refers to a heightened capacity to be aware of the phenomenal features of experience, including of the processes of thinking, feeling and

perceiving itself. Meta-awareness enables a change in perspective from being immersed within experience onto that experience. It is this change in perspective that allows thoughts to be experienced as mere mental events, rather than as accurate depictions of reality, a process labeled dereification. The phenomenological model, like other theoretical and clinical mindfulness accounts (e.g. Chambers et al., 2009; Kabat-Zinn 1982), holds that the cognitive processes of meta-awareness and dereification are two core mechanisms of action underlying mindfulness-based emotion regulation (Lutz et al., 2015). However, the novelty of the phenomenological model is that it provides testable predictions about how these two metacognitive capacities (and other phenomenological dimensions) are affected by specific mindfulness practices and levels of expertise (see the next section of a further discussion of this in relation to meta-awareness and dereification). The present work was embedded in a broader research project (see methods) which aimed to test some of these predictions. Here, we adopted the phenomenological model to inform predictions in studying the impact of mindfulness meditation on pain regulation. This provided us a solid framework to guide research questions while also allowing us to test some of the predictions made in the model; thus contributing to the research aim of the broader project. Note that while we framed our research questions in terms of meta-awareness and dereification, as of yet, no well-validated measures are available for these constructs. Therefore, in this work, we studied both constructs under the proxy of cognitive defusion, which collapses both constructs into a single construct (see section 1.7).

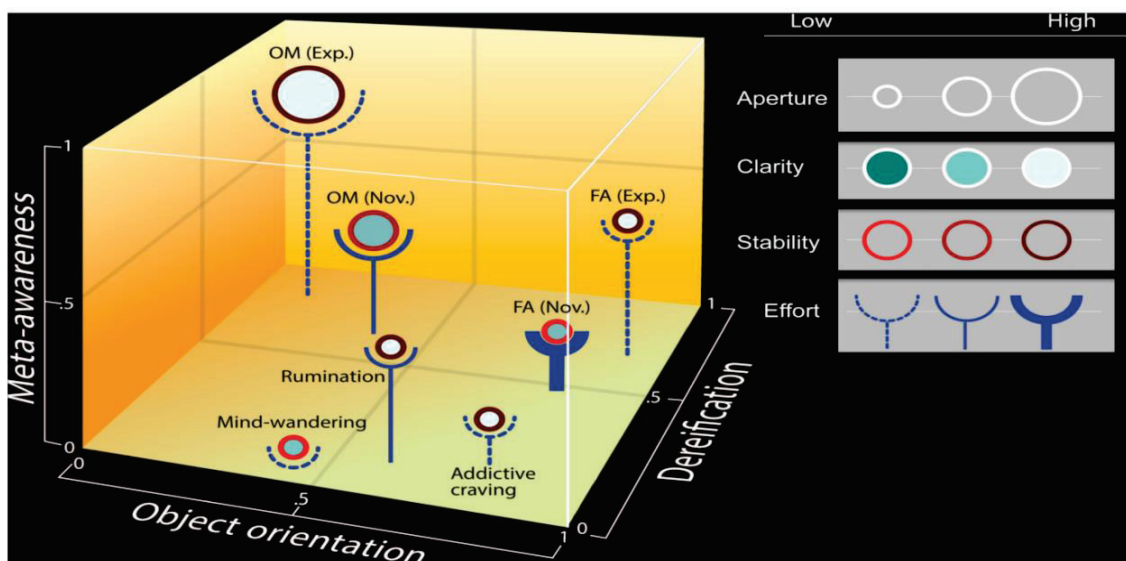


Figure 1. The phenomenological matrix of mindfulness practices. The figure maps hypothetically two broad styles of mindfulness meditation, Focused attention meditation (FA) and Open Monitoring meditation (OM), and three mental states relevant for psychopathology on a multi-dimensional phenomenological space. “Exp” and “Nov” stand for expert and novice practitioners. The three primary dimensions of the space are Object Orientation, Dereification and Meta-awareness which are mapped on the Euclidean space. The model also identifies four secondary dimensions: Aperture, Clarity, Stability and Effort. These four qualities are represented, respectively, by the diameter of a circle, fill color of the circle, color of the perimeter of the circle, and by the width of a supporting stalk. See the text for details on all presented dimensions and meditation states. Mind-wandering is represented as an effortless state (dashed line) of absorption (low Meta-awareness) where the contents of experience are phenomenally interpreted as accurate depictions of reality (low Dereification). Addictive craving is depicted as a state strongly and repeatedly oriented toward the object of addiction (high Object Orientation). Ruminations is represented as a state where the person is aware of stable intrusive thoughts (some Meta-awareness) that are however still experiences as ‘real’ (low Dereification). [Figure and adapted text from Lutz et al., 2015].

1.4 Description of mindfulness practices

In this section I will introduce the mindfulness practices relevant to the present work and detail their relation to the meta-cognitive capacities of meta-awareness and dereification, but first I will introduce some axioms that have been suggested to underlie all meditation practices that provide a useful framework for the neuroscientific investigation of mindfulness practices. It has been suggested that all meditation practices, however diverse, share the following features and aims (Lutz et al., 2006):

- 1) The intended cultivation of a certain desirable and phenomenally reportable state.
- 2) The premise that the repeated cultivation of a given state eventually induces trait change.
- 3) The claimed progression from novice to expert meditator.

With these axioms in mind, I now turn to the mindfulness practices relevant to the present work. Based on traditional Buddhist texts, two broad styles of mindfulness practices can be discerned, which, for neuroscientific purposes, have been described in terms of their defining features. These include: Focused Attention (FA) meditation, which involves the focusing of attention on a selected object, and Open Monitoring (OM) meditation, which involves the non-reactive monitoring of the content of moment to moment experience. Both styles are found in several Buddhist meditation traditions, including Vipassana, Zen and Tibetan Buddhism, as well as in secular MBIs (Lutz et al., 2008). An advanced form of OM is so called Open Presence (OP) meditation, which involves a turning of awareness on itself in order to transcend subject-object duality (Lutz et al., 2006; Dunne, 2011). OP is a highly specific meditation practice relevant to the present work. Each of these practices will be further discussed below.

1.4.1 Focused attention

FA meditation involves a narrowing of attention and the cultivation of a one-pointed concentration on a single object, often involving a localized subset of sensations (e.g. the movement of the breath at the nostrils). The main task-set consists of sustaining attention on the chosen object, becoming aware when the mind has wandered, non-judgmentally letting go of the distracter, and subsequently reallocating attention to the intended object. Thus, FA not only requires a focusing of attention, but also a continuous monitoring of the quality of attention to verify whether attention is still focused on the intended object or whether focus has been lost (Lutz et al., 2008). The latter involves a type of meta-awareness that is not focused on an object *per se*, but is instead monitoring the intentional relation itself (Lutz et al., 2006). This monitoring capacity provides the basis for OM practice that involves a further development of meta-awareness (Lutz et al., 2006; Dahl et al., 2015). Furthermore, FA also involves some degree of dereification but not as much as in OM (see the description of OM below). More specifically, in novices, FA involves some degree of dereification that is needed to disengage from distracters, while with

increasing expertise in FA, meta-awareness and dereification become developed to the point where it becomes possible to note minor perturbations in attention before they develop into full-blown distractions (Lutz et al., 2015). FA is said to calm the mind and reduces distractions (see Lutz et al. 2008, for an overview of empirical evidence supporting this claim). Hence, FA is often recommended to novice practitioners who may still frequently contend with distractions. However, at all levels of expertise FA serves as preparatory practice for OM (Lutz et al., 2008), as will be further discussed below.

1.4.2 Open monitoring

This style of meditation involves the non-reactive monitoring of moment to moment experience without explicit focus (Lutz et al., 2008). As mentioned above, it relies on the initial application of FA as a means to calm the mind, stabilize attention and strengthen the monitoring faculty. When the monitoring faculty has been sufficiently strengthened with FA, either between sessions or within a session, the focus on an explicit object can be reduced and the monitoring faculty correspondingly emphasized to gradually incorporate the flow of all present moment sensations, emotions and thoughts. Thus, in contrast to FA, OM involves no strong distinction between selection and deselection, or between what is on the foreground and background of awareness (Lutz et al., 2008; Lutz et al., 2015). In OM, it is possible to become aware of new experiential content (e.g. emotional tone or thought) without it becoming the primary focus of attention. It is as if the emotional tone or thought remain in the background even though there is no contrasting foreground. In this way, the “effortful” selection or “grasping” of objects is gradually reduced and replaced by an “effortless” sustaining of awareness without explicit focus. In typical OM instructions, one is encouraged to become aware of a large field of awareness that includes stimuli from the body, mind and environment, without giving particular attention to any one of them. This is said to provide access to the rich features of each experience, such as the degree of phenomenal intensity, affective tone, and active cognitive schema, that often remain implicit. OM practices aim to deliberately strengthen this metacognitive perspective or meta-awareness thereby simultaneously strengthening the capacity for dereification (see previous section). According to the phenomenological model, both processes are higher in OM compared to FA (due to the broader scope of monitoring) and become further strengthened with increasing expertise in OM, up to the point where meta-awareness (the monitoring state and dereification can be sustained effortlessly (see Figure 1). In later sections I will detail how these processes might be beneficial to pain regulation, but first I will discuss the case of OP meditation, which can be considered an advanced form of OM, below.

1.4.3 Open presence

At the highest levels of OM, when the monitoring state continues effortlessly, meta-awareness and dereification have almost reached their maximum, and the grasping of mental objects is reduced to a

minimum, it is possible and even recommended to make awareness an object of meditation itself (Chambers et al., 2009; Lutz et al., 2006). A canonical example of this type of meditation is so called Open Presence (OP) meditation: a highly advanced form of OM found in the Tibetan Buddhist meditation traditions under study in the present work. OP (and ultimately all Buddhist meditation practices) aim(s) for a direct understanding of “reflexive” awareness or the fundamental Awareness that is said to be the basis nature and structure of consciousness itself. This can be better understood when taking into account the central Buddhist tenet that the mind is comprised of two unified aspects: awareness and objects of awareness, where awareness is understood as that which gives rise to the experience of mental phenomena or qualia itself. According to Buddhist notions, mental phenomena or stimuli (e.g. thoughts and emotions) always emerge within awareness and are de facto inseparable from it. However, this relationship is usually obscured by a strong habitual tendency to identify with mental objects, which incurs a separation between these two aspects of the mind. This reportedly gives rise to a false sense of separation between the perceiver and that what is perceived, also known as subject-object duality, which is said to be at the basis of all mental suffering (Chambers et al., 2009). OP aims to undo this false sense of separation and related subject-object duality. It is claimed that when the monitoring state continuous almost effortlessly there comes a point where awareness can be directed back on itself and the mind released in its natural, effortless state that is Open Presence or fundamental Awareness. This reportedly leads to a complete suspension of subject-object duality (including of all conceptual features and space-time categories) (Lutz et al., 2006). As such, OP is considered a non-dual practice (Lutz et al., 2006; Dunne, 2011). However, it should be noted that OP is a highly advanced practice and even experienced practitioners might only be able to sustain a true non-dual state for shorts period of time (Lutz et al., 2006). In terms of metacognitive processes, OP can be considered an advanced form of OM, where the capacities for meta-awareness and dereification have been developed to their maximum (akin to the representation of OM in experts in Figure 1).

To summarize, FA and OM are two complementary meditation practices. FA is utilized to calm the mind, stabilize attention and strengthen the monitoring faculty. The augmented monitoring capacity then forms the basis for OM practice that involves a monitoring of all experience. OP, in turn, is an advance style of OM that reportedly involves an effortless resting in “reflexive” awareness and a complete suspension of subject-object duality. Although these practices are diverse, they share the common characteristic that they all systematically train the capacity to intentionally initiate, direct and/or sustain attentional processes while progressively strengthening the capacity to be aware of the processes of thinking, feeling and perceiving (Dahl et al., 2015), or meta-awareness, and the capacity to perceive thoughts as mere mental events instead of as accurate reflections of reality, or dereification; two complementary processes purported to have beneficial effects on emotion regulation, cultivated to their maximum with OM (OP).

For the scope of the present work, we investigated the effect of OM style meditation on pain regulation. This choice was motivated by three main reasons: i) while traditionally FA is considered to lead to some desirable traits, it mainly OM that has been associated with beneficial effects on the regulation of emotions in traditional contexts (via meta-awareness and dereification) (Lutz et al., 2006), ii) the task-set of OM is most closely related to the definition of mindfulness most often provided in clinical pain contexts (i.e. pay attention to the present moment, as non-reactively, non-judgmentally, and open-heartedly as possible), iii) the present study is a continuation of previous work that reported preferential effects of OM over FA on subjective pain experience (Perlman et al., 2010) (see section 1.8.2). Nonetheless, FA is also relevant to the present work in that we recruited experienced meditation practitioners (simply referred to as experts henceforth) that were extensively familiar with both FA and OM. Similarly, we recruited meditation-naïve participants that underwent formal meditation training in both FA and OM, both for the reason that FA practice is considered a necessarily precursor to OM and to enable a better matching with experts. Finally, the notion of state is relevant to the present work in that we contrasted a state of OM with a non-meditative attentional distraction state which we expected to differ in terms of relevant cognitive processes, including the level of meta-awareness, as will be further detailed below.

Lastly, it should be noted that novice and experts differed in their way of practicing OM. Experts were extensively familiar with OP (awareness-oriented OM) while novices were trained in OM (object-oriented OM). This difference was inevitable, as it would not have been possible to train novices in OP and experts would probably not have been able to practice a pure form of OM. However, as already mentioned above, OP is considered a highly advanced practice and even experts might not have been able to sustain a true OP state for more than short periods of time. Therefore, we could not be certain whether experts' actual practice was more akin to OM or OP. For this reason, we will use the term OM for both novices and experts below, while acknowledging that for experts actual meditation might also have qualified as OP, which at places will be discussed more explicitly.

I will now turn to the relevance of these specific cognitive processes -cultivated as part of a developmental trajectory with FA and OM- to pain regulation. To this end, I will first introduce basic concepts and definitions related to pain. I will then, discuss the concept of pain catastrophizing and make the case that it is a paradigmatic example of a maladaptive mental state that is low in meta-awareness and dereification, before discussing how cognitive defusion, which includes the subprocesses of meta-awareness and dereification (as cultivated with mindfulness practice), has the potential to oppose pain catastrophizing-related processes and their detrimental effects on pain experience.

1.5 Pain: definition and basic concepts

The International Association for the Study of Pain (IASP) defines pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (Merskey and Bogduk, 1994). This definition highlights the subjective nature of pain and its multidimensionality as both a distinct sensation and motivational drive (Craig, 2003ab). Indeed, pain does not simply reflect sensory input, but rather arises from the complex interaction between sensory-discriminative (location, magnitude, duration), affective-motivational (unpleasantness, fight and flight response) and cognitive-evaluative (appraisal) factors (Melzack and Casey, 1968). It is for this reason that psychological factors as diverse as attention, emotion, expectations, beliefs, and the meaning attributed to pain, have the power to amplify or attenuate pain experience and that identical nociceptive stimuli can produce widely varying pain reports across individuals (Atlas and Wager, 2012; Hu and Iannetti, 2019). Importantly, over the last two decades, a mental set, known as pain catastrophizing, has risen to prominence as one of the most potent predictors of increased pain experience, as will be further discussed below.

1.6 Pain catastrophizing

Pain catastrophizing is broadly conceived as “an exaggerated negative 'mental set' brought to bear during actual or anticipated Pain catastrophizing pain experience” (Sullivan et al., 2001). The construct incorporates three dimensions: the tendency to magnify the threat value of pain sensations (pain magnification), a relative inability to inhibit pain-related thoughts in anticipation of, or during a painful encounter (pain rumination), and feeling helpless in the context of pain (helplessness) (Quartana et al., 2009). A growing literature shows that the tendency to catastrophize during pain is linked to increased pain and emotional distress. More specifically, in experimental pain contexts, pain catastrophizing has been associated with a number of indices of pain sensitivity in both healthy individuals and chronic pain patients (Sullivan et al., 2001; Edwards et al., 2006). Moreover, in clinical contexts, pain catastrophizing has been robustly associated to a number of clinical pain-related outcomes including disability, affective distress and increased pain severity (Sullivan et al., 2001; Edwards et al., 2006), and the maintenance and exacerbation of chronic pain (Gatchel et al., 2007; Edwards et al., 2016). Pain catastrophizing is also a core component of theories of pain-related fear and avoidance. These theories are among the most well accepted and empirically supported in explaining the etiology of chronic pain, and hold that a tendency to misinterpret pain sensations, such as following an injury, in a catastrophizing manner, leads to excessive pain-related fear and avoidance, with increased pain, disability and suffering as a result (Crombez, 2013; Vlaeyen et al., 1995; Vlaeyen et al., 2000). Conversely, a tendency to interpret pain as non-threatening has been associated with faster recovery (Crombez, 2013).

1.7 Cognitive defusion: a candidate cognitive mechanism underlying mindfulness-based pain regulation

The above discussed notion that avoidance of pain is maladaptive is in line with clinical and mindfulness theory which holds that cultivating an open and accepting attitude towards pain, especially when chronic and inescapable, is more adaptive than experiential avoidance (Kabat-Zinn, 1982, 1990; Chambers et al., 2009). More specifically, whereas pain catastrophizing involves the cognitive-affective amplification of pain, mindfulness practice is a process designed to oppose or undermine the effect of pain catastrophizing. One standard phenomenological description of this practice reports that by opening up to sensory experience and deliberately cultivating a nonjudgmental and nonelaborative mindset, one might become aware of distressing thoughts and emotional reactivity as mere mental events instead of as accurate representations of reality (Kabat-Zinn, 1982). This meta-cognitive stance (akin to meta-awareness and dereification) might reduce secondary elaborative processing. Assuming this stance has been suggested to lead to an uncoupling of the affective and cognitive dimensions of pain from the sensory dimension (Kabat-Zinn, 1982). An important aim of the present work was to more closely examine this claim and implicated cognitive processes. As mentioned before, since no well-validated measures for meta-awareness and dereification are available, we did this using the proxy of cognitive defusion. This construct will be briefly further discussed below.

Cognitive defusion is a process similar to decentering and metacognitive awareness (Bernstein et al., 2015, Forman et al., 2012), and refers to the ability to gain psychological distance from internal experiences such as thoughts and feelings, seeing them as mere events in the mind rather than as accurate, truth-based reflections of reality (Forman et al., 2012; Blackledge, 2007; Masuda et al., 2004). As becomes apparent from this definition, cognitive defusion collapses the constructs of meta-awareness (ability to gain psychological distance from experiences) and dereification (seeing them as mere events in the mind rather than as accurate truth-based reflections of reality) into a single construct (see Lutz et al., 2015). The relation of meta-awareness and dereification to mindfulness practice has been extensively discussed before (see section 1.4). Cognitive defusion can reasonably be expected to map onto the different meditation styles and levels of expertise on a similar manner (i.e. increased cognitive defusion with OM and increasing expertise).

The opposite of cognitive defusion, is experiential fusion, a state of mind where one is so entangled in thoughts that they are taken literal and take precedence over behavior and function (McCracken et al., 2014; Hayes et al., 1999). A variety of clinical disorders such as depression, anxiety and chronic pain are marked by states of high experiential fusion with negative thoughts and feelings (Lo et al., 2015; Hoge et al., 2014, McCracken et al., 2014). Conversely, the ability to step back from being entangled in thoughts and feelings through the cultivation of meta-awareness is considered an important predecessor to mental

health in the clinical domain (Hayes 2004; Segal et al., 2014; Kabat-Zinn 2013). For instance, in traditional cognitive therapy (CT), this capacity is believed to be achieved implicitly through cognitive restructuring (Teasdale et al., 2001). In contrast, more recent adaptations of CT, so-called third-wave behavioral interventions, have made the ability to step back from thoughts their centerpiece and hold that it is not necessary to change the content of experience as long as one changes one's relationship to experience (Forman et al., 2012). These interventions include Acceptance-based Commitment Therapy (ACT), a complex behavioral package that incorporates mindfulness-based elements from which the concept of cognitive defusion originates (see Hayes et al., 1999 for an account of defusion techniques in ACT), and MBIs; in which the capacity or cognitive defusion is trained at the hand of specific mindfulness practices (see section 1.4).

While the concept of cognitive defusion has been around for some time (Hayes et al., 1999), it is only since fairly recently that the construct really gained traction (see Bernstein et al., 2015 for an overview of positive associations with cognitive-defusion related constructs and mental health gains, including reduced anxiety, depression and negative affect). This might be related to the fact that well-validated measures of cognitive defusion have only recently become available. The relatively few studies that have begun to explore relationships between defusion-related constructs and pain-related outcomes, have found associations with better pain-related outcomes in chronic pain patients (McCracken et al., 2013a,b, 2014). However, to our knowledge, no studies to date have examined interrelations between cognitive defusion and pain catastrophizing, as well as their respective relations to pain-related outcomes.

From the perspective of cognitive defusion pain catastrophizing is an example of high fusion. For example, a typical pain-related catastrophizing thought is "It's terrible and it's never going to get better" (Sullivan et al., 1995). When this thought occurs and appears as a realistic it may induce fear and pain amplification (Crombez et al., 2013). This is an instance of experiential fusion in that the thought present itself as if the situation it represents is real. Cognitive defusion then refers to the process of changing one's perspective to thoughts through meta-awareness, through which they lose their representational integrity and being experienced simply as mental events. In the context of pain catastrophizing, this may translate to reduced emotional reactivity, and sensory-affective uncoupling of pain (Kabat-Zinn, 1982). Thus, cognitive defusion and pain catastrophizing are possibly antithetical constructs with an inverse relationship to sensory-affective uncoupling of pain. This tentative hypothesis has not been explored so far, which was an explicit aim of the present work.

Below, I will briefly review the clinical and experimental studies, focusing on what is known to date of the effect of mindfulness-based pain regulation on subjective pain experience and underlying cognitive mechanisms, based on which I will detail some of the aims of the present work.

1.8 Clinical and experimental research on mindfulness meditation and pain

1.8.1 Clinical studies

In the early 1980s the first mindfulness-based intervention for chronic pain management was introduced (Kabat-Zinn 1982). The 10-week program was offered to chronic pain patients who failed to improve with traditional medical care, and comprised weekly 2-hr meetings and teachings on meditation practices (akin to FA and OM) and gentle yoga, accompanied by discussions on stress and coping and home meditation assignments (45 min/day). As discussed before, the basic premise underlying the program was that mindfulness meditation could help chronic patients learn to “uncouple” the affective/evaluative alarm reaction of pain from the sensory dimension (Kabat-Zinn 1982). In line with this notion, this first study reported promising outcomes on pain symptoms, mood disturbance, anxiety and depression that were relatively stable at follow-up (up to 7 months) (Kabat-Zinn, 1982).

Similar more recent adaptations of the above program, so called mindfulness-based interventions (MBIs) (see Baer et al., 2003), have since been implemented for a wide variety of chronic pain disorders, including but not limited to chronic back pain, fibromyalgia and musculoskeletal pain (Hilton et al., 2017). These include several well-controlled studies that have reported promising outcomes of MBIs on several mental health indices related to chronic pain (e.g. Morone et al, 2008; Turner et al., 2016). Nevertheless, systematic reviews and meta-analyses generally echo the view that there is only limited evidence for the efficacy of mindfulness-based interventions on chronic pain due to methodological issues (e.g. small sample size, lack of active control groups, no intention to treat etc.) (Chiesa and Serreti, 2011; Bawa et al., 2015). Nevertheless, one of the most comprehensive reviews to date included a meta-analysis of 30 randomized controlled trials investigating the effect of mindfulness-based interventions on various pain disorders, and found that, collectively, evidence for an effect on: depression is high (small effect size: SMD 0.15, but with high precision/reliability), mental health-related quality of life is moderate (medium effect size: SMD 0.49, with moderate precision/reliability), physical quality of life/functional impairment is low (medium effect sizes: SMD 0.30-0.34, but with high imprecision/unreliability) (Hilton et al., 2017).

To summarize, more high-quality studies are clearly needed before any definite conclusions can be drawn. However, while not directly examined, the results of the reviewed clinical studies are at least in line with the notion that mindfulness meditation primarily impacts the affective dimension of pain as opposed to the sensory dimension. Nevertheless, clinical studies are focusing primarily on mental health outcomes or measures of symptoms reductions. They are not well-suited for studying specific mechanisms of mindfulness meditation or indeed in establishing whether mindfulness meditation per se is the active factor at all. This is because MBIs are complex and multifaceted and incorporate elements of various meditation techniques including, breath awareness, body scans, mindful walking, physical

exercises and stretching, and cognitive reappraisal. An additional confound is that MBIs include social interactions with the group and teacher which may also contribute to non-specific effects (Kabat-Zinn, 1982; as noted in Perlman et al., 2010). For these and other reasons, the mechanisms of mindfulness meditation can be better investigated with experimental studies targeting well-defined meditative states and specific cognitive mechanisms.

1.8.2 Experimental studies

In parallel to clinical studies investigating the efficacy of MBIs, experimental studies have begun to explore the mechanisms underlying mindfulness-based pain regulation. The majority of these studies have been neuroimaging-oriented and collected pain intensity and unpleasantness reports with the aim of performing brain-behavior correlations. Here, I review findings with respect to the impact of mindfulness meditation on subjective pain experience, while associated neuroimaging results will be reviewed in later sections.

One of the first studies in the field, by Grant and Rainville, compared a group of long term meditators practitioners in the Zen tradition (>1000 hours of practice) to meditation-naïve controls (Grant et al., 2009). Compared to baseline, meditators, but not controls, reported a reduction in both pain intensity and unpleasantness, both while concentrating on the pain sensation (akin to FA) and while performing a mindful instruction (akin to OM). Another study by Brown and Jones, included subjects from diverse meditation traditions and with widely ranging meditation experience (39-1820 hours of practice), who were compared against meditation-naïve controls (Brown and Jones, 2010). No active meditation instructions were provided in this study. At first, the authors observed no group differences. However, when comparing a subgroup of the most experienced meditators (> 6 years of experience) to controls, meditators were found to report significantly lower pain unpleasantness (intensity reports were not collected). Another study by Gard and colleagues included experienced Vipassana practitioners (910 to 20855 hours of practice) and meditation-naïve controls (Gard et al., 2012). Meditators but not controls, reported a reduction in pain unpleasantness but not pain intensity when performing a mindfulness instruction (akin to OM) as compared to baseline. Another study by Perlman and colleagues, of which the present work is a continuation, compared Tibetan Buddhism practitioners to formerly meditation-naïve controls who received written meditation instructions and were instructed to practice at home for 30 minutes a day 7 days prior to the experiment (Perlman et al., 2010). This study investigated the effect of FA and OM practice (OP for experts) on subjective pain experience. During FA, groups reported no differences in pain intensity and pain unpleasantness. During OM, experts reported significantly lower pain unpleasantness, as well as marginally lower pain intensity, both compared to the FA condition, as well as compared to novices, with much larger effects on the affective as compared to the sensory dimension. Finally, in a series of experiments by Zeidan and colleagues, meditation-naïve participants

underwent 4 brief 20-minute sessions of formal meditation training in a practice that involved sustained focused attention on the breath (akin to FA) (Zeidan et al., 2011, 2015, 2016). After the intervention, but not before, participants reported a marked overall reduction in pain, including in pain intensity and unpleasantness, while focusing attention on the breath.

To summarize, the reviewed experimental studies have yielded mixed results, with some studies reporting a clear pattern of sensory-affective uncoupling (Gard et al., 2012; Perlman et al., 2010), while others reported marked overall reductions in pain intensity and pain unpleasantness (Grant and Rainville, 2009; Zeidan et al., 2011, 2015, 2016). As such, the notion of mindfulness-related sensory-affective uncoupling of pain remains debatable.

The above discrepancy may arise from the diversity of styles of and expertise in mindfulness meditation. For instance, the type of meditation instructions provided to novices in the studies by Zeidan and colleagues, involved a focusing of attention on the breath, which in the context of pain, might involve components more akin to distraction, which has been linked to attentional gating mechanisms and overall pain reductions (Miron and Duncan 1989; Sprenger et al., 2012), as was observed in these studies. However, at the same time, the studies by Zeidan and colleagues are the only ones who provided formal meditation training to novices (in all other studies meditation-naïve participants received written meditation instructions). Hence, it is also plausible that novices tend to show a different pattern of pain regulation when they begin to meditate as compared to experts. As mindfulness instructions and level of formal training differed between the studies at hand, this remains an open question. Furthermore, the finding that experts reported sensory-affective uncoupling of pain during OM in the study by Perlman and colleagues needs itself to be replicated.

The current work aimed to address the above issues, first, by recruiting a sample of expert meditators from the same Tibetan Buddhist meditation traditions as in the study by Perlman and colleagues, which allowed for a replication of results, second, by including formerly meditation-naïve participants who received brief formal training in OM, which allowed us to examine whether novices show an effect after formal training in OM, which none of the studies have provided so far. The latter also allowed us to make a preliminary comparison of the pattern of pain regulation of novices trained with that of novices trained in the studies by Zeidan and colleagues. Note that in this light, we could have opted to instruct participants to perform FA in addition to OM, which would have allowed us to directly compare the pain regulatory effect of OM and FA in formally trained novices. However, we instead chose to implement a non-meditative attentional distraction control state. This choice was motivated by our wish to compare a state that is high in meta-awareness and dereification in relation to pain-related processes to one where these cognitive processes are low (at least in relation to pain). That is, where the distraction condition might still have involved some degree of meta-awareness and dereification to enable a focusing on the task-set,

this task-set was away from pain, thus preventing the recruitment of these cognitive capacities in relation to pain itself.

1.8.3 Studies examining interrelations between mindfulness and pain catastrophizing

Interestingly, none of the above reviewed experimental studies have investigated the cognitive mechanisms underlying mindfulness-based pain regulation. Nevertheless, another line of clinically-oriented studies has investigated interrelations between mindfulness and pain catastrophizing. The majority of these studies have hypothesized that mindfulness and pain catastrophizing can be construed as antithetical constructs; where pain catastrophizing refers to a type of conceptual processing that is reactive and judgmental and leads to the cognitive-affective amplification of pain, whereas mindfulness involves a specific cognitive attitude that is non-judgmental and nonelaborative and assumed to lead to a diffusion of emotional responses. As such, most reviewed studies expected to find an inverse relationship between mindfulness and pain catastrophizing measures. Methodologically, the majority of these type of studies (and the ones reviewed below) have examined statistical relationships between pain catastrophizing, as assessed by the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995), and the different facets of the Five Facet Mindfulness Questionnaire (FFMQ) (Baer et al., 2006); the most widely implemented mindfulness questionnaire in clinical pain research. The latter purports to measure five mindfulness dimensions including: Observing (noticing or attending to internal and external experiences), Describing (labeling internal experiences with words), Acting with awareness (attending to present moment experience), Non-Judging (adopting a non-evaluative stance towards thoughts and feelings) and Non-Reacting (allowing thoughts and feelings to pass, without getting caught up in them). From these studies, a consistent picture has emerged as will be reviewed further below.

Of the different FFMQ facets, the Non-judging and Non-reacting facets have repeatedly been found to correlate negatively with PCS, in both clinical (Day et al., 2015, Turner et al., 2016; Schutze et al., 2010), and healthy samples (Elvery et al., 2016), with the Non-judging facet generally showing the strongest correlations. The Act with awareness facet was also found to correlate negatively with PCS in the majority of studies, albeit less strongly (Day et al., 2015, Turner et al., 2016, Elvery et al., 2016). In contrast, correlations with Observe and Describe facets are generally not observed (Day et al., 2015; Turner et al., 2016; Schutze et al., 2010; Elvery et al., 2016). Collectively, these studies suggest that in particular the Non-judging and Non-reacting facets of the FFMQ capture dimensions of mindfulness antithetical to pain catastrophizing. Importantly, the specificity of these findings has been questioned by one of the studies, which found that none of the significant relationships between FFMQ facets and PCS survived when controlling for worry, a general anxiety-related construct (Day et al., 2015). This finding underlines the need to control for other more general cognitive-emotional constructs to assess specificity when

examining relations between mindfulness and pain catastrophizing (Day et al., 2015). Importantly, the non-specificity of the relationship between FFMQ facets and pain catastrophizing raises the question whether other mindfulness-related constructs show a more specific relationship to pain catastrophizing. A better understanding of whether there are any specific mindfulness-related constructs that overlap with pain catastrophizing would be of great benefit to the field as it could help optimize the implementation of mindfulness-based interventions in the clinical domain. Interestingly, as mentioned before, none of the studies reviewed in this section have examined the role of cognitive defusion (or meta-awareness and dereification) in mindfulness-based pain regulation. This was another central aim of the present work.

1.9 Summary and general aims

In this chapter, I introduced the phenomenological matrix, a heuristic framework that allows to reconceptualize mindfulness as an assembly of cognitive processes that can be mapped onto different practice styles and levels of expertise. Based on this model, I highlighted the hypothesized central role of meta-awareness and dereification as two core cognitive processes underlying mindfulness-based emotion regulation, and detailed their presumed developmental trajectory with mindfulness practice, coming to full fruition with expertise in OM. I then discussed how both constructs are more commonly studied under the single construct of cognitive defusion and how it has been hypothesized that this metacognitive capacity underlies sensory-affective uncoupling of pain during mindfulness meditation by its opposing effects on pain catastrophizing-related processes. Subsequently, I reviewed an experimental literature which indicates that mindfulness meditation may indeed result in sensory-affective uncoupling of pain, but that discrepancies remain, possibly related to a diversity of styles of and expertise in mindfulness meditation. Finally, I reviewed clinically-oriented studies that have started exploring relationships between mindfulness and pain catastrophizing, but have so far not examined the role of cognitive defusion in mindfulness-based pain regulation.

The aim of the present work was to bridge the above three literatures: i) mindfulness theory focusing on the phenomenology of mindfulness practices and emphasizing cognitive defusion (i.e. meta-awareness and dereification) as a core cognitive process underlying mindfulness-based emotion regulation, ii) experimental studies examining the impact of mindfulness meditation on subjective pain experience and sensory-affective uncoupling of pain, and iii) clinical studies investigating interrelations between pain catastrophizing and mindfulness-related processes. To this end, we implemented a multidimensional approach, where we: i) investigated the role of meditation state and expertise on sensory-affective uncoupling of pain experience, and ii) examined the impact of mindfulness mediation on pain catastrophizing and cognitive defusion in relation to sensory-affective uncoupling of pain experience.

Chapter 2: Neuronal mechanism underlying sensory-affective uncoupling of pain during mindfulness meditation

This chapter starts with a review of pain processing in the human nervous system, from peripheral nociceptive processing to nociceptive processing in the spinal cord and in the brain. I then describe how, nociceptive information is transduced to a final conscious pain percept. In doing so, I focus on the role of the anterior insula as a critical hub of the salience network, implicated in bottom-up (including pain processing) and top-down salience processing (including pain anticipation). I then, review some studies on mindfulness-based pain regulation to date, showing that mindfulness meditation has been associated with altered anterior insula processing during the anticipation and experience of pain. I then proceed to outlining some of the aims and hypotheses of this work.

2.1 Pain processing in the human nervous system

2.1.1. Nociceptors

The body's ability to detect harmful stimuli relies on a specialized part of the somatic sensory system that responds to potentially damaging mechanical, chemical and thermal stimuli (Purves, 2004). This process is initiated by nociceptors: primary sensory neurons that have their cell bodies located in the dorsal root ganglion (or the trigeminal ganglion for the face) and project one axon peripherally to their target organ and the other centrally to the dorsal horn of the spinal cord (or the brainstem for the face) (Basbaum et al. 2009; Purves, 2004).

Nociceptors are present in all tissues of the body except the central nervous system, but especially the skin is densely innervated. Two major classes of nociceptors exist. The first class includes medium diameter myelinated A δ -fibers that possess relatively rapid conducting velocities (5-30 m/s). These fibers mediate so called 'first' pain: the acute phase of the pain response that is brief, sharp and well-localized. The second class includes small diameter unmyelinated C-fibers that possess much lower conducting velocities (0.4–1.4 m/s). These fibers mediate so called 'second' pain that is longer-lasting, dull and less well-localized (Basbaum et al., 2009). The different classes of nociceptive fibers also exhibit different response properties. A δ -fibers generally respond either to dangerously intense mechanical or mechanothermal stimuli. Specifically, so called Type I A δ -fibers are mechanosensitive but have high pain thresholds (>50° C), whereas type II A δ -fibers have much lower heat thresholds (>43° C) but very high mechanical thresholds. By contrast, most C-fibers respond to mechanical, thermal and chemical noxious stimuli and are therefore said to be polymodal (Basbaum, 2009; Purves, 2004).

2.1.2. Integration in the spinal cord

When activated, nociceptors send an afferent volley to the dorsal horn of the spinal cord where they terminate on second-order spinal neurons (Basbaum et al, 2009). The dorsal horn is a major site for integration of primary sensory input and descending supraspinal modulation (Peirs and Seal, 2012). Pain processing in the dorsal horn is incredibly complex and a vast area of research is dedicated to understanding how primary sensory afferents and their interactions in the dorsal horn contribute to clinically relevant pain disorders. Hence, a full review of this topic is well beyond the scope of the present thesis (see Julius and Basbaum 2001 & Craig 2003a for reviews). Notwithstanding this complexity, a few key organizing principles can be noted.

As displayed in figure 1, the dorsal horn is organized in a precise laminar manner and different classes of nociceptors tend to target spinal neurons in different laminae (Basbaum et al., 2009). Specifically, anatomical evidence indicates that A δ -fibers primarily project to superficial lamina I and lamina V deeper in the dorsal horn, C-fibers generally project to superficial laminae I and II, and A β -fibers -which process innocuous sensory information- primarily terminate in deep laminae III, IV, and V (Basbaum et al., 2009). Accordingly, electrophysiological studies show that spinal cord neurons within lamina I and II primarily respond to noxious stimulation (via A δ - and C-fibers), whereas neurons in lamina III, IV and V are more responsive to sensory touch (Peirs and Seal, 2016). In addition, spinal projection neurons in lamina V generally have large receptive fields (allowing for the convergence of multiple inputs) (Craig 2003a). These types of neurons are called wide-dynamic-range (WDR) neurons because they respond to a broad range of stimulus intensities (Basbaum et al., 2009). In contrast, most projection neurons in lamina I have small receptive fields and form monosynaptic connections with primary sensory afferents (Craig, 2003). Neurons of this type are called nociceptive-specific (NS).

The precise role of these different types of neurons is still elusive. However, WDR-neurons are likely integral to intensity coding functions and NS-neurons to encoding precise somatotopic information. Accordingly, it has been suggested that different types of pain emerge as a function of the integration of multiple types of second-order neurons, i.e. from the combined characteristics (or population coding) of NS and WDR neurons (as well as other neurons) (Price, Greenspan and Dubner 2003), although this notion is still subject to debate (see Craig 2003ab; Wercberger & Basbaum, 2019). Regardless of the exact contributions of the respective neurons, projection neurons from lamina I and V constitute the major output from the dorsal horn to the brain (Basbaum et al. 2009), as will be further discussed in the next section.

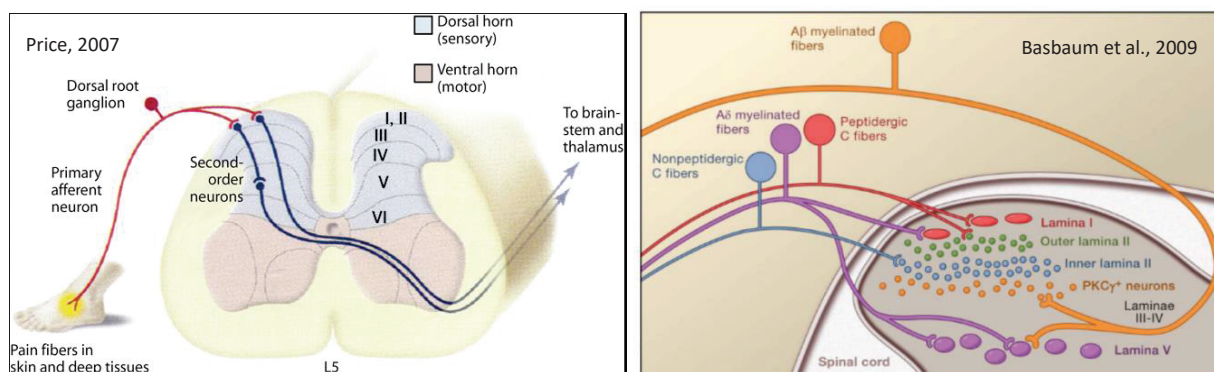


Figure 1. (Left) First-order nociceptive neurons project from the periphery to superficial (I-II) and deep (V-VI) laminae. **(Right)** The dorsal horn is organized in a precise laminar manner and different classes of nociceptors target spinal neurons in different laminae.

2.1.3 Ascending pathways of the spinal cord

From the dorsal horn of the spinal cord, several afferent bundles convey nociceptive information to distinct supraspinal sites. The majority of these tracts pass through the thalamus, which constitutes a major relay station for nociceptive input to the rest of the brain. Additionally, several tracts target limbic areas directly. The main nociceptive tracts and their supraspinal targets will be briefly described below.

The spinothalamic tract (STT): constitutes the major ascending pathway for information about temperature and pain. Originating mainly from lamina I and V of the dorsal horn, axons from second-order neurons in this pathway first decussate the spinal cord through the anterior white commissure, before ascending along the spinal cord in the ventrolateral funiculus, through the brainstem, to several thalamic target sites (Almeida, 2004).

- A component of this pathway, the neospinothalamic pathway, directly projects to lateral thalamic nuclei, which include the ventroposterior lateral (VPL), medial (VPM) and inferior (VPI) thalamic nuclei (Almeida, 2004; Lenz, 2010). Neurons in this pathway are primarily nociceptive-specific and convey precise topographic information to projection sites (Lenz, 2010). These include the primary somatosensory cortex (S1) in the parietal lobe and the secondary somatosensory cortex (S2) in the parietal operculum, which are involved in the sensory-discriminative aspects of pain processing (i.e. in encoding information about the intensity, location, quality and duration of pain).
- Another component of the STT, originates from lamina I of the dorsal horn and projects to a thalamocortical relay nucleus in the posterolateral thalamus — the posterior part of the ventromedial nucleus, or VMpo, which in turn projects to a specific site in the dorsal posterior insula (Craig 2002). This pathway has been the subject of considerable controversy as some authors have disputed its very existence, whereas others consider it a key interoceptive pathway (and the posterior insula as key interoceptive cortex) that conveys an internal representation of the physiological status of the body

(based on observations that this pathway is consistently activated by a range of visceral sensations including pain, among others).

- A third component of the STT projects to specific medial intralaminar thalamic nuclei (the central lateral nucleus (CL), medial dorsal nucleus (MDvc) and the parafascicular nucleus (Pf)), and then on to several limbic and cortical regions including the striatum, area 24 of the anterior cingulate cortex (ACC) and prefrontal cortex (Lenz, 2010). This pathway is not somatotopically organized and contributes to the affective-motivational aspects of pain processing (i.e. pain aversiveness and escape and avoidance behaviors), in part through coordinated activity with other limbic areas (see below).

Other nociceptive tracts

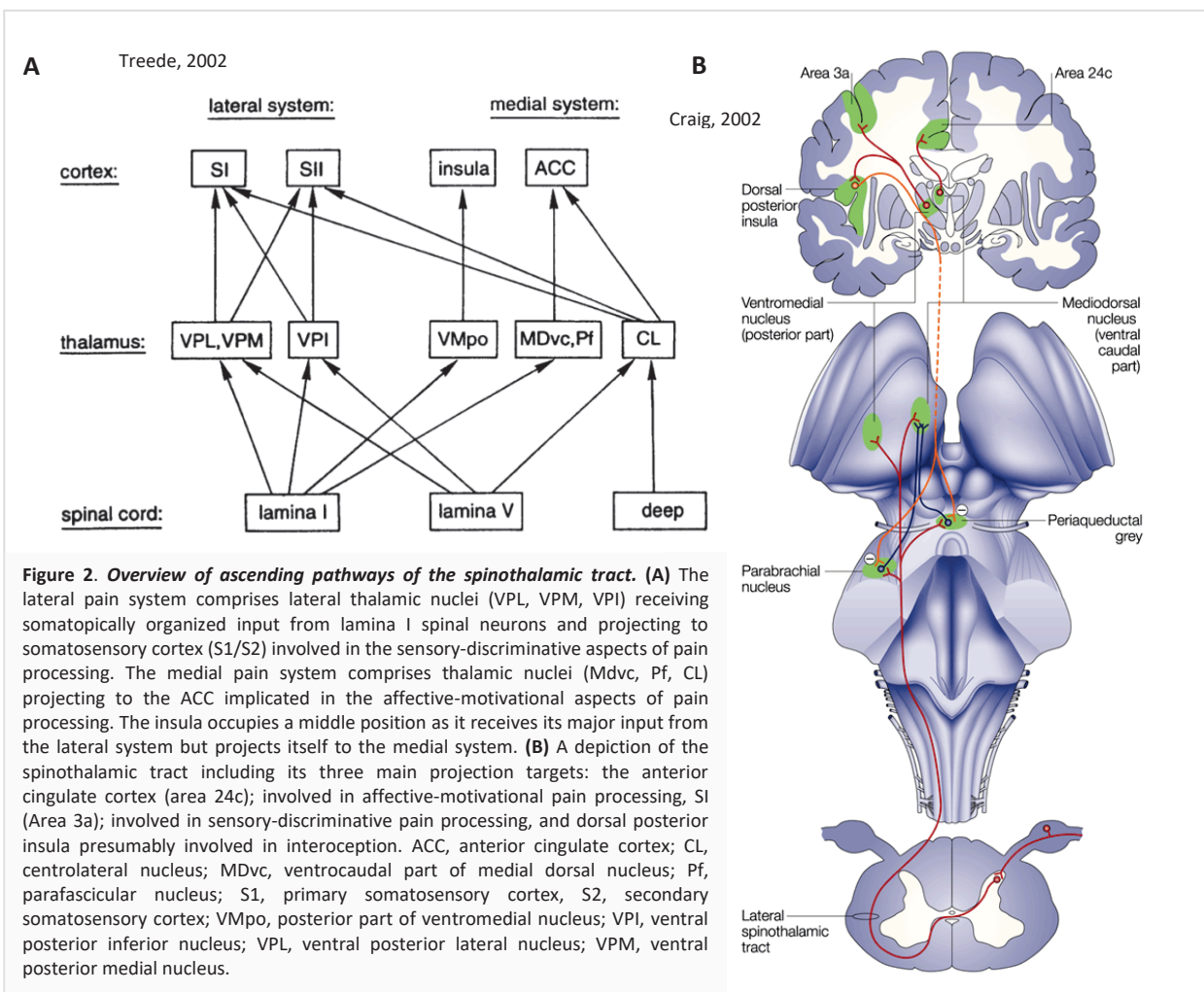
The spinoreticular tract: originates mainly from lamina V, VII and VIII of the dorsal horn. This tract largely parallels the spinothalamic tract, except that it passes through the reticular formation of the brainstem before ascending to medial thalamic nuclei. Its projections to the reticular formation are thought to contribute to motor control, neurovegetative functions and descending pain inhibition, whereas its projections to the medial thalamic nuclei are implicated in the affective-motivational components of pain processing. However, the extent to which the spinoreticular tract contributes to the latter remains unclear as its thalamic projections are relatively sparse (Almeida, 2004).

The spinomesencephalic tract: originates mainly in laminae I, II, IV, V, VI of the dorsal horn. Its main projection site is the periaqueductal gray (PAG) of the midbrain. The PAG plays a central role in the descending control of pain activity and spinomesencephalic projections likely contribute to this function (Basbaum, 2009). Stimulation studies also suggest a role for this tract in autonomic, cardiovascular, and motivational-affective responses related to pain (Almeida, 2004).

The spinobrachial and spinohypothalamic tract: are both extrathalamic tracts with direct projections to their target sites. Both tracts first project to the parabrachial nucleus (PN). From there, the spinoparabrachial-amygdaloid tract projects to the amygdala and the spinoparabrachial-hypothalamic tract to the ventromedial nucleus of the hypothalamus. These projections are thought to contribute to the neuroendocrine, autonomic, motivational and affective regulation of pain (Almeida, 2004).

Medial and lateral pain system

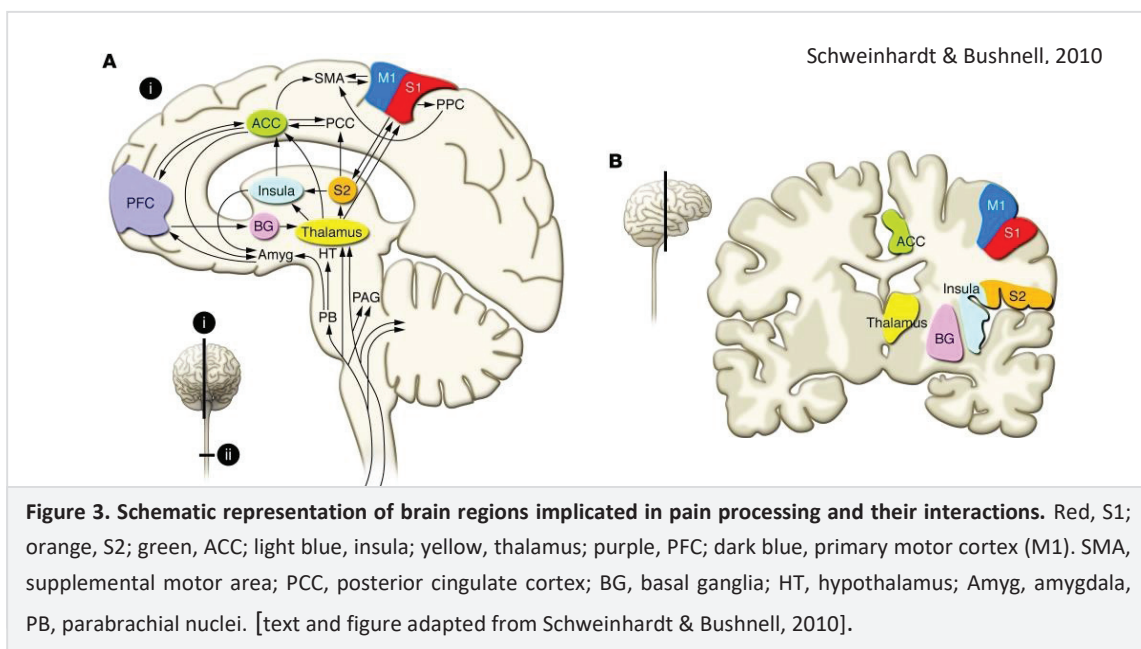
Based on the above described thalamic projections, the nociceptive system is commonly divided into a lateral and medial pain system according to the thalamic nuclei involved (see Figure 2). The lateral system involves the lateral thalamic nuclei (VPL, VPM, VPI) and their main cortical projection sites: the primary and secondary somatosensory cortex (S1 and S2 respectively), thought to be involved in the sensory-discriminative aspects of pain processing. The medial system includes the medial thalamic nuclei (CL, MDvc, Pf) and their main cortical projection site: the anterior cingulate cortex (ACC), thought to be involved in the affective-motivational aspects of pain processing. The insula occupies a middle position in this classification as it receives its major input from the lateral system, but projects itself to the medial system. Thus, the sensory-discriminative and affective motivational aspects of pain processing seem to depend on partly dissociable neural substrates. However, it should be emphasized that the division of the nociceptive system in a lateral and medial system is an oversimplification as the lateral system can for example influence affective-motivational functions through several pathways. Nevertheless, the distinction is considered useful and valid (Treede et al., 2002).



2.1.4 The cortical integration of pain

The pain matrix

The advent of neuroimaging (employing techniques such as functional magnetic resonance imaging (fMRI); measuring changes in blood oxygenation, and positron emission topography (PET); measuring changes in cerebral blood flow; both presumably reflecting underlying changes in neural activity) has revealed that nociceptive processing activates a large-scale distributed brain network, consistent with the complex and multidimensional nature of pain (Tracy and Mantyh, 2007; Garcia-Larrea and Peyron, 2013). Brain structures activated by painful stimuli are commonly referred to as the “pain matrix”: a concept derived from the notion of the “neuromatrix” put forward by Ronald Melzack, who proposed that the physical self or the feeling of the “body self” is produced by the distributed activity of neurons, each experience, including pain, being associated with a different output pattern or “neurosignature” (Melzack, 1989; 2001). Consistent with the idea of the neuromatrix, pain is not associated with a fixed pattern of brain activation. Rather, pain results from activity that is dependent on the complex interplay between physical, emotional and cognitive factors influencing pain perception. Cortical and subcortical regions commonly activated by nociceptive stimulation are displayed in Figure 3, and include the ACC, insular cortex, S1 and S2 (all primary recipients of nociceptive information; see previous section), as well as frontal and prefrontal cortices, thalamus, basal ganglia, cerebellum, amygdala, hippocampus, and regions within the parietal and temporal cortices (Tracey, 2005; see meta-analyses by Peyron et al., 2000; Apkarian et al., 2005). Some of these regions, including the ACC, insular cortex, and S2, are more commonly activated than others during painful stimulation (Duerden and Albanese, 2013; Jensen et al., 2016), and are therefore commonly taken to represent the core of the pain matrix and as indicating nociceptive processing is sufficient for the generation of a pain percept (which critically depends on the involvement of other areas, see below) (Tracey, 2005).



Sensory-discriminative and affective-motivational processing

A classical distinction, already briefly touched upon above, is that between a lateral sensory-discriminative system and a medial affective-motivational system. Specifically, while the activity of most regions constituting the core pain matrix typically correlates with both objective stimulus temperature and perceived pain intensity (Coghill et al., 1999, 2001, 2003; Wager et al., 2013; see further below), sensory-discriminative pain processing is commonly considered to be restricted to the posterior insula (pINS) and S1, S2 (Bushnell, 1999; Hofbauer et al., 2001; Timmerman et al., 2001; Maihöfner et al., 2006; Mazolla et al., 2012). Noxious stimulation consistently activates localized regions situated at the upper bank of the lateral sulcus (sylvian fissure), including portions of the S2 and pINS (Treede 2000). As distinguishing these regions with fMRI is challenging, they are collectively referred to as the operculo-insular cortex (Mazolla, 2012). While activation of the operculo-insular cortex is not unique to nociception and is also commonly observed with other somatosensory stimulation (consistent with the idea of its role as an interoceptive cortex, see below) (Treede 2000; Garcia-Larrea, 2012; Mazolla, 2012), pain stimulation is associated with stronger bilateral activation with activity being strongest on the contralateral side of stimulation (Mazolla, 2012). Furthermore, while noxious and innocuous stimuli activate overlapping regions in the operculo-insular cortex, pain stimulation has been shown to uniquely activate small sites at the contralateral posterior insula (I_g area) and anterior part of bilateral (OP 4) (Mazolla et al., 2012). Activation of S1 is less consistently observed, possibly due to larger interindividual anatomical variability and its activity being context-dependent (e.g. attentional/hypnotic modulations towards or away from pain sensations respectively increase or decrease S1 activity; Bushnell et al., 1999). In addition, noxious versus innocuous stimulation is known to increase functional connectivity between S1 and pINS (Peltz et al., 2011). Combined with observations that activity of pINS strongly correlates with objective stimulus intensity (Craig, 2000; Kong et al., 2006), and of somatotopic organization within these regions (Craig, 2003; Brooks et al., 2005), reviewed findings converge to suggest an important role of the operculo-insular cortex (pINS/S2) and S1 in sensory-discriminative aspect of pain processing.

The medial affective-motivational system, on the other hand, has been typically equated with the ACC (but see below), which receives coarse somatotopically unorganized nociceptive information (e.g. Vogt et al., 1993). Initial evidence for its role in the affective-motivational aspects of pain processing came from research in animals and humans. For instance, studies showing that cingulotomy in animals impaired aversive learning, and that cingulotomy in humans (for the alleviation of chronic pain) caused a reduction in pain affect but not in one's ability to appraise the sensory aspects of noxious stimuli (see Vogt et al., 1993). Other evidence for the involvement of the ACC in affective-motivational pain processing comes from functional neuroimaging studies. For instance, a hypnotic manipulation to selectively reduce the unpleasantness but not intensity of noxious stimuli specifically led to changes in ACC but not in sensory regions (Rainville, 1997). Yet more recently, an attempt has been made to synthesize findings of 939

neuroimaging studies including studies on pain and negative affect (i.e. fear, anger, disgust) (Shackman et al., 2011). Results of this large scale review and meta-analysis show that both pain and negative affect activate an overlapping region in the anterior midcingulate cortex (aMCC; (BA32/24). Other observations in support of the aMCC in the affective-motivational aspects of pain processing, are its robust connection to subcortical regions implicated in pain and negative affect (e.g. amygdala, nucleus accumbens), and it being situated directly next to the motor cortex with which it shares extensive connections, thus allowing the initiation of motivated behaviors, including pain-related avoidance (Shackman et al., 2011).

From nociception to pain

While the distinction between a sensory-discriminative and affective-motivational pain system is still valid to some degree, it is also limited. For example, it does not take into account the critical role of the anterior insula (aINS) in pain processing other than stating it occupies a middle position between the two systems. Furthermore, it does not explain how primary nociceptive information is translated to a conscious pain percept or how cognitive manipulations can affect pain experience. Finally, it does not account for the involvement of the aMCC in cognitive control, and attentional/evaluative functions important to pain, or observations that pain is better predicted when taking into account distributed activity in multiple brain regions.

To account for the countless nuances inherent to pain, Garcia-Larrea and Peyron, have conceptualized the pain matrix as a fluid system composed of several interacting networks, in line with the original concept of the neuromatrix (Garcia-Larrea and Peyron, 2013).

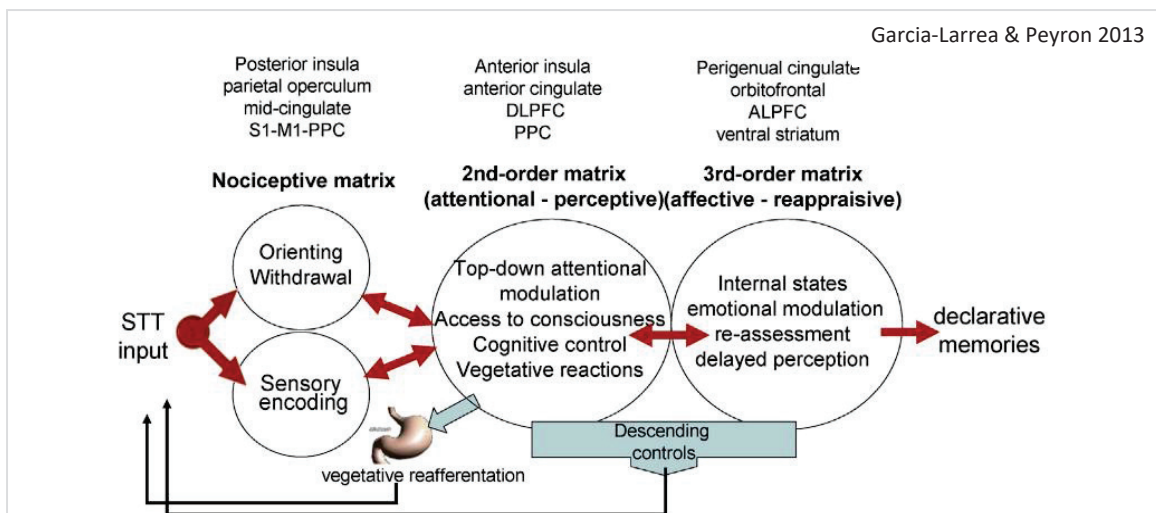


Figure 4. Schematic representation of the three interacting subnetworks underlying pain perception proposed by Garcia-Larrea and Peyron. A first-order nociceptive matrix is primarily involved in sensory encoding. A 2nd-order perceptual matrix underlies attentional/evaluative and modulatory aspects of pain and is involved in the transduction of sensory information to a conscious pain percept. A 3rd-order reappraisal matrix is largely composed of regions outside the classic pain matrix and is primarily involved in the emotional regulation of primary pain experience (reappraisal) [from Garcia-Larrea & Peyron, 2013].

Garcia-Larrea and Peyron distinguish a first-order nociceptive matrix that includes regions receiving primary afferents, including the aMCC, pINS and S1/S2. While the nociceptive matrix, and especially pINS and S1/S2 are responsible for the generation of sensory pain experience, they cannot by themselves generate a conscious pain experience. This requires association of the nociceptive matrix with a second-order perceptual network.

A second-order perceptual network comprises the mid and anterior insula, the aMCC and prefrontal and posterior parietal regions (Garcia-Larrea and Peyron, 2013). Particularly the mid and anterior insula participate almost consistently to pain. As will be discussed more extensively below, these integrative regions are crucial to interoception and in the conscious monitoring of internal body states (Craig et al., 2002; Critchley et al., 2004). The latter requires that the aINS, which receives sensory information from the pINS, engages with brain structures implicated in attention and cognitive control. These include the aMCC (in addition to its role in negative affect), and prefrontal and posterior parietal regions. Relationships between these regions are complex and context-dependent. However, broadly these brain structures are involved in sustaining attentional, evaluative and cognitive control processes (see Garcia-Larrea and Peyron, 2013 for a review). Specifically, the aMCC and aINS are part of a functionally coupled “salience network”, whose function is to detect behaviorally relevant stimuli from the internal and external environment to select them for further processing (Menon and Uddin, 2010). These regions can then recruit prefrontal and posterior parietal regions essential for declarative awareness and the generation of conscious pain percepts (see Garcia-Larrea and Bastuji 2018: Garcia-Larrea and Peyron, 2013 for reviews). This salience network also mediates top-down influences on low-level sensory processes (Garcia-Larrea and Peyron, 2013; Menon and Uddin, 2010). As the aMCC and aINS, as part of the salience network, integrate bottom-up and top-down processes and are involved in a wide-range of functions, their activity during pain varies enormously depending on contextual factors (Garcia-Larrea and Peyron, 2013). For this same reason, activity in a large part of the “pain matrix”, including the second-order perceptual matrix, is not specific to pain experience, but rather reflects general functions such as salience detection (including of stimuli from all sensory modalities) (Legrain et al., 2011).

Finally, Garcia-Larrea and Peyron, distinguish a third-order reappraisal matrix, which comprises several regions that fall outside the classic pain matrix and whose activity has been shown to exert a powerful influence on pain. This includes regions such as the perigenual cingulate, the orbitofrontal cortex, the temporal pole, and anterolateral prefrontal areas (Garcia-Larrea and Peyron, 2013), which have been implicated in affective regulation and contextual evaluation of stimuli (Roy et al., 2012; Rolls et al., 2008). As noted by Garcia-Larrea and Peyron, the pain-relieving effects of placebo, self-regulation of pain, and positive beliefs have been primarily associated with activity in those regions (see Wiech et al., 2008 for a review). Importantly, these regions, and particularly the ventromedial prefrontal cortex (perigenual cingulate, orbitofrontal cortex) (Roy et al., 2012), are heavily connected to regions implicated in the

descending control of pain (i.e. periaqueductal grey and brainstem), and can thus indirectly affect first- and second-order pain matrices through causing inhibition of ascending nociceptive information (Garcia-Larrea and Peyron, 2013; see Bushnell et al., 2013 for a review). Consistent with the original idea of the neuromatrix, the final pain percept is proposed to arise from the coordinated activity between these different matrices whose activity is subject to constant change (Garcia-Larrea and Peyron, 2013).

In line with the model proposed by Garcia-Larrea and Peyron, Wager and colleagues used a machine-learning approach to predict predicted perceived pain intensity in healthy participants (Wager et al., 2013). They identified a neurologic signature (pattern of activity across brain regions with positive and negative weights), comprising brain regions such as the thalamus, pINs, aINS, S2, mACC, which had a specificity of about 90% in discriminating painful heat from other salient and aversive events. Yet more recent findings show that the identified neurological pain signature (NPS) is largely specific for encoding nociceptive pain i.e., the pattern of activation and pain intensity produced by a noxious event (Woo et al., 2017). Note that the regions in the NPS largely correspond to the first-order nociceptive and second-order perceptual matrix proposed by Garcia-Larrea and Peyron, in line with the idea that association of these two matrices is necessary for the generation of a conscious pain percept. More recently, a second neurologic signature has been identified that predicts changes in pain experience independent from activity in the NPS. This second signature has been shown to mediate the effects of voluntary pain regulation and comprises the vmPFC and nucleus accumbens as core regions. Note that this is largely consistent with the third-order reappraisal matrix proposed by Garcia-Larrea and Peyron.

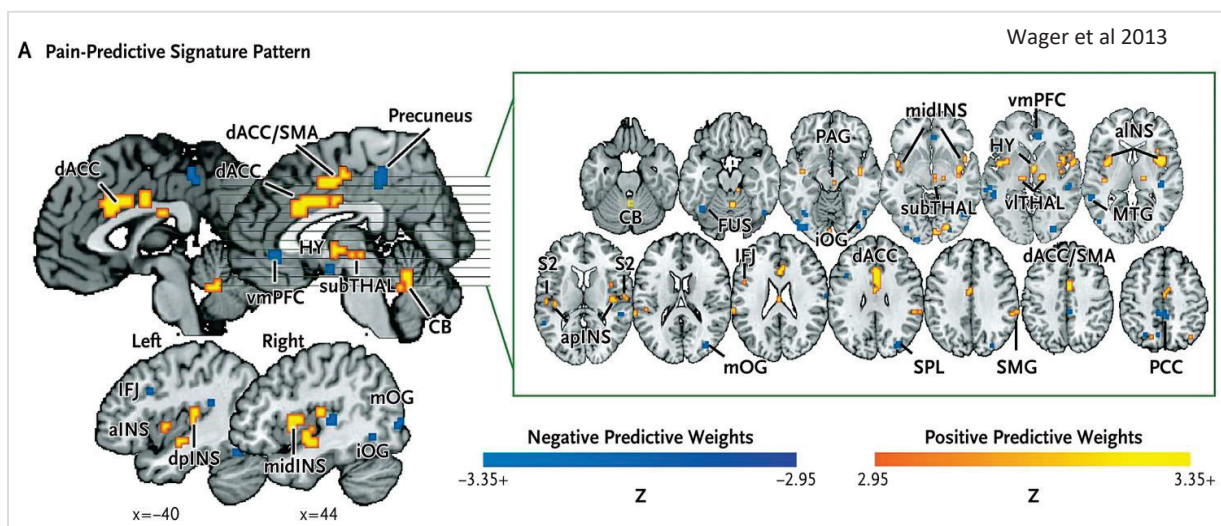


Figure 4. The neurological pain signature. The figure shows a signature map, consisting of a pattern of positive and negative weights that reliably predict pain. ACC denotes anterior cingulate cortex, CB cerebellum, FUS fusiform, HY hypothalamus, IFJ inferior frontal junction, INS insula, MTG middle temporal gyrus, OG occipital gyrus, PAG periaqueductal gray matter, PCC posterior cingulate cortex, PFC prefrontal cortex, S2 secondary somatosensory cortex, SMA supplementary motor area, SMG supramarginal gyrus, SPL superior parietal lobule, TG temporal gyrus, and THAL thalamus. [text and figure adapted from Wager et al., 2013]

2.1.5 The anterior insula: a critical salience network hub involved in current and predictive feeling states

In the previous section, I have discussed how the salience network, comprising the aINS and aMCC as core nodes, is crucial to the detection of bottom-up salient events, such as noxious events, and in providing access to working memory resources for further processing. However, the role of the salience network is not limited to bottom-up salience processing. Instead, ample evidence indicates that activity in the salience network can also be driven by top-down processing. This is for instance the case during pain anticipation. Importantly, such top-down processing in the salience network is known to influence subsequent pain perception. This dual role of the salience network, and especially of aINS, can be better understood when taking into account its integrative function as a critical interface between sensory, affective and cognitive structures. This section briefly reviews the role of aINS as a critical hub in the salience network and its importance to pain processing.

Structural and functional organization of the insular cortex

Functional connectivity analyses based on a clustering-approach have identified three functional subdivisions (see Figure 5A). A posterior region (yellow) primarily connected with pINS and somatosensory cortices; a dorsoanterior region functionally connected with aMCC and other regions in a previously described control network (CEN; see below); and a ventral anterior region, primarily connected with pregenual anterior cingulate cortex and other affective region (Deen et al., 2011). This finding has been replicated (Chang et al., 2013), and is also reflected in underlying structural connectivity (Nomi et al., 2016), and in large scale reverse-inference analyses showing that the pINS is mainly associated with somatomotor processing, the dorsoanterior insula with cognitive/attentional control, and the ventroanterior insula with emotive functions (Chang et al., 2013; Uddin et al., 2014). Importantly, in addition to this functional subdivision, some subregions in the aINS have been identified that show overlap in functions (see Figure 5B) (Uddin et al., 2014). These regions correspond with the salience network, in line with the function of this network as a critical integrative hub (see below).

The salience network

The brain is intrinsically organized into functionally coupled subnetworks with different functionality. The three main functional networks are the default mode network (DMN), including the vmPFC and posterior cingulate cortex (PCC), and implicated in self-referential processing (among other functions); the salience network (SN), including the aINS and aMCC as main nodes, and implicated in salience processing and switching between other networks; and the central executive network (CEN), including the dIPFC and posterior parietal cortex (PPC), and implicated in attentional and cognitive control functions (Menon and

Uddin, 2010). The SN occupies a central position between the DMN and CEN, and has been implicated in dynamically switching between the other two networks (whose activity alternates in rest) (see Figure 5C). The SN is unique in that it receives sensory and limbic information in the aINS (from pINS), which is continuously filtered for the detection of salient events. In case such an event (e.g. pain) is detected, the aINS triggers appropriate control signals for the adaptive regulation of behavior via the mACC (and CEN). In addition, to its role in bottom-up processing the aINS as part of the SN is also sensitive to top-down-influences such as during pain anticipation (see further below).

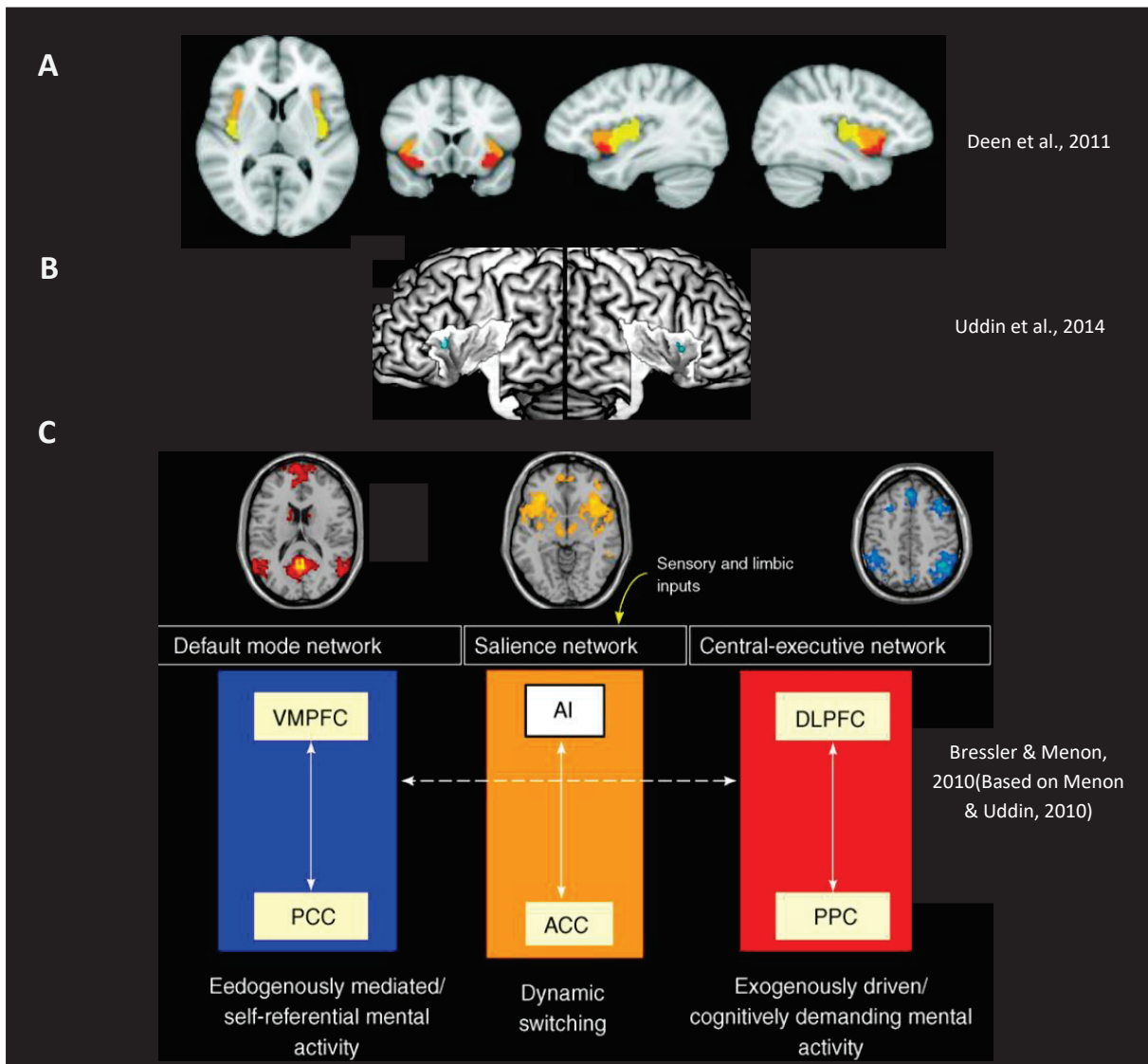
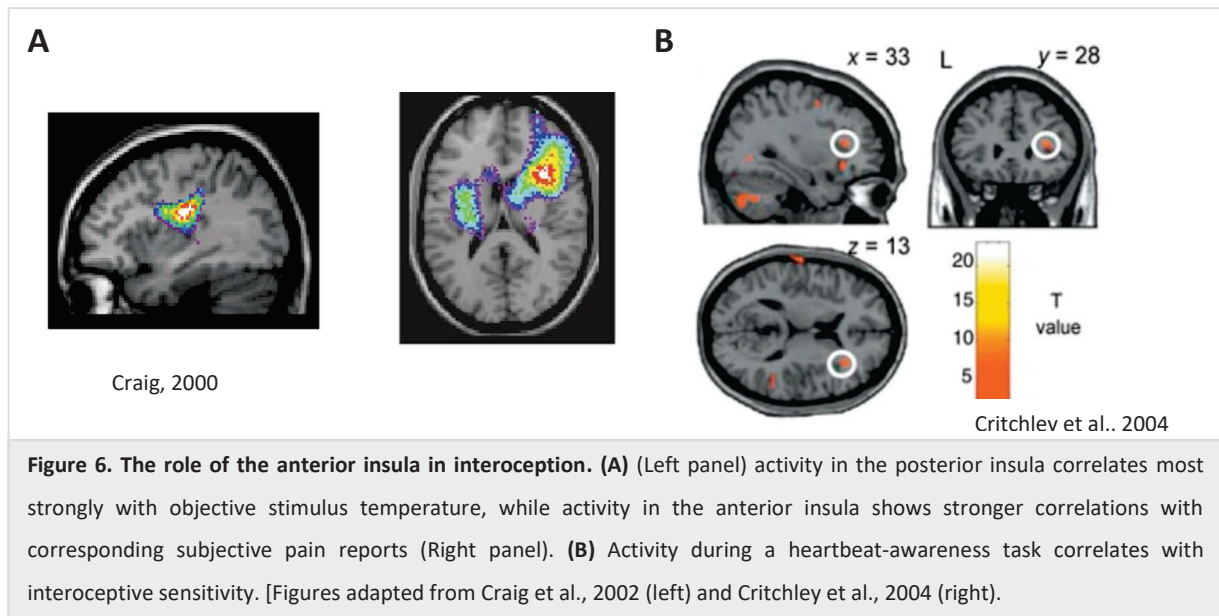


Figure 5. Insular subdivisions and the salience network. (A) The insula has three functional subdivisions: a posterior “somatomotor” insula (yellow), anteriordorsal “cognitive” insula and ventroanterior “affective” insula. (B) Some subregions in the anterior insula show overlap in functions and correspond to the salience network, (C) the salience network occupies a middle position between the default mode and central-executive network (see text) and is implicated in switching between these networks and in detecting salient events by virtue of its input of sensory and limbic information. vmPFC, ventromedial prefrontal cortex; PCC posterior cingulate cortex; AI, anterior insula; ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex.

The role of the anterior insula in bottom-up salience detection

The insular cortex (posterior to anterior) has been attributed a critical role in interoception i.e., sensing the internal state of the body. Specifically, it has been proposed that primary nociceptive information from the piNS is re-mapped in the aINS to give rise to a consciously accessible feeling state (Craig, 2002; 2009). This proposal is now strongly supported by the literature. Supporting its role in awareness of subjective feeling states, the aINS is consistently activated (with the aMCC) during emotions including, maternal and romantic love, anger, fear, sadness, happiness, sexual arousal, disgust and aversion and many others (see Craig, 2002 for an overview). Furthermore, whereas graded objective stimulus intensity of painful stimuli correlate strongly with activity in piNS, corresponding subjective pain reports correlate more strongly with activity in aINS (see Figure 6A) (Craig, 2000; Kong et al., 2006). Yet other studies indicate that activity in aINS correlates with interoceptive awareness of heartbeat (see Figure 6B) (Critchley et al., 2004). Another line of work provides additional insight into the function of the aINS. Specifically, the aINS has been found to respond strongly to novel and deviant stimuli (Crottaz-Herbette and Menon 2006; Downar et al. 2000, 2001; 2002). As such, the aINS has been attributed a critical role in the facilitation of detection of bottom-up salient events (Mennon and Udin, 2010). Importantly, in the context of pain, activity in the salience network –which is largely overlapping with the pain matrix- is taken to reflect such general salience processing, rather than specific pain-related activity (Legrain 2011). Collectively, these findings establish the aINS as key integrative hub of the salience network implicated in the bottom-up detection of salient events including noxious stimuli.

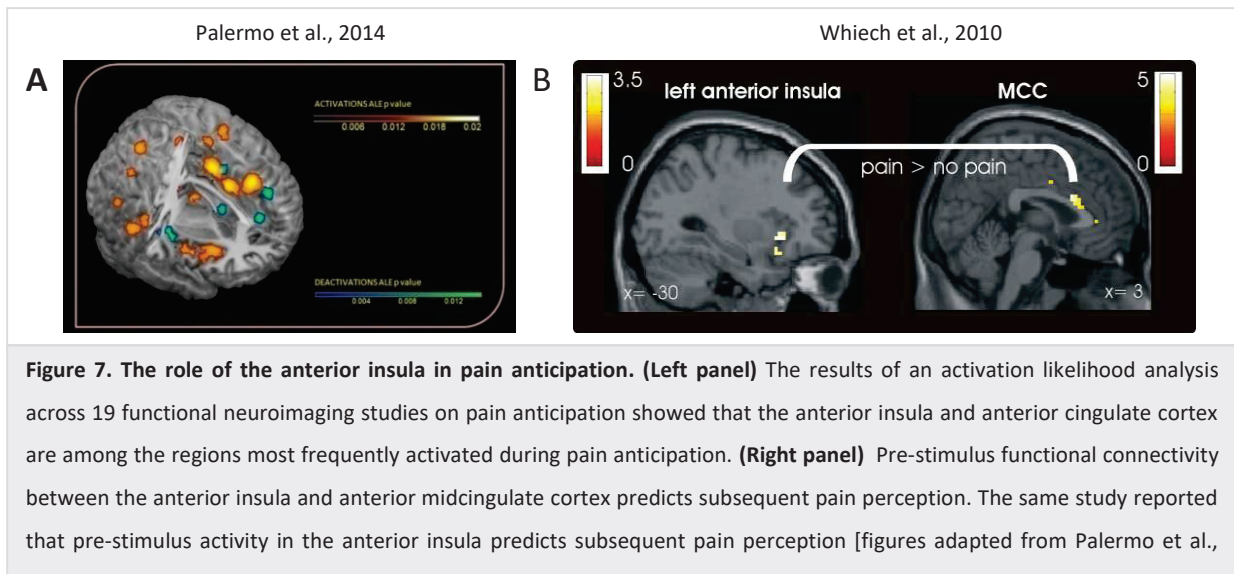


The role of the anterior insula in top-down salience processing

In addition to its role in bottom-up salience processing, ample evidence indicates that the AI additionally processes predictive feeling states, consistent with a role in top-down salience processing (Singer et al., 2009). For example, the aINS is commonly activated during pain anticipation (see Figure 7A) (Palermo et al., 2015), and anticipation of other aversive events (Sege et al., 2017). In the case of pain anticipation, the aINS frequently co-activates with the mACC and dorsolateral prefrontal cortex (dlPFC) (Palermo et al., 2015), and activity in these regions scales with the magnitude of expected pain (Koyama et al., 2005). It has been speculated that this pattern of activation represent the dlPFC (known to be able to generate representational knowledge; Arnsten, 2009) initiating a pain expectation, which then brings the aINS and aMCC, as part of the salience network, in a vigilant monitoring state to facilitate the detection of menacing events (Palermo et al., 2015).

Importantly, anticipatory activity, especially in regions of the salience network, can powerfully bias pain perception. Specifically, it has been shown that positive and negative expectancy respectively reduce and increase aINS activity (Whiech, 2008; Sarinopoulos et al., 2010; Atlas et al., 2010), and that this activity predicts subsequent pain reports (Atlas et al., 2010; Whiech et al., 2010). For example, Atlas and colleagues showed that low and high pain expectations for identical moderate pain stimuli, respectively decreased and increased pain reports, which was mediated by activity in aINS and aMCC (during pain), indicating a role for these regions in the integration of top-down predictions for a subsequent decision about pain (Atlas et al., 2010). This notion received further support by Whiech and colleagues, who showed that the classification of near-threshold pain stimuli as painful or non-painful was biased by threat-related information and was predicted by pre-stimulus activity in aINS, while threat-related bias was associated with pre-stimulus functional connectivity between aINS and aMCC (see Figure 7B) (Whiech et al., 2010). These findings mimicked that of another report which found that pre-stimulus activity in aINS predicted subsequent pain (Ploner et al., 2010), and were interpreted as suggesting that the aINS, as a critical hub salience network hub, integrates information about the significance of a stimulus in the decision about pain (Whiech et al., 2010). More recently, studies implementing predictive coding frameworks, demonstrated that pre-stimulus activity in aINS is best explained by a combination of actual pain intensity and expected pain intensity, while activity in pINS only represented pain intensity (Fazeli and Büchel, 2018; Geuter et al., 2017).

To summarize, a wealth of evidence across a variety of brain imaging studies and task domains indicates that the aINS (and aMCC) respond to the degree of subjective salience, whether cognitive, homeostatic or emotional (Mennon and Udin, 2010; Craig 2009; Craig 2002). Importantly, preliminary evidence indicates that mindfulness meditation impacts both bottom-up and top-down salience processing during the anticipation and reception of painful stimuli, as will be reviewed in the next section.



2.2 Neuroimaging studies on mindfulness-based pain regulation

The field of contemplative neuroscience is still relatively nascent. As such, only a handful of neuroimaging studies on mindfulness-based pain regulation are available. These studies have provided mixed results, possibly due to a diversity of styles and expertise in mindfulness meditation. Nevertheless, some commonalities can be distinguished especially when considering studies investigating mindfulness-based pain regulation as a function of mindfulness expertise. Below, I will briefly review the current state of the field on the basis of which I will detail some of the aims and scope of the present work

One of the first studies by Grant and Rainville compared a group of long term meditators practitioners in the Zen tradition (>1000 hours of practice) to meditation-naïve controls (Grant et al., 2011). They observed that experienced practitioners required significantly higher noxious stimulation to elicit moderate pain as compared to age-matched-controls (49.9 vs 47.9 °C). Compared to controls, long-term meditators, also reported reduced pain and exhibited a pattern of decoupling between primary pain processing regions (increased activity in insula, ACC, thalamus) and areas involved in executive, evaluative and emotive functions (decreased activity in prefrontal cortex, amygdala, hippocampus) (see Figure 1; lower panel). This pattern of decoupling (decreased dlPFC/ACC-connectivity) predicted higher pain tolerance in the Zen group. Additionally, experts but not novices showed dissociation between activity in the core pain matrix (insula, ACC) and subjective pain reports. Notably, this study involved no explicit meditation instruction, possibly indicating that experts' extensive meditation experience had induced a trait change in their capacity to regulate pain. The study authors suggested that the Zen practitioners were able to decouple the sensory-discriminative dimensions of pain from the cognitive-evaluative dimension allowing them to view painful stimuli more neutrally. The observed pattern of pain regulation in this study seemed markedly different from that of other known pain regulation strategies at the time (i.e. attentional distraction, placebo) that typically involve a decrease or no change in activity in

the core pain matrix and/or prefrontal regulation (Bushnell et al., 2013). A similar profile for mindfulness-based pain regulation has since been observed multiple times (see below).

A second study by Gard and colleagues examined the effect of a mindfulness instruction in experienced Vipassana practitioners ($M = 5979$; $SD = 5114$ hours of meditation practice) compared to meditation-naïve controls. They reported that a mindful state (akin to OM) specifically reduced pain unpleasantness but not pain intensity compared to a baseline condition. This decrease in unpleasantness was associated with reduced activity in lateral prefrontal cortex and increased activity in right pINS during stimulation (Gard et al., 2012). The authors interpreted this finding as suggesting that a mindful state is associated with decreased cognitive control during pain regulation. Nevertheless, slightly at odds with this interpretation, is that the authors also investigated pain anticipation and observed that a mindful state increased activity in the rostral ACC (rACC), a region frequently implicated in cognitive control (Shackman et al., 2011). Zeidan and colleagues investigated the effect of a brief mindfulness intervention in which meditation-naïve controls were trained to sustain focused attention on the breath (akin to FA) during 4 brief 20-minute sessions of formal meditation (Zeidan et al., 2011, 2015). Following the intervention, novices showed a marked reduction in pain intensity and unpleasantness ratings (potentially relating to the specific mindfulness technique employed, see section 1.8.2). The mindfulness instruction to focus attention on the breath during pain stimulation was associated with increased activity in insula and ACC (both compared to pre-intervention and rest) in novice meditators. However, in stark contrast to the earlier reviewed studies with expert meditators, novice meditators, showed clear reductions in activity in primary pain processing regions, including in SI and thalamus, but increased activity in regions implicated in appraisals and affect, including the orbitofrontal cortex (OFC); implicated in contextual evaluation (Rolls et al., 2008), and the rACC; implicated in the top-down regulation of negative affect and affective modulation of pain (Rainville, 2002) (see Figure 3; upper panel). The authors interpreted these findings as suggesting that mindfulness-based pain regulation recruits multiple neural mechanisms, which, at least in novices, includes descending pain inhibition (reduced activity sensory regions) and contextual reappraisal (OFC). However, given that this study employed a meditation instruction differed from that in other studies (investigating OM-styles of meditation, it remains an open question whether the observed results pertained to the FA-technique or the beginner level of expertise. Indeed, focusing attention on the breath during pain mimics attentional distraction, which has been linked to attentional gating mechanisms (Miron and Duncan 1989; Sprenger et al., 2012), as was observed in the studies by Zeidan and colleagues.

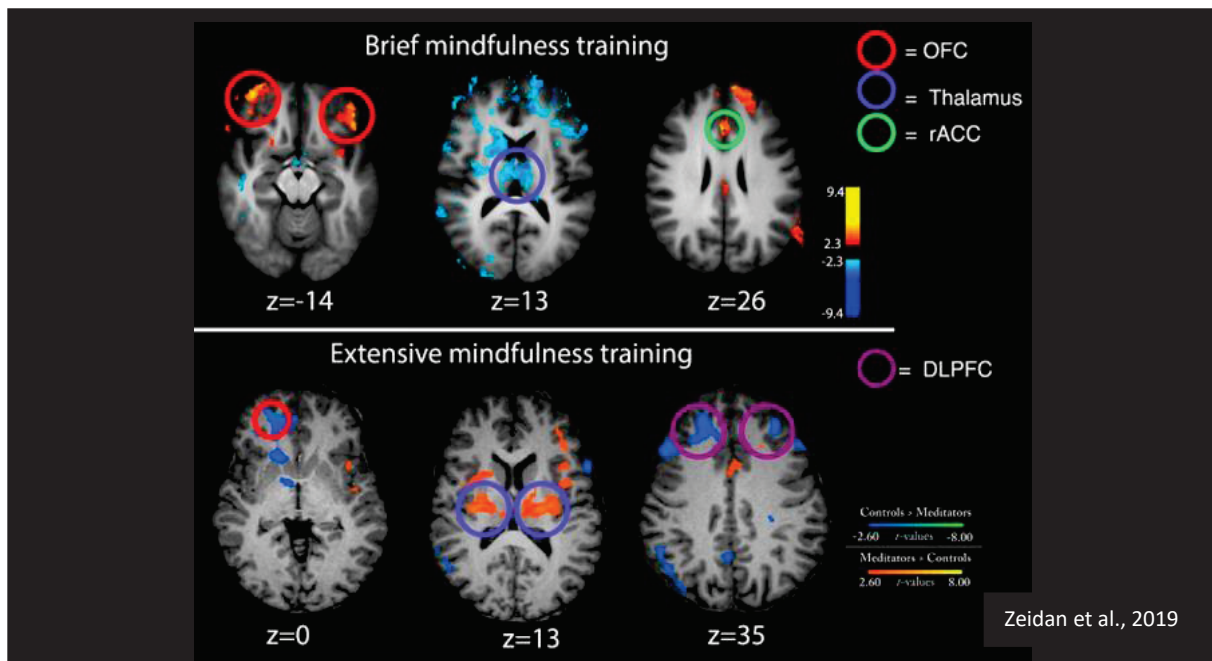
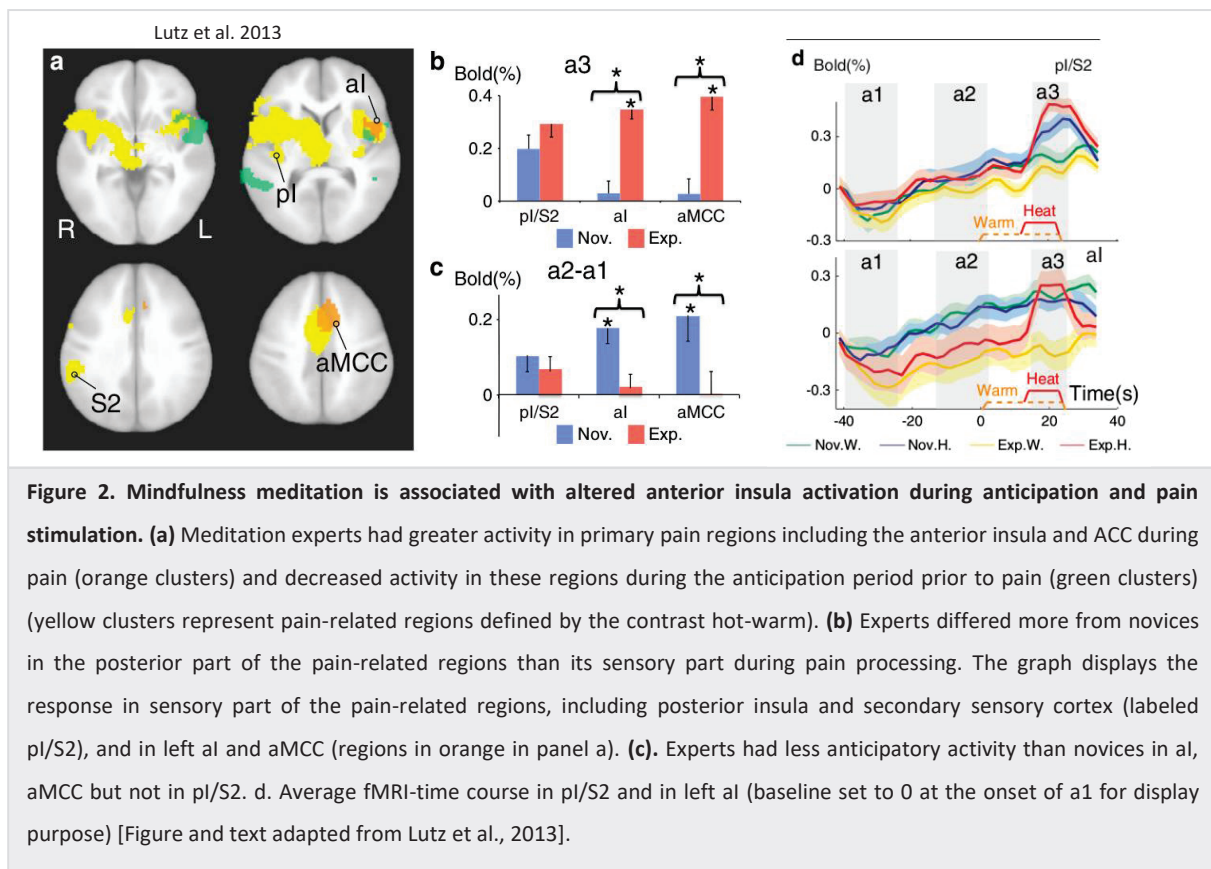


Figure 1. (Upper panel): Brief mindfulness training has been associated with higher mindfulness meditation-induced activation of the bilateral orbitofrontal cortex (OFC) and rostral anterior cingulate cortex (rACC), and with greater thalamic deactivation (Zeidan et al., 2011; 2015), **(Lower panel):** Extensive mindfulness training has been associated with significant decoupling, involving increased activity in primary pain processing regions including the thalamus and insula and reduced deactivation in brain structures processing appraisals and affect including the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (dlPFC) during noxious heat stimulation (Grant et al., 2011) [Figure and text adapted from Zeidan et al., 2019].

Finally, a study by Lutz and colleagues, of which the present work is a continuation, investigated the effect of OM mindfulness practice on the anticipation and appraisal of pain in experienced meditation practitioners in the Tibetan Buddhist tradition (mean 27,000 h, SD 12,500 hours of practice) as compared to controls (who had received written meditation instructions and practiced for 7 days at home). The experienced practitioners reported lower pain unpleasantness but not pain intensity as compared to controls while performing OM during pain stimulation. This pattern of pain reduction was associated with lower activity in left aINS and aMCC (i.e. the core nodes of the salience network) during pain, but decreased activity in these regions and the amygdala during pain anticipation (see Figure 2a-c); in line with another report of a meditation-related decrease in anticipatory brain activity using electroencephalography (EEG) (Brown et al., 2010) (but see Gard et al., 2012 reviewed above). For experts, reduced baseline activity in left aINS correlated with lifetime meditation experience. Furthermore, the pattern of low baseline activity coupled with high response in the aINS and aMCC during pain was associated with enhanced neural habituation in amygdala and pain-related regions before painful stimulation and in the pain-related regions during painful stimulation. Finally, similar to the study by Grant and colleagues (Grant et al., 2011), experts but not novices showed a dissociation between activity in the core pain matrix (aINS, aMCC) and subjective pain reports suggesting that the quality of attention to pain

was different for experts. The authors interpreted these findings as suggesting that ‘cultivating experiential openness down-regulates anticipatory representation of aversive events, and increases the recruitment of attentional resources during pain, which is associated with faster neural habituation. A potential caveat of this study was that it did not involve an explicit manipulation of pain anticipation. That is, participants were not informed about the temperature of the upcoming stimulation (nonpainful warm or painful hot). As such participants were likely to anticipate to the same degree during warm and hot baseline periods as is suggested by the plots of the fMRI-time course (see Figure 2d), which could have affected the pain contrasts (hot-warm) especially since groups showed differential baseline activity. Explicitly manipulating pain anticipation as we did it the present work can control this issue.



To summarize, neuroimaging studies on mindfulness-based pain regulation in experienced meditation practitioners to date have yielded relatively consistent results, whereas studies investigating mindfulness-based pain regulation in novice meditators have reported markedly different results, possibly the result of the specific FA-technique employed. The relative consistency across studies investigating mindfulness-based pain regulation in experienced practitioners is remarkable as meditation traditions and the amount of meditation expertise examined differed considerably between studies. Two of the three studies with expert meditators associated mindfulness-based pain regulation to increased activity in sensory regions as well as with a simultaneous decrease in prefrontal regions (Grant et al., 2011; Gard et al., 2012).

However, the most consistent finding across these studies (including the studies on novices by Zeidan et al.), is that mindfulness meditation is associated with increased activity in the aINS and aMCC, two core nodes of the salience network during pain (Grant et al., 2011; Gard et al., 2012; Zeidan et al., 2011, 2015; Lutz et al., 2013). Unlike as is typical, activity in these regions did not correlate with subjective pain reports for experienced practitioners (as opposed to novices) in two of the studies (Grant et al., 2011; Lutz et al., 2013). In addition to this more increased response in regions of the salience network during pain, one of the studies found that mindfulness meditation is associated with decreased activity in regions of the salience network (AI, ACC) during pain anticipation, with one other study linking mindfulness-based meditation to decrease anticipatory brain activity (Brown et al., 2010; but see Gard et al., 2012).

Collectively, the above studies suggest that the chronometry of the aINS is a sensitive marker of present-centeredness (increased activation during pain) vs mental projection in the future (increased activation during pain anticipation). This, pattern may be explained by taking into account the dual function of the aINS, in processing both current feeling states (i.e. increased attention to bottom-up salient stimuli at pain onset) and predictive feeling states (i.e. decreased top-down salience) during pain anticipation. Furthermore, if increased aINS activity with meditation during early pain indeed reflects increased attention to bottom-up salience, then one could expect that aINS activity during the late phase of tonic-like pain stimuli would be more reflective of top-down factors such as pain rumination and aversion to pain, as bottom-up salience processing is usually limited to unexpected or novel events (Corbetta et al., 2008, Corbetta and Shulman, 2002). Studies suggest that aINS responds with sustained salience to pain (Downar et al, 2003). However, it is unclear whether this response can be modulated by contextual factors, although preliminary evidence indicates that this might indeed be the case. Specifically, Wager and colleagues examined the effect of a placebo manipulation on the temporal processing of pain, and found that the expectation of lower pain was associated with a faster recovery of aINS-activity to baseline during the late phase of pain stimulation (Wager et al, 2004). To our knowledge, no studies to date have examined the impact of mindfulness meditation on this process.

Finally, given that mindfulness meditation and pain catastrophizing can be construed as opposite processes (see section 1.8.3), we aimed to additionally examine the impact of pain catastrophizing on the chronometry of the AI.

2.3 Summary and aims

In this chapter I described how nociception gives rise to a conscious pain percept in the brain. I particularly zoomed in on the role of the aINS, as part of the salience network, in both bottom-up and top-down salience processing during the reception and anticipation of painful stimuli respectively. I reviewed studies on mindfulness-based pain regulation to show that preliminary evidence suggests that mindfulness meditation is associated with altered anterior insula activation during the anticipation

(decreased activity) and experience (increased activity) of painful stimuli. These findings suggest that the chronometry of the aINS is a sensitive marker of present-centeredness (increased activation during pain) vs mental projection in the future (increased activation during pain anticipation). One of the aims of the present work was to examine this hypothesis, and to explore its relation to mindfulness meditation, pain catastrophizing and sensory-affective uncoupling of pain.

Aims and hypotheses

3.1 General aims and hypotheses

The general aim of the present thesis was to study the cognitive and neuronal mechanisms underlying the pain-regulatory qualities of mindfulness meditation. Our core hypothesis was that the specific meta-cognitive stance, labeled cognitive defusion (which includes the subprocesses of meta-awareness and dereification important for monitoring and control of the mind), underlies sensory-affective uncoupling of pain in meditation, by opposing pain catastrophizing-related processes (see Figure 1).

Mindfulness practices aim to deliberately cultivate meta-awareness and dereification thus promoting cognitive defusion. Accordingly, we expected that the degree of sensory-affective of pain would be a function of a mindfulness instruction (state) and expertise (trait) (see Figure 2). More specifically, we expected that experts would be higher in trait cognitive defusion (and lower in pain catastrophizing) as compared to novices, resulting in higher trait sensory-affective uncoupling of pain. In addition to this trait effect, we expected that an OM instruction would induce a state increase in cognitive defusion as compared to a distraction control condition (where meta-awareness and dereification and thus cognitive defusion would be allocated away from pain, leaving pain catastrophizing-related processes relatively unchecked). Furthermore, we expected this state effect to be larger for experts compared to novices due to their expertise in OM (in the form of OP). Note that while we focused on the role of cognitive defusion in these predictions, we expected cognitive defusion and pain catastrophizing to be antithetical processes exhibiting an inverse relationship to each other and sensory-affective uncoupling of pain, making it possible to substitute cognitive defusion on the x-axis of Figure 2 by pain catastrophizing with an opposite sign.

In study 1, we tested the above predictions on the modulatory effects on meditation state and expertise on sensory-affective uncoupling of subjective pain experience. We also tested the predictions that trait pain catastrophizing would be lower for experts compared to novices and that trait pain catastrophizing would negatively predict the degree of sensory-affective uncoupling of pain experience.

In study 2, we tested the prediction that trait cognitive defusion would be inversely correlated to trait pain catastrophizing and examined the respective relationship of both constructs to sensory-affective uncoupling of pain experience, while also phenomenally exploring cognitive defusion.

In study 3, we tested the above predictions on the modulatory effects of meditation state and expertise on putative neuronal markers of sensory-affective uncoupling of pain (i.e. the chronometry of the anterior

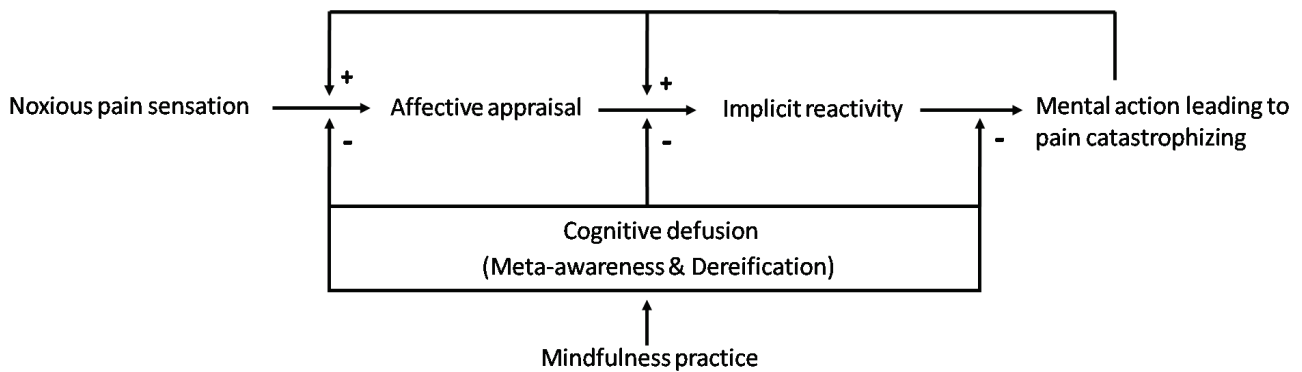


Figure 1. Schematic illustration of the core hypothesis. Shown is a typical pain response that involves a noxious stimulus and accompanying cognitive-affective appraisals. Pain catastrophizing is an exaggerated mental set that builds on implicit reactivity and feeds back to amplify cognitive-affective pain processing, thereby strengthening sensory-affective coupling of pain. Conversely, mindfulness practice aims to deliberately cultivate cognitive defusion (which includes the subprocesses of meta-awareness and dereification) involving a detached observation of the contents of experience, allowing distressing thoughts/feelings to be seen as mere mental events instead of as accurate reflections of reality that need to be reacted upon. This may reduce secondary elaborative processing and result in sensory-affective uncoupling of pain.

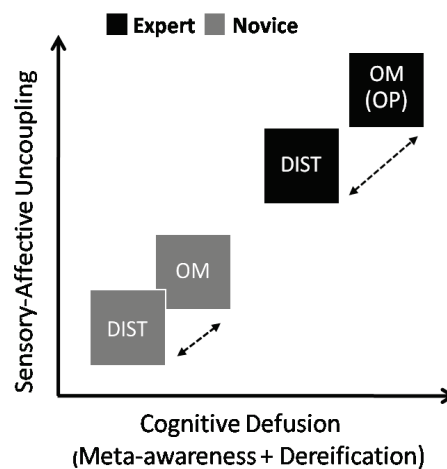


Figure 2. Schematic illustration of some of the general hypotheses. Expected relationships of both task conditions (OM, Dist) and meditation expertise (Expert, Novice) to cognitive defusion (x-axis) and sensory-affective uncoupling of pain (y-axis). Note that it is possible to substitute cognitive defusion on the x-axis by pain catastrophizing with an opposite sign. Dist: Distraction, OM: Open Monitoring, OP: Open Presence.

3.2 Hypotheses for Study 1

In Study 1 we aimed to replicate previous results on sensory-affective uncoupling of pain experience during OM in experienced meditators (experts) (Perlman et al., 2010). We also aimed to extend and further substantiate these findings by: 1) examining whether novices who underwent formal meditation training would show a pattern of sensory-affective uncoupling of pain experience during OM similar to what has been observed before in experts (Perlman et al., 2010), 2) implementing long painful stimuli which have been suggested to better mimic chronic pain states (Racine et al., 2012), and 3) examining the role of trait pain catastrophizing in sensory-affective uncoupling of pain experience in the context of mindfulness meditation.

We expected that long painful stimuli in particular would exacerbate pain catastrophizing-related processes, which would be counteracted by meditation state and expertise. In line with the cognitive attitude cultivated by mindfulness meditation, we expected this regulation to be mainly reflected in a reduction in pain unpleasantness as opposed to pain intensity. Our specific hypotheses were the following:

- Experts would rate painful stimuli as overall less unpleasant but equally intense compared to novices (trait effect).
- A mindfulness instruction would reduce pain unpleasantness but not pain intensity compared to attentional distraction (state effect); and to a larger degree for long compared to short painful stimuli and for experts compared to novices (interaction effect).
- Experts would be more resilient to pain amplification by long painful stimuli than novices as reflected in a lower increase in pain unpleasantness but not pain intensity between short and long painful stimuli and larger sensory-affective uncoupling for long painful stimuli in particular (trait effect).
- Experts would be lower in trait pain catastrophizing compared to novices which would be able to explain the above two effects related to pain amplification.

3.3 Hypotheses for Study 2

The overarching aim of Study 2 was to investigate the role of cognitive defusion in mindfulness-based pain regulation. A first aim was to examine interrelations between cognitive defusion and pain catastrophizing while controlling for variance shared with several other mindfulness-related and more general cognitive-emotional constructs. A second aim was to investigate the respective relationship of cognitive defusion and pain catastrophizing to pain experience.

- Given the strong theoretical foundation for cognitive (de)fusion as a primary construct at the root of pain catastrophizing, cognitive defusion would be specifically and uniquely correlated to pain catastrophizing, even when controlling for variance shared with other mindfulness-related and more general cognitive-emotional constructs such as anxiety, worry and depression.
- Cognitive defusion and pain catastrophizing would both primarily predict pain unpleasantness as opposed to pain intensity, but in opposite direction: negatively and positively respectively.

Parts of this study were more explorative and involved no specific hypotheses including:

- An examination of the respective relationship of cognitive defusion and pain catastrophizing to pain self-reports (i.e. the unique predictive value of both constructs with regard to pain reports while controlling for shared variance).

3.4 Hypotheses for study 3

In Study 3, we aimed to replicate previous findings of experts showing decreased aINS activation during pain anticipation but increased activation during pain as compared to novices during OM, which was associated with a specific reduction in pain unpleasantness as opposed to in pain intensity (Lutz et al., 2013). This pattern displayed by experts could be explained by taking into account the dual function of aINS, in the processing of both current feeling states (i.e. increased attention to bottom-up salient stimuli at pain onset reflecting interoception) and predictive feeling states (i.e. decreased top-down salience during pain anticipation reflecting decreased anxious anticipation) (Singer et al., 2009). If increased aINS activity for experts during early pain indeed reflects increased attention to bottom-up salience, then one would expect that anterior insula activity during the late phase of tonic-like pain stimuli would be more reflective of top-down factors such as pain rumination and aversion to pain, as bottom-up salience processing is usually limited to unexpected or novel events (Corbetta et al., 2008, Corbetta and Shulman, 2002).

Based on the above considerations, our general hypothesis was that the chronometry of the anterior insula is a sensitive marker of present-centeredness vs top-down conceptual processing. One of the aims of the present work was to examine this hypothesis, and to explore its relation to mindfulness meditation, pain catastrophizing and sensory-affective uncoupling of pain.

Specifically, we hypothesized that:

- During pain anticipation, a mindfulness state and expertise would be associated with lower aINS and amygdala activation (including the interaction effect).
- During early pain, a mindfulness state and expertise would be associated with increased aINS activation (including the interaction effect).
- During late pain, a mindfulness state and expertise would be associated with decreased aINS activation (including the interaction effect).
- We additionally aimed to explore the hypothesis that decreased aINS activity during pain anticipation and during late pain could be linked to lower pain catastrophizing scores and increased sensory-affective uncoupling of pain (taking into account the balance between sensory (pINS/S2) and affective systems (aINS) during late pain).

General methods

Data in the present work are presented in the form of three different studies that all centered on the same pain paradigm which included an OM and Distraction condition. This experiment itself was part of a broader project that investigated the impact of mindfulness meditation on experiential, cognitive and affective processes in novice and expert meditators through several experimental paradigms. The three studies differed in measurements studied and subjects included. Specifically, in Study 1, we performed a detailed analysis of pain self-reports in relation to trait pain catastrophizing. Hence, we included all eligible subjects that participated to the pain paradigm. In Study 2, the main focus was on investigating interrelations between trait cognitive defusion and pain catastrophizing. Hence, to increase power for this analysis, we included novices and experts that participated to the broader protocol but were excluded for the pain paradigm. Finally, Study 3 contained the sample as Study 1, except for subjects excluded due to MRI-related exclusion criteria (see Figure 1 for a schematic overview of methods implemented in each study).

This chapter is a general overview of some of the methods implemented in the present work. Specifically, I provide information on: 1) the selection and inclusion procedure for expert meditators, 2) the meditation training protocol for novice meditators, 3) the experimental paradigm including task conditions, 4) the main questionnaires implemented in the presented work, 5) the fMRI-method. Specific information on the data-preprocessing and analyses methods are provided in the methods sections of each of the studies.

Further information on inclusion procedures, paradigms and measurements of the larger protocol of which this work was part are provided in Annex I of this manuscript (“Brain & Mindfulness Project Manual”, available online at: <https://osf.io/dbwch/>)

	Study 1	Study 2	Study 3
Paradigm	Pain paradigm conducted in an fMRI-scanner		
Conditions	OM, Distraction		
Subjects	35 novices; 26 experts	43 novices; 27 experts	30 novices; 25 experts
Measures	self-reports, questionnaires	self-reports, questionnaires	MRI, self-reports, questionnaires

Figure 1. Overview of the studies included in the present work. All studies centered on the same pain paradigm conducted in an fMRI-scanner and included an OM and Distraction condition. Further information is provided on subjects and measurements included in each study.

4.1 Expert practitioners

In the past meditation studies have included mixed samples with meditators from different traditions and with widely varying practice experience; complicating the attribution of effects to specific practice styles and/or levels of expertise, as well as study replication (Davidson and Kaszniak, 2015). The present work aimed to avoid this pitfall by the inclusion of a qualitatively high and uniform group of expert practitioners, which we intended to achieve through the implementation of a rigorous selection procedure detailed here.

For the present work, we recruited long-term meditation practitioners within French and European Tibetan Buddhist communities that were trained in either the Nyingma school (Mahamudra) or the Karma Kagyu (Dzogchen) school or both. Importantly, these meditators belonged to the same meditation traditions as those in an earlier study that we wished to replicate (Perlman et al., 2010).

Eligible experts needed to have:

- a minimum of 10 000 hours of meditation practice
- followed at least one traditional 3 year meditation retreat
- sustained a daily practice of a minimum of 45 minutes over the past year

To ensure that all experts matched these criteria, experts were contacted by one of our team members who herself was an experienced practitioner in the meditation traditions under study. In this contact moment, it was also verified that experts were sufficiently familiar with the practice of OP and had the right motivation to participate. Experts' meditation experience was estimated based on detailed information on lifetime meditation retreats and (daily) practice acquired during this interview. The sample of experts included in Study 1 had an average lifetime meditation experience of 41357 hours (\pm 17999 SD; range: 13110-94535) (see Annex I for more detailed information regarding the selection procedure).

4.2 Novice meditation training protocol

A critical effort of the Brain & Mindfulness project was to refine the matching between the control group and expert practitioners. This was done primarily by training novices in different styles of meditation practice and by familiarizing them to different phenomenological dimensions of interest. Here I highlight only the main features of this novel training protocol that we exhaustively described in a separate publication (Abdoun et al., 2018; see Annex II including further information on the rationale, day program, practice metrics, as well as a verification of the claim that the experiential exercises helped novices to more accurately report on their meditation experience).

At the heart of the novice training protocol was a two-day meditation weekend that was designed to equip formerly meditation-naïve participants with a theoretical background and experiential knowledge of meditation that enabled them to share their experience with the experimenters. This was of crucial importance to the neurophenomenological approach implemented in the present work as it relied on the capacity for novices to reliably report on their experience, which involved having an adequate understanding of some of the probed phenomenological dimensions. Practically, this involved that, during the training, participants were introduced to various styles of meditation practices and acquainted with phenomenological categories through various experiential exercises that will be further described below.

4.2.1 Meditation practice

The training protocol was based on Joy of Living (Rinpoche & Swanson 2007; Tergar 2018), a secular meditation program aimed at Western audiences authored by Yongey Mingyur Rinpoche, a renowned master of Karma Kagyü and Nyingma schools of Tibetan Buddhism. This program was selected for its shared background with experts' training. The training was provided by a qualified instructor with thirteen years of practice under the guidance of Mingyur Rinpoche, and eight years of teaching experience with the Joy of Living program. The training included teachings with the support of instruction videos, guided meditations and experiential exercises, question and answer sessions, as well as sufficient time to reflect and share within the group. Introduced meditation styles included FA and OM (and compassion). After the meditation weekend, novices were invited to carry on their meditation practice for a minimum of 20 minutes a day, equally balancing between the different practices, and keeping track of their practice with a logbook, until they had finished all experiments in the larger protocol. As this required substantial motivation, novices were recruited for their interest to learn and their willingness to sustain a regular meditation practice for several months (see Annex I for detailed information on other inclusion procedures).

4.2.2 Experiential exercises

Throughout the training weekend, subjects were prompted to familiarize themselves with the dimensions of subjective experience of interest to the neuroscientific experiments. This familiarization was carried out through various experiential exercises; either in the context of guided meditation session and teachings or during specific exercises aimed at familiarizing subjects with a given phenomenological dimension. Exercises of particular relevance to the present work involved switching between Focused Attention on, and Open Monitoring of, pain, and experiential exercises on the phenomenological dimensions of Absorption and Meditative awareness and Openness. At the end of the weekend, novices received a

document that briefly described each phenomenological dimension and reminded them of how it was introduced by corresponding exercises during the weekend.

4.3 Experimental paradigm

To test the hypotheses presented in this work, we designed a novel fMRI-scanner acute pain paradigm specifically devised to amplify the cognitive-affective aspects of pain experience. Specifically, we implemented periods of pain anticipation and long tonic-like pain stimuli which have been suggested to better mimic chronic pain states (Racine et al., 2012). We additionally implemented shorter pain stimuli with the purpose of introducing uncertainty (about whether the stimulation would be short or long), as well as contextual relief (i.e. being informed that stimulation will end soon instead of lasting much longer), and potentially further distress (i.e. being informed that a stimulation will last much longer instead of ending soon). Finally, we collected, self-reports of pain intensity, unpleasantness and relief after stimulations. Each of these aspects of the experimental paradigm and their underlying rationales will be further discussed below. However, I will first provide a brief general description of the experimental design.

4.3.1 Brief description of experimental paradigm

The experimental design is presented in Figure 1. A fixation cross was displayed on the screen when no other visual stimuli were presented. Each trial started with a 5-8 sec introductory period. A 2 sec predictive cue then indicated whether the upcoming stimulation would be warm or hot and was followed by a 5 to 8 sec anticipatory period. A thermal stimulation was then delivered which was either hot, at the participant's painful temperature, or warm, at a non-painful temperature 6 degrees cooler. 3 to 6 sec after stimulus onset, a second cue indicated whether the stimulation would be short (8 sec, relief) or long (16 sec, non-relief). Warm stimuli were always long (16 sec) and served as a baseline control condition for the MRI. Five to eight seconds after the thermal stimulation ended, two rating scales were presented for 5 sec each (see rating scale section below). After 1 sec the next trial started. Baseline temperature for the thermode was 32°C. Ramp-up and ramp-down periods were 1.5 sec for the warm and 2.5 sec for hot stimuli. Temperature of the long hot stimuli dropped slightly by 1 ° C (0.5 ° C/sec) after 2 sec of stimulation (not depicted) as initial pilot sessions revealed they would otherwise be unbearable. Subjects received a total of 60 thermal stimuli; 20 short hot (SH), 20 long hot (LH) and 20 long warm (LW), applied to the palmar side of the left wrist. All thermal stimuli were delivered during one experimental session consisting of six blocks of ten trials each. Subjects rested 1.5 minute between the blocks. Each block was further subdivided into two subblocks, one for each state condition, in randomized order: Open Monitoring (OM) or a control addition task (Distraction). Each trial type (SH, LH, LW) was set to occur at least once during each subblock. Each subblock started with a 20 s auditory and visual state induction during which

participants received instructions for the experimental condition. For OM, participants were instructed to keep an open and accepting awareness (see methodsS1 for full instructions). Experts specifically were also told that the OM instructions referred to the practice of OP. For Distraction, subjects were instructed to mentally add simple single-digit numbers (1-3) that were presented on the center of the screen (replacing the fixation cross) from the start of each trial until rating scales were shown (see Fig. 1). Numbers were presented for 1 sec with a variable interval of 3, 4 or 5 sec between numbers. Subjects were asked to maintain a tight focus on the screen in order not to miss any numbers, while blocking all pain-related sensations, emotions and thoughts. In order to minimize visual differences between task conditions, numbers were also presented on the screen during OM. However, subjects were instructed to abstain from mental addition, but to nonetheless keep their gaze fixed at the screen at all times, in a relaxed manner, in order to not miss any visual cues. Prior to the experiment, participants were familiarized with the task and performed one full block of trials using non-painful stimuli only.

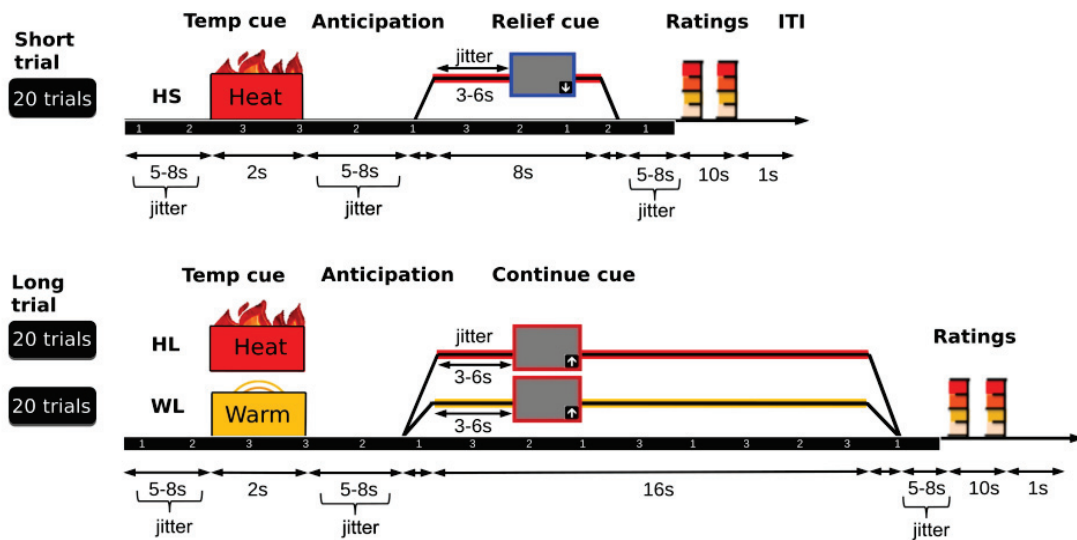


Figure 1. Schematic illustration of the experimental paradigm. Each trial started with a 5-8 sec introductory period. A 2 sec predictive cue then indicated the temperature of the upcoming stimulation (warm or hot) and was followed by a 5-8 sec anticipatory period. A thermal stimulation was then delivered that was either short (8 sec) or long (16 sec). After 3-6 sec of thermal stimulation, a second visual cue informed subjects about the duration of the stimulation. Non-painful warm stimuli were always long and served as baseline control for the fMRI. Following stimulus offset, a 5-8 sec rest period preceded the presentation of two rating scales (5 sec each). Rating scales probed pain intensity, unpleasantness, relief and task performance. During each trial, a single-digit number (1-3) was presented every 2 sec from the start of the trial until rating scales were shown (see black horizontal bars). Subjects randomly alternated between two task conditions: Distraction, involving the mental addition of the numbers and the blocking of all pain experience; or OM involving the cultivation of an open attitude to pain (and no mental addition). Subjects received a total of 60 thermal stimuli: 20 short hot (SH), 20 long hot (LH) and 20 long warm (LW) equally distributed across the two task conditions. ITI: intertrial interval.

4.3.2 Motivation of design choices

The employed experimental design built on a previous fMRI-paradigm (Lutz et al., 2013), but incorporated a number of important adaptations. In contrast to the referred study, the paradigm employed in the present work was designed to separate the brain's response to pain from its anticipation of pain through the implementation of veridical visual cues about the temperature of the upcoming stimulation (nonpainful warm or painful hot) and the implementation of temporal jitters to reduce collinearity of regressors in the fMRI-based general linear models (following Ploghaus et al., 1999 and Wager et al., 2004).

The design also implemented a contextual relief manipulation, which was inspired by previous work (see Leknes et al., 2012), and was designed to study reward-related activity. Specifically, at the beginning of painful stimuli, participants did not know whether painful stimuli would be short (8s) or long (16s), which was only signaled a couple of seconds (3-6s) into the stimulation with a second visual cue, which let the participants know whether the stimulation would be short (end thus end soon) or long (and continue considerably longer). The idea was that this would provide a contrast for contextual relief (impending relief vs non-relief during painful stimuli). This aspect of the design and associated relief ratings (see below) have not been analyzed for the present work. However, our specific manner of implementing contextual relief (i.e. contrasting short and long pain stimuli), had the additional advantage that long stimuli could be used to study hypotheses on the cognitive and neuronal mechanisms underlying the counteracting effect of meditation on pain catastrophizing-related processes, which we expected to occur most prominently during tonic-like pain stimuli.

Another design choice related to the warm nonpainful stimuli. These were implemented as a baseline control for the MRI. Ideally, we had wanted to implement both short and long nonpainful warm stimuli. However, doing so would have made total scan time for the pain paradigm well over an hour (90 minutes) which we found undesirable in terms of subject load pertaining to pain stimulations (and in terms of total scan time taking into account other acquired scans). Hence, our choice of only implementing long nonpainful warm stimuli.

A final design choice that deserves mention related to the temperature of long painful stimuli. Long painful stimuli started at participants' pre-calibrated temperature evoking moderate pain (see section on calibration procedures below). However, initial pilot sessions revealed that for long pain stimuli specifically, maintaining this temperature for the entire 16s duration led to unsupportable pain. Hence, it was decided to drop the temperature of long hot stimuli slightly by 1 ° C (0.5 ° C/sec) after 2 sec of stimulation (not depicted in figure 1). This adjustment reflects the best compromise we empirically found to use a long painful stimulation in this design without distressing or hurting participants. This choice posed a potential limitation for the interpretation of the chronometry of the fMRI analyses, but we did not think it poses a limitation for Study 1 and 2 on self-reports as our main hypotheses were based on state

and group effects and there is no reason to believe the temperature drop would interact with these factors.

4.3.3 Rating scales

After each trial, two different rating scales were presented in randomized order. We collected ratings of pain intensity, unpleasantness and relief using 1-9 item Likert scales (see table below for the frequency of presentation). We further checked task performance by regularly asking the total sum of the addition task in the Distraction condition, or, in case of OM, to what degree participants were able to follow meditation instructions. The specific questions are provided below.

Different self-report questions:

‘Intensity: How hot was the stimulation?’

Labels: 1 = Not at all, 9: Extremely hot

‘Unpleasantness: How much did the stimulation bother you?’

Labels: 1 = Not at all, 9: Extremely

‘Relief’: How relieved were you by the end of the stimulation?’

Labels: 1 = Not at all, 9: Extremely

‘Meditation Instruction’: To what degree were you able to follow the instruction?’

Presentation frequency:

<u>OM condition:</u>		
10 x Warm Long	10 x Hot Long	10 x Short Long
6 x Unpleasantness	6 x Unpleasantness	6 x Unpleasantness
6 x Relief	6 x Relief	6 x Relief
4 x Intensity	4 x Intensity	4 x Intensity
4 x Meditation	4 x Meditation	4 x Meditation
<u>Distraction condition:</u>		
10 x Warm Long	10 x Hot Long	10 x Short Long
6 x Unpleasantness	6 x Unpleasantness	6 x Unpleasantness
6 x Relief	6 x Relief	6 x Relief
4 x Intensity	4 x Intensity	4 x Intensity
4 x Addition	4 x Addition	4 x Addition

4.3.4 Pain calibration procedure

Painful stimuli were provided by a TSA 2001-II thermal stimulator (Medoc Advanced Medical Systems, Haifa, Israel) with a 30 mm × 30 mm flat thermode applied to the palmar side of the left wrist. All participants underwent a calibration procedure for stimulus temperature. Using the method of limits (Fruhstorfer et al., 1976), the temperature was increased from 32° C to 50° C maximum at 0.7 C° C/sec. Participants were instructed to indicate with a button press when the pain level reached a 7 on a scale of 0 (“no pain”) – 10 (“the worst pain imaginable”). At button press, temperature returned to the 32° C baseline at maximum rate. The temperature remained at baseline for 5 sec before rising again. Subjects received 10 stimulations. The average temperature over the last five trials was used as an indication of that participant’s pain sensitivity (except when 50° C was reached at three consecutive trials in which case the procedure was stopped and pain sensitivity set at 50° C; 3 novices, 2 experts). A second, finer calibration procedure was performed on the day of the experiment to determine the optimal temperature for a 16 sec long heat stimulation that would be used during the experiment itself. This calibration started with the temperature that best matched the participant’s previously determined pain sensitivity, but was confined to a limited range of four possible temperatures: 47.0, 47.5, 48.0, and 48.5° C. Subjects received the best matching temperature for 16 sec, after which they were asked to rate their pain using the same scale as before. If rating was at 7, temperature was kept at that level; else the temperature was adapted until the targeted pain level of 7 was reached. Note that we only included novices with an initial pain sensitivity above 47 ° C (see also the Brain & Mindfulness Project Manual; Annex I). This choice was motivated by the existing literature on meditation expertise. Specifically, our group and others have previously found that expert meditators usually have a higher pain threshold (Grant et al., 2011; Lutz et al., 2013). This issue is particularly relevant for the interpretation of group differences in brain imaging data. For instance, Grant et al., 2011 had difficulty interpreting fMRI group differences because novice and expert groups had very different stimulus temperatures.

4.4 Psychometric scales

Across studies in the present work, we implemented two main questionnaires of central relevance to our hypotheses: the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995), and the Drexel Defusion Scale (DDS) (Forman et al., 2012). We also implemented several control questionnaires (see Study 2), including the Five Facet Mindfulness Questionnaire (FFMQ) as main control in light of its widespread use in the mindfulness literature (see section 1.8.3). Given the importance of these three questionnaires to the present work, I will here discuss them in greater detail.

4.4.1 Pain Catastrophizing Scale (PCS)

The PCS is the standard reference psychometric tool for the assessment of pain catastrophizing (Quartana et al., 2009). This 13-item questionnaire asks respondents to reflect on past painful feelings and to indicate to what degree they experienced each of 13 negative pain-related thoughts or feelings on a 5-point Likert-scale from 0 (not at all) to 4 (all the time). The item structure of the PCS is based on previous experimental and clinical work identifying different components of pain catastrophizing (Spanos et al., 1979; Chaves and Brown, 1987; Rosenstiel and Keefe, 1983). Consistent with this work, factor analyses of the PCS have shown that catastrophizing is a multidimensional construct comprising elements of rumination (“I can’t stop thinking about how much it hurts”), magnification (“I worry that something serious may happen”), and helplessness (“There is nothing I can do to reduce the intensity of the pain”) (Sullivan, 1995). The factor structure of the PCS has subsequently been replicated in several studies (Osman et al., 1997, 2000; Sullivan et al., 1995, 2000; Van Damme et al., 2002). Correspondingly, the PCS comprises three subscales of rumination, magnification and helplessness that are most frequently combined to yield an overall catastrophizing score (Sullivan et al., 1995). Higher scores reflect higher levels of pain catastrophizing and a total PCS score above 30 has been shown to reflect clinically relevant levels of catastrophizing (Sullivan et al., 1995). The PCS has been found to show excellent internal consistency ($\alpha = 0.93$), concurrent and discriminant validity (Osman et al., 1997), and good test-retest reliability over a 6-week period ($r = 0.75$) (Sullivan et al., 1995).

4.4.2 Drexel Defusion Scale (DDS)

The DDS is a relatively recently developed questionnaire that measures one’s ability to gain psychological distance from psychological experiences including thoughts, feelings and sensations, seeing them as mere mental events rather than as truth-based reflections of reality. The DDS is a 10-item questionnaire that starts with an extensive explanation of the concept of defusion that is intended to help respondent’s understand the relatively complex construct. Subsequently, participants are asked to indicate the degree to which they would be able to defuse from hypothetical situations, including from: negative thoughts and feelings, physical pain and bodily urges (e.g. “To what extent would you normally be able to defuse from” : “negative thoughts about yourself” / “feelings of anger” / “physical pain” / “cravings for food?”) (respectively), indicating their responses on a 6-point Likert scale ranging from “Not at all” (0) to “Very much” (5). Higher scores indicate higher ability to defuse from inner experiences. The DDS is relatively unique in that it not only measures one’s ability to gain distance from thoughts but also from other internal experiences (in contrast to other similar measures, e.g. CFQ; Gillanders et al., 2014). Furthermore, it has been assessed that the DDS items reflect meta-awareness and dereification (disidentification) from internal experiences, matching our aim to investigate these two cognitive processes. The DDS showed good internal consistency ($\alpha = 0.83$), and high convergent and divergent validity (Forman et al., 2012).

4.4.3 Five Facet Mindfulness Questionnaire (FFMQ)

The FFMQ measures five purported mindfulness dimensions including: Observing (noticing or attending to internal and external experiences), Describing (labeling internal experiences with words), Acting with awareness (attending to present moment experience), Non-Judging (adopting a non-evaluative stance towards thoughts and feelings) and Non-Reacting (allowing thoughts and feelings to pass, without getting caught up in them). The FFMQ is a 39-item questionnaire and participants are asked to rate to what degree they experience these dimensions in their daily life on a 5-point Likert-type scale ranging from 1 (never or very rarely true) to 5 (very often or always true). Scores are calculated separately for the subscales, with higher scores reflecting higher levels of mindfulness. The five different facets have been found to demonstrate adequate to good internal consistency, with alpha coefficients ranging from .75 to .91 (Baer et al., 2006). The FFMQ is one of the most popular mindfulness measures, especially in the clinical domain. However, the FFMQ has also received strong criticism (see Grossman, 2011; van Dam et al., 2012). First, the FFMQ, like many similar mindfulness measures, suffers from method effects, related to positive and negative wording of response items (van Dam et al. 2012). Specifically differences in endorsement of negative and positive items have been observed that are suggestive of greater susceptibility to method effects in non-meditators compared to meditators (e.g., Baer et al., 2011; Van Dam et al., 2009), thus introducing systemic variance irrelevant to the construct under study. Further criticisms include a lack of specificity. The FFMQ, like similar mindfulness measures, poses relatively general questions (e.g. "When I do things, my mind wanders off and I'm easily distracted." Or "I tell myself I shouldn't be feeling the way I'm feeling."), instead of taxing precise psychological characteristics or processes. Related, are doubts about its construct validity (whether the construct is measuring what it purports to measure, namely mindfulness, a complex and multifaceted hard to define process) (see section 1.2), among other criticisms (see Grossman, 2011).

EXPERIMENTAL RESULTS

Mindfulness meditation is related to sensory-affective uncoupling of pain in trained novice and expert practitioners

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Zorn J., Abdoun O., Bouet R., Lutz A.

Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR5292, Lyon 1 University,
Lyon, France

Abstract

Background: Mindfulness meditation can alleviate acute and chronic pain while pain catastrophizing can exacerbate them. The interrelations between mindfulness meditation and pain catastrophizing during acute pain remain little known. It has been proposed that mindfulness meditation reduces pain by uncoupling sensory and affective pain dimensions. However, studies to date have reported mixed results, possibly due to a diversity of styles of and expertise in mindfulness meditation. The current study aimed to test for a positive (resp. negative) impact of mindfulness meditation (resp. pain catastrophizing) on sensory-affective uncoupling as a function of meditation expertise. **Methods:** This cross-sectional study investigated the effect of a style of mindfulness meditation called Open Monitoring on sensory and affective pain experience by comparing novice (2-day formal training; average ~20h home practice) to expert practitioners (>10.000h practice). We implemented a paradigm that was designed to amplify the cognitive-affective aspects of pain experience by the manipulation of pain anticipation and uncertainty of stimulus length (8s or 16s thermal pain stimuli). We collected pain intensity and unpleasantness ratings and assessed trait pain catastrophizing with the Pain Catastrophizing Scale (PCS). **Results:** Across groups, mindfulness meditation reduced unpleasantness but not intensity ratings compared to attentional distraction. Experts reported a lower score on PCS, reduced amplification of unpleasantness by long painful stimuli, and larger sensory-affective uncoupling than novices particularly during long painful stimuli. In experts, meditation-induced uncoupling spilled over the control condition. Across groups and task conditions, a higher score on PCS predicted lower sensory-affective uncoupling during long painful stimuli and higher ratings of pain intensity during short painful stimuli. **Conclusion:** These findings suggest that OM, a style of mindfulness meditation, specifically down-regulates pain affect as opposed to pain intensity, and that pain catastrophizing undermines sensory-affective uncoupling of pain. **Significance:** In this study, we found that a style of mindfulness meditation referred to as Open Monitoring reduced unpleasantness but not intensity ratings compared to attentional distraction in trained novice (state effect) and expert meditators (state and trait effects). We also observed that trait pain

catastrophizing scores predicted this sensory-affective uncoupling. These findings advance our understanding of the cognitive mechanisms underlying mindfulness meditation and can inform treatment strategies for chronic pain.

Keywords: Mindfulness meditation, pain catastrophizing, sensory intensity, pain affect, thermal pain.

1. Introduction

Pain includes partly dissociable sensory and affective-motivational components. Sensory qualities relate to pain intensity, location and duration, whereas the affective-motivational component refers to pain unpleasantness that produces a motivation to avoid pain and seek relief (Melzack and Casey, 1968). The affective-motivational component is intertwined with cognitive-evaluative processes that can exacerbate or reduce pain (Sullivan et al., 2001). One such factor is pain catastrophizing, “an exaggerated negative ‘mental set’ brought to bear during actual or anticipated pain experience” (Sullivan et al., 2001), which predicts increased pain in healthy and clinical populations (Quartana et al., 2009; Sullivan et al., 2001), as well as the maintenance and exacerbation of chronic pain (Edwards et al., 2016; Gatchel et al., 2007).

A process designed to undermine or oppose effects of pain catastrophizing is mindfulness, which has been defined as a “nonelaborative, nonjudgmental, present-centered awareness” (Bishop et al., 2014). Contrary to pain catastrophizing, a mindful stance is thought to deflate the negative cognitive-affective elaboration of pain, by becoming aware of distressing thoughts and automatic emotional reactivity and by observing them as mere mental events. Opening up to sensory experience is thought to support this process (Bernstein et al., 2015; Hayes et al., 2012; Kabat-Zinn, 2013; Lutz et al., 2015).

Mindfulness meditation can indeed alleviate acute and chronic pain (Zeidan et al. 2019). In line with the cognitive stance cultivated by mindfulness meditation, one of the most consistent findings has been a reduction in pain affect as opposed to intensity (Gard et al., 2012; Hilton et al., 2017; Perlman et al., 2010). This suggests that mindfulness meditation reduces pain by “uncoupling” sensory and affective/evaluative pain dimensions. However, despite that some meditation studies have reported neural substrates for sensory-affective uncoupling (as reviewed by Grant 2014), this notion remains debatable, as some studies have reported marked overall pain reductions for novice (Zeidan et al., 2011, 2015, 2016) and expert meditators (Grant and Rainville, 2009). This discrepancy may arise from the diversity of styles of and expertise in mindfulness meditation. Furthermore, interrelations between mindfulness and pain catastrophizing during acute pain remain little known.

In the present work, we implemented a paradigm that was designed to amplify the cognitive-affective aspects of pain while participants performed Open Monitoring meditation (Lutz et al., 2008), a style of mindfulness meditation known to impact sensory-affective uncoupling of pain (Perlman et al., 2010).

Specifically, we collected pain intensity and unpleasantness ratings, while novices (2-day formal training; average ~20h home practice) and expert practitioners (>10.000h practice) performed OM meditation, or a distraction control condition, during the anticipation and reception of short (8s) and long (16s) thermal pain stimuli.

We expected that long painful stimuli in particular would exacerbate pain catastrophizing related processes, which would be counteracted by meditation state and expertise. In line with the cognitive attitude cultivated by mindfulness meditation, we expected this regulation to be mainly reflected in a reduction in pain unpleasantness as opposed to pain intensity. Specifically, we hypothesized that mindfulness meditation would reduce pain unpleasantness but not pain intensity compared to attentional distraction (state effect); and to a larger degree for long compared to short painful stimuli and experts compared to novices. Furthermore, we expected that experts would rate painful stimuli as overall less unpleasant but equally intense compared to novices (trait effect). We also expected that experts would be more resilient to pain amplification by long painful stimuli than novices, as reflected in a lower increase in unpleasantness but not intensity between short and long painful stimuli and larger sensory-affective uncoupling for long painful stimuli in particular. Finally, we expected that the latter two effects could be explained by lower pain catastrophizing for experts compared to novices.

2. Material and Methods

2.1 Participants

Participants were recruited for the Brain and Mindfulness ERC-funded project, which includes a cross-sectional observational neuroscientific study on the effect of mindfulness meditation on experiential, cognitive and affective processes conducted in the city of Lyon from 2015 to 2018. Participants included novice and long term meditation practitioners (experts), who were recruited through multiple screening stages which are reported in detail elsewhere (see the Brain & Mindfulness Project Manual, Abdoun et al., 2018). Inclusion criteria were: aged between 35 and 65 years, no psychotropic drug use, no neurological or psychiatric disorder, a Beck Depression Inventory (BDI) score below 20, no family history of epilepsy, no severe hearing loss, MRI compatibility (the experiment was carried out in an MRI scanner) and affiliation to the social security system. Pregnant and breastfeeding women were also excluded. Experts needed to have: a minimum of 10.000 hours of formal practice in the Kagyu or Nyingma school of Tibetan Buddhism, followed at least one traditional 3-year meditation retreat, a regular daily practice in the year preceding inclusion. They also had to be able to distinguish between OM meditation and Open Presence (OP) meditation, a more advanced non-dual form of OM (see meditation practices below for details) and to be familiar with the practice of OP. Novices were included if they did not have significant experience with meditation or other mind-body training techniques and a pain sensitivity above 47 ° C

comparable to experts in our previous study (Lutz et al., 2013). Long-term meditation practitioners under a tradition comparable to the one in the current study also exhibited very low pain sensitivity (~50 ° C to elicit moderate pain), further speaking to the need to match controls and experts on pain sensitivity. The study by Lutz et al., 2013 was also used in a power-analysis to determine the optimum sample size for the current study. While the power analysis for the fMRI data was based on a group size of 25 participants (plus 3 participants to accommodate for artifactual data), we oversampled the novice group to increase our power for correlation analyses with questionnaire measures. A total of 37 novices and 27 expert practitioners were included. Two novices were excluded from the analyses because of a technical error with the log file and non-compliance with task instructions. One expert was excluded because of poor control task performance (33 % correct responses only). Hence, the final sample included 35 novices (52.3 ± 7.5 years old, 16 females) and 26 expert practitioners (52.2 ± 8.1 years old, 12 females). No significant group differences were present in age, gender and temperature of painful stimuli used during the experiment (see Table 1). Experts had an average lifetime meditation experience of 41357 hours (± 17999 SD; range: 13110-94535, missing data for one participant). All participants provided written informed consent before participating in the study. The study was approved by the regional ethics committee on Human Research (CPP Sud-Est IV, 2015-A01472-47).

	Novices	Experts	P-value
Age (years)	52.3 (7.5)	52.2 (8.1)	p = .95
Temperature (experiment)	47.89 (0.49)	47.79 (0.49)	p = .45
Sex	35 (16F/19M)	26 (12F/14M)	P = .97

Table 1. Group characteristics. Continuous variables are presented as mean (standard deviation), and P-values were calculated using Welch's t-test. For categorical variables, P-values were calculated using chi-squared test.

2.2 Meditation practices

As has been discussed elsewhere (Lutz et al., 2013), states of openness and acceptance central to Mindfulness Based Interventions (MBI, Kabat-Zinn, 1982, 1985, 1986) and Acceptance Commitment Therapy (ACT, Hayes, 2004) are also at the heart of mindfulness-related meditation practices labeled here Open Monitoring (OM) (Chambers et al., 2009; Dunne 2011; Hayes, 2004; Lutz et al., 2006, 2015). OM practices aim to cultivate a non-reactive, open and accepting awareness of present moment experience. Traditionally, initial training in Focused Attention (FA) meditation is considered a prerequisite for OM practice (Lutz et al., 2008). Hence, novices also received training in FA (for details on the training protocol see Abdoun et al. 2019). Specifically, novices may still frequently 'grasp' mental objects, causing

them to become absorbed in experiential content, resulting in a reduction or loss of moment-to-moment attention and observation. FA, which involves sustained focused attention on a selected object of choice, increases the capacity to detect distractions and sustain attention, which is said to stabilize the mind (Lutz et al., 2008). The resulting improved monitoring capacity supports OM practice, which involves the non-selective, non-judgmental, and non-elaborative monitoring of all ongoing sensory, affective and cognitive experience (Chambers et al., 2006; Lutz et al., 2008; see methodsS1 for OM instructions provided during the experiment). It has been suggested that the cultivation of such a meta-cognitive perspective allows one to become aware of subtle distressing thoughts that may accompany the perception of a nociceptive stimulus (e.g. thoughts such as “It is killing me” or “this lasts forever”) that may otherwise go unnoticed. This awareness, together with the realization that thoughts are simply mental events and not accurate reflections of reality –a process known as “cognitive defusion” or “dereification” assumed integral to OM– is thought to cut subsequent emotional reactivity and pain amplification (Bishop et al., 2014; Hayes 2004; Kabat-Zinn, 1982; Lutz et al., 2015; Lutz et al., 2008). As a result of these two processes, it has been proposed that, during a state of OM, sensory pain dimensions might be perceived with equal or increased vividness, without the affective distress that usually accompanies such experience (Lutz et al., 2013; Perlman et al., 2010), leading to an ‘uncoupling’ of sensory and affective pain dimensions (Kabat-Zinn, 1982).

Novices and experts differ in the way of practicing objectless meditation. Specifically, with expertise the capacity to sustain an open monitoring state becomes increasingly effortless, at which point it becomes possible to make awareness an object of meditation itself (Chambers et al., 2009; Lutz et al., 2008). Expert practitioners were intensively trained in this advanced style of OM labeled open presence (OP) (Tib. rig pa) (Lutz et al, 2006) and were explicitly asked to do it. In this state, theoretically at least, the phenomenological qualities of effortlessness, openness and acceptance are vividly experienced and control-oriented elaborative processes reduced to a minimum. A suspension of subject-object duality (non-duality) is also reportedly involved (Dunne, 2011; Lutz et al., 2006). As this state is considered a relatively advanced one, even expert practitioners might not be able to sustain it for more than a short time (Lutz et al., 2006). For the sake of simplicity, we will use the term OM for both novices and experts below, acknowledging that for experts actual meditation might also have qualified as OP.

2.3 Meditation training novices

An important aim of the Brain and Mindfulness project was to have a high-quality control group for expert practitioners. To this end, meditation naïve participants underwent a weekend-long formal meditation training program (see Abdoun et al., 2019 for in depth information on the novice training protocol), that was provided by a qualified MBSR teacher, with 13 years of practice and 8 years of teaching experience in the meditation tradition under study and 3 years of experience as a teacher of a 18 month meditation-based intervention (Poisnel et al., 2018). The training included teachings with the support of instruction

videos, guided meditations and experiential exercises, question and answer sessions, as well as sufficient time to reflect and share within the group. During the weekend, novices were introduced to various styles of meditation, including FA and OM practice: two complementary styles of meditation (see section above), also extensively practiced by expert practitioners. One specific exercise involved switching between focused attention on, and open monitoring of, pain. During such exercises, novices were additionally familiarized with several experiential dimensions relevant to mindfulness meditation (e.g. absorption vs. meditative awareness). Through this approach, we aimed to assure that novices gained an adequate understanding of the practices, while simultaneously addressing another issue in the literature, namely that studies that did not include formal meditation training failed to observe effects for meditation-naïve control participants (Gard et al., 2012; Grant and Rainville, 2009; Perlman et al., 2010). After the training weekend, novices were invited to keep up a daily practice of minimum 20 minutes a day until the day of the last experiment, to balance FA, OM and compassion meditations (relevant to other experiments, and also practiced by the experts), and to keep track of their practice with a logbook (n = 29). Novices had on average 63.2 days (\pm 31.8 SD) to practice before participating to the experiment (range: 15-124 days), during which they engaged for a daily average of 18.3 minutes (\pm 7.8 SD, range: 6.4 to 36.7 minutes) in the three meditations, including in OM practice for a daily average of 7.7 minutes (\pm 3.8 SD; range: 1.4 to 15.1 minutes). Total meditation practice at the day of the experiment was 19.4 hours (\pm 12.9 SD; range: 2.2 to 49.2 hours), including 8.1 (\pm 6.1 SD; range: 0.4 to 26.5 hours) of OM.

2.4 Pain calibration procedure

Painful stimuli were provided by a TSA 2001-II thermal stimulator (Medoc Advanced Medical Systems, Haifa, Israel) with a 30 mm \times 30 mm flat thermode applied to the palmar side of the left wrist. All participants underwent a calibration procedure for stimulus temperature. Using the method of limits (Fruhstorfer et al., 1976), the temperature was increased from 32° C to 50° C maximum at 0.7 C° C/sec. Participants were instructed to indicate with a button press when the pain level reached a 7 on a scale of 0 (“no pain”) – 10 (“the worst pain imaginable”). At button press, temperature returned to the 32° C baseline at maximum rate. The temperature remained at baseline for 5 sec before rising again. Subjects received 10 stimulations. The average temperature over the last five trials was used as an indication of that participant’s pain sensitivity (except when 50° C was reached at three consecutive trials in which case the procedure was stopped and pain sensitivity set at 50° C; 3 novices, 2 experts). A second, finer calibration procedure was performed on the day of the experiment to determine the optimal temperature for a 16 sec long heat stimulation that would be used during the experiment itself. This calibration started with the temperature that best matched the participant’s previously determined pain sensitivity, but was confined to a limited range of four possible temperatures: 47.0, 47.5, 48.0, and 48.5° C. Subjects received the best matching temperature for 16 sec, after which they were asked to rate their pain using the same scale as before. If rating was at 7, temperature was kept at that level; else the temperature was adapted

until the targeted pain level of 7 was reached (see methodsS2 for more details on the results of the two calibration procedures).

2.5 Experimental design, pain stimuli and task instructions

Visual stimuli were presented using Psychopy v1.83.04 (Peirce, 2009). The experimental design is presented in Figure 1. Temporal jitters in the presentation of the stimuli were introduced to reduce collinearity of regressors in the fMRI-based general linear models. A fixation cross was displayed on the screen when no other visual stimuli were presented. Each trial started with a 5-8 sec introductory period. A 2 sec predictive cue then indicated whether the upcoming stimulation would be warm or hot and was followed by a 5 to 8 sec anticipatory period. A thermal stimulation was then delivered which was either hot, at the participant's painful temperature, or warm, at a non-painful temperature 6 degrees cooler. 3 to 6 sec after stimulus onset, a second cue indicated whether the stimulation would be short (8 sec, relief) or long (16 sec, non-relief). Warm stimuli were always long (16 sec) and served as a baseline control condition for the MRI. Hence, they will not be analyzed for the current work. Five to eight seconds after the thermal stimulation ended, two rating scales were presented for 5 sec each (see rating scale section below). After 1 sec the next trial started. Baseline temperature for the thermode was 32°C. Ramp-up and ramp-down periods were 1.5 sec for the warm and 2.5 sec for hot stimuli. Temperature of the long hot stimuli dropped slightly by 1 ° C (0.5 ° C/sec) after 2 sec of stimulation (not depicted) as initial pilot sessions revealed they would otherwise be unbearable. Subjects received a total of 60 thermal stimuli; 20 short hot (SH), 20 long hot (LH) and 20 long warm (LW), applied to the palmar side of the left wrist. All thermal stimuli were delivered during one experimental session consisting of six blocks of ten trials each. Subjects rested 1.5 minute between the blocks. Each block was further subdivided into two subblocks, one for each state condition, in randomized order: Open Monitoring (OM) or a control addition task (Distraction). Each trial type (SH, LH, LW) was set to occur at least once during each subblock. Each subblock started with a 20 s auditory and visual state induction during which participants received instructions for the experimental condition. For OM, participants were instructed to keep an open and accepting awareness (see methodsS1 for full instructions). Experts specifically were also told that the OM instructions referred to the practice of OP. For Distraction, subjects were instructed to mentally add simple single-digit numbers (1-3) that were presented on the center of the screen (replacing the fixation cross) from the start of each trial until rating scales were shown (see Fig. 1). Numbers were presented for 1 sec with a variable interval of 3, 4 or 5 sec between numbers. Subjects were asked to maintain a tight focus on the screen in order not to miss any numbers, while blocking all pain-related sensations, emotions and thoughts. In order to minimize visual differences between task conditions, numbers were also presented on the screen during OM. However, subjects were instructed to abstain from mental addition, but to nonetheless keep their gaze fixed at the screen at all times, in a relaxed manner, in order to not miss any

visual cues. Prior to the experiment, participants were familiarized with the task and performed one full block of trials using non-painful stimuli only.

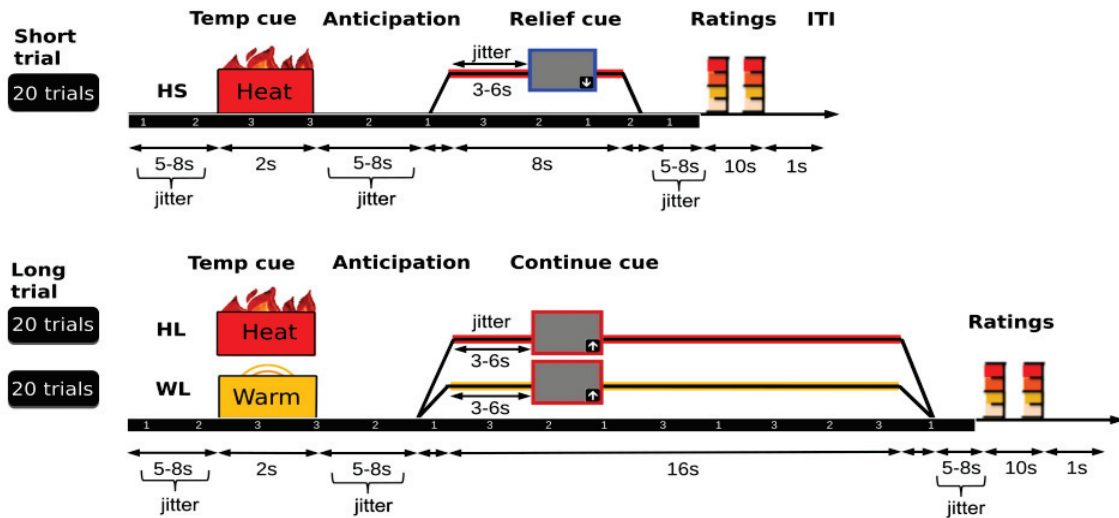


Figure 1. Schematic illustration of the experimental paradigm. Each trial started with a 5-8 sec introductory period. A 2 sec predictive cue then indicated the temperature of the upcoming stimulation (warm or hot) and was followed by a 5-8 sec anticipatory period. A thermal stimulation was then delivered that was either short (8 sec) or long (16 sec). After 3-6 sec of thermal stimulation, a second visual cue informed subjects about the duration of the stimulation. Non-painful warm stimuli were always long and served as baseline control for the fMRI. Following stimulus offset, a 5-8 sec rest period preceded the presentation of two rating scales (5 sec each). Rating scales probed pain intensity, unpleasantness, relief and task performance. During each trial, a single-digit number (1-3) was presented every 2 sec from the start of the trial until rating scales were shown (see black horizontal bars). Subjects randomly alternated between two task conditions: Distraction, involving the mental addition of the numbers and the blocking of all pain experience; or OM involving the cultivation of an open attitude to pain (and no mental addition). Subjects received a total of 60 thermal stimuli: 20 short hot (SH), 20 long hot (LH) and 20 long warm (LW) equally distributed across the two task conditions. ITI: intertrial interval.

2.6 Rating scales

Throughout the blocks, we collected ratings of pain intensity and unpleasantness using 1-9 Likert items. Similarly, we collected ratings of pain relief (how relieved were you when the stimulation stopped) which will not be analyzed here, but in a future publication in the context of studying reward-related activity in the neuroimaging analysis. We further checked task performance by regularly asking the total sum of the addition task in the Distraction condition, or, in case of OM, to what degree participants were able to

follow meditation instructions. After each trial, two different rating scales were presented in randomized order (see methodsS3 for the specific questions and frequency of presentation).

2.7 Questionnaires and other measurements

To characterize interindividual trait differences in cognitive and affective processes involved in our paradigm, we measured the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995). 33 novices and 26 experts completed the PCS before participating in the experiment. Other measurements relevant to the current experiment were collected. These included the Drexel Defusion Scale which measures cognitive defusion (see the Brain & Mindfulness project manual, Abdoun et al., 2018, for all questionnaires collected), several phenomenological scales collected at the end of the fMRI-session (e.g. openness, avoidance, vividness), and a qualitative interview about worldview and pain and suffering coping strategies. These will be the subject of a future publication.

2.8 Statistical analysis

We used R 3.3.2 for statistical analyses (R core team, 2017).

Group comparisons: Welch's t-test was used to compare group means for age, pain sensitivity, experimental temperature, task performance and trait pain catastrophizing. Chi-squared test was used to test for differences in categorical variables between groups.

Outlier removal pain ratings: We first removed no-response trials and subsequently removed extreme outlier points that were more than 3.5 standard deviations away from the median for each grouping of Subject by Rating Type (Intensity, Unpleasantness).

Linear mixed models (LMMs): LMMs were fitted to the data using lme4 (Bates et al., 2015). The main advantage of these models is that they are able to handle missing data and complex unbalanced designs (e.g. different ratings being asked at different trials as in the current study) (Bates et al., 2015; Molenberghs and Lesaffre, 2014). Another characteristic of LMMs is that they contain a fixed and random effects structure. Usually, the fixed effects structure estimates the explanatory variables (i.e. effects of interests or covariates), while the random effects structure estimates subject-level effects for repeated measures, thus accounting for heterogeneity between subjects and non-independence within subjects (Singmann and Kellen, 2019). Fixed effect terms for each model are specified in the results section. Time (different blocks) was additionally included as fixed effect covariate in all models. We kept the random effects structures maximal, by including subject-level random intercepts and random slopes for each within-subject fixed effect (including the Time covariate) (Barr et al., 2013). Models were fitted using restricted maximum likelihood, and type II Wald chi-square tests were used to assess significance of fixed

effects (Bates et al., 2015; Bolker et al., 2019; Luke, 2017). Post-hoc tests were performed using the emmeans package version 1.2.2, using Tukey multiple comparison corrections.

Effects size calculations: For informative, replicative and meta-analytic purposes, we provide effect size measures for the effects of interest. As of yet, no generally accepted method exists for the calculation of effect sizes within LMMs. As a workaround for estimation of the effect sizes for interaction and post-hoc effects observed within LMMs, we fitted simpler models to the data and calculated effect sizes on them. More specifically, for LMM interaction effects, we fitted the equivalent ANOVA model, that included the factors involved in the interaction, and data averaged per subject for each possible combination of the factor levels (as usual for ANOVA). We subsequently calculated the partial eta-squared (η^2) effect-size measure for the interaction term (Maher et al., 2013). For the estimation of effect sizes of post-hoc LMM pairwise comparisons, we grouped data according to the levels under comparison, and averaged data per subject. We subsequently calculated Cohen's (d) effect-size measure (Maher et al., 2013). Cohen's (d) was also calculated for group differences in pain catastrophizing analyzed with a t-test.

3. Results

3.1. Manipulation check

The percentage of correct responses on the Distraction task did not differ between experts ($M=0.87$, $SD=0.13$) and novices ($M=0.88$, $SD=0.11$), ($t(49.9) = 0.6$, $p = 0.57$), suggesting equal control task compliance between groups. However, when participants were asked to what degree they could follow meditation instructions, experts ($M = 7.46$, $SD = 1.21$) provided significantly higher ratings than novices ($M = 6.66$, $SD = 1.38$), ($t(57.3) = 2.4$, $p = 0.020$; $d = 0.61$), potentially reflecting differing levels of expertise.

3.2 Effects of meditation state and expertise on pain experience

We tested the effect of meditation state and expertise on pain experience with a model that included Group (Experts, Novices), State (OM, Distraction), Rating Type (Intensity, Unpleasantness) and Trial Type (Short, Long) as fixed effects (see Fig. 2a for an overview of the data). We observed a State x Rating Type ($\chi^2(1) = 1.0$, $p = .001$; $\eta^2=0.11$), a Group x Rating Type interaction ($\chi^2(1) = 1.3$, $p < .001$; $\eta^2=0.18$) and a Group x Rating Type x Trial Type interaction ($\chi^2(1) = 8.6$, $p = .003$; $\eta^2=0.08$).

First, we conducted post-hoc tests on the State x Rating Type interaction (Fig. 2b). In line with what was predicted, we observed an overall state effect across groups (Novices, Experts) and trial types (Short, Long). Interpreting the overall state effect, we found that relative to Distraction, OM significantly reduced the unpleasantness but not intensity of pain across all participants (unpleasantness: estimate = -0.25,

95% ci = [-0.39,-0.11], $t(102) = -3.5$, $p < .001$, $d = -0.14$; intensity: estimate = 0.03, 95% ci = [-0.19,0.13], $t(173) = 0.3$, $p = .74$). To test whether this effect of state was also present in each group, we performed follow up tests on the novice and expert groups separately. We found that the state effect was present in both novice and expert groups (novices: State x Rating Type ($\chi^2(1) = 6.36$, $p = .012$, $\eta^2=0.12$; unpleasantness: estimate = -0.21, 95% ci = [-0.38,-0.04], $t(65) = -2.4$, $p = .018$, $d = -0.15$; intensity: estimate = 0.08, 95% ci = [-0.11,0.28], $t(118) = 0.8$, $p = .43$), (experts: State x Rating Type ($\chi^2(1) = 3.85$, $p = .05$, $\eta^2=0.10$; unpleasantness: estimate = -0.29, 95% ci = [-0.53,-0.05], $t(39) = -2.4$, $p = .021$, $d = -0.18$; intensity: estimate = -0.03, 95% ci = [-0.29,0.24], $t(60) = -0.19$, $p = .85$). Additional supplementary analyses revealed that, for novices, none of the usual practice metrics could predict the state effect. Instead, time elapsed since the meditation weekend was found to be a significant predictor, such that novices who participated in the experiment closer to the meditation weekend reported larger state effects (see resultsS1). The significance of this finding will be further detailed in the discussion.

Next, we performed post-hoc tests on the Group x Rating Type interaction of the main model (Fig. 2c). Across the different task conditions (OM, Distraction) and trial types (Short, Long), experts rated painful stimuli as significantly less unpleasant compared to novices (estimate = -1.75, 95% ci = [-2.45,-1.05], $t(59) = -5.0$, $p < .0001$; $d = -1.33$), whereas averaged reports of pain intensity did not differ between groups (estimate = -0.66, 95% ci = [-1.38,0.05], $t(59) = -1.8$, $p = .070$). Thus, in line with our predictions expert practitioners reported a larger reduction in the unpleasantness but not intensity of pain compared to novices during OM meditation, but contrary to our predictions, this effect also extended to a non-meditative control state.

Finally, we examined the Group x Rating Type x Trial Type interaction of the main model (Figs 2d-e). A first post-hoc test revealed that, as predicted, experts, reported a significantly lower increase in pain unpleasantness between short and long painful stimuli compared to novices (estimate = -0.46, SE = 0.15, $t(103) = -3.2$, $p < .01$; $d = -0.98$), whereas the reported increase in pain intensity did not differ between groups (estimate = 0.05, SE = 0.16, $t(172) = 0.3$, $p = .74$) (Fig. 2d). Second, we performed post-hoc tests to examine group differences in the reported degree of sensory-affective uncoupling of pain; operationalized as the within-subject difference between sensory intensity and unpleasantness ratings of pain (intensity-unpleasantness). As predicted, experts, compared to novices, reported significantly larger sensory-affective uncoupling of pain, already during short (estimate = 0.83, SE = 0.32, $t(70) = 2.6$, $p = .01$; $d = -0.73$) but most pronouncedly during long painful stimuli (estimate = 1.3, SE = 0.32, $t(70) = 4.2$, $p = .0001$; $d = -1.02$) (see solid lines Fig. 2e). Expert, but not novice practitioners, additionally reported larger sensory-affective uncoupling of pain for long compared to short painful stimuli (experts: estimate = 0.69, SE = 0.13, $t(2078) = 5.2$, $p < .0001$; $d = 0.40$; novices: estimate = 0.18, SE = 0.11, $t(2075) = 1.5$, $p = .12$) (see dashed lines Fig. 2e). Collectively, these results confirmed our hypotheses on meditation state and expertise related sensory-affective uncoupling of pain.

We also anticipated a modulation of the state-effect by meditation-expertise and trial type, such that experts would report larger OM-related sensory-affective uncoupling than novices, particularly during long painful stimuli, which we failed to observe. This could have been due to cross-over effects between task conditions, as it has been previously observed that a meditation state can affect the post-meditative baseline (Lutz et al., 2004). Specifically, experts' larger sensory-affective uncoupling of pain cultivated during meditation might have lingered on to the control state: thereby attenuating overall differences between states in this group. To test this possibility, we performed an exploratory analysis to examine whether the magnitude of reported sensory-affective uncoupling of pain, for the two different task conditions, depended on the order of task performance within blocks. We fitted a model that included Group (Experts, Novices), State (OM, Distraction), Subblock (First, Second) and Block (1 to 6) as fixed effect terms, and an Uncoupling index (within-subject difference intensity-unpleasantness for long painful stimuli) as dependent variable. Consistent with this hypothesis, we observed a Group x State x Subblock interaction ($\chi^2(1) = 4.44, p = .035$). Post-hoc tests revealed an order effect for experts only, who reported increased sensory-affective uncoupling of pain for OM relative to Distraction, during first but not second experimental subblocks after resting breaks (first subblock: estimate = 0.73, 95% ci = [0.06, 1.39], $t(137) = 2.2, p = .032$; second subblock: estimate = -0.15, 95% ci = [-0.82, 0.51], $t(122) = -0.45, p = .65$) (see Fig. 3). No such order effect was present for novices (first subblock: estimate = 0.11, 95% ci = [-0.43, 0.66], $t(125) = 0.4, p = .68$; second subblock: estimate = 0.51, 95% ci = [-0.09, 1.10], $t(142) = 1.7, p = .094$). The fact that experts reported larger sensory-affective uncoupling of pain for OM compared to Distraction during first but not second experimental subblocks after 2-minute during resting breaks, suggests that a spillover effect of OM within blocks, that attenuated overall state differences, was present for the expert group specifically.

3.3 Relationship between pain catastrophizing and meditation expertise

Next, we tested for group differences in trait pain catastrophizing as measured by the pain catastrophizing scale (PCS). As predicted, experts had significantly lower trait pain catastrophizing compared to novices (experts: $M = 6.96, SD = 5.39$; novices: $M = 18.27, SD = 9.35, t(52.7) = -5.8, p < .0001, 95\% \text{ ci} = [-15.20, -7.42]; d = -1.44$) (see resultsS2 for figure). To explore the relationship of this expertise effect to meditation practice, we tested whether experts' lifetime meditation experience could predict pain catastrophizing scores, which was not the case ($r(23) = -0.08, p = .70$). This might have been due to non-linearity of training, or a ceiling effect introduced by the high level of experience of expert practitioners (~40,000 hours).

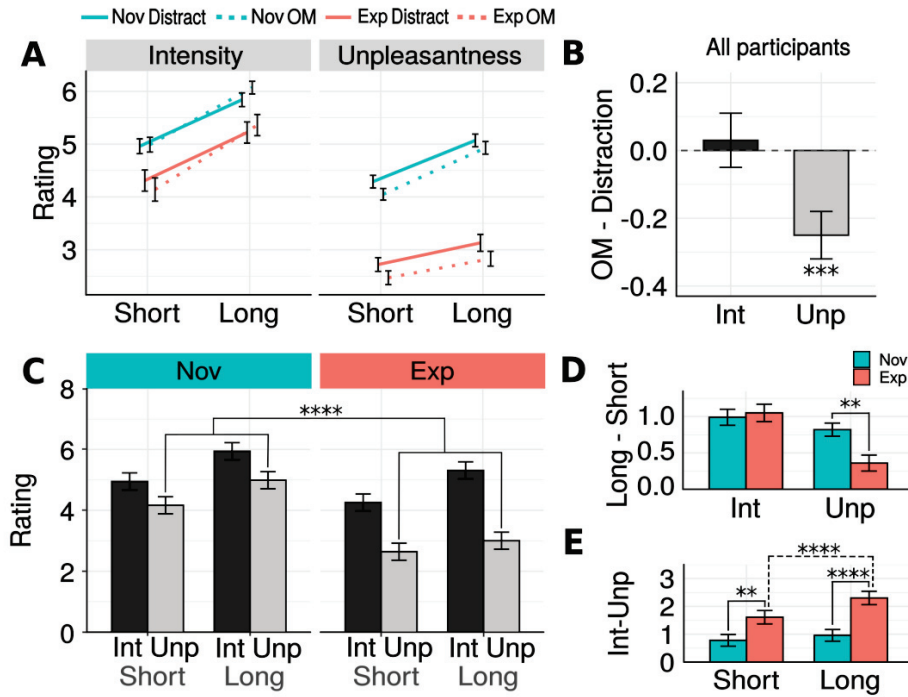


Figure 2. Effect of meditation state and expertise on subjective pain experience. (A) Overview of pain self-report data. (B) Relative to Distraction, OM reduced the unpleasantness but not intensity of pain, across groups (Novices and Experts) and trial types (Short, Long); Subsequent results are averaged across the levels of states (OM, Distraction). (C) Compared to novices, experts rated painful stimuli as less unpleasantness but equally intense across trial types (Short, Long). (D) Experts, compared to novices, reported a comparable increase in pain intensity but a lower increase in pain unpleasantness between short and long painful stimuli. (E) Experts, compared to novices, reported larger sensory-affective uncoupling of pain, already during short, but particularly during long painful stimuli (solid lines). Experts additionally reported larger sensory-affective uncoupling of pain for long compared to short painful stimuli (dashed lines). Pain ratings were provided on 1-9 Likert scales. Results are model-derived estimates. OM: Open Monitoring, Int: Intensity, Unp: unpleasantness. Error bars are standard errors. Significance levels *: $p < .05$; **: $p < .01$; ***: $p < .001$; ****: $p < .0001$.

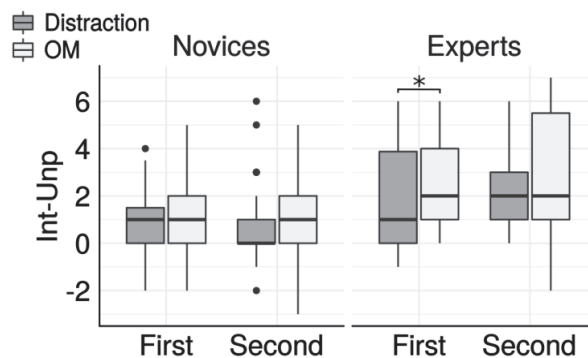


Figure 3. Effect of task order within blocks on reported sensory-affective uncoupling of pain. A state-effect specific to experts was present when controlling for task order within blocks, with experts but not novices reporting increased sensory-affective uncoupling of pain for OM compared to Distraction for first but not second subblocks after resting breaks.

3.4 Relationships between pain catastrophizing and pain experience

Finally, and as hypothesized, we examined whether the group difference in trait pain catastrophizing could explain the observed group differences in increase in pain unpleasantness between short and long painful stimuli, as well as in reported degree of sensory-affective uncoupling for long painful stimuli. To test this, we divided participants in a low (Low PCS) and high (High PCS) pain catastrophizing subgroup (median split), and examined whether the newly created PCS subgroups showed similar group differences in the specified effects. The Low PCS group included 22 experts and 7 novices while the High PCS group included 26 novices and 4 experts (see blue (novices) and red (experts) dots in upper panels Fig. 4A). Groups did not differ in mean pain sensitivity (low PCS: $M = 47.5$, $SD = 2.1$, high PCS: 47.8 , $SD = 1.5$, $t(50) = -0.7$, $p = .49$, 95% ci = [-1.30,0.63]) or experimental pain temperature (low PCS: $M = 47.9$, $SD = 0.49$, high PCS: 47.8 , $SD = 0.50$, $t(57) = 0.48$, $p = .63$, 95% ci = [-0.20,0.32]). We fitted a model that included PCS (Low PCS, High PCS), Trial Type (Short, Long), State (OM, Distraction) and Rating Type (Intensity, Unpleasantness) as fixed effects, and observed a PCS x Rating Type interaction ($\chi^2(1) = 7.1$, $p < .01$; $\eta^2 = 0.11$), and a PCS x Rating Type x Trial Type interaction ($\chi^2(1) = 1.7$, $p < .001$; $\eta^2 = 0.17$).

First, we conducted post-hoc tests on the PCS x Rating Type interaction (Fig. 4A). Across the different task conditions (OM, Distraction) and trial types (Short, Long), the Low PCS group rated painful stimuli as significantly less unpleasant than the High PCS group (estimate = -1.54, SE = 0.37, $t(57) = -4.2$, $p < .0001$, 95% ci = [-2.29,-0.80]; $d = -1.12$), whereas averaged reports of sensory pain intensity did not differ between PCS groups (estimate = -0.70, SE = 0.36, $t(57) = -1.9$, $p = .057$, 95% ci = [-1.42,0.02]). This result was conceptually similar to that of the equivalent test for the novice and expert groups.

Subsequently, we examined the PCS x Rating Type x Trial Type (Figs 4b-c). A first post-hoc test showed that, contrary to what was predicted, the Low compared to High PCS group reported a lower increase in pain unpleasantness between short and long painful stimuli only at a trend level (estimate = -0.27, SE = 0.15, $t(95) = -1.8$, $p = .075$). Also, the Low PCS group reported a higher increase in pain intensity (estimate = 0.45, SE = 0.17, $t(154) = 2.7$, $p < .01$) (Fig. 4b). To help interpret this unexpected finding we conducted follow-up tests on short and long pain stimuli separately. Interestingly, we found that the High PCS group rated short painful stimuli as significantly more intense compared to the Low PCS group (estimate: 0.93, 95% ci = [0.20,1.65], $t(60) = 2.6$, $p = .013$) (dashed lines Fig. 4a), whereas intensity reports were not different between groups for long painful stimuli (estimate: 0.47, 95% ci = [-0.28,1.23], $t(59) = 1.3$, $p = .22$) (the equivalent test for novice and expert groups did not show such an effect). The larger increase in pain intensity between short and long painful stimuli for the Low compared to High PCS group was not what we initially predicted. This effect could reflect either a ceiling effect for the high PCS group due to increased baseline pain sensitivity, or alternatively, an enhanced opening up to pain sensation during long painful stimuli for the Low PCS group.

Further continuing the interpretation of the PCS x Rating Type x Trial Type interaction, we finally conducted post-hoc tests on differences between PCS groups in reported degree of sensory-affective uncoupling of pain (Fig. 4c). As predicted, the Low compared to High PCS group reported more pronounced sensory-affective uncoupling of pain for long painful stimuli [(estimate = 1.21, SE = 0.34, $t(66) = 3.6$, $p < .001$; $d = 0.88$) (solid lines Fig. 4c), whereas reported sensory-affective uncoupling of pain did not differ between PCS groups for short painful stimuli (estimate = 0.48, SE = 0.34, $t(66) = 1.44$, $p = .15$). The Low but not High PCS group additionally reported larger sensory-affective uncoupling of pain for long compared to short painful stimuli (Low PCS: estimate = 0.69, SE = 0.13, $t(2078) = 5.2$, $p < .0001$, $d = 0.45$; High PCS: estimate = 0.18, SE = 0.11, $t(2075) = 1.5$, $p = .12$) (see dashed lines Fig. 4c).

These results suggest that the group differences in trait pain catastrophizing could indeed explain the observed group differences in sensory-affective uncoupling of pain for long painful stimuli, as predicted. In order to further assess the specificity of this finding, we tested whether pain catastrophizing could also predict sensory-affective uncoupling of pain for long painful stimuli, across participants, when controlling for the effect of meditation expertise. We found that this was indeed the case (see resultsS3). This suggests that the above findings were not simply driven by group differences in meditation expertise unrelated to pain catastrophizing.

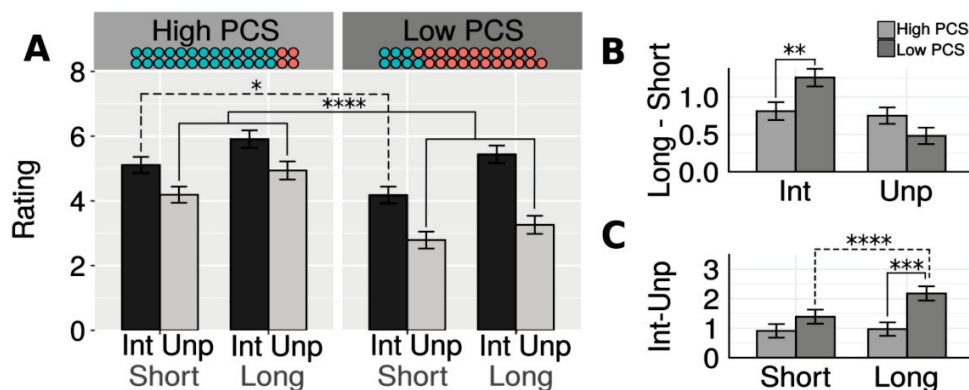


Figure 4. Effect of pain catastrophizing on subjective pain experience. Results are averaged across the levels of states (OM, Distraction). **(A)** The low (right panel) compared to high PCS group (left panel) rated painful stimuli as less unpleasant (solid lines) across trial types (Short, Long). However, the high compared to low PCS group rated painful stimuli as more intense only when they were short (dashed lines). Dots in upper panels represent the composition in novices (blue) and experts (red) of each PCS group. **(B)** The increase in pain unpleasantness between short and long painful stimuli did not differ between groups. Instead the low PCS group reported a higher increase in pain intensity. **(C)** The low compared to high PCS group reported larger sensory-affective uncoupling of pain, specifically during long painful stimuli (solid lines), as well as a larger increase in sensory-affective uncoupling of pain between short and long painful stimuli (dashed lines). Pain ratings were provided on 1-9 Likert scales. Results are model-derived estimates. Int: Intensity, Unp: unpleasantness. Error bars are standard errors. Significance levels *: $p < .05$; **: $p < .01$; ***: $p < .001$; ****: $p < .0001$.

4. Discussion

The present study aimed to better characterize the pain regulatory mechanism of OM mindfulness meditation; a meditation practice analogous to that employed in mindfulness-based interventions for the treatment of chronic pain. To this end, we investigated the impact of an OM meditation state and expertise on sensory and affective pain experience during short (8s) and long (16s) painful stimuli.

4.1 Effect of the state manipulation

We found that OM meditation compared to attentional distraction, reduced ratings of unpleasantness but not intensity for novice and expert practitioners. This finding replicates several studies that reported lower pain unpleasantness as a result of mindfulness training or expertise (Brown and Jones, 2010; Gard et al., 2012; Grant et al., 2011; Grant and Rainville, 2009; Perlman et al., 2010; Zeidan et al., 2011, 2015, 2016), and extends this work in multiple ways.

The within-subject contrast of two opposing cognitive and attentional stances allowed us to better understand the relative regulatory efficacy of each. In the context of the current study, mindfulness meditation emerged as the more adaptive strategy. This finding is in line with clinical and mindfulness theory which holds that cultivating an open and accepting attitude towards pain, especially when chronic and inescapable, is more adaptive than experiential avoidance (Bishop et al, 2014; Hayes et al., 2012; Kabat-Zinn, 2013). This notion has gathered empirical support from the clinical domain which has consistently linked excessive fear and avoidance behaviors to poorer clinical outcomes (Crombez et al., 2013; Edwards et al., 2016). Our finding that both expert and novice practitioners reported lower pain unpleasantness during mindfulness-meditation, including for long tonic-like pain stimuli which have been suggested to better mimic chronic pain states (Racine et al., 2012), further supports this notion.

The finding on meditation-induced sensory-affective uncoupling of pain for experts, corroborates two other studies with long-term meditation practitioners, the first by Gard and colleagues on experienced Vipassana practitioners (Gard et al., 2012), and the second by Perlman and colleagues on Tibetan Buddhism practitioners (Perlman et al., 2010), that observed similar results.

Our finding of a reduction in pain unpleasantness during mindfulness-meditation for novices is also salient as other studies, with similar instructions, failed to observe effects for control participants (Gard et al., 2012; Grant and Rainville, 2009; Perlman et al., 2010). This difference is perhaps most readily attributed to the larger dose of meditation training for novices in our study, which included 2 days of formal training in OM and FA meditations with a teacher, and several weeks of home practice (2-18 weeks) (Abdoun et al., 2019). By contrast, other studies only provided written meditation instructions. Hence, it can be

speculated that the capacity to non-judgmentally monitor (pain) experience is not trivial and requires at least some familiarity with and training in OM (and likely FA); a view also traditionally held (Lutz et al., 2006, 2008). However, practice metrics for novices could not predict the state effect (reduced unpleasantness with OM). Instead, time elapsed since the meditation weekend emerged as the sole significant predictor: novices who participated closer to the meditation weekend reported larger state effects. Although surprising at first, further inspection revealed a potential explanation. Specifically, we have reported before that novices who enrolled in the training protocol initially showed high motivation, but that the intensity of practice linearly decreased over weeks (Abdoun et al. 2019). This may well explain the observed decline in the state effect over weeks. If indeed true, this finding has several important implications. First, it suggests that, for beginner meditators, a continuous and disciplined effort may be required to achieve sustained effects on pain regulation. Second, the finding points to the importance of taking into account sustainability of effects as initial results might be overly optimistic. Lastly, the results beg the question how much effort is required to maintain effects and whether the capacity to non-judgmentally monitor pain can become learned and effortless (as the findings on experts suggest), and if so, at which stage. These are interesting avenues for future research.

Notably, the only other studies that also reported mindfulness-related reductions in pain ratings for novices provided formal training too. Specifically, in a series of experiments by Zeidan and colleagues, meditation-naive participants underwent 4 brief 20-minute sessions of meditation training in a practice that involved sustained focused attention on the breath (Zeidan et al., 2011, 2015, 2016), a type of practice that qualifies as FA. When used in the context of pain, this might involve components more akin to distraction, which has been linked to attentional gating mechanisms and overall pain reductions (Miron and Duncan 1989; Sprenger et al., 2012), as was observed in these studies. The present results suggest that novices can also be successfully trained in OM meditation and that this yields a different regulatory profile characterized by sensory-affective uncoupling, consistent with earlier work with expert practitioners (Perlman et al., 2010). However, this interpretation warrants caution as the present study lacked a baseline control condition, and reported results were relative to a distraction condition that in itself may have reduced pain intensity. Furthermore, in the studies by Zeidan and colleagues, mindfulness meditation also impacted the affective dimension of pain more than the sensory dimension. Nonetheless, the observed reductions in pain intensity (up to 27-40%) in those studies seem an order of magnitude larger than what has been reported in most studies on OM meditation, suggesting that different mechanisms are at play. Future research is needed to clearly delineate the respective beneficial effects of these different meditative practices, especially in a clinical context.

Finally, we hypothesized larger state effects for long compared to short painful stimuli and for experts compared to novices, which we did not observe. For experts, this may have had several possible reasons. First, across task conditions, experts showed a trait-like tendency towards larger sensory-affective uncoupling. Hence, for experts, sensory-affective uncoupling of pain may no longer have been

state-dependent, a notion supported by the relation to trait pain catastrophizing (see below). Secondly, an exploratory analysis suggested that for experts larger sensory-affective uncoupling cultivated during OM spilled over to the control condition and thus attenuated overall state differences. As effortlessness is said to be key feature of non-dual mindfulness (i.e. OP meditation), this spill-over of sensory decoupling following meditation in experts only could be a signature of this process. Further work is needed to explore this possibility.

4.2 Effect of meditation expertise and relation to trait characteristics

The basic premise of mindfulness practice is that the repeated cultivation of a meditative state can eventually induce desirable changes in behavioral and psychological traits (Lutz et al., 2006). In accordance with this notion, several trait-like effects related to meditation expertise were observed across both task conditions. Specifically, experts reported lower overall pain unpleasantness but not pain intensity, reduced amplification of unpleasantness by long painful stimuli, and larger sensory-affective uncoupling particularly during long painful stimuli. Supporting the idea that these group differences reflected trait effects was that experts' lower trait pain catastrophizing, compared to novices, could explain several of the effects, although not all. Hence, pain catastrophizing may not fully exhaust all mechanisms underlying expertise; this possibility will be explored through a more refined, qualitative approach in a future publication. Regardless, experts showed increased resilience to pain amplifying processes, which was partly relatable to lower trait pain catastrophizing. Contrary to our expectation, lifetime meditation experience did not predict trait pain catastrophizing. Our findings corroborate other studies that reported reduced pain catastrophizing following mindfulness-based interventions (Turner et al., 2016), and negative relations between measures of mindfulness and pain catastrophizing (Day et al., 2015; Elvery et al., 2017; Schutze et al., 2009; Dorado et al., 2018; Jensen et al. 2018). In addition, the observed pattern of pain reduction is remarkably in line with the specific cognitive attitude cultivated by mindfulness meditation that emphasizes openness to sensory experience and deliberate disengagement from cognitive-affective appraisals. The possibility that one can open up to the sensory aspects of pain experience while simultaneously reducing emotional distress is particularly relevant in the context of chronic pain conditions. Nevertheless, more research is clearly warranted to further substantiate these findings and to examine the extendibility of these findings to clinical pain contexts.

4.3 Limitations

The current study had several limitations. First, the study built on subjective pain reports. Although more readily accepted in pain research, they are also susceptible to demand characteristics (Orne 1962; Weber and Cook 1972). However, we consider it unlikely that these were primarily driving results as we reported complex relations between various experimental factors and trait variables. Second, the study design did

not allow to conclusively disentangle state and trait effects. An inclusion of a baseline control condition would have made it clearer whether effects observed across task conditions were state-induced or trait-like. Third, we selected participants with low pain sensitivity, which decreases the generalizability of the findings. Finally, the cross-sectional design rendered it unclear whether meditation expertise was the causal factor of lower trait pain catastrophizing in expert practitioners.

5. Conclusion

This study associated mindfulness meditation with sensory-affective uncoupling of pain in trained novice and expert meditators and identified trait pain catastrophizing as a predictor of sensory-affective uncoupling. These findings help to illuminate the cognitive mechanisms of mindfulness-based pain-regulation and provide a better understanding of its relation to other pain-regulation strategies.

Author contributions

AL conceived the study. JZ, OA and AL were responsible for the study design. JZ executed the study and was responsible for data analysis. AL, OA and RB contributed to the data analysis and data interpretation. JZ drafted the manuscript in close collaboration with OA and AL. RB provided feedback on the manuscript. All authors have read and approved the manuscript and contributed substantially to the manuscript.

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References

1. Abdoun O, Zorn J, Fucci E, Perraud E, Aarts K, Lutz, A. Brain & Mindfulness Project Manual. 2018. OSF. <https://osf.io/dbwch/>
2. Abdoun O, Zorn J, Poletti S, Fucci E, Lutz A, Training novice practitioners to reliably report their meditation experience using shared phenomenological dimensions. *Consciousness and Cognition*. 2019. Feb 68: 57-72. <https://doi.org/10.1016/j.concog.2019.01.004>

3. Barr DJ, Levy R, Scheepers C, Tily HJ. Random effects structure for confirmatory hypothesis testing: Keep it maximal. *Journal of Memory and Language*. 2013. 68, 255-278. <https://doi.org/10.1016/j.jml.2012.11.001>
4. Bates D, Maechler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015. 67(1), 1-48. doi:10.18637/jss.v067.i01
5. Bernstein A, Hadash Y, Lichtash Y, Tanay G, Shepherd K, Fresco DM. Decentering and Related Constructs: A Critical Review and Metacognitive Processes Model. *Perspect Psychol Sci*. 2015. 10(5): 599–617. doi: 10.1177/1745691615594577
6. Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, Segal ZV, Abbey S, Speca M, Velting D, Devins G. Mindfulness: A proposed operational definition. *Clin Psychol Sci Prac*. 2014. 11: 230–241. <https://doi.org/10.1093/clipsy.bph077>
7. Bolker BM, Brooks ME, Clark CJ, Geange SW, Poulsen JR, Stevens MHH, White JS. Generalized linear mixed models: a practical guide for ecology and evolution. *Trends in Ecology and Evolution*. 2019. 24, 127-35. <https://doi.org/10.1016/j.tree.2008.10.008>
8. Brown CA, Jones AK. Meditation experience predicts less negative appraisal of pain: electrophysiological evidence for the involvement of anticipatory neural responses. *Pain*. 2010. 150(3): 428–438. <https://doi.org/10.1016/j.pain.2010.04.017>
9. Cassidy EL, Atherton RJ, Robertson N, Walsh DA, Gillet R. Mindfulness, functioning and catastrophizing after multidisciplinary pain management for chronic low back pain. *Pain*. 2012. 153: 644–650. <https://doi.org/10.1016/j.pain.2011.11.027>
10. Chambers R, Gullone E, Allen NB. Mindful emotion regulation: an integrative review. *Clin Psychol Rev*. 2009. 29, 560–572. <https://doi.org/10.1016/j.cpr.2009.06.005>
11. Crombez G, Eccleston C, Van Damme S, Vlaeyen JW, Karoyl P. Fear-avoidance model of chronic pain: the next generation. *Clin J Pain*. 2013. 28(6): 475-483. doi: 10.1097/AJP.0b013e3182385392
12. Day MA, Smitherman A, Ward LC, Thorn BE. An investigation of the associations between measures of mindfulness and pain catastrophizing. *Clin J Pain*. 2015. 31:222–8. doi: 10.1097/AJP.000000000000102
13. Delacre M, Lakens D, Leys C. Why Psychologists Should by Default Use Welch's t-test Instead of Student's t-test. *International Review of Social Psychology*. 2017. 30(1), 92–101. doi: <http://doi.org/10.5334/irsp.82>

14. Dorado K, Schreiber KL, Koulouris A, Edwards RR, Napadow V, Lazaridou A. Interactive effects of pain catastrophizing and mindfulness on pain intensity in women with fibromyalgia. *Health Psychol Open*. 2018. Jul-Dec; 5(2). doi: 10.1177/2055102918807406
15. Dunne J. Toward an understanding of non-dual mindfulness. *Contemp. Buddhism*. 2011. 12, 71–88. doi: 10.1080/14639947.2011.564820
16. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The role of psychosocial processes in the development and maintenance of chronic pain. *The Journal of Pain*. 2016.17(9):T70-T92. <https://doi.org/10.1016/j.jpain.2016.01.001>
17. Elvery N, Jensen MP, Ehde DM, Day MA. Pain catastrophizing, mindfulness, and pain acceptance: What's the difference? *The Clinical Journal of Pain*. 2017. 33: 485–495. doi: 10.1097/AJP.0000000000000430
18. Fruhstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry*. 1976. 39: 1071–1075. doi: 10.1136/jnnp.39.11.1071
19. Gard T, Hölzel BK, Sack AT, Hempel H, Lazar SW, Vaitl D, Ott U. Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. *Cereb. Cortex*. 2012. 11: 2692–2702. doi: 10.1093/cercor/bhr352
20. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. 2007. 133(4):581-624. doi: 10.1037/0033-2909.133.4.581
21. Grant JA, Courtemanche J, Rainville P. A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain*. 2011. 152:150–156. <https://doi.org/10.1016/j.pain.2010.10.006>
22. Grant JA, Rainville P. Pain sensitivity and analgesic effects of mindful states in Zen meditators: a cross-sectional study. *Psychosomatic Medicine*. 2009. 71:106–114. doi: 10.1097/PSY.0b013e31818f52ee
23. Hayes S, Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies. *Behavior Therapy*. 2004. 35, 639–665. [https://doi.org/10.1016/S0005-7894\(04\)80013-3](https://doi.org/10.1016/S0005-7894(04)80013-3)
24. Hayes SC, Strosahl KD, Wilson KG. *Acceptance and commitment therapy: The process and Practice of Mindful Change*. New York, NY: Guilford Press; 2012.
25. Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, Colaiaco B, Maher AR, Shanman RM, Sorbero ME, Maglione MA, *Mindfulness Meditation for Chronic Pain: Systematic Review*

and Meta-analysis, *Annals of Behavioral Medicine*. 2017. 51(2); 199-213. <https://doi.org/10.1007/s12160-016-9844-2>

26. Jensen MP, Thorn BE, Carmody J, Keefe FJ, Burns JW. The role of cognitive content and cognitive processes in chronic pain: An important distinction? *The Clinical Journal of Pain*. 2018. 34: 391–401. doi: 10.1097/AJP.0000000000000559.

27. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen. Hosp. Psychiatry*. 1982. 4, 33–47. [https://doi.org/10.1016/0163-8343\(82\)90026-3](https://doi.org/10.1016/0163-8343(82)90026-3)

28. Kabat-Zinn J, Lipworth L, Burney R. The clinical use of mindfulness meditation for the self-regulation of chronic pain. *J. Behav. Med.* 1985. 8, 163–190. doi: 10.1007/BF00845519

29. Kabat-Zinn J, Lipworth L, Burney R, Sellers W, Four year follow-up of a meditation-based program for the self-regulation of chronic pain: treatment outcomes and compliance. *Clin. J. Pain*. 1986. 2, 159–173. DOI: 10.1097/00002508-198602030-00004

30. Kabat-Zinn J. *Full catastrophe living: using the wisdom of your body and mind to face stress, pain, and illness*. New York: Bantam Books; 2013.

31. Luke SG. Evaluating significance in linear mixed-effects models in R. *Behav Res*. 2017. 49:1494-1502. doi: 10.3758/s13428-016-0809-y

32. Lutz A, Dunne J, Davidson R. Meditation and the neuroscience of consciousness: an introduction. *The Cambridge Handbook of Consciousness*, 2006. 19.

33. Lutz A, Greischar LL, Rawlings NB, Ricard M, Davidson RJ. Long-term meditators self-induce high-amplitude gamma synchrony during mental practice. 2004. 101 (46) 16369-16373; <https://doi.org/10.1073/pnas.0407401101>

34. Lutz A, Jha AP, Dunne JD, Saron CD, Investigating the phenomenological matrix of mindfulness-related practices from a neurocognitive perspective. *Am Psychol*. 2015. 70(7): 632–658. doi: 10.1037/a0039585

35. Lutz A, McFarlin DR, Perlman DM, Salomons TV, Davidson RJ. Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *Neuroimage*. 2013. 1;64:538-46. <https://doi.org/10.1016/j.neuroimage.2012.09.030>

36. Lutz A, Slagter HA, Dunne JD, Davidson RJ. Attention regulation and monitoring in meditation. *Trends Cogn Sci*. 2008. 12, 163–169. <https://doi.org/10.1016/j.tics.2008.01.005>

37. Maher JM, Markey JC, Ebert-May D. The Other Half of the Story: Effect Size Analysis in Quantitative Research. *CBE Life Sci Educ.* 2013. 12(3): 345–351. doi:10.1187/cbe.13-04-0082
38. Melzack R, Casey KL. Sensory, motivational and central control determinants of chronic pain: A new conceptual model. In: Kenshalo DR. *The skin senses: Proceedings of the first International Symposium on the Skin Senses, held at the Florida State University in Tallahassee, Florida.* 1968. P432-439.
39. Miron D, Duncan GH, Bushnell MC. Effects of attention on the intensity and unpleasantness of thermal pain. *Pain.* 1989. 39(3):345-52. [https://doi.org/10.1016/0304-3959\(89\)90048-1](https://doi.org/10.1016/0304-3959(89)90048-1)
40. Molenberghs G, Lesaffre E. Missing Data. *Methods and Applications of Statistics in Clinical Trials, Volume 1: Concepts, Principles, Trials, and Designs* by N. Balakrishnan. Chapter 42. Pages 522-535.
41. Orne MT. On the social psychology of the psychological experiment: With particular reference to demand characteristics and their implications. *American Psychologist.* 1962. 17(11), 776–783. <https://doi.org/10.1037/h0043424>
42. Peirce JW. Generating stimuli for neuroscience using PsychoPy. *Frontiers in Neuroinformatics.* 2009.2 (10), 1-8. doi: 10.3389/neuro.11.010.2008
43. Perlman DM, Salomons TV, Davidson RJ, Lutz A. Differential effects on pain intensity and unpleasantness of two meditation practices. *Emotion.* 2010. 10:65–71. doi: 10.1037/a0018440
44. Quartana PJ, Campbell CM, Edwards RR, Pain catastrophizing: a critical review. *Expert Rev Neurother.* 2009. 9(5): 745–758. DOI: 10.1586/ern.09.34
45. R core team. *R: A language and environment for statistical computing.* R Found. Stat. Comput. 2017. Vienna Austria.
46. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception – Part 1: Are there really differences between women and men? *PAIN.* 2012. 153; 602–618. <https://doi.org/10.1016/j.pain.2011.11.025>
47. Schutze R, Rees C, Preece M, Schutze M. Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. *Pain.* 148: 120–127. <https://doi.org/10.1016/j.pain.2009.10.030>.
48. Singmann H, Kellen D. (in press). An Introduction to Mixed Models for Experimental Psychology. In Spieler DH, Schumacher E (Eds.), *New Methods in Neuroscience and Cognitive Psychology.* Psychology Press.

49. Sprenger C, Eippert F, Finsterbusch J, Bingel U, Rose M, Büchel C. Attention Modulates Spinal Cord Responses to Pain. *Current Biology*. 2012. 22; 1019–1022. <https://doi.org/10.1016/j.cub.2012.04.006>
50. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*. 1995. 7(4), 524-532. doi:10.1037//1040-3590.7.4.524
51. Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*. 2001. 17:52-64. doi: 10.1097/00002508-200103000-00008.
52. Turner JA, Anderson ML, Balderson BH, Cook AJ, Sherman KJ, Cherkin DC. Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain: similar effects on mindfulness, catastrophizing, self-efficacy, and acceptance in a randomized controlled trial. *PAIN*. 2016. 157:2434–44. doi: 10.1097/j.pain.0000000000000696
53. Weber SJ, Cook T. Subject effects in laboratory research: An examination of subject roles, demand characteristics, and valid inference. *Psychological Bulletin*. 1972. 77(4), 273–295. <https://doi.org/10.1037/h0032351>
54. Zeidan F, Adler-Neal AL, Wells RE, Stagnaro E, May LM, Eisenach JC, McHaffie JG, Coghill RC. Mindfulness-meditation-based pain relief is not mediated by endogenous opioids. *J. Neurosci.*, 2016. 36(11):3391–3397. doi: 10.1523/JNEUROSCI.4328-15.2016
55. Zeidan F, Martucci KT, Kraft RA, Gordon NS, McHaffie JG, Coghill RC. Brain mechanisms supporting the modulation of pain by mindfulness meditation. *J. Neurosci.* 2011.31:5540–5548. doi: 10.1523/JNEUROSCI.5791-10.2011
56. Zeidan F, Emersion NM, Farris SR, Ray JN, Jung Y, McHaffie JG, Coghill RC. Mindfulness-meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness-meditation induced analgesia. *The Journal of Neuroscience*. 2015. 35(46):15307–15325. doi: 10.1523/JNEUROSCI.2542-15.2015
57. Zeidan F, Grant JA, Brown CA, McHaffie JG, Coghill RC, The neural mechanisms of mindfulness-based pain relief: a functional magnetic resonance imaging-based review and primer. *PAIN Reports*. 2019. 7;4(4):e759. Volume 4 - Issue 4 - p e759. doi: 10.1097/PR9.0000000000000759

Supplementary information

MethodsS1. State instructions

Written instructions

Distraction condition: Concentrate your mind on the numbers and visual cues on the screen. Whenever a new number appears, mentally add it to the total sum of the previous number(s). You should focus your attention only on the numbers and the cues. Block all other emotions, sensations, or thoughts that may arise during the calculation task. Be very focused so that you don't miss any number or cue.

OM condition: Start to anchor your attention in your body. Simply rest your body. Relax your muscles. Rest your mind without blocking anything. Allow everything to arise in the field of awareness as it is in the present moment. The body and the mind rest in unity. Gently watch the numbers and the cues appear on the screen. Pay attention to cues, while not doing anything in particular with the numbers. When the thermal stimulus arises, gently let it be a support for your attention. You know that you are feeling the sensation; you recognize it, while resting the mind on this support. While resting your attention on the thermal sensation, thoughts, or emotions may arise. Just let them be in the vast field of your awareness while remaining at ease in the present moment.

Auditory instructions

Distraction condition: Concentrate your mind on the number and the visual cues on the screen. You should focus your attention completely on the screen and the counting task. Block all the emotions, sensations and thought that arise during this task. Be very concentrated so that you don't miss any number or visual cue.

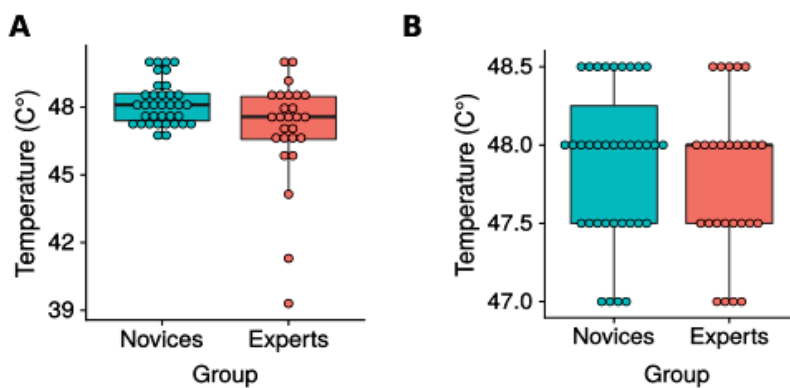
OM condition: Relax your body and your mind, there is no need to block anything. When the heat stimulation starts, gently be aware of it. Be aware of your experience of this sensation and let your mind relax with it. When any thoughts or emotions arise, let them be there in the vast space of your awareness.

MethodsS2. Pain calibration results

Supplementary Table 1. Temperature characteristics of pain calibration procedures.

	Novices	Experts	t-value	p-value
Temperature (pain threshold)	48.2 (1.0)	47.0 (2.4)	2.3	p = .027
Temperature (experiment)	47.9 (0.5)	47.8 (0.5)	0.8	p = .45

Data are presented as mean (standard deviation).



Supplementary Figure 1. Combined box-and-whisker dot plots for temperature characteristics pain calibration procedures. (A) Calibration results for pain threshold determination. **(B)** Calibration results for experimental pain temperature determination.

Note. Three experts had low pain sensitivity (<45 C°, see Fig. S1a). Further examination revealed that these data points were from three consecutive experts in terms of lab visit. Their visits also coincided with the arrival of a new student responsible for pain sensitivity calibration. We noticed that this student initially used unnecessary frightening language to explain the pain sensitivity calibration procedure to experts (novices did the pain sensitivity calibration at an earlier time point during the meditation weekend). This issue was corrected upon noticing but might explain the low pain sensitivity for these experts. This notion seems supported by the fact that the same experts had no problem tolerating the experimental temperature (≥ 47 C°) during the second calibration procedure, which was performed by the first author. It is unlikely that this issue will have influenced the results in an undue manner, as it were only some experts with relatively higher pain sensitivity (not novices), but findings mainly relate to larger sensory-affective uncoupling for experts, which goes in the other direction of what higher pain sensitivity for experts is expected to influence the results. Once we removed these 3 expert meditators, all interaction effects of the main model were still present, and post-hoc test yielded similar significant results.

MethodsS3. Self-reports

Different self-report questions:

‘Intensity: How hot was the stimulation?’

Labels: 1 = Not at all, 9: Extremely hot

‘Unpleasantness: How much did the stimulation bother you?’

Labels: 1 = Not at all, 9: Extremely

‘Relief’: How relieved where you by the end of the stimulation?’

Labels: 1 = Not at all, 9: Extremely

‘Meditation Instruction’: To what degree where you able to follow the instruction?’

Labels: 1 = Not at all, 9: Completely

‘Addition’: What is the total sum of the numbers that were presented?’

5 different two digit-numbers were presented, one of which was the correct answer.

Presentation frequency:

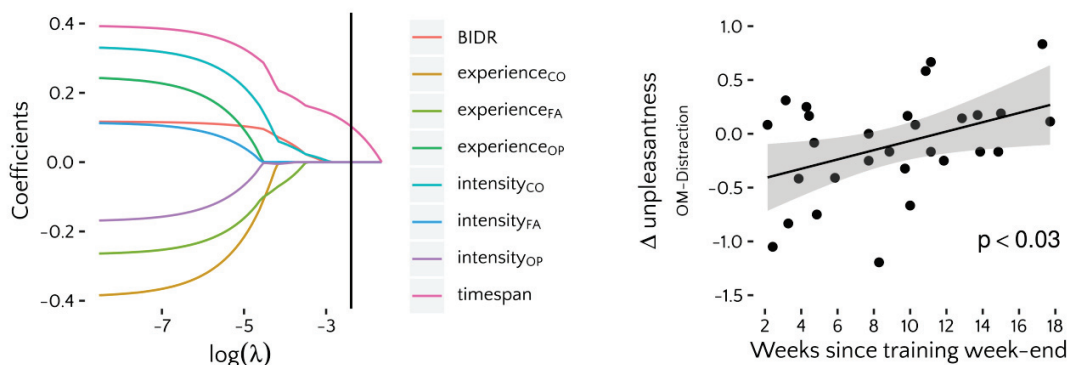
<u>OM condition:</u>		
10 x Warm Long	10 x Hot Long	10 x Short Long
6 x Unpleasantness	6 x Unpleasantness	6 x Unpleasantness
6 x Relief	6 x Relief	6 x Relief
4 x Intensity	4 x Intensity	4 x Intensity
4 x Meditation	4 x Meditation	4 x Meditation
<u>Distraction condition:</u>		
10 x Warm Long	10 x Hot Long	10 x Short Long
6 x Unpleasantness	6 x Unpleasantness	6 x Unpleasantness
6 x Relief	6 x Relief	6 x Relief
4 x Intensity	4 x Intensity	4 x Intensity
4 x Addition	4 x Addition	4 x Addition

ResultsS1. Relation between state effect and novice practice metrics

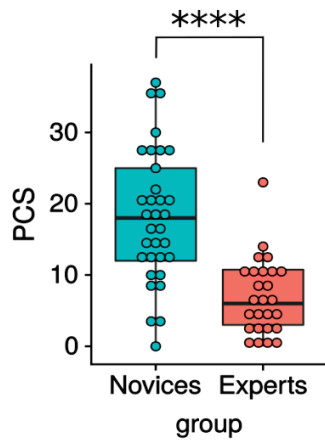
Our novice participants showed a reduction in unpleasantness in OM compared to the Distraction condition. In order to assess whether such effect is associated to novices' meditation home practice, we modeled the individual state effect on unpleasantness (difference in self-reported unpleasantness between OM and Distraction) as a function of two metrics of practice: the average daily practice in minutes (thereafter referred to as Intensity) and the total amount of practice in hours since the meditation training (Experience). In previous work we found highly specific associations between effects on self-reports on one hand, and metrics (Intensity or Experience) and practices (e.g. FA or OM) on the other hand (Abdoun et al. 2019). Therefore, we computed Intensity and Experience separately for each of the 3 practices that our participants were trained at (FA, OM and compassion - CO). An evident hypothesis for the present experiment is that the practice of OM would be the best predictor of the observed reduction in unpleasantness during OM. As control variables, we also included participants' score to the Balanced Inventory of Desirable Responding (BIDR), and the time elapsed since the meditation week-end (timespan).

Given the high number of predictors (8) compared to the small sample size (29), we used a LASSO regression to select the best predictors. LASSO regression uses a penalty on the regressors to force certain coefficients to be set to zero. This regularization process produces a sparse model that optimizes prediction while reducing overfitting (Tibshirani, 1996). We used the R glmnet package to perform the LASSO regression (Friedman et al. 2019). glmnet performs LASSO regression for a whole range of regularization parameter values and selects the optimal one using a cross-validation scheme.

The model selected by the LASSO regression contains a single predictor, timespan. Contrary to our prediction, metrics of OM practice were not selected (Fig. S2a). A post-hoc correlational analysis shows that timespan significantly predicts the state effect on unpleasantness ($r=.41$, $p=.027$, Fig. S2b).



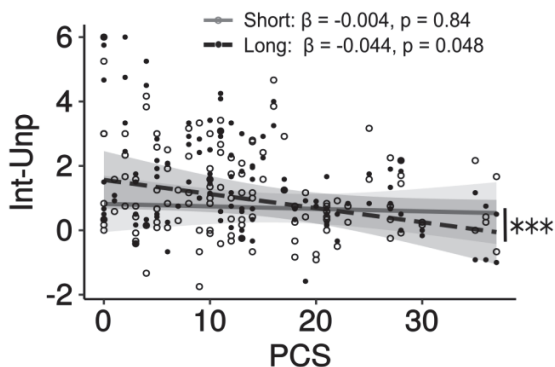
Supplementary Figure 2. Predictors of the state effect on unpleasantness in novices. (A) Standardized coefficients as a function of the regularization parameter λ . At the optimal value of λ (black line), timespan is the only selected predictor. **(B)** Timespan significantly predicts the state effect on unpleasantness.



Supplementary Figure 2. Group difference in pain catastrophizing

ResultsS3. Complementary PCS analysis

To test the specificity of the relationship between pain catastrophizing and sensory-affective uncoupling of pain, we performed an additional analysis to examine whether pain catastrophizing could predict the degree of sensory-affective uncoupling of pain, specifically for long painful stimuli, up and above the effect of meditation expertise. To this end, we fitted a model that included Trial Type (Short, Long), State (OM, Distraction) and PCS (continuous variable) as fixed effects and a Decoupling index (within subject difference intensity-unpleasantness) as dependent measure, as well as Group (Novices, Experts) as additional fixed effect covariate. We observed a PCS x Trial Type interaction ($\chi^2(1) = 13.0, p < .001$). Post-hoc tests revealed that, across participants, pain catastrophizing negatively predicted the degree of reported sensory-affective uncoupling of pain, specifically for the long but not short painful stimulations (long: estimate = -0.044 , SE = 0.02 , $t(61) = -2.01$, $p = .048$, 95% CI $[-0.09, -0.00]$; short: estimate = -0.004 , SE = 0.02 , $t(57) = -0.2$, $p = .83$, 95% CI $[-0.05, 0.04]$) (Fig. S4).



Supplementary Figure 4. Relationship between pain catastrophizing and reported sensory-affective uncoupling of pain. Across participants, pain catastrophizing specifically predicted the degree of sensory-affective uncoupling of pain for long painful stimuli, even after controlling for the effect of meditation expertise.

Cognitive defusion is a core cognitive mechanism for the sensory-affective uncoupling of pain during mindfulness meditation

In review at *Psychosomatic Medicine*

Zorn J., Abdoun O., Sonié S., Lutz A.

Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR5292, Lyon 1 University,
Lyon, France

Abstract

Objective: Mindfulness meditation can downregulate the experience of pain. However, its specific underlying regulatory mechanisms are still largely unknown. Here, we aimed to investigate the role of cognitive defusion in mindfulness-based pain regulation. **Methods:** We implemented a thermal heat paradigm that was designed to amplify the cognitive-affective aspects of pain experience in novice (2-day formal training; average ~20h home practice) and expert meditators (>10.000h practice). We collected pain intensity and unpleasantness reports, and trait measures of pain catastrophizing assessed by the Pain Catastrophizing Scale (PCS), cognitive defusion assessed by the Drexel Defusion Scale (DDS), and cognitive fusion assessed by the Cognitive Fusion Questionnaire (CFQ), as well as of several other constructs commonly reported in the literature. **Results:** Experts reported significantly lower PCS but higher DDS than novices. Furthermore, across participants, the PCS and DDS were negatively correlated and shared unique variance that survived controlling for other mindfulness-related and other cognitive-emotional constructs. Conversely, the relationships between PCS and other constructs commonly reported in the literature did not appear specific as none of the relationships survived controlling for DDS. In further support of the relevance of DDS to pain, both the DDS and PCS specifically predicted pain unpleasantness as opposed to pain intensity. However, DDS appeared a more specific predictor of pain unpleasantness than PCS, as the relationship between DDS and unpleasantness survived controlling for PCS, but not vice versa. At a reviewer's request we further included the CFQ. While this measure behaved very similarly to DDS in relationship to PCS and pain self-reports, it showed a less specific relationship with questionnaire measures compared to DDS. **Conclusions:** Collectively, these findings highlight the central role of cognitive defusion in mindfulness-based pain regulation.

Keywords: Mindfulness meditation, cognitive defusion, pain catastrophizing, pain affect, dereification, cognitive distancing, emotion regulation, meta-awareness.

1. Introduction

An early Buddhist account describes pain as being composed of two distinct “arrows”: an immediate physical sensation and a secondary response linked to negative mentation. It is claimed that although negative mentation often habitually follows awareness of unpleasant physical stimuli, this need not be necessarily so, as for individuals trained in mindfulness meditation it is possible to uncouple the immediate pain sensation from the affective reactivity to it, allowing the physical component to be fully experienced without concomitant emotional distress (Bodhi, 2005).

In line with early contemplative notions, pain is now generally considered a multidimensional experience comprising, sensory-discriminative, affective-motivational and cognitive-evaluative dimensions (Melzack and Casey, 1968; Tracey and Mantyh, 2007). Furthermore, the efficacy of mindfulness-based interventions (MBIs) for chronic pain management is increasingly supported by the clinical literature (Hilton et al., 2017), whereas experimental studies indicate that mindfulness meditation is indeed primarily associated with reductions in pain unpleasantness as opposed to intensity in healthy participants, as reviewed by Zeidan et al., 2019. However, the specific cognitive mechanisms underlying mindfulness-based pain regulation still remain largely debated (e.g. Zeidan et al., 2019).

It has been proposed that mindfulness meditation may reduce pain by counteracting the detrimental effects of pain catastrophizing, which refers to “an exaggerated negative 'mental set' brought to bear during actual or anticipated pain experience” (Sullivan et al., 2001), and is a key predictor of increased pain in healthy and clinical samples (Quartana et al., 2009; Sullivan et al., 2001), as well as of the maintenance and exacerbation of chronic pain (Edwards et al., 2016; Gatchel et al., 2007); making it an important clinical treatment target. Pain catastrophizing, refers to a type of conceptual processing that is reactive, judgmental and, often, implicit. This can be contrasted with the specific cognitive attitude cultivated during mindfulness meditation, which consists of a “nonelaborative, nonjudgmental, present-centered awareness” (Bishop et al., 2004). Thus, mindfulness and pain catastrophizing can be construed as antithetical constructs.

Several studies have examined statistical relations between pain catastrophizing as measured by the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995), a reference standard psychometric tool for pain catastrophizing; and mindfulness (most frequently) as measured by the Five Facet Mindfulness Questionnaire (FFMQ) (Baer et al., 2006), a popular mindfulness questionnaire that purports to measure five mindfulness dimensions: Non-Judging, Non-Reacting, Act Aware, Observing and Describing. Supporting the idea that mindfulness and pain catastrophizing are antithetical constructs, these studies have typically observed inverse correlations between the PCS and Non-Judging, Non-Reacting and Act Aware (but not Observing and Describing) FFMQ facets (Day et al., 2015, Turner et al., 2016; Schutze et al., 2010; Elvery et al., 2017). However, the specificity of these findings is questioned by one of the studies, which found that none of the significant relationships between PCS and FFMQ facets survived

controlling for worry -an anxiety-related construct- thus underlining the need to control for other more general cognitive-emotional constructs when examining relations between PCS and mindfulness-related constructs (Day et al., 2015). Importantly, the non-specificity of the relationship between PCS and FFMQ facets raises the question whether there are other mindfulness-related constructs that show a more specific relationship to PCS.

The question of specificity is not only relevant to elucidating the mechanisms of mindfulness-based pain regulation, but could also inform a larger debate. Specifically, a question at the forefront of the field is whether different psychosocial treatments act by specific or common mechanisms of action (Jensen, 2011; Thorn et al., 2011). As pointed out by Day et al., 2015, addressing this question first requires a clear understanding of how the different statistical instruments used to measure relevant psychological constructs overlap before any treatment intervention. Given the centrality of pain catastrophizing to chronic pain, it would be particularly useful to identify psychological constructs that show a specific inverse relationship to -i.e. share unique variance with- pain catastrophizing, so that it can be studied how such constructs are similarly or differently affected by different treatment interventions.

Another candidate cognitive mechanism underlying mindfulness-based pain regulation -with potential cross intervention and transdiagnostic relevance- is cognitive defusion, which refers to “the ability to gain psychological distance from internal experiences such as thoughts and feelings, seeing them as mere events in the mind rather than as accurate, truth-based reflections of reality” (Forman et al. 2012). Cognitive fusion (the antithesis of defusion) refers to a mental state where one is entangled in thoughts to the extent that they are taken literal and dominate feelings and behavior (Hayes et al., 1999; 2006). With mindfulness meditation, the capacity for cognitive defusion is presumably developed through the non-reactive monitoring of experience (Lutz et al., 2015). Specifically, the sustained cultivation of a mental state that notices but does not engage in conceptual elaboration -facilitated by paying attention to present moment sensory experience- is thought to foster a change in perspective from being entangled into the contents of experience onto that experience. This allegedly enables one to become aware of the usually implicit features of one’s mental life, including the thinking process itself -a process known as meta-awareness. This, in turn, allows for the recognition that thoughts are simply mental events and not the things that they seem to represent -a capacity labeled dereification or metacognitive insight. Notably, while some mindfulness accounts (e.g. Lutz et al. 2015), clearly distinguish meta-awareness and dereification as core cognitive mechanisms of mindfulness meditation, these constructs are commonly treated as identical in the psychological literature of “cognitive defusion” (Hayes, 2004) and “decentering” (e.g., Fresco et al., 2007a). Given that we aimed to test the importance of meta-awareness and dereification to (mindfulness-based) pain regulation (and well-validated measures for these constructs are lacking), we chose to focus on cognitive defusion rather than on decentering, as, to our knowledge, the former is largely limited to these dimensions, whereas the latter also includes acceptance/compassion dimensions (see Hadash et al., 2017); which, although both relevant to mindfulness meditation, are

beyond the scope of the present work. Of note, cognitive defusion is not only a hypothesized action mechanism of mindfulness meditation, but also of acceptance-based therapies -from where the construct derives (Hayes et al., 1999), and of cognitive behavioral therapy (CBT), for which incidental increases in defusion-related constructs have been observed (Teasdale et al., 2001). Furthermore, changes in defusion-related constructs have already been shown to underlie therapeutic change in depression (Bieling et al., 2012), and social anxiety disorder (Hayes-Skelton and Lee, 2018). Nevertheless, the construct has received little attention in pain research, although some studies have reported positive associations between defusion-related constructs and improved pain outcomes in chronic pain patients (McCracken et al., 2013a/b, 2014).

From the perspective of cognitive defusion, pain catastrophizing is an example of a state of high cognitive fusion, where pain-related thoughts such as “It’s killing me” or “this lasts forever” appear realistic and thus provoke fear and emotional distress (McCracken et al., 2014; Hayes et al., 1999), and, consequently, pain amplification (Leeuw et al., 2007). Conversely, in a meditation-related cognitively defused state, the same thoughts or feelings may still occur, but can be perceived from a distanced perspective as mere mental events that are not necessarily accurate, making them lose their representational integrity, diffusing emotional responding and secondary elaborative processing as a result (Kabat-Zinn, 1982, Chambers et al., 2009). It has been suggested that this process might produce an uncoupling of the sensory component of pain from its affective and cognitive dimensions (Kabat-Zinn, 1982). Thus, cognitive defusion and pain catastrophizing are possibly antithetical constructs with an inverse relationship to pain experience. The present work aimed to test this hypothesis.

Previously, we reported evidence that low pain catastrophizing is a marker of mindfulness-related sensory-affective uncoupling of pain (Zorn et al. 2020). Specifically, when comparing novice (2-day formal training; average ~20h home practice) to expert meditators (>10.000h meditation training) during an acute pain task that was designed to amplify the cognitive-affective aspects of pain experience –through the implementation of (16s) long pain stimuli and the manipulation of pain anticipation, we found that experts reported significantly lower pain catastrophizing (PCS) and PCS negatively predicted sensory-affective uncoupling of pain (defined as the difference between intensity and unpleasantness ratings). Thus, participants from this experiment, and from a larger sample that did not participate in the specific pain experiment, provided an interesting sample to test our hypotheses. We collected two self-report measures of cognitive (de)fusion: the Drexel Defusion Scale (DDS; Forman et al., 2012) and the Cognitive Fusion Questionnaire (CFQ; Gillanders et al., 2014). Whereas the DDS is designed to measure defusion, the CFQ has been designed to measure cognitive fusion (Gillanders et al., 2014). As we were primarily interested in the regulatory mechanisms underlying mindfulness meditation (i.e. cognitive defusion), we chose to focus on the DDS in this work. At the request of a reviewer, we also reported CFQ in an exploratory manner.

The purpose of the current study was twofold. A first aim was to examine the relationships between pain catastrophizing as assessed by the PCS, and several mindfulness-related constructs, including: 1) the FFMQ scales, 2) the DDS, and 3) interoceptive awareness as assessed by the MAIA scale (Mehling et al., 2012). Based on previous research, we hypothesized that all included mindfulness constructs (except the Observing and Describing FFMQ scales) would be negatively correlated with the PCS. However, based on the theoretical notion that cognitive fusion (the antithesis of cognitive defusion) is at the root of what causes one to catastrophize about pain (i.e. entanglement/believing in thoughts), we expected the strongest negative overlap between PCS and DDS. For this reason, we also expected that the DDS would share unique variance with the PCS that would survive controlling for variance shared with other cognitive-emotional constructs such as anxiety, worry and depression, as well as for interoceptive awareness. A second aim was to investigate the relation of DDS and PCS to pain-related outcomes. To this end, we first examined their association with pain intensity and unpleasantness reports of novice and expert meditators collected during the acute pain task. In line with our previous report, we expected that PCS and DDS would both primarily predict pain unpleasantness as opposed to intensity, but in the opposite direction: positively and negatively respectively. We also examined the specific relationship of both constructs to pain self-reports, i.e. the unique predictive value of PCS and DDS to pain ratings, controlling for shared variance. This exploration was open-ended.

2. Material and Methods

2.1 Participants

Participants were recruited for the *Brain and Mindfulness* ERC-funded project, which includes a cross-sectional observational study on mindfulness meditation conducted at the Lyon Neuroscience Research Center from 2015 to 2018. Participants included novice and long-term meditation practitioners (hereafter referred to as experts), who were recruited through multiple screening stages which have been reported into detail elsewhere (see the Brain & Mindfulness Project Manual, Abdoun et al., 2018). Meditation-naïve participants were recruited locally through flyers and posters in public spaces, mailing lists, Facebook, and notifications to research participant databases. Experts were recruited through networking by a long-term meditation practitioner with extensive contacts with communities in multiple Buddhist meditation centers, predominantly in France but also internationally. Inclusion criteria included: age between 35 and 65 years, no psychotropic drug use, no neurological or psychiatric disorder, a Beck Depression Inventory (BDI) score below 20, no family history of epilepsy, no severe hearing loss and affiliation to the social security system (mandatory for research participation in France). Pregnant and breastfeeding women were excluded. Novices were additionally required not to have significant experience with meditation or other mind-body training techniques. Experts were required to have: a minimum of 10.000 hours of formal practice in the Kagyu or Nyingma schools of Tibetan Buddhism, ii) followed at least one traditional 3-year

meditation retreat, iii) a regular daily practice in the year preceding inclusion. For experts, inclusion criteria were checked during a phone-interview by the long-term meditation practitioner in charge of expert recruitment who was extensively familiar with the meditation traditions at hand. A total of 43 novices (53.2 ± 7.0 years old, 22 females) and 27 experts (51.9 ± 8.4 years old, 12 females) were included in the present study. All participants underwent a medical check and provided written informed consent before participating in the study. The study was approved by the regional ethics committee on Human Research (CPP Sud-Est IV, 2015-A01472-47).

2.2 Power analysis

We conducted a power analysis to determine the effect sizes we had the power to detect with N = 70 (the number of subjects available). This revealed that we had 80% power to detect correlation coefficients with medium effect sizes ($r = .33$) at $\alpha=0.05$ (two-tailed). We reckoned that this was at the low end for these types of studies: correlations between PCS and relevant FFMQ-scales (Non-Reacting/Non-Judging) are usually between $r = -.20$ to $-.35$ (Day et al., 2015; Schutze et al., 2010; Elvery et al., 2017; Turner et al., 2016). However, our study differed from these other studies in that our sample of novices and experts was expected to cover an extended range of trait values compared to other more conventional samples. Such increased sample variance is associated with an increase in correlation coefficients and hence power (see methods). For this reason, and because assumptions were met (we observed an extended range of trait values by the inclusion of experts and higher correlation coefficients compared to the literature), we considered statistical power to be within acceptable levels.

2.3 Meditation practices and novice training protocol

Two broad styles of mindfulness meditation are Open Monitoring (OM) and Focused Attention (FA) meditation. Both styles are complementary and central to MBIs. Traditionally, initial FA practice is considered a prerequisite for OM (Lutz et al., 2008). FA involves the sustained focusing of attention of a selected object (e.g. the breath), non-judgmentally noticing when the mind has wandered, and redirecting attention back to the intended object. This is said to increase the capacity to detect distractions and to calm the mind. The resulting improved monitoring capacity (i.e. meta-awareness), forms the transition point to OM, which involves the non-selective and non-reactive monitoring of all present moment experience (Chambers et al., 2009; Lutz et al., 2008). The purpose of OM practices is to gain insight into cognitive-emotional patterns, including the realization that thoughts are not necessarily real, but mere mental events (i.e. dereification). It is in this sense that OM practice may promote cognitive defusion - i.e. psychological distance from thoughts and feelings, seeing them as mere mental events rather than as intrinsically real (Forman et al., 2012). Importantly, repeated meditation practice is thought to foster trait change, including in the capacity for cognitive defusion (Lutz et al., 2015). Novices were initially

meditation-naïve -including when trait measures were obtained, but extensively familiarized with both practices during a meditation weekend led by an experienced meditation teacher (see Abdoun et al., 2019 for an extensive description of the training protocol). Subsequently, novices participated in the pain paradigm having, on average, ~20h of home (FA and OM) practice experience (see Zorn et al., 2020). Experts were extensively familiar with both practices, including with an advanced style of OM labeled Open Presence (OP) (Rangdrol, 2011). In this state, control-oriented elaborative processes are reduced to a minimum and a suspension of subject-object duality (non-duality) is also reportedly involved. These features are thought to further strengthen the practitioner's capacity for cognitive defusion. To summarize, the total sample could be expected to range from low to moderate (novices) to high (experts) cognitive defusion, which we considered a strength of the present work as it provided an extended range to study relationships between constructs.

2.4 Questionnaires

All participants filled a battery of self-administered questionnaires (for a complete overview, see the Brain & Mindfulness Project Manual, Abdoun et al., 2018). Novices filled the questionnaires prior to participation in the meditation weekend. Experts filled their questionnaires either during their visit or from home afterwards. Questionnaires included in the present work are listed below.

Drexel Defusion Scale (DDS)

The DDS is a 10-item questionnaire that measures one's ability to distance themselves from a variety of psychological experiences. The questionnaire starts with an extensive introduction on the concept of defusion that is intended to help respondent's understand the construct. Participants are asked to indicate the degree to which they would be able to defuse from hypothetical situations with negative thoughts or feelings on a 6-point Likert scale ranging from "not at all" (0) to "very much" (5). Higher scores indicate higher cognitive defusion. The DDS has shown good preliminary internal consistency ($\alpha = 0.83$), and high convergent and divergent validity (Forman et al., 2012).

Cognitive Fusion Questionnaire (CFQ)

The CFQ is a 7-item questionnaire that measures cognitive fusion (Gillanders et al., 2014). Participants are asked to indicate to what degree statements about cognitive fusion apply to them in general on a 7-point Likert (1= Never true; 7 = Always true). Items are combined to yield a total score. The CFQ showed good internal consistency ($\alpha = .88$ to $.93$ for different samples) and convergent and divergent validity in its initial validation (Gillanders et al., 2014).

Pain Catastrophizing Scale (PCS)

The PCS is a 13-item questionnaire that asks respondents to reflect on past painful feelings and to indicate to what degree they experienced different pain-related thoughts or feelings on a 5-point Likert-scale from 0 (not at all) to 4 (all the time). The PCS comprises three subscales of rumination, magnification and helplessness which are combined to yield a total score. Higher scores reflect higher pain catastrophizing (Sullivan et al., 1995). The PCS has been found to show excellent internal consistency ($\alpha = 0.93$), concurrent and discriminant validity (Osman et al., 1997), and good test-retest reliability over a 6-week period ($r = 0.75$) (Sullivan et al., 1995).

Five Facet Mindfulness Questionnaire (FFMQ)

The FFMQ is a 39-item questionnaire that measures five purported mindfulness dimensions including: Observing (noticing or attending to internal/external experiences), Describing (labeling internal experiences with words), Acting with awareness (attending to present moment experience), Non-Judging (adopting a non-evaluative stance towards thoughts and feelings) and Non-Reacting (allowing thoughts and feelings to pass). Participants indicate to what degree they experience these dimensions in their daily life on a 5-point Likert-type scale ranging from 1 (never or very rarely true) to 5 (very often or always true). Scores are calculated separately for subscales, with higher scores reflecting higher mindfulness. The FFMQ facets have been found to demonstrate adequate to good internal consistency, with alpha coefficients ranging from .75 to .91 (Baer et al., 2006).

Multidimensional Assessment of Interoceptive Awareness (MAIA)

The MAIA is a 32-item questionnaire that measures different aspects of interoceptive body awareness including: Noticing, Not Distracting, Not Worrying, Attention Regulation, Emotional Awareness, Self-Regulation, Body Listening, Trusting. Responses are provided on 6-point Likert-scales that range from 0 (Never) to 5 (Always). The different subscales have adequate to excellent internal consistency ($\alpha = .66$ to $.87$). Scales can be combined to yield a total score. Higher scores indicate higher positive interoceptive awareness (Mehling et al., 2012).

Penn-State Worry Questionnaire (PSWQ)

The PSWQ is a 16-item questionnaire that measures the propensity to worry, using Likert rating from 1 (not at all typical of me) to 5 (very typical of me). A total score can be calculated, and higher scores indicate higher trait worry (Meyer et al., 1990). The PSWQ has shown good internal consistency with alpha coefficients ranging from .88 to .95 (Startup and Erickson, 2006), and good test-retest reliability over 8-10 weeks ($r = 0.92$) (Meyer et al., 1990).

State-Trait Anxiety Inventory (STAI)

The STAI is a 40-item questionnaire that measures state and trait anxiety. For the purpose of the current study we only used the STAI trait scale (20-items) which asks respondents to describe how they generally feel. All items are rated on a 4-point scale, from 1 (almost never) to 4 (almost always). Higher scores indicate greater anxiety. The STAI has shown good internal consistency with alpha coefficients ranging from .86 to .95, and test-retest reliability coefficients ranged from .65 to .75 over a 2-months period (Spielberger., 1983).

Beck Depression Inventory (BDI)

The BDI is a 21-item questionnaire that measures characteristic attitudes and symptoms of depression. Each question has four scores ranging from 0 (symptom not present) to 3 (symptom very intense). A total sum score is calculated to reflect depression severity (Beck, et al., 1961). The BDI-I has shown good internal consistency with alpha coefficients of .86 and .81 for psychiatric and non-psychiatric populations respectively, and good concurrent and discriminant validity (Beck et al . 1988).

2.5 Acute pain paradigm

2.5.1 Inclusion

A subsample of included participants participated in an acute pain paradigm that was conducted in an fMRI-scanner (neuroimaging results will be published in a separate publication). To be eligible for this experiment, participants had to be MRI-compatible (absence of claustrophobia/internal magnetic objects). Novices were additionally required to have a pain sensitivity equal to or higher than 47 C°: comparable to the higher pain thresholds that have been observed for experienced practitioners in previous studies (Lutz et al., 2013; Grant et al., 2011). This served to avoid the introduction of artificial group differences in neuroimaging analyses. A subset of 29 novices (13 females) and 25 experts (12 females) met the additional inclusion criteria and participated in the acute pain paradigm.

2.5.2 Pain calibration

The pain calibration procedure has been described in detail elsewhere (Zorn et al., 2020). Briefly, painful stimuli were provided by a TSA 2001-II thermal stimulator (Medoc Advanced Medical Systems, Haifa, Israel) with a 30 mm × 30 mm flat thermode applied to the palmar side of the left wrist. Using the method of limits (Fruhstorfer et al., 1976), all participants underwent an initial calibration procedure to determine their pain sensitivity corresponding to a subjective pain level of 7 on a scale of 0 (“no pain”) – 10 (“the worst pain imaginable”). A second finer calibration procedure was performed to determine the optimal temperature for a 16s long heat stimulation that would be used during the experiment itself.

2.5.3 Experimental design

The experimental setup and behavioral results of the acute pain paradigm have been reported into detail elsewhere (Zorn et al., 2020). Briefly, the task was designed to amplify the cognitive-affective aspects of pain experience: through the implementation of long tonic-like pain stimuli, which have been suggested to better mimic chronic pain states (Racine et al., 2012), and the manipulation of pain anticipation, which may induce anxious pain anticipation (e.g. Ploghaus et al., 2001). Participants received short (8s) and long (16s) noxious thermal heat stimuli (pain level of 7) intermixed with 16s nonpainful warm control stimuli (6 degrees cooler). All stimuli were applied to the palmar side of the left wrist. During anticipation and reception of thermal stimuli, participants performed one of two task conditions: Open Monitoring meditation (OM) or a Distraction control condition (DIS) that was intended to prevent participants from cultivating a meditative stance towards pain. See Figure 1 for more details on the experimental paradigm. See Supplementary Information 1 for full task instructions.

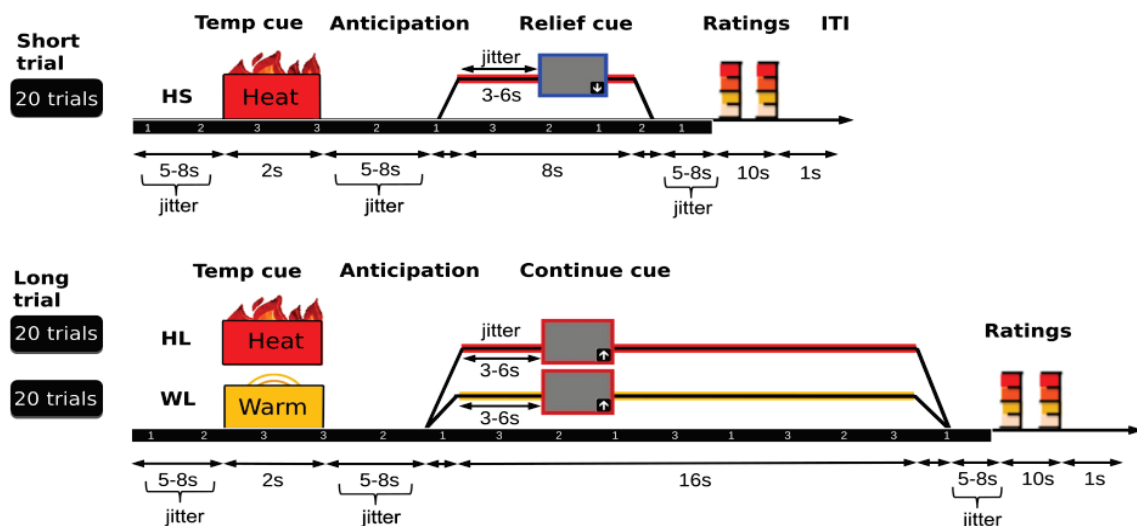


Figure 1. Schematic illustration of the experimental paradigm. Each trial started with a 5-8 sec introductory period. A 2s veridical visual cue then appeared that indicated whether the temperature of the upcoming stimulation would be nonpainful warm (image of radiating heat) or painful hot (image of burning flames), followed by a 5-8 s anticipation period before stimulus onset. A thermal stimulation (to the palmar side of the left wrist) was then delivered. A second visual cue (3-6 s after stimulus onset) informed participants about whether the unfolding stimulation would be short (8 s) or long (16 s) (and served a psychological relief manipulation not reported here). Nonpainful warm stimuli were always long and provided a baseline control condition for the MRI. Following stimulus offset, a 5-8 s rest period preceded the presentation of two rating scales (5 s each) (see main text for rating types). During each trial, a simple single-digit number (1-3) was presented every 2 s from the start of the trial until rating scales were displayed (see black horizontal bars). Subjects randomly alternated between two task conditions: Distraction, involving the mental addition of the numbers and a blocking of all pain experience or OM involving the cultivation of an open attitude to pain (and no mental addition). Participants received a total of 10 thermal stimuli for each combination of trial type (Short Hot; Long Hot; Long Warm) by task condition (OM; Distraction); 60 thermal stimuli in total. ITI: intertrial interval (adapted from Zorn et al. 2020).

2.5.4 Pain ratings

After each thermal stimulation, participants provided two self-reports using 1-9 Item Likert scales. Questions were presented randomly and included questions on pain intensity, unpleasantness (and relief not reported here). Participants were informed that pain intensity referred to the sensory aspect of stimuli; whereas pain unpleasantness related to their affective reaction to it (i.e. how much it bothered them). Additionally, task performance was probed (OM: quality of meditation; DIS: final sum addition task) and analyzed as part of our previous report (Zorn et al., 2020), leading to the exclusion of 1 expert due to poor counting task performance. This expert was also excluded from the analyses of the associations between pain ratings and trait scores in the present work. See Supplementary Information 2 for an overview of rating scale questions and frequency of presentation.

2.6 Analysis

All statistical analyses were performed using R version 3.4.4 (R Core Team, 2017).

Correlations. We used zero-order correlations and partial correlations to explore the relationships between traits, and between traits and pain ratings. One benefit of our sample combining novices and experts is that it offers extended ranges of values on all measures, and therefore provides higher sensitivity for correlational analyses (Bland and Altman 2011). However, a limitation of such a sample is that it cannot be directly compared to the existing literature, as the extended range is expected to produce higher correlation coefficients compared to typical samples composed of either healthy or clinical participants, with more restricted ranges. In order to allow for a quantitative comparison of our results with those previously reported in the literature (notably between PCS and other trait questionnaires), we re-estimated the correlation coefficients after restricting the range of our data to typical ranges by mean-centering each group of participants. As most of the measures could be affected by age (Cassidy et al., 2012) or sex (Keogh, 2006), covariates (e.g. sex, age) were regressed out by adding them as controlling variables. Group differences on these scores were tested using Wilcoxon-Mann-Whitney tests which are more robust to violations of assumptions required by equivalent parametric tests.

Pain ratings. Pain self-reports have been analyzed in depth in a separate publication (Zorn et al., 2020), in which we showed that, across task conditions and groups, PCS negatively predicted sensory-affective uncoupling of pain specifically for long but not short trial types -in line with the idea that tonic-like pain stimuli better mimic chronic pain states (Racine et al., 2012). Given that the present work aimed to study the respective relationship of PCS and DDS to sensory and affective pain dimensions, we here chose to limit our analyses to long pain stimuli, which provided the most sensitive test. Furthermore, given that we were interested in studying the relationship between trait measures and pain experience, pain ratings were averaged across states to obtain trait-like scores for each subject, for each pain dimension (intensity and unpleasantness). Finally, to allow us to test specifically whether trait measures predicted pain

intensity, unpleasantness or both - usually complicated by the high correlation between these measures, pain intensity was partialled out from the correlations between trait scores and pain unpleasantness (and vice versa).

3. Results

3.1 Concurrent validity of DDS and PCS

As Table 1 shows, all scales and subscales had good to excellent internal consistency as indexed by their Cronbach's alpha coefficients. In addition, Table 1 shows, for each scale and subscale, means, standard deviations and sample size for the total sample (first row), and Novice (second row) and Expert (third row) group, including a test for group differences as assessed by Wilcoxon-Mann-Whitney tests and Cohen's *d* standardized measure of effect size (fourth row). All group differences reached statistical significance, with experts scoring higher on mindfulness-related measures including DDS, CFQ, MAIA and FFMQ scales, but lower on measures of general negative cognitive-emotional constructs including, PCS, PSWQ, STAI and BDI compared to novices.

		FFMQ												
		PCS	DDS	CFQ	FFMQ						MAIA	PSWQ	STAI	BDI
					OBS	DESC	ACT	nJDG	nRCT	total				
All (n=70)	α	.93	.88	.92	.80	.92	.90	.86	.89	.95	.96	.92	.93	.80
	M	13.2	33.0	20.5	30.6	27.5	28.6	30.9	24.0	141.6	102.4	44.8	36.8	4.0
	SD	8.9	8.3	7.5	4.9	6.4	6.2	5.5	5.7	24.0	27.9	11.4	8.8	3.9
Novices (n=43)	M	17.2	28.9	24.0	28.7	25.4	26.4	28.8	21.2	130.4	89.0	49.6	39.5	5.1
	SD	8.5	6.6	6.7	4.6	5.6	5.8	5.4	4.5	20.3	25.6	11.4	9.0	4.3
Experts (n=27)	M	6.9	39.4	14.9	33.8	31.0	32.1	34.1	28.4	159.4	123.7	37.3	32.5	2.3
	SD	5.2	6.4	4.8	3.6	6.3	5.0	4.0	4.3	18.0	15.2	6.4	6.8	2.4
Group difference	<i>d</i>	1.40	1.61	1.50	1.19	0.95	1.05	1.10	1.63	1.50	1.56	1.26	0.85	0.75
	<i>p</i>	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	.001

Table 1. Summary data for psychometric scales. The first line displays Cronbach's alpha coefficients (α) for each scale and subscale. Further displayed for each scale and subscale are means, standard deviations and sample sizes for all participants (first row), Novices (second row) and Experts (third row), including a test for group differences as assessed by Wilcoxon-Mann-Whitney tests and Cohen's *d* standardized measure of effect size (fourth row). *Pain Catastrophizing Scale*, *DDS*: *Drexel Defusion Scale*, *CFQ*: *Cognitive Fusion Questionnaire*, *FFMQ*: *Five Facet Mindfulness Questionnaire* (subscales: *OBS*: *Observing*, *DESC*: *Describing*, *ACT*: *Acting with Awareness*, *nJDG*: *Non-Judging*, *nRCT*: *Non-Reacting*), *MAIA*: *Multidimensional Assessment Interoceptive Awareness*, *PSWQ*: *Penn-State Worry Questionnaire*, *STAI*: *State-Trait Anxiety Inventory*, *BDI*: *Beck Depression Inventory*.

For further analyses, data from Novice and Expert groups were combined (see methods). Pooled data showed a smooth bivariate distribution (see Supplementary Figure 1), legitimating the use of correlation coefficient as a measure of association between trait variables across the entire pool of participants. Table 2 shows correlations between PCS and other commonly associated psychological constructs after regressing out gender and age from all variables. First, we assessed correlations between PCS and other constructs (top two rows), with and without controlling for groups (see methods). As predicted, the mindfulness-related construct that showed the highest correlation with PCS was the DDS ($R=-.64$), which was higher than the correlation of the MAIA ($R=-.55$) and the different FFMQ scales (Non-Judging: $R=-.45$; Non-Reacting: $R=-.55$; the FFMQ scales typically showing the highest correlations with PCS as here). Of note, the PCS also showed moderate to strong positive correlations with other general negative cognitive-emotional constructs including PSWQ ($R=.58$), STAI ($R=.52$) and BDI ($R=.47$). Controlling for groups (allowing correlation coefficients to be compared with existing literature; see methods), did not fundamentally change these results, except that PCS was no longer correlated with the FFMQ facets of Observing ($R=-.20$) and Describing ($R=-.16$) (as predicted) and Acting with Awareness ($R=-.13$) (contrary to prediction). These findings provided initial support for our hypothesis that DDS is a core antithetical construct to PCS. As a next step, we explored the concurrent validity between DDS and PCS. Partial correlations (third row) showed that correlations between PCS and other scales were no longer significant when controlling for DDS, with the notable exception of PSWQ (worry) (.25), suggesting that relationships between PCS and other commonly associated constructs are not specific but underlain by a single construct captured by DDS. In contrast, the relationship between PCS and DDS was found to be highly specific as it survived controlling for each of the other scales (fourth row). In accord with these findings, DDS demonstrated (moderate to) high correlation (i.e. shared variance) with all other constructs (see fifth row), that was maintained when controlling for groups (bottom row). Collectively, these findings offer compelling support for the concurrent validity of DDS in relation to PCS, in line with our central hypothesis.

At a reviewers' request, analyses were repeated in an exploratory manner, exchanging DDS for CFQ - another measure of cognitive (de)-fusion; see Table 3. In doing so, we found that CFQ demonstrated a very similar pattern of correlations with other constructs compared to DDS (first two rows). This is consistent with CFQ being highly correlated with DDS in our sample ($R=-.79$; $R=-.65$ controlling for groups). Further in line with these findings, CFQ also behaved very similarly to the DDS with respect to PCS. Specifically, after controlling for CFQ, the relationships between PCS and all other constructs were strongly attenuated and only the associations with MAIA, PSWQ and the Non-Reacting facet of FFMQ remained significant (third row). In further similarity to DDS, the relationship between PCS and CFQ was robust to controlling for variance shared with each other construct (last row). However, what set the DDS and CFQ apart was that the DDS explained most of the shared variance between PCS and CFQ, while the reverse was not true (see third and fourth row of first column respectively).

	FFMQ											
	DDS	CFQ	OBS	DESC	ACT	nJDG	nRCT	total	MAIA	PSWQ	STAI	BDI
<i>R</i> _{PCS,·}	-.64***	.59***	-.43***	-.35**	-.35**	-.45***	-.55***	-.51***	-.55***	.58***	.52***	.47***
95% CI	[-.76,-.47]	[.41,.73]	[-.60,-.21]	[-.55,-.12]	[-.54,-.12]	[-.62,-.24]	[-.70,-.36]	[-.67,-.31]	[-.70,-.35]	[.39,.72]	[.31,.67]	[.26,.64]
<i>R</i> _{PCS,· group}	-.45***	.37**	-.20	-.16	-.13	-.25*	-.31*	-.27*	-.32**	.40***	.39**	.36**
95% CI	[-.62,-.23]	[.15,.57]	[-.42,-.04]	[-.38,-.09]	[-.36,-.12]	[-.46,-.01]	[-.52,-.08]	[-.48,-.03]	[-.52,-.08]	[.17,.58]	[.17,.58]	[.13,.56]
<i>R</i> _{PCS,· DDS}	.19	-.06	.09	.00	-.10	-.16	-.06	-.06	-.17	.25*	.10	.19
95% CI	[-.06,.41]	[-.30,.18]	[-.16,.32]	[-.24,.24]	[-.33,.15]	[-.39,.08]	[-.29,.19]	[-.40,.07]	[-.40,.07]	[.01,.46]	[-.14,.33]	[-.05,.41]
<i>R</i> _{PCS,· group DDS}	-.35**	-.53***	-.57***	-.57***	-.51***	-.41***	-.45***	-.45***	-.42***	-.41***	-.45***	-.52***
95% CI	[-.54,-.12]	[-.68,-.33]	[-.72,-.39]	[-.71,-.38]	[-.67,-.31]	[-.60,-.19]	[-.62,-.23]	[-.60,-.20]	[-.59,-.18]	[-.62,-.23]	[-.62,-.23]	[-.67,-.31]
<i>R</i> _{DDS,·}	-.79***	.60***	.64***	.54***	.61***	.73***	.76***	.71***	-.69***	-.72***	-.72***	-.54***
95% CI	[-.86,-.67]	[.43,.74]	[.47,.76]	[.35,.69]	[.44,.75]	[.59,.82]	[.63,.84]	[.57,.81]	[-.79,-.53]	[-.82,-.58]	[-.82,-.58]	[-.69,-.35]
<i>R</i> _{DDS,· group}	-.65***	.44***	.53***	.38**	.46***	.56***	.62***	.54***	-.54***	-.67***	-.67***	-.46***
95% CI	[-.77,-.49]	[.22,.61]	[.33,.68]	[.15,.57]	[.24,.63]	[.37,.71]	[.44,.75]	[.34,.69]	[-.69,-.34]	[-.78,-.51]	[-.78,-.51]	[-.63,-.24]

Table 2. Correlations between pain catastrophizing and commonly associated psychological constructs and zero-order and partial correlations DDS. The top two rows display zero-order correlations between PCS and other scales (controlling and not controlling for groups). Subsequently displayed are partial correlations between PCS and each other scale, controlling for DDS (third row), and between PCS and DDS controlling for each other scale (fourth row). The bottom two rows display zero-order correlations between DDS and other scales (controlling and not controlling for groups). Gender and age were regressed out from all variables. *PCS*: Pain Catastrophizing Scale, *DDS*: Drexel Defusion Scale, *CFQ*: Cognitive Fusion Questionnaire, *FFMQ*: Five Facet Mindfulness Questionnaire (subscales: *OBS*: observe, *DESC*: describe, *ACT*: act with awareness, *nJDG*: non-judgment, *nRCT*: non-reactivity), *MAIA*: Multidimensional Assessment of Interoceptive Awareness, *PSWQ*: Penn-State Worry Questionnaire, *STAI*: State-Trait Anxiety Inventory, *BDI*: Beck Depression Inventory. Significance values: *: $p < .05$, **: $p < .01$, ***: $p < .001$.

	FFMQ										
	DDS	OBS	DESC	ACT	nJDG	nRCT	total	MAIA	PSWQ	STAI	BDI
<i>R</i> _{CFQ,·}	-.79***	-.66***	-.59***	-.68***	-.72***	-.66***	-.80***	-.66***	.71***	.77***	.59***
95% CI	[-.86,-.67]	[-.78,-.50]	[-.72,-.40]	[-.79,-.52]	[-.82,-.58]	[-.77,-.49]	[-.87,-.69]	[-.78,-.50]	[.56,.81]	[.65,.85]	[.41,.73]
<i>R</i> _{CFQ,· group}	-.65***	-.52***	-.46***	-.57***	-.61***	-.44***	-.68***	-.46***	.57***	.74***	.53***
95% CI	[-.77,-.49]	[-.68,-.32]	[-.63,-.24]	[-.71,-.38]	[-.74,-.43]	[-.62,-.22]	[-.79,-.52]	[-.63,-.24]	[.38,.71]	[.61,.83]	[.33,.68]
<i>R</i> _{PCS,· CFQ}	-.35**	-.05	-.01	.09	-.04	-.27*	-.08	-.26*	.28*	.11	.18
95% CI	[-.54,-.12]	[-.29,.19]	[-.25,.23]	[-.16,.32]	[-.28,.20]	[-.48,-.03]	[-.32,.16]	[-.47,-.02]	[.04,.49]	[-.13,.35]	[-.06,.41]
<i>R</i> _{PCS,· CFQ DDS}	.19	.46***	.51***	.51***	.43***	.36**	.35**	.37**	.32**	.35**	.44***
95% CI	[-.06,.41]	[.24,.63]	[.30,.67]	[.31,.67]	[.21,.61]	[.13,.56]	[.12,.55]	[.14,.56]	[.08,.52]	[.12,.55]	[.22,.61]

Table 3. Zero-order and partial correlations CFQ. The top two rows display zero-order correlations between DDS and other scales (controlling and not controlling for groups). Subsequently displayed are partial correlations between PCS and each other scale, controlling for CFQ (third row), and between PCS and CFQ controlling for other scales (fourth row). Gender and age were regressed out from all variables. *PCS*: Pain Catastrophizing Scale, *DDS*: Drexel Defusion Scale, *CFQ*: Cognitive Fusion Questionnaire, *FFMQ*: Five Facet Mindfulness Questionnaire (subscales: *OBS*: observe, *DESC*: describe, *ACT*: act with awareness, *nJDG*: non-judgment, *nRCT*: non-reactivity), *MAIA*: Multidimensional Assessment of Interoceptive Awareness, *PSWQ*: Penn-State Worry Questionnaire, *STAI*: State-Trait Anxiety Inventory, *BDI*: Beck Depression Inventory. Significance values: *: $p < .05$, **: $p < .01$, ***: $p < .001$.

3.2 Relationship between traits (PCS, DDS) and sensory and affective pain self-reports

Next, we investigated the unique and respective roles of DDS and PCS in predicting pain-related outcomes. To this end, we assessed their respective correlation with intensity and unpleasantness ratings of novice and expert meditators collected during an acute pain task. We first re-analyzed pain self-reports for long pain stimuli only (see methods). A simple ANOVA model of subjects' average long pain ratings yielded a significant Group (Novices/Experts) x Rating Type (Intensity/Unpleasantness) interaction ($\chi^2(1) = 13.16, p < .001$). In line with our previous report (Zorn et al., 2020), this interaction was driven by experts reporting significantly lower pain unpleasantness than novices (estimate = -1.81, 95% CI = [-2.52, -1.05], $t(59) = -5.1, p < .0001$), whereas pain intensity reports did not differ between groups (estimate = -0.70, 95% CI = [-1.42, 0.02], $t(59) = -1.9, p = .057$). We then tested our hypothesis that PCS and DDS would both primarily predict pain unpleasantness as opposed to pain intensity but in opposite direction. Pooled data again followed a smooth bivariate distribution (see Supplementary Figure 2). Results for the respective relationship of DDS and PCS to pain outcomes are displayed in Figure 1. As predicted, pain intensity was not significantly correlated with neither DDS ($R = .21, 95\% \text{ CI } [-.06, .45], p > .13$) nor PCS ($R = -.18, 95\% \text{ CI } [-.43, .09], p > .19$) (upper left plot, controlled for pain unpleasantness). By contrast, pain unpleasantness was significantly negatively correlated with DDS ($R = -.55, 95\% \text{ CI } [-.71, -.32], p < .0001$), and positively with PCS ($R = .49, 95\% \text{ CI } [.25, .67], p < .001$) (upper right plot; values outside brackets, controlled for pain intensity). Further assessing the specificity of these relationships, we found that the relationship between DDS and unpleasantness survived controlling for PCS ($R = -.33, 95\% \text{ CI } [-.55, -.06], p = .016$), whereas the relationship between PCS and unpleasantness, was not significant when controlling for DDS ($R = .20, 95\% \text{ CI } [-.08, .45], p > .16$) (upper right plot; values between brackets). Taken together, these findings suggest that PCS and DDS indeed both specifically predict pain unpleasantness as opposed to pain intensity, but in the opposite direction, positively and negatively respectively, and that DDS is a more specific predictor of pain unpleasantness than PCS.

At a reviewers' request, analyses were again repeated in an exploratory manner, exchanging DDS for CFQ (see Figure 1). Like DDS, CFQ was not significantly correlated with pain intensity ($R = -.09, 95\% \text{ CI } [-.35, .18], p > .51$) (lower left plot, controlling for pain unpleasantness). In further similarity to DDS, CFQ was significantly correlated with pain unpleasantness ($R = .46, 95\% \text{ CI } [.22, .65], p < .001$) (lower right plot; values outside brackets, controlling for pain intensity). However, the CFQ differed from the DDS in that its relationship with the unpleasantness did not appear specific as it did not survive controlling for PCS ($R = -.24, 95\% \text{ CI } [-.04, .48], p > .09$), while, conversely, the relationship between PCS and unpleasantness did survive controlling for CFQ ($R = .30, 95\% \text{ CI } [.03, .53], p = .033$) (lower right plot; values between brackets).

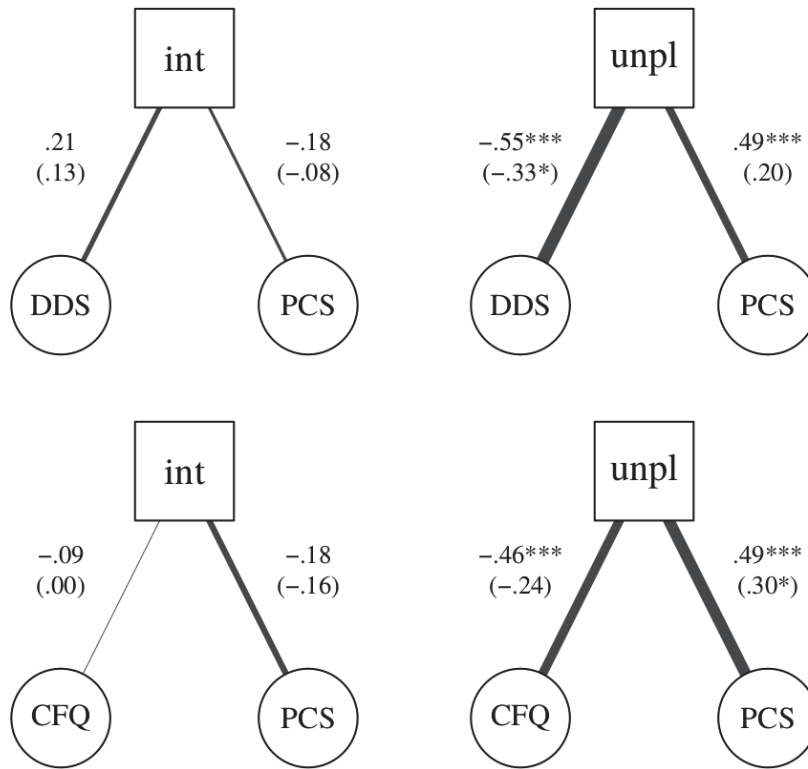


Figure 2. Relationships between trait and pain self-reports. The top two plots display the relationships of DDS and PCS (circles) to pain ratings (squares) of pain intensity (controlled for pain unpleasantness) (left) and pain unpleasantness (controlled for pain intensity) (right). Values outside brackets zero-order correlation coefficients and values inside brackets are partial correlation coefficients (controlled for the respective other trait construct). Line widths are proportional to the corresponding partial correlation coefficients. The bottom two plots display the equivalent results for CFQ. *int*: pain intensity, *unpl*: pain unpleasantness, *PCS*: Pain Catastrophizing Scale, *DDS*: Drexel Defusion Scale. Significance values: *: $p < .05$, **: $p < .01$, ***: $p < .001$.

4. Discussion

This study built on previous work in which we presented preliminary evidence that lower trait pain catastrophizing (PCS) is an important marker of mindfulness-based sensory-affective uncoupling of pain experience. Using the same sample of novice (~20h of practice) and expert meditators (>10,000h of experience), we here aimed to explore the regulatory cognitive mechanisms of mindfulness meditation underlying such effects: testing the hypothesis that cognitive defusion, as measured by the DDS, is a core cognitive mechanism underlying mindfulness-based pain regulation with a unique and specific inverse

relationship to PCS and an opposite relation to (affective) pain experience. At reviewer's request, analyses were repeated, substituting DDS for CFQ, another measure of cognitive (de-)fusion.

As predicted, the DDS emerged as a core antithetical construct to PCS. Specifically, we found that DDS and PCS were negatively correlated and shared unique variance that survived controlling for other mindfulness-related constructs, including FFMQ facets and interoceptive awareness (MAIA), and common negative-affective cognitive-emotional constructs, including anxiety (STAI), depression (BDI), and worry (PSWQ). Conversely, the relationships between PCS and other constructs, with the exception of the PSWQ (but including Non-Judging/Non-Reacting FFMQ facets), were no longer significant when controlling for DDS: questioning the specificity of these relationships to PCS. The CFQ, designed to measure cognitive fusion, behaved very similarly to DDS: also strongly attenuating the relationship between PCS and other constructs and showing a specific relationship to PCS that survived controlling for the other constructs. However, the relationship between DDS and PCS survived controlling for CFQ, but not vice versa, suggesting that DDS in particular captured variance unique to PCS. The significance of DDS to pain was further supported by the finding that DDS was a more specific predictor of pain unpleasantness than PCS. This was not the case for CFQ, again suggesting that DDS was the more relevant construct in relation to pain. The significance of these findings will be discussed further below.

Firstly, the results supported the hypothesis that cognitive defusion is a core cognitive mechanism of mindfulness-based pain regulation. Experts reported markedly higher DDS than novices, the DDS showed a specific negative association with PCS across participants, and, like the PCS, the DDS specifically predicted pain unpleasantness as opposed to pain intensity, but positively and negatively respectively. Hence, the results offer compelling preliminary evidence that cognitive defusion (DDS) is an important psychological process underlying the positive pain regulatory effects of mindfulness meditation (i.e., sensory-affective uncoupling of pain). It is noteworthy that DDS appeared as a more specific predictor of pain unpleasantness than PCS (which was reduced to non-significance after controlling for DDS). This is remarkable, given that the PCS is widely regarded as one of the most potent predictors of increased pain (e.g. Keefe et al., 2004; Gatchel et al., 2007). Nevertheless, replication in longitudinal studies and other samples, including clinical populations, is warranted before any conclusive results can be drawn.

Secondly, we included both the DDS (Forman et al., 2012), designed to measure cognitive defusion, and the CFQ (Gillanders et al., 2014), designed to measure cognitive fusion, which allowed a respective comparison of these constructs. Both measures are fairly recent and lack extensive validation. However, two recent reports performing factor analyses on decentering/defusion-related constructs (Naragon et al., 2017; Hadash et al., 2017), are reassuring concerning their construct validity. Briefly, both studies found very similar two-factor solutions, where the DDS largely mapped onto the first factor and the CFQ largely onto the second. Both studies interpreted the first factor as reflecting disidentification from internal

experience and the second factor as reflecting (reduced) automatic reactivity to thought content. Both studies also observed similar expected divergent associations with criterion variables. Specifically, the first factor (intentional disidentification from internal experience) was primarily associated with FFMQ Non-Reactivity, whereas the second factor (reduced) (automatic reactivity to thought content) was primarily associated with measures of negative thinking, including worry, rumination, anxiety and depression symptoms. Collectively, these studies suggest that DDS reflects disidentification with experience and the CFQ automatic reactivity (Hadash et al., 2017). In further support of this interpretation, the first factor (DDS) but not second factor (CFQ) predicted self-reported disidentification during a meta-awareness with disidentification manipulation in one of the studies (Hadash et al., 2017). In line with this earlier work, we found largely similar association patterns, with DDS showing strongest associations with FFMQ Non-Reactivity, and the CFQ (mildly) stronger associations with indices of emotional reactivity (anxiety and depression). Interestingly, our results, additionally, suggest that the DDS (but not CFQ) has incremental predictive power in predicting PCS over FFMQ Non-Reactivity, as the relationship between DDS and PCS survived controlling for the latter but not vice versa. The FFMQ Non-Reactivity scale specifically measures non-reactive observation of inner experience (Baer et al., 2006). Therefore, one interesting possibility is that the incremental validity of DDS (to FFMQ-Non-Reactivity) reflects disidentification with experience (rather than mere non-reactivity). This would be in line with some mindfulness accounts (Lutz et al., 2015) hypothesizing that dereification (i.e. not taking thoughts to be real) together with meta-awareness are critical aspects underlying the beneficial effects of mindfulness-meditation, such as non-reactivity or equanimity, on emotion regulation. Future research, ideally aided by the development of psychometric scales measuring dereification/disidentification with experience, is required to further investigate this interesting possibility. This research should also include an effort to develop a measure of cognitive defusion in expert meditators in non-dual mindfulness as the ones studied in the present study. According to them, cognitive defusion is a capacity which can apply not only to the contents of experience (thoughts, emotions, bodily sensations), as measured by the DDS, but also to subjective features such as the sense of being a permanent self, or the duality subject and object (Dunne et al. 2011). One noteworthy observation is that the CFQ and DDS were highly correlated in the present work (-.65; controlling for groups), but not in previous work (0.07 to 0.28) (Naragon et al., 2017; Hadash et al., 2017). The reason for this difference is unclear. However, we included a sample that was highly familiar with the concept of cognitive defusion (experts) and a sample interested in the subject of meditation (novices), as opposed to more regular healthy or clinical samples in other studies, which might have influenced these results. More research in diverse samples could potentially clarify this issue.

Thirdly, our findings inform a larger literature interested in identifying antithetical constructs to PCS. Most such studies to date have explored relationships between PCS and FFMQ facets in clinical (Day et al., 2015, Turner et al., 2016; Schutze et al., 2010), and healthy samples (Elvery et al., 2017). Although these studies all found that PCS correlated negatively with Non-Judging/Non-Reacting FFMQ facets in particular, one of the studies also found that these were no longer significantly related to PCS when

controlling for worry as assessed by the PSWQ (Day et al., 2015). According to the authors of that study this finding might be explained by the fact that many of the FFMQ facets have content that appear related to anxiety, worry, or negative affectivity. Such lack of sufficient divergent validity is congruent with a high degree of correspondence reported between mindfulness scores, on the one hand, and stress (Goldberg et al., 2014; Stanley et al., 2011), and personality factors (Siegling and Petrides, 2014), on the other. And could as well explain other counterintuitive results in the literature, for instance, Non-Reactivity being associated with a stronger association between pain intensity and pain catastrophizing (Jensen et al., 2018), and Non-Judging and Acting with Awareness with amplified negative effects of catastrophizing (Dorado et al., 2018). Our finding suggests that the relationship between DDS and PCS is a more specific one, as was expected based on our, and others (Kabat-Zinn, 1982; McCracken et al., 2013a), theorizing that cognitive defusion, or rather the lack thereof, is a construct at the root of what causes one to catastrophize about pain: namely being entangled in thoughts and consequently taking thoughts to be phenomenologically real instead of mere mental events that do not necessarily need to be reacted upon.

Fourthly, our findings contribute to a larger discussion on whether different effective psychosocial treatment interventions act by distinct or common cognitive mechanisms of action. Illuminating this question first entails achieving a better insight into the specific mechanisms underlying different treatment effects (Jensen, 2011; Thorn et al., 2011). Our finding that the DDS is a specific antithetical construct to PCS that might underlie mindfulness-based pain regulation is particularly interesting in this light, because defusion/decentering-related constructs have been hypothesized to be transdiagnostic therapeutic mechanisms of change that are shared across different psychosocial treatment interventions (e.g. Mennin et al., 2013; Bernstein et al., 2015). In line with this idea, Baquedano et al. found that, compared to self-immersion, a cognitive defusion stance reduces food-related salivation and automatic food bias (Papies et al., 2012; Baquedano et al., 2017). Segal and colleagues showed that the posttreatment growth of mindfulness-related regulatory capacity decreases depression relapse, and that this growth was mediated specifically by the capacity to develop the skill to decenter thoughts, a construct overlapping with cognitive defusion (Farb et al., 2018). In this special issue, Barnhofer et al, further reported that a MBI compared to psycho-education and rest specifically increased decentering, decreased brooding and decreased symptoms in depressed patients and that these changes were correlated to a reduced dorsolateral prefrontal cortex activation during an implicit emotion regulation (Barnhofer et al. in press). Similar, results have been observed with other treatment interventions including CBT (Teasdale, 2001; Fresco et al., 2007b). Our results suggest that these effects extend to the context of pain regulation, which is congruent with the fact that cognitive defusion, by its very definition, is a construct relevant to emotion regulation in general. That is, the construct of defusion focuses on a cognitive process rather than on cognitive content, and thus all emotional disorders where maladaptive cognitive schema are central (irrespective of their content) should be amenable to positive change by the promotion of cognitive defusion.

Limitations

This study had several limitations. First, the very specific sample under study, including healthy novice and expert meditators, warrants more research into the transferability of findings to the clinical domain. Second, the cross-sectional nature of the study did not allow for causality attributions, which requires future longitudinal work. Third, the study built on self-reports, which although readily accepted in pain research, are also susceptible to demand characteristics (Orne, 1962; Weber and Cook, 1972). However, we consider it unlikely that these were primarily driving the results, given that the main interest of this work was the specificity of effects which is less likely to be influenced by this type of effect. Fourth, novices engaged in a meditation intervention in between the collection of trait self reports and pain self-reports, which posed a potential confound. However, given the brevity of the intervention (~20h), we consider it unlikely that this unduly influenced results (see also previous point). A last limitation arose from the DDS, which includes an extensive introduction on the concept of cognitive defusion, which might induce desirable responding and asks respondents to indicate to what degree they would be able to defuse from hypothetical vignettes, which might cause overlap with (estimated) self-efficacy (e.g. Gillanders et al., 2014). Future work should assess whether these concerns are justified.

5. Conclusion

This study shows that cognitive defusion specifically and negatively correlated with pain catastrophizing and has an inverse and positive relationship to sensory-affective uncoupling of pain. Overall, these findings highlight the central role of cognitive defusion as a positive regulatory mechanism of mindfulness-related pain regulation. These findings are promising to the clinical domain and warrant more research on this interesting construct.

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References

1. Abdoun O, Zorn J, Fucci E, Perraud E, Aarts K, Lutz, A. Brain & Mindfulness Project Manual. 2018. OSF. <https://osf.io/dbwch/>
2. Abdoun O, Zorn J, Poletti S, Fucci E, Lutz A, Training novice practitioners to reliably report their meditation experience using shared phenomenological dimensions. *Consciousness and Cognition*. 2019. Feb 68: 57-72. <https://doi.org/10.1016/j.concog.2019.01.004>

3. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment*. 2006; 13:27–45. doi: 10.1177/1073191105283504
4. Baquedano C, Vergara R, Lopez V, Fabar C, Cosmelli D, Lutz A. Compared to self-immersion, mindful attention reduces salivation and automatic food bias. *Scientific Reports*. 2017. 2017; 7: 13839. <http://doi.org/10.1038/s41598-017-13662-z>
5. Barnhofer T, Reess TJ, Fessler M, Winnebeck E, Grimm S, Gärtner M, Fan Y, Huntenburg JM, Schroeter TA, Gummersbach M, Bajbouj M, Hölzel BK. Effects of Mindfulness Training on Emotion Regulation in Patients with Depression: Reduced Dorsolateral Prefrontal Cortex Activation Indexes Early Beneficial Changes (This special issue).
6. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. 1988. *Clinical Psychology Review*, 8(1), 77-100. [https://doi.org/10.1016/0272-7358\(88\)90050-5](https://doi.org/10.1016/0272-7358(88)90050-5)
7. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry*. 1961. 4:561-571. doi:10.1001/archpsyc.1961.01710120031004
8. Bernstein A, Hadash Y, Lichtash Y, Tanay G, Shepherd K, Fresco DM. Decentering and Related Constructs: A Critical Review and Metacognitive Processes Model. *Perspect Psychol Sci*. 2015. 10(5): 599–617. doi: 10.1177/1745691615594577
9. Bieling PJ, Hawley LL, Bloch RT, Corcoran KM, Levitan RD, Young LT, MacQueen GM, Segal ZV. Treatment Specific Changes in Decentering Following Mindfulness-Based Cognitive Therapy Versus Antidepressant Medication or Placebo for Prevention of Depressive Relapse. *J Consult Clin Psychol*. 2012. 80(3): 365–372. doi: 10.1037/a0027483
10. Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, Segal ZV, Abbey S, Speca M, Velting D, Devins G. Mindfulness: A proposed operational definition. *Clin Psychol Sci Pract*. 2004. 11: 230–241. <https://doi.org/10.1093/clipsy.bph077>
11. Bland JM, Altman DG. Correlation in restricted ranges of data. *BMJ*. 2011. 342. <https://doi.org/10.1136/bmj.d556>
12. Bohdi B. *In the Buddha's words: an anthology of discourses from the pali canon*. Boston: Wisdom Publications; 2005.
13. Cassidy EL, Atherton RJ, Robertson N, Walsh DA, Gillett R. Mindfulness, functioning and catastrophizing after multidisciplinary pain management for chronic low back pain. *PAIN*. 2012. 153:644–50. <https://doi.org/10.1016/j.pain.2011.11.027>

14. Chambers R, Gullone E, Allen NB, Mindful emotion regulation: an integrative review. *Clin Psychol Rev.* 2009. 29, 560-572. <https://doi.org/10.1016/j.cpr.2009.06.005>
15. Day MA, Smitherman A, Ward LC, Thorn BE. An investigation of the associations between measures of mindfulness and pain catastrophizing. *Clin J Pain.* 2015. 31:222–8. doi: 10.1097/AJP.000000000000102
16. Dorado K, Schreiber KL, Koulouris A, Edwards RR, Napadow V, Lazaridou A. Interactive effects of pain catastrophizing and mindfulness on pain intensity in women with fibromyalgia. *Health Psychol Open.* 2018. 5(2). doi: 10.1177/2055102918807406
17. Dunne J, Toward an understanding of non-dual mindfulness. *Contemporary Buddhism.* 2011. 12 (1), 71-88. <http://dx.doi.org/10.1080/14639947.2011.564820>
18. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The role of psychosocial processes in the development and maintenance of chronic pain. *The Journal of Pain.* 2016.17(9):T70-T92. <https://doi.org/10.1016/j.jpain.2016.01.001>
19. Elvery N, Jensen MP, Ehde DM, Day MA. Pain catastrophizing, mindfulness, and pain acceptance: What's the difference? *The Clinical Journal of Pain.* 2017. 33: 485–495. doi: 10.1097/AJP.0000000000000430.
20. Farb N, Anderson A, Ravindran A, Hawley L, Irving J, Mancuso E, Gulamani T, Williams G, Ferguson, A, Segal ZV. Prevention of relapse/recurrence in major depressive disorder with either mindfulness-based cognitive therapy or cognitive therapy. *Journal of Consulting and Clinical Psychology.* 2018. 86(2), 200–204. <https://doi.org/10.1037/ccp0000266>
21. Forman EM, Herbert JD, Juarascio AS, Yeomans PD, Zebell JA, Goetter EM, Moitra E. The Drexel defusion scale: A new measure of experiential distancing. *Journal of Contextual Behavioral Science.* 2012. 1(s 1-2):55-65. doi: 10.1016/j.jcbs.2012.09.001
22. Fresco DM, Moore MT, van Dulmen MHM, Segal ZV, Ma SH, Teasdale JD, Williams JMG. Initial psychometric properties of the experiences questionnaire: validation of a self-report measure of decentering. *Behavior Therapy.* 2007a. 38(3):234–246. <http://doi.org/10.1016/j.beth.2006.08.003>.
23. Fresco DM, Segal ZV, Buis T, Kennedy S. Relationship of posttreatment decentering and cognitive reactivity to relapse in major depression. 2007b. 75(3):447-55. doi: 10.1037/0022-006X.75.3.447.
24. Fruhstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry.* 1976. 39: 1071–1075. doi: 10.1136/jnnp.39.11.1071

25. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull.* 2007. 133(4):581-624. doi: 10.1037/0033-2909.133.4.581
26. Gillanders DT, Bolderston H, Bond FW, Dempster M, Flaxman PE,..... Remington B. The development and initial validation of The Cognitive Fusion Questionnaire. *Behavior Therapy.* 2014. 45,83–101. doi: <http://dx.doi.org/10.1016/j.beth.2013.09.001>.
27. Goldberg SB, Del Re AC, Hoyt WT, Davis JM. The Secret Ingredient in Mindfulness Interventions? A Case for Practice Quality Over Quantity. *Journal of Counseling Psychology.* 2014. 61(3):491-7. doi: 10.1037/cou0000032.
28. Grant JA, Courtemanche J, Rainville P. A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain.* 2011. 152:150–156. <https://doi.org/10.1016/j.pain.2010.10.006>
29. Hadash Y, Lichtash Y, Bernstein A: Measuring decentering and related constructs: capacity and limitations of extant assessment scales. *Mindfulness.* 2017. 8:1674-1688 doi: <http://dx.doi.org/10.1007/s12671-017-0743-9>
30. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behav Res Ther.* 2006;4:1–25. doi: 10.1016/j.brat.2005.06.006
31. Hayes SC, Shenk C. Operationalizing mindfulness without unnecessary attachments. *Clinical Psychology: Science and Practice.* 2004. 11(3), 249–254. <https://doi.org/10.1093/clipsy.bph079>
32. Hayes-Skelton SA, Lee CS, Changes in Decentering across Cognitive Behavioral Group Therapy for Social Anxiety Disorder. *Behav Ther.* 2018 49(5): 809–822. doi: 10.1016/j.beth.2018.01.005
33. Hayes SC, Strosahl K, Wilson KG. *Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change.* New York: Guilford Press; 1999.
34. Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, Colaiaco B, Maher AR, Shanman RM, Sorbero ME, Maglione MA, Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis, *Annals of Behavioral Medicine.* 2017. 51(2); 199-213. <https://doi.org/10.1007/s12160-016-9844-2>
35. Jensen MP. Psychosocial approaches to pain management: an organizational framework. *Pain.* 2011. 152:717–725. doi: 10.1016/j.pain.2010.09.002

36. Jensen MP, Thorn BE, Carmody J, Keefe FJ, Burns JW. The role of cognitive content and cognitive processes in chronic pain: An important distinction? *The Clinical Journal of Pain*. 2018. 34: 391–401. doi: 10.1097/AJP.0000000000000559.
37. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen. Hosp. Psychiatry*. 1982. 4, 33–47. [https://doi.org/10.1016/0163-8343\(82\)90026-3](https://doi.org/10.1016/0163-8343(82)90026-3).
38. Keefe FJ, Rumble ME, Scipio, CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science. *J Pain*. 2004;5(4):195-211. doi: <https://doi.org/10.1016/j.jpain.2004.02.576>
39. Keogh E. Sex and gender differences in pain: a selective review of biological and psychosocial factors. *J Mens Health Gend*. 2006. 3:236–43. <https://doi.org/10.1016/j.jmhg.2006.03.006>
40. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med*. 2007. 30:77–94. doi: 10.1007/s10865-006-9085-0
41. Lutz A, Slagter HA, Dunne JD, Davidson RJ. Attention regulation and monitoring in meditation. *Trends Cogn Sci*. 2008. 12, 163–169. <https://doi.org/10.1016/j.tics.2008.01.005>
42. Lutz A, McFarlin DR, Perlman DM, Salomons TV, Davidson RJ. Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *Neuroimage*. 2013. 1;64:538-46. <https://doi.org/10.1016/j.neuroimage.2012.09.030>
43. Lutz A, Jha AP, Dunne JD, Saron CD, Investigating the phenomenological matrix of mindfulness-related practices from a neurocognitive perspective. *Am Psychol*. 2015. 70(7): 632–658. doi: 10.1037/a0039585
44. McCracken L, Estelle B, Joseph C, Decentering, rumination, cognitive defusion, and psychological flexibility in people with chronic pain. *Journal of Behavioral Medicine*. 2014. 37(6). doi: 10.1007/s10865-014-9570-9
45. McCracken LM, DaSilva P, Skillicorn B, Doherty R. The Cognitive Fusion Questionnaire: A preliminary study of psychometric properties and prediction of functioning in chronic pain. *The Clinical Journal of Pain*. 2013a. doi:10.1097/AJP.0000000000000047
46. McCracken LM, Gutierrez-Martinez O, Smyth C. “Decentering” reflects psychological flexibility in people with chronic pain and correlates with their quality of functioning. *Health Psychology*. 2013b. 32, 820–823. doi: 10.1037/a0028093

47. Mehling WE, Price C, Daubenmier JJ, Acree M, Bartmess E, Stewart A. The multidimensional assessment of interoceptive awareness (MAIA). *PLoS ONE*. 2012. 7:e48230. doi: 10.1371/journal.pone.0048230
48. Melzack R, Casey KL. Sensory, motivational and central control determinants of chronic pain: A new conceptual model. In: Kenshalo DR. *The skin senses: Proceedings of the first International Symposium on the Skin Senses*, held at the Florida State University in Tallahassee, Florida. 1968. P432-439.
49. Mennin DS, Ellard KK, Fresco DM, Gross JJ. United We Stand: Emphasizing Commonalities Across Cognitive-Behavioral Therapies. *Behav Ther*. 2013. 44(2): 234–248. doi:10.1016/j.beth.2013.02.004.
50. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the penn state worry questionnaire. *Behavior Research and Therapy*. 1990. 28, 487-495. doi:10.1016/0005-7967(90)90135-6
51. Naragon-Gainey K, DeMarree KG. Structure and validity of measures of decentering and defusion. *Psychological Assessment*. 2017. 29, 935–954. doi: <http://dx.doi.org/10.1037/pas0000405>
52. Orne MT. On the social psychology of the psychological experiment: With particular reference to demand characteristics and their implications. *American Psychologist*. 1962. 17(11), 776–783. <https://doi.org/10.1037/h0043424>
53. Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med*. 1997 20(6):589-605. doi: 10.1023/a:1025570508954
54. Papiies EK, Barsalou LW, Custers R. Mindful attention prevents mindless impulses. *Social Psychological and Personality Science*. 2012. 3, 291–299. doi: <https://doi.org/10.1177/1948550611419031>
55. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *Journal of Neuroscience*. 2001;21:9896–9903. doi: 10.1523/JNEUROSCI.21-24-09896.2001_
56. Quartana PJ, Campbell CM, Edwards RR, Pain catastrophizing: a critical review. *Expert Rev Neurother*. 2009. 9(5): 745–758. doi: 10.1586/ern.09.34
57. R Core Team (2017). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org>.
58. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception – Part 1: Are there really

differences between women and men? PAIN. 2012. 153; 602–618.
<https://doi.org/10.1016/j.pain.2011.11.025>

59. Rangdrol, T.N., 2011. Heart Lamp: Lamp of Mahamudra and Heart of the Matter, 3 ed. Calif.: Rangjung Yeshe Publications, Boudhanath: Berkeley

60. Schutze R, Rees C, Preece M, Schutze M. Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. *Pain*. 2010. 148: 120–127. <https://doi.org/10.1016/j.pain.2009.10.030>.

61. Siegling AB, Petrides KV. Measures of trait mindfulness: Convergent validity, shared dimensionality, and linkages to the five-factor model. *Front Psychol*. 2014. 5: 1164. 2014. doi: 10.3389/fpsyg.2014.01164

62. Spielberger C. Manual for the State-Trait Anxiety Inventory (rev. ed.). Palo Alto (CA): Consulting Psychologists Press. 1983.

63. Stanley EA, Schaldach JM, Kiyonaga A, Jha AP, Mindfulness-based Mind Fitness Training: A Case Study of a High-Stress Predeployment Military Cohort. *Cognitive and behavioral practice*. 2011. 18:566-576. <https://doi.org/10.1016/j.cbpra.2010.08.002>

64. Startup HM, Erickson TM. The Penn State Worry Questionnaire (PSWQ). In Davey GCL, Wells A (Eds.), *Worry and Its Psychological Disorders: Theory, Assessment and Treatment*. 2006. 101-119. Chichester: Wiley.

65. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*. 1995. 7(4), 524-532. doi:10.1037//1040-3590.7.4.524

66. Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*. 2001. 17:52-64. doi: 10.1097/00002508-200103000-00008.

67. Teasdale JD, Scott J, Moore RG, Hayhurst H, Pope M, Paykel ES. How does cognitive therapy prevent relapse in residual depression? Evidence from a controlled trial. *Journal of Consulting and Clinical Psychology*. 2001. 69(3), 347–357. doi: 10.1037//0022-006x.69.3.347

68. Thorn BE, Burns JW. Common and specific treatment factors in psychosocial pain management: the need for a new research agenda. *Pain*. 2011. 152:705–706. doi: 10.1016/j.pain.2010.12.017

69. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron*. 2007. 2;55(3):377-91. <https://doi.org/10.1016/j.neuron.2007.07.012>

70. Turner JA, Anderson ML, Balderson BH, Cook AJ, Sherman KJ, Cherkin DC. Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain: similar effects on

mindfulness, catastrophizing, self-efficacy, and acceptance in a randomized controlled trial. *PAIN*. 2016. 157:2434–44. doi: 10.1097/j.pain.0000000000000696

71. Weber SJ, Cook T. Subject effects in laboratory research: An examination of subject roles, demand characteristics, and valid inference. *Psychological Bulletin*. 1972. 77(4), 273–295. <https://doi.org/10.1037/h0032351>

72. Zeidan F, Grant JA, Brown CA, McHaffie JG, Coghill RC, The neural mechanisms of mindfulness-based pain relief: a functional magnetic resonance imaging-based review and primer. *PAIN Reports*. 2019. 7;4(4):e759. Volume 4 - Issue 4 - p e759. doi: 10.1097/PR9.0000000000000759

73. Zorn J, Abdoun O, Bouet R, Lutz A. Mindfulness meditation is related to sensory-affective uncoupling of pain in trained novice and expert practitioners. *European Journal of Pain*.

Supplementary Information 1

Written instructions

Distraction condition: Concentrate your mind on the numbers and visual cues on the screen. Whenever a new number appears, mentally add it to the total sum of the previous number(s). You should focus your attention only on the numbers and the cues. Block all other emotions, sensations, or thoughts that may arise during the calculation task. Be very focused so that you don't miss any number or cue.

OM condition: Start to anchor your attention in your body. Simply rest your body. Relax your muscles. Rest your mind without blocking anything. Allow everything to arise in the field of awareness as it is in the present moment. The body and the mind rest in unity. Gently watch the numbers and the cues appear on the screen. Pay attention to cues, while not doing anything in particular with the numbers. When the thermal stimulus arises, gently let it be a support for your attention. You know that you are feeling the sensation; you recognize it, while resting the mind on this support. While resting your attention on the thermal sensation, thoughts, or emotions may arise. Just let them be in the vast field of your awareness while remaining at ease in the present moment.

Auditory instructions

Distraction condition: Concentrate your mind on the number and the visual cues on the screen. You should focus your attention completely on the screen and the counting task. Block all the emotions, sensations and thought that arise during this task. Be very concentrated so that you don't miss any number or visual cue.

OM condition: Relax your body and your mind, there is no need to block anything. When the heat stimulation starts, gently be aware of it. Be aware of your experience of this sensation and let your mind relax with it. When any thoughts or emotions arise, let them be there in the vast space of your awareness.

Supplementary Information 2

Different self-report questions:

'Intensity: How hot was the stimulation?'

Labels: 1 = Not at all, 9: Extremely hot

'Unpleasantness: How much did the stimulation bother you?'

Labels: 1 = Not at all, 9: Extremely

'Relief': How relieved were you by the end of the stimulation?'

Labels: 1 = Not at all, 9: Extremely

'Meditation Instruction': To what degree were you able to follow the instruction?'

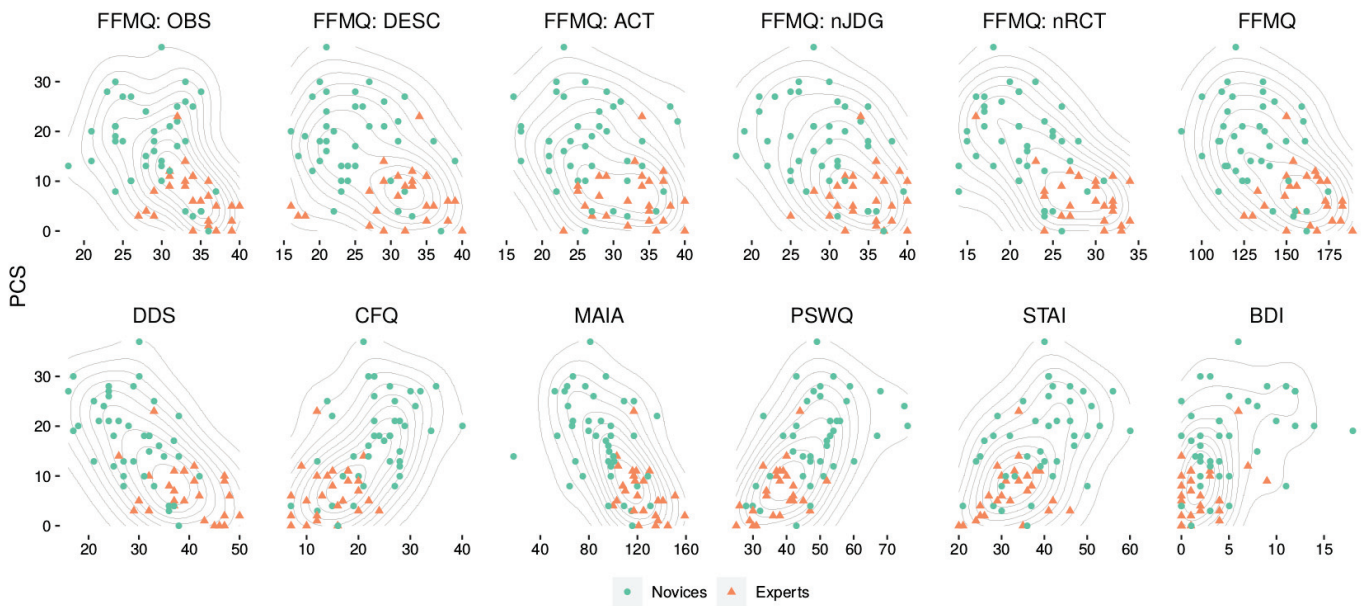
Labels: 1 = Not at all, 9: Completely

'Addition': What is the total sum of the numbers that were presented?'

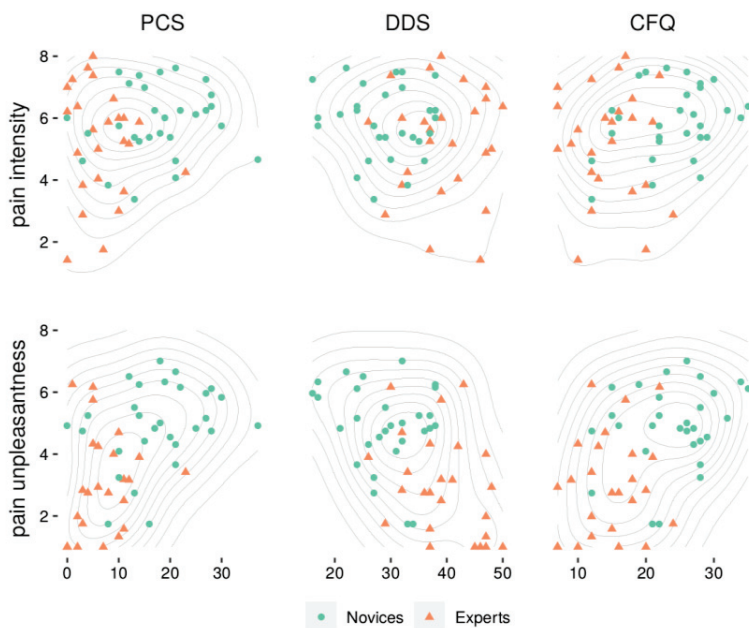
5 different two digit-numbers were presented, one of which was the correct answer.

Presentation frequency:

<u>OM condition:</u>		
10 x Warm Long	10 x Hot Long	10 x Short Long
6 x Unpleasantness	6 x Unpleasantness	6 x Unpleasantness
6 x Relief	6 x Relief	6 x Relief
4 x Intensity	4 x Intensity	4 x Intensity
4 x Meditation	4 x Meditation	4 x Meditation
<u>Distraction condition:</u>		
10 x Warm Long	10 x Hot Long	10 x Short Long
6 x Unpleasantness	6 x Unpleasantness	6 x Unpleasantness
6 x Relief	6 x Relief	6 x Relief
4 x Intensity	4 x Intensity	4 x Intensity
4 x Addition	4 x Addition	4 x Addition



Supplementary Figure 1. Distribution of trait self-reports in relation to PCS. Pooled data showed a smooth bivariate distribution across Novices and Experts. *PCS: Pain Catastrophizing Scale, DDS: Drexel Defusion Scale, Cognitive Fusion Questionnaire, FFMQ: Five Facet Mindfulness Questionnaire (subscales: OBS: observe, DESC: describe, ACT: act with awareness, nJDG: non-judgment, nRCT: non-reactivity), MAIA: Multidimensional Assessment of Interoceptive Awareness, PSWQ: Penn-State Worry Questionnaire, STAI: State-Trait Anxiety Inventory, BDI: Beck Depression Inventory.*



Supplementary Figure 2. Distribution of trait self-reports in relation to pain ratings. Pooled data showed a smooth bivariate distribution across Novices and Experts. *PCS: Pain Catastrophizing Scale, DDS: Drexel Defusion Scale, CFQ: Cognitive Fusion Questionnaire.*

Expertise in mindfulness meditation is associated with decreased anterior insula activation during pain anticipation which predicts increased sensory-affective uncoupling of pain

Zorn J., Meunier D, Fauchon C, Lambertson F, Lutz A.

Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR5292, Lyon 1 University,
Lyon, France

Abstract

Background: We previously reported that a mindfulness instruction (state) and mindfulness expertise (trait) both led to increased self-reported sensory-affective uncoupling of pain and that this uncoupling was negatively predicted by trait pain catastrophizing (Zorn et al., 2020). Here, we aimed to explore the neuronal correlates of these findings by analyzing the functional magnetic resonance imaging (fMRI)-data corresponding to this previous report. We hypothesized that the chronometry of the anterior insula during pain anticipation and early and late pain periods is a sensitive marker of present centeredness (increased response to bottom-up salience during early pain) vs conceptually-driven top-down processing (increased top-down salience during pain anticipation and late pain) that could be related to self-reported sensory-affective uncoupling of pain and pain catastrophizing scores. **Methods:** we implemented a novel acute pain fMRI-scanner paradigm that was designed to amplify the cognitive-affective aspects of pain, while participants performed Open Monitoring meditation (Lutz et al., 2008), a style of mindfulness meditation known to impact sensory-affective uncoupling of pain (Perlman et al., 2010; Zorn et al., 2020). Specifically, we collected pain intensity and unpleasantness ratings, while novices (2-day formal training; average) and expert practitioners (>10.000h practice) performed OM meditation, or a distraction control condition, during the anticipation and reception of short (8s) and long tonic-like (16s) thermal pain stimuli. Pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS). **Results:** We found evidence for a modulation of mindfulness expertise but not state on brain activity during pain anticipation. Specifically, experts showed lower pre-stimulus activity in the left anterior insula (aINS) as well as in bilateral dorsolateral prefrontal cortex (dlPFC) and medial cingulate cortex (aMCC). Lower pre-stimulus activity in left aINS predicted increased sensory-affective uncoupling of pain across participants. However, contrary to our predictions, pain catastrophizing scores could not predict pre-stimulus activity in this region. Hypotheses on early and late pain periods could not be tested due to methodological limitations. **Conclusion:** Mindfulness expertise is associated with decreased anticipatory brain activity, including in left AI, and lower pre-stimulus activity in this region positively predicts sensory-affective uncoupling of pain.

1. Introduction

Pain is not a direct read-out of sensory input, rather it is shaped by cognitive-affective factors that can amplify or reduce pain (Tracey and Mantyh, 2007). One of the best predictors of increased pain is pain catastrophizing, an “exaggerated negative mental set brought to bear during actual or anticipated pain experience” (Sullivan et al., 2001). Pain catastrophizing refers to a type of conceptual processing that is reactive, judgmental and often implicit. This can be contrasted with mindfulness, a “nonelaborative, nonjudgmental, present-centered awareness” (Bishop et al., 2004), cultivated with certain meditation practices (Lutz et al., 2015; Dahl et al., 2015). In contrast to pain catastrophizing, a mindful stance presumably deflates the negative cognitive-affective elaboration of pain by allowing one to become aware of distressing thoughts and emotions as mere mental events that do not necessarily need to be reacted to (Bishop et al., 2004; Chambers et al., 2009). Cultivating this attitude, together with increased openness to sensory experience, has been suggested to lead to sensory-affective uncoupling of pain (Kabat-Zinn, 1982). Supporting this notion, several clinical studies on mindfulness-based interventions have reported mindfulness-related pain reductions with the largest effects on the affective compared to sensory dimension of pain (Hilton et al., 2017). Moreover, we previously reported that a mindfulness instruction (state) and mindfulness expertise (trait) both led to increased self-reported sensory-affective uncoupling of pain and that this uncoupling was negatively predicted by trait pain catastrophizing (Zorn et al., 2020). Here, we aimed to explore the neuronal correlates of these findings by analyzing the functional magnetic resonance imaging (fMRI)-data corresponding to this previous report.

Consistent with the multidimensional nature of pain, noxious stimulation results in widespread cortical activation, including of the thalamus, primary (S1) and secondary (S2) somatosensory cortices, mid cingulate cortex, insula and prefrontal regions (Tracey and Mantyh, 2007; Duerden and Albanese, 2013). Although the activity of most of these regions typically correlates with perceived pain intensity (Coghill et al., 2001, 2003; Wager et al., 2013), sensory-discriminative pain processing is thought to be restricted to S1 and S2 and the posterior insula (pINS) (Bushnell, 1999; Hofbauer et al., 2001; Timmerman et al., 2001; Maihöfner et al., 2006; Mazolla et al., 2012). In contrast, affective-motivational components of pain processing are ascribed to limbic regions such as the amygdala, and anterior mid cingulate cortex (aMCC) and anterior insula (aINS) (Treede, 1999; Rainville, 1997), with activity in the latter two regions frequently correlating with perceived pain unpleasantness (as well as pain intensity) (Rainville, 1997; Tolle 1999; Lorenz et al., 2003; Schreckenberger., 2005). In addition, prefrontal regions such as the dorsolateral prefrontal cortex (dlPFC) and posterior parietal regions have been implicated in the attention, evaluation and cognitive control aspects of pain processing (along with AI and aMCC) (Garcia-Larrea and Peyron, 2010).

While all of the above brain regions uniquely contribute to pain experience, the aINS has received particular attention as it is critically situated at the interface between homeostatic, afferent and cognitive brain networks, and works together with the aMCC as a functionally coupled 'salience' network to help integrate bottom-up stimulus driven processing with top-down control and biasing of sensory input (including about the decision of pain) (Mennon and Udin, 2010; Fazeli and Büchel, 2018). Specifically, from the pINS, primary nociceptive information about the body's physiological state is thought to be re-represented and integrated with affective and cognitive information in the aINS particularly it's right side, to give rise to a consciously accessible feeling state (Craig 2002; 2003). Supporting this claim, the aINS is consistently activated during awareness of emotionally-loaden subjective feeling states (Craig, 2002), and pain-related activity in pINS typically correlates with objective stimulus intensity, whereas activity in aINS usually correlates more strongly with subjective pain reports (Craig, 2000; Kong et al., 2006). Yet other studies indicate that aINS-activity correlates with interoceptive awareness (Critchley et al., 2004), thus firmly implicating the aINS in bottom-up attention to salient sensory stimuli. In addition to processing current feeling states, the aINS also processes predictive feeling states (Singer et al., 2009). For example, the aINS is frequently activated during pain anticipation and anticipation of other aversive events (Palermo, 2014; Sege, 2017), and this activity is modulated by trait and contextual factors. For example anxious and depressed subjects show aberrant anticipatory activity in aINS (Paulus and Stein, 2010), and positive and negative expectancy reduce and increase anticipatory aINS-activity respectively (Whiech, 2008; Sarinopoulos et al., 2010; Atlas et al., 2010), and this activity is known to predict subsequent pain reports (Atlas et al., 2010; Whiech et al., 2010). More recently, studies on predictive coding have directly shown that the aINS integrates sensory input with top-down predictions into a decision about pain (Fazeli and Büchel, 2018; Geuter et al., 2017). To summarize, a wealth of evidence across a variety of brain imaging studies and task domains indicates that the aINS (and aMCC) respond to the degree of subjective salience, whether cognitive, homeostatic or emotional (Mennon and Udin, 2010; Craig 2009; Craig 2002).

Based on the involvement of aINS in both bottom-up and top-down salience processing, it could be speculated that the present-centered state cultivated during mindfulness meditation is reflected in the chronometry of the aINS as reduced activity during pain anticipation (reflecting diminished anxious anticipation) but increased activation during pain onset (reflecting increased attention to bottom-up sensory stimuli). Several studies support this notion. For example, Grant et al., found reduced pain ratings and increased activity in insula (posterior to anterior) and dorsal ACC (dACC) during pain for experienced meditators compared to controls. Similarly, Gard and colleagues reported decreased unpleasantness during a mindful state for experienced meditators but not controls, which was associated with decreased activation in lateral prefrontal cortex and increased activation in right PINS during stimulation (Gard et al., 2012). Furthermore, Zeidan et al., observed overall pain reductions following brief mindfulness training in novices, which was associated with greater activation in bilateral aINS (among

other regions) (Zeidan et al., 2011; 2015). Finally, Lutz and colleagues, found that experienced meditators reported lower pain unpleasantness compared to controls during a mindful monitoring state, which was associated with lower activity in left aINS and aMCC during pain, but decreased activity in these regions and amygdala during pain anticipation, congruent with another report of a meditation-related decrease in anticipatory brain activity (Brown et al., 2010) (but see Gard et al., 2012). Notably, whereas pain-related activity in aINS and aMCC normally correlates with pain unpleasantness (Craig, 2010; Rainville et al., 1997), as was the case for controls in two of the studies (Grant et al., 2011; Lutz et al., 2013), this association was not present for meditators, suggesting a different quality of attention to pain.

Collectively, studies on mindfulness-based pain regulation to date suggest that the chronometry of the aINS is a sensitive marker of present-centeredness (increased activation during pain) vs mental projection in the future (increased activation during pain anticipation), in line with other work indicating that a present-centered mindful state reduces activity in self-referential cortical midline regions and increases activity in a right lateralized viscerosomatic network (Farb et al., 2007). However, the reviewed studies were not designed to disentangle pain from its anticipation (Ploghaus et al., 1999, Wager et al., 2004), thus posing a potential confound. Furthermore, if increased aINS-activity with meditation during early pain indeed reflects increased attention to bottom-up salience, then one could expect that aINS-activity during the late phase of tonic-like pain stimuli would be more reflective of top-down factors such as pain rumination and aversion to pain, as bottom-up salience processing is usually limited to unexpected or novel events (Corbetta et al., 2008, Corbetta and Shulman, 2002). Studies suggest that aINS responds with sustained salience to pain (Downar et al., 2003). However, it is unclear whether this response can be modulated by contextual factors, although preliminary evidence indicates that this might indeed be the case (Wager et al., 2004). To our knowledge, no studies to date have examined the impact of mindfulness meditation on this process. Therefore, following Lutz et al., we aimed to explore the impact of mindfulness meditation on aINS-chronometry (and concomitant activity in sensory and cognitive regions) in relation to mindfulness-related sensory-affective uncoupling of pain. Finally, given that we previously reported a negative association between mindfulness expertise and pain catastrophizing and between pain catastrophizing and sensory-affective uncoupling of pain, we also aimed to explore the relation of pain catastrophizing to this process.

In order to address these questions, we implemented a novel acute pain fMRI-scanner paradigm that was designed to amplify the cognitive-affective aspects of pain, while participants performed Open Monitoring meditation (Lutz et al., 2008), a style of mindfulness meditation known to impact sensory-affective uncoupling of pain (Perlman et al., 2010; Zorn et al., 2020). Specifically, we collected pain intensity and unpleasantness ratings, while novices (2-day formal training; average) and expert practitioners (>10,000h practice) performed OM meditation, or a distraction control condition, during the anticipation and reception of short (8s) and long tonic-like (16s) thermal pain stimuli.

Our hypotheses pertained to pain anticipation and early and late pain periods. Our first hypothesis was that the present-centered state associated with mindfulness meditation (state and expertise) would downregulate anticipatory pain representations in aINS and amygdala (replicating Lutz et al., 2013), and that the degree of aINS-activation would negatively predict sensory-affective uncoupling of pain and would positively correlate with trait pain catastrophizing, which we previously found to be lower in experienced practitioners (Zorn et al., 2020). Our second hypothesis was that increased openness to sensory experience during mindfulness meditation (state and expertise) would result in increased aINS-activation during early pain (replicating Grant et al., 2009; Lutz et al., 2013). In an exploratory fashion we intended to examine the relationship of aINS-activation during early pain to uncoupling and pain catastrophizing scores. Finally, our third hypothesis was that the present centered state cultivated during mindfulness meditation (state and expertise) would be reflected in lower aINS-activation during late pain, reflecting decreased top-down salience processing. Therefore, we expected that aINS-activity during late pain, would be positively correlated with pain unpleasantness as well as with pain catastrophizing. More broadly, based on our previous report (Zorn et al., 2020), we aimed to identify the neuronal correlates underlying mindfulness-related sensory-affective uncoupling of pain.

2. Material and Methods

2.1. Participants

Participants included novice and long term meditation practitioners (experts), who were recruited through multiple screening stages which are reported into detail elsewhere (see the Brain & Mindfulness Project Manual, Abdoun et al., 2018). Inclusion criteria were: aged between 35 and 65 years, no psychotropic drug use, no neurological or psychiatric disorder, a Beck Depression Inventory (BDI) score below 20, no family history of epilepsy, no severe hearing loss, MRI compatibility and affiliation to the social security system. Pregnant and breastfeeding women were also excluded. Experts needed to have: a minimum of 10.000 hours of formal practice in the Kagyu or Nyingma school of Tibetan Buddhism, followed at least one traditional 3-year meditation retreat, a regular daily practice in the year preceding inclusion. They also had to be able to distinguish between OM and OP meditation and to be familiar with the practice of OP. Novices were included if they did not have significant experience with meditation or other mind-body training techniques and a pain threshold above 47 C° comparable to experts in our previous study (Lutz et al., 2013). In a prior report on this study (Zorn et al., 2020), we reported preliminary behavioral results from 35 novices and 26 experts. Of this sample, 5 participants were excluded because of motion exceeding a predefined threshold (> 2mm or > 2 degree absolute movement in more than 2 runs) and 1 participant because of missing anatomical scans. The final sample included 30 novices (17 males/13 females; mean age 52.5 ± 7.6 years, pain threshold 48.3 ± 1.0 ; experimental temperature 48.0 ± 0.5) and

25 experts (13 males/12 females; mean age 52.6 ± 8.0 years, pain threshold 47.0 ± 2.4 ; experimental temperature 47.8 ± 0.5). 6 included participants had 1 out of 6 runs discarded due to the movement criterion. All participants provided written informed consent before participating to the study. The study was approved by the regional ethics committee on Human Research (CPP Sud-Est IV, 2015-A01472-47).

2.2 Meditation practices

All participants who participated to the experiment were familiar with two styles of meditation: Open Monitoring meditation (OM) and Focused attention meditation (FA): experts because of longstanding experience and novices because they were familiarized with the practices through an extensive novice meditation training protocol (see section 2.3 meditation training novices). Initial training in FA meditation is considered a prerequisite for OM in both traditional and clinical contexts (Lutz et al., 2008). Specifically, FA, involves a sustained focusing of attention on a selected object of choice and is said to increase the capacity to detect distractions and sustain attention, thus improving the monitoring capacity (Lutz et al., 2008). The resulting improved monitoring capacity supports OM practice, which involves the non-selective, non-judgmental, and non-elaborative monitoring of all ongoing experience, whether sensory, affective or cognitive (Chambers et al., 2009; Lutz et al., 2008; see supplementary information 1 for instructions provided during the experiment). The cultivation of this present-centered metacognitive perspective is thought to allow one to become aware of subtle distressing thoughts that may accompany the anticipation or perception of painful stimuli that may otherwise go unnoticed. This awareness itself, together with the realization that thoughts are mere mental events and do not necessarily need to be reacted upon is thought to reduce secondary elaborative processing and may thus result in reduced mental absorption and pain-related distress (Bishop et al., 2004; Hayes 2004; Kabat-Zinn, 1982; Lutz et al., 2015; Lutz et al., 2008). As a result of these two processes, has been suggested that during a mindful state, sensory pain dimensions might be experienced with equal or increased vividness, without concomitant emotional distress (Lutz et al., 2013; Perlman et al., 2010), thus inducing an 'uncoupling' of sensory and affective pain experience (Kabat-Zinn, 1982).

It should be noted that novices and experts differed in the way of practicing objectless meditation. Specifically, with increasing expertise the capacity to sustain an open monitoring state purportedly becomes increasingly effortless, at which point awareness can be made an object of meditation itself (Chambers et al., 2009; Lutz et al., 2008). Expert practitioners were intensively familiar with this advanced style of OM labeled as open presence (OP) (Tib. rig pa) (Lutz et al, 2006) and were explicitly asked to do it. In this state, theoretically at least, the phenomenological qualities of effortlessness, openness and acceptance are vividly experienced and control-oriented elaborative processes reduced to a minimum. A suspension of subject-object duality (non-duality) is also reportedly involved (Dunne, 2011; Lutz et al., 2006). As this state is considered a relatively advanced one, even expert practitioners might not be able to sustain it for more than a short time (Lutz et al., 2006). For the sake of simplicity, we will use the term

OM for both novices and experts below, acknowledging that for experts actual meditation might also have qualified as OP.

2.3 Meditation training novices

We aimed to have a high-quality control group for expert practitioners as well as to investigate the effect of mindfulness-based pain regulation in trained novices. To this end, meditation-naïve participants underwent a weekend-long formal meditation training program (see Abdoun et al., 2019 for detailed information on the novice training protocol), provided by a qualified MBSR teacher, with 13 years of practice and 8 years of teaching experience in the meditation tradition under study as well as 3 years of experience as a teacher of a 18 month mindfulness-based intervention (Poissnel et al., 2018). The training included teachings with the support of instruction videos, guided meditation sessions and experiential exercises, question and answer sessions, as well as sufficient time to reflect and share with the group. During the training, novices were introduced to various styles of meditation, including FA and OM; two complementary styles of meditation (see section 2.2) also extensively practiced by the expert practitioners. One specific exercise involved alternating between focused attention on, and open monitoring of, pain. During such exercises, novices were additionally familiarized with several experiential dimensions relevant to mindfulness meditation (e.g. absorption vs. meditative awareness). Through this approach, we aimed to assure that novices gained an adequate understanding of the practices. After the training weekend, novices were invited to keep up a daily practice of minimum 20 minutes a day until the day of the last experiment, to balance FA, OM and compassion meditations (relevant to other experiments, and also practiced by the experts), and to keep track of their practice with a logbook.

2.4 Pain calibration procedure

Painful stimuli were provided by a TSA 2001-II thermal stimulator (Medoc Advanced Medical Systems, Haifa, Israel) with a 30 mm × 30 mm flat thermode applied to the palmar side of the left wrist. All participants underwent a calibration procedure for stimulus temperature. Using the method of limits (Fruhstorfer et al., 1976), the temperature was increased from 32° C to 50° C maximum at 0.7 C° C/sec. Participants were instructed to indicate with a button press when the pain level reached a 7 on a scale of 0 (“no pain”) – 10 (“the worst pain imaginable”). At button press, temperature returned to the 32° C baseline at maximum rate. The temperature remained at baseline for 5 sec before rising again. Subjects received 10 stimulations. The average temperature over the last five trials was used as an indication of that participant’s pain sensitivity (except when 50° C was reached at three consecutive trials in which case the procedure was stopped and pain sensitivity set at 50° C; 3 novices, 2 experts). A second, finer calibration procedure was performed on the day of the experiment to determine the optimal temperature for a 16 sec long heat stimulation that would be used during the experiment itself. This calibration started

with the temperature that best matched the participant's previously determined pain sensitivity, but was confined to a limited range of four possible temperatures: 47.0, 47.5, 48.0, and 48.5° C. Subjects received the best matching temperature for 16 sec, after which they were asked to rate their pain using the same scale as before. If rating was at 7, temperature was kept at that level; else the temperature was adapted until the targeted pain level of 7 was reached.

2.5 Experimental design, pain stimuli and task instructions

Visual stimuli were presented using Psychopy v1.83.04 (Peirce, 2009). The experimental design is presented in Figure 1. Temporal jitters in the presentation of the stimuli were introduced to reduce collinearity of regressors in the fMRI-based general linear models. A fixation cross was displayed on the screen when no other visual stimuli were presented. Each trial started with a 5-8 sec introductory period. A 2 sec predictive cue then indicated whether the upcoming stimulation would be warm or hot and was followed by a 5 to 8 sec anticipatory period. A thermal stimulation was then delivered which was either hot, at the participant's painful temperature, or warm, at a non-painful temperature 6 degrees cooler. 3 to 6 sec after stimulus onset, a second cue indicated whether the stimulation would be short (8 sec, relief) or long (16 sec, non-relief). Warm stimuli were always long (16 sec) and served as a baseline control condition for the MRI. Five to eight seconds after the thermal stimulation ended, two rating scales were presented for 5 sec each (see rating scale section below). After 1 sec the next trial started. Baseline temperature for the thermode was 32°C. Ramp-up and ramp-down periods were 1.5 sec for the warm and 2.5 sec for hot stimuli. Temperature of the long hot stimuli dropped slightly by 1 ° C (0.5 ° C/sec) after 2 sec of stimulation (not depicted) as initial pilot sessions revealed they would otherwise be unbearable. Subjects received a total of 60 thermal stimuli; 20 short hot (SH), 20 long hot (LH) and 20 long warm (LW), applied to the palmar side of the left wrist. All thermal stimuli were delivered during one experimental session consisting of six blocks of ten trials each. Subjects rested 1.5 minute between the blocks. Each block was further subdivided into two subblocks, one for each state condition, in randomized order: Open Monitoring (OM) or a control addition task (Distraction). Each trial type (SH, LH, LW) was set to occur at least once during each subblock. Each subblock started with a 20 s auditory and visual state induction during which participants received instructions for the experimental condition. For OM, participants were instructed to keep an open and accepting awareness (see supplementary information 1 for full instructions). Experts specifically were also told that the OM instructions referred to the practice of OP. For Distraction, subjects were instructed to mentally add simple single-digit numbers (1-3) that were presented on the center of the screen (replacing the fixation cross) from the start of each trial until rating scales were shown (see Fig. 1). Numbers were presented for 1 sec with a variable interval of 3, 4 or 5 sec between numbers. Subjects were asked to maintain a tight focus on the screen in order not to miss any numbers, while blocking all pain-related sensations, emotions and thoughts. In order to minimize visual differences between task conditions, numbers were also presented on the screen during OM. However,

subjects were instructed to abstain from mental addition, but to nonetheless keep their gaze fixed at the screen at all times, in a relaxed manner, in order to not miss any visual cues. Prior to the experiment, participants were familiarized with the task and performed one full block of trials using non-painful stimuli only (note information on meditation practices, pain calibration procedure and experimental design adapted from Zorn et al., 2020).

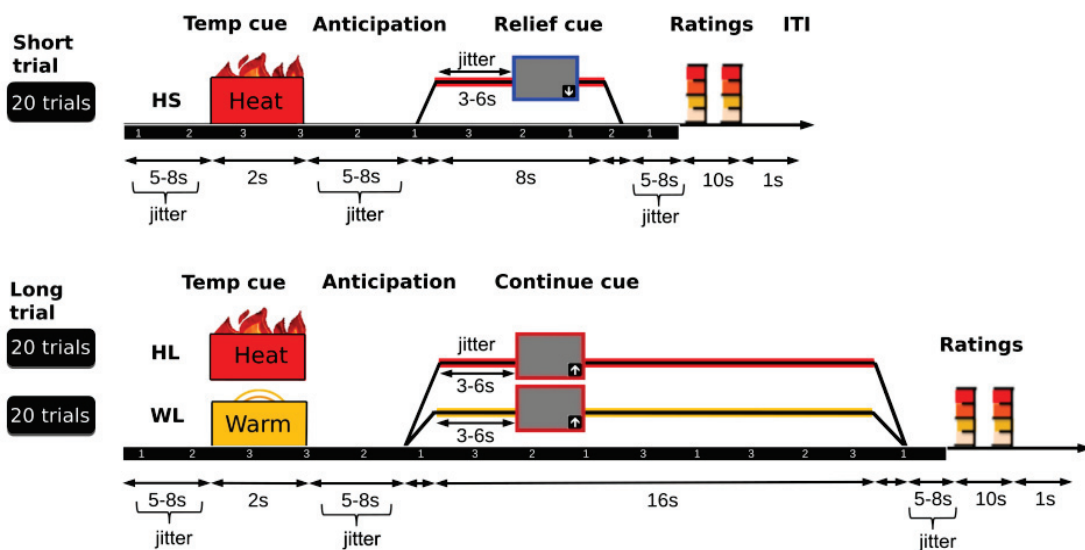


Figure 1. Schematic illustration of the experimental paradigm. Each trial started with a 5-8 sec introductory period. A 2 sec predictive cue then indicated the temperature of the upcoming stimulation (warm or hot) and was followed by a 5-8 sec anticipatory period. A thermal stimulation was then delivered that was either short (8 sec) or long (16 sec). After 3-6 sec of thermal stimulation, a second visual cue informed subjects about the duration of the stimulation. Non-painful warm stimuli were always long and served as baseline control for the fMRI. Following stimulus offset, a 5-8 sec rest period preceded the presentation of two rating scales (5 sec each). Rating scales probed pain intensity, unpleasantness, relief and task performance. During each trial, a single-digit number (1-3) was presented every 2 sec from the start of the trial until rating scales were shown (see black horizontal bars). Subjects randomly alternated between two task conditions: Distraction, involving the mental addition of the numbers and the blocking of all pain experience; or OM involving the cultivation of an open attitude to pain (and no mental addition). Subjects received a total of 60 thermal stimuli: 20 short hot (SH), 20 long hot (LH) and 20 long warm (LW) equally distributed across the two task conditions. ITI: intertrial interval.

2.6 Rating scales

Throughout the blocks, we collected ratings of pain intensity and unpleasantness using 1-9 Likert items. Similarly, we collected ratings of pain relief (how relieved were you when the stimulation stopped) which were not analyzed here due to time constraints. We further checked task performance by regularly asking the total sum of the addition task in the Distraction condition, or, in case of OM, to what degree participants were able to follow meditation instructions. After each trial, two different rating scales were presented in randomized order (see supplementary information 2 for the specific questions and frequency of presentation).

2.7 Behavioral analysis

For the behavioral analysis, we refer to our previous report (Zorn et al., 2020), where pain ratings and pain catastrophizing scores were extensively analyzed with the following results: a) a general state effect with OM being associated with lower pain unpleasantness but not pain intensity as compared to the attentional distraction control condition across groups and trial types, b) experts reporting larger sensory-affective uncoupling (intensity-unpleasantness) as compared to controls already during short, but particularly during long trial types, (c) lower pain catastrophizing scores for experts compared to novices, and d), pain catastrophizing scores predicting sensory-affective uncoupling across participants specifically for long trial types.

2.8 BOLD data analysis

Data acquisition

Scanning was performed on a 3-T scanner (Prisma Siemens, Erlangen, Germany) with a 64 channel head/neck coil.

Functional imaging data were acquired using a simultaneous multi-slice (SMS) EPI pulse sequence with a multiband factor of 4 which allowed for the acquisition of data with a high temporal resolution (TR = 1000 ms, TE = 30 ms). Each volume comprised 52 axial slices of 2.3 mm thickness. A 10% gap between slices resulted in 2.5 x 2.5 x 2.6 mm³ voxel size (FOV = 1680 x 1680 mm, flip angle = 65°).

For anatomical reference, we acquired structural T1-weighted (TR = 2500 ms, TE = 2.83 ms, flip angle = 6°, voxel size = 1x1x1 mm³), non-EPI T2*-weighted (TR = 3680 ms, TE = 30 ms, flip angle = 90°, voxel size 2 x 2 x 2 mm³) and T2-weighted (TR = 2500 ms, TE = 261 ms, flip angle = 120°, voxel size 1 x 1 x 1 mm³) images.

fMRI data preprocessing

Neuroimaging data were preprocessed using Nipype Python (Gorgolewski et al. 2011) and SPM12 (Wellcome Trust Centre for Neuroimaging, UK). The first four volumes of each run were discarded to allow for magnetization to reach equilibrium. No slice timing correction was performed as this is not critical to SMS-EPI acquisitions, where all slices in a volume are acquired relatively close in time (Glasser 2013). In addition, SMS-EPI acquisitions have relatively low tissue contrast (due to incomplete T1 relaxation), and require a different preprocessing strategy for accurate registration to structural data (Glasser 2013). Hence, the preprocessing pipeline described by Villain et al. (2010), developed to improve anatomical mapping of functional data, was applied. Briefly, images were first realigned. The mean image of the functional runs was then coregistered onto the (non-distorted) non-EPI T2* image, the non-EPI T2* image then onto the T2 image, and the T2 image then onto the T1 acquisition. Resulting coregistration parameters were successively applied to all SMS-EPI images. Subsequently, the T1 image was segmented and normalized to MNI-space, and resulting parameters applied to the coregistered T1, EPI and non-EPI T2* images. Normalized images were smoothed with a 7.5 x 7.5 x 8 FWHM Gaussian kernel.

The artifact detection toolbox (ART) was used in order to detect outlier volumes (> 3 mm scan-to-scan motion or global signal intensity deviations more than 5 standard deviations away from the mean). Identified outliers were modeled as knock-out regressors and added to the general linear model (GLM) as confound regressors together with the 6 realignment parameters.

Using aCompCor an additional denoising step was performed in order to remove physiological noise from the data. This method consists of principal components analysis on voxels in a noise mask, which comprised CSF and white matter segmentation maps, eroded by 1 voxel. Additionally, following Bezdade et al. 2017, voxels that correlated with the convolved task regressors, as determined by a conservative threshold of $p < 0.2$, were excluded from the mask in order to avoid including stimulus correlated components. The 5 principal components were added as confound regressors to the GLM.

Single subject analyses

Two general linear models (GLM) were constructed to test the different hypotheses.

The first GLM addressed questions about anticipation and relief. Regressors in this model were convolved with a canonical BOLD-response. Modeled regressors of interest were: i) the first 5 seconds of the anticipation period; ii) the full length of the pain stimuli: 13 s for short painful stimuli, 21 s for long painful stimuli and 19 s for long warm stimuli (including ramp-up and -down periods). iii) the relief cue, 2 s duration. In addition, several regressors of non-interest were modeled including the rating scales, state

cues, intro cues and intro audio. Events for each of these event types were collapsed into a single regressor. The temperature cue was not modeled as it was orthogonal to the anticipation period.

The second GLM was constructed in order to compare early and late pain periods of long painful stimuli. Following Wager et al. 2004, regressors in this model included unconvolved epochs (to avoid assuming a particular response shape) shifted 4 s in time to account for the hemodynamic response delay. To maximize the contrast between early and late pain periods, it was chosen to model three time windows: i) early-pain, 7,5 s duration (4-11.5 s after stimulus onset); mid-pain, 6 s duration (11,5-17,5 s after stimulus onset); late-pain, 7,5 s duration (17,5–25 s) after stimulus onset (stimulus offset was at 21 s). Long warm stimuli were modeled similar to long painful stimuli. Short painful stimuli were modeled as one event, 4-17 s after stimulus onset. For all heat stimuli, we additionally modeled the full length of the anticipation period 4-12 s after the temperature cue (5-8 s duration) and a recovery period, 4-11,5 s after stimulation offset (7,5 s duration). In addition, several effects of no interest were modeled by convolving events with a canonical BOLD response. These included the rating scales, state cues, intro cues, and intro audio. Events for each of these event types were collapsed into a single regressor. The temperature and relief cue were not modeled as they were orthogonal to anticipation and pain periods respectively.

Second-level analyses

Functional activation analyses

Each participant's first-level t-contrasts were entered into second-level GLMs to investigate contrasts of interest. We first verified whether pain stimulation activated the typical pain-processing regions by analyzing the BOLD-signal (contrast Hot – Warm) across task conditions (OM, Distraction), trial types (Short, Long) and groups (Novices, Experts). Subsequently, we analyzed the pain anticipation period using a 2x2 factorial ANOVA with factors State(OM, Distraction) and Group (Novice, Expert) (contrast Hot – Warm), first in bilateral aINS and amygdala using small-volume correction (SVC) and then on a whole-brain basis in an exploratory manner. Similarly, we analyzed the early pain period of long pain stimuli (as short stimuli overlapped with the relief cue posing a possible confound), using a 2x2 factorial ANOVA with factors State (OM, Distraction) and Group (Novice, Expert) (contrast Hot – Warm), first in bilateral aINS using small-volume correction (SVC) and then on a whole-brain basis in an exploratory manner. All whole-brain analyses were carried out at a $p < 0.001$ uncorrected at the voxel-level and cluster-level family-wise error-corrected pFWE < 0.05 values were reported as significant. Regions were classified using the Hammersmith atlas (Hammers et al., 2003; Faillenot et al., 2017), and the Human Connectome Project atlas (HCP MMP 1.0) (Glasser et al., 2016).

ROI definition

Based on our hypotheses we restricted our primary analyses to bilateral aINS, which was defined based on the Hammersmith atlas (Hammers et al., 2003; Faillenot et al., 2017), and included the insula inferior cortex and the anterior and middle short anterior gyrus, which together cover the portion of the insula anterior to $y = 4$. For the analyses on pain anticipation, we additionally included the bilateral amygdala to the mask as defined by the Hammersmith atlas.

Outlier removal

In some functional analyses we detected strong outliers after extracting beta-estimates (never more than one and for different subjects for different contrasts). To prevent that activation clusters were driven by outlier points, we implemented a retrospective and conservative outlier removal method. If extreme outlier points more than 3.5 standard deviations away from the mean across the levels of a given comparison (e.g. novice and expert groups were detected, we re-performed the GLM-analyses excluding the subject corresponding to the outlier point. In all cases, this led to a decrease of significant clusters indicating that clusters were false positives driven by outlier participants.

Correlational analyses

We performed two types of correlation analyses: brain-behavior correlations with extracted beta-estimates and whole-brain voxel-wise correlations. Correlations with extracted beta-estimates were performed using Spearman's ρ as well as bisquare robust regressions (following Rudolf et al., 2018). Correlational analyses are particularly sensitive to outliers that can result in false-positive and negatives (Rousselet and Pernet., 2012), an issue that might be particularly present with neuroimaging data prone to outliers (Wager et al., 2005). Several statistical techniques have been proposed to reduce the influence of outliers, including robust regression techniques (Rousselet and Pernet, 2012; Wager et al., 2005). We implemented bisquare-regressions using the R-package robustbase (Maechler et al., 2020). This robust regression technique iteratively downweights points with high leverage (i.e. influence on the regression line) so that these points have less influence on the regression parameters estimates. Spearman's correlations were included as reference. We additionally performed whole-brain voxel-wise analyses with pain catastrophizing and uncoupling scores that were carried out at a threshold of $p < 0.005$ uncorrected at the voxel-level and a family-wise error-correction of $pFWE < 0.05$ at the cluster-level.

3. Results

3.1 Behavioral results

We first tested whether experts reported larger sensory-affective uncoupling (intensity – unpleasantness) compared to novices for short and long painful stimuli in line with our previous behavioral report (Zorn et al., 2020). Running a 2x2 factorial ANOVA with the factors Group and Trial Type we found a main effect of Group ($F(1, 106) = 15.0, p < 0.001$), but no effect of Trial Type ($F(1, 106) = 3.7, p = 0.13$) or Group x Trial Type interaction ($F(1, 106) = 1.9, p = 0.28$). Confirmatory follow-up test showed that experts reported larger uncoupling than novices during short (estimate = 0.7, 95% ci = [-1.33, -0.02], $t(46) = -2.1, p = 0.045$) and long trial types (estimate = 1.2, 95% ci = [-1.91, -0.39], $t(40) = -3.0, p < 0.01$).

We subsequently test whether novices and experts in the included sample differed in trait pain catastrophizing similar to our previous report (Zorn et al., 2020). In line with this report, Trait pain catastrophizing was significantly lower in Experts (6.8 +- 5.4) compared to novices (17.2 +- 9.2) (estimate = 10.4, 95% ci = [6.3, 14.5], $t(46.5) = 5.2, p < 0.001$).

3.2 Pain Anticipation

Activation analyses

To evaluate our first hypothesis -that mindfulness meditation downregulates neural representations of pain anticipation- we examined the effect of State (OM/Distraction) and Group (Novice/ Expert) on fMRI-activity in the anticipation period (Hot-Warm) using a 2x2 factorial ANOVA. We first restricted the analysis to bilateral aINS and left amygdala based on our hypothesis. We observed a main effect of Group for a cluster in the left aINS (see top rows Table 1 and Figure 1; cluster marked in red). A post-hoc test revealed that, in line with our hypothesis, this region was more strongly activated for novices compared to experts (estimate = 0.78, 95% ci = [0.32, 1.26], $t(51.0) = 3.4, p < 0.01$; see Figure 1A). This effect was also present at a trend level in the right aINS. However, contrary to our hypothesis we failed to observe a State or interaction effect or an effect on the amygdala. In an exploratory manner, we also ran the same ANOVA on a whole-brain basis to identify potential regions we might have missed with our more restricted approach based on previous work. This again yielded only a main effect of Group, but this time for a large activation cluster with significant peaks in bilateral dIPFC and right frontopolar cortex (FPC) and extending into bilateral aMCC (see middle rows Table 1 and Figure 1; cluster marked in yellow). A post-hoc test revealed that this cluster was also more strongly activated for novices than experts (estimate = 0.47, 95% ci = [0.24, 0.71], $t(49.9) = 4.0, p < 0.001$; see Fig. 1B). Note that we removed one outlier subject (novice, > 5std away from the mean for aINS cluster) for this and corresponding

correlational analyses (see methods). Keeping this subject further increased the significance of all reported clusters.

Correlational analyses

As a next step, we performed correlation analyses, to test whether the observed decreased anticipatory brain activity for experts compared to novices could be linked to experts' lower trait pain catastrophizing and increased self-reported sensory-affective uncoupling of pain. We first addressed these questions in relation the left AI cluster that was part of our primary regions of interest. We first tested whether activity in this cluster could predict sensory-affective uncoupling of pain (calculated as self-reported intensity - unpleasantness across states and trial types; using demeaned scores to control for group effects). This was indeed the case with lower left aINS-activity during pain anticipation predicting increased self-reported sensory-affective uncoupling of pain across subjects (Spearman's $\rho = -0.29$, $p = 0.035$; robust $R^2 = -0.13$, $p < 0.01$; see Fig. 1C). To test the specificity of this finding we subsequently tested whether left aINS-activity during pain anticipation could predict intensity and unpleasantness scores. This was not the case (Intensity: Spearman's $\rho = -0.19$, $p = 0.15$; robust $R^2 = 0.03$, $p = 0.23$; Unpleasantness: Spearman's $\rho = 0.04$; robust $R^2 < 0.0$, both $p > 0.75$). We then tested whether across subjects (demeaned) pain catastrophizing scores could predict activation in this cluster. This was not the case (Spearman's $\rho < 0.01$, robust $R^2 < 0.01$, both $p > 0.7$). In an exploratory manner, we then performed the same correlation analyses for the prefrontal cluster that was identified through the whole-brain analysis. This cluster did not correlate with pain catastrophizing scores (Spearman's $\rho = 0.09$, robust $R^2 = 0.01$, both $p > 0.4$), nor predicted self-reported sensory-affective uncoupling of pain experience (Spearman's $\rho = -0.03$, robust $R^2 < 0.01$, both $p > 0.7$). Reperforming the analyses with null findings for groups separately and with sex and age as covariate did not change the results.

Finally, and in a further exploratory manner, we performed whole-brain correlation analyses with pain catastrophizing and sensory-affective uncoupling scores at FWE-correction rate of $p < 0.005$. The analysis with pain catastrophizing scores yielded no significant clusters. In contrast, the analysis with uncoupling scores yielded one significant cluster that had its peak activation in the left pINS and extended from the operculoinsula (PI/SII) anteriorly to middle insula and into the inferior frontal gyrus (IFG) see Table 1 bottom row and Figure 1; cluster marked in green). For descriptive purposes, we performed a post-hoc test on this cluster, correlating extracted parameter-estimates with self-report sensory-affective uncoupling scores (Spearman's $\rho = -0.45$, $p < 0.001$; robust $R^2 = 0.24$, $p < 0.01$; see Figure 1D). To test the specificity of this finding we subsequently performed whole-brain analyses with intensity and unpleasantness instead of sensory-affective uncoupling scores. This yielded no significant clusters.

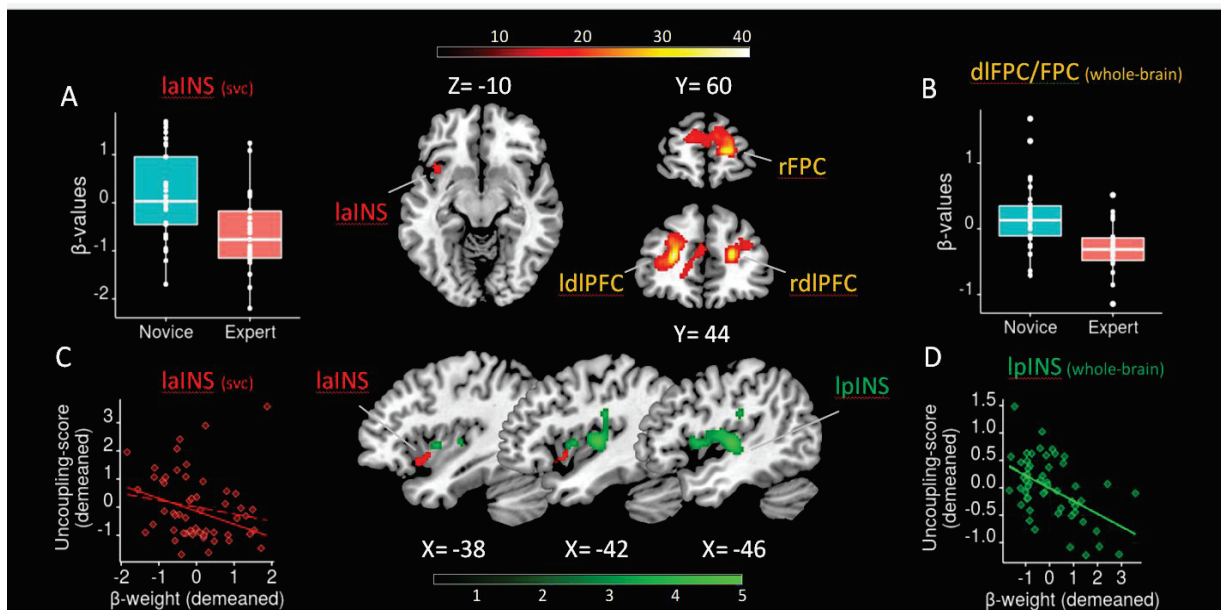


Figure 2. Pain anticipation. (A) experts showed lower activation in left AI compared to experts during pain anticipation, see red cluster, (B) experts additionally showed lower activation in several prefrontal regions including in bilateral *dlPFC* and *rPFC* extending into bilateral *ACC*, see yellow cluster, (C) Across subjects, anticipatory activity in *laINS* negatively predicted self-reported sensory-affective uncoupling of pain, (D) Across subjects, lower activity in a large cluster extending from *lpINS* and *STG* anteriorly into the *IFG* negatively predicted self-reported sensory-affective uncoupling of pain. Analyses were performed using small-volume correction (svc) or whole-brain voxel analysis (whole-brain). *laINS*; left anterior insula, *dlPFC*: dorsolateral prefrontal cortex, *FPC*; frontopolar cortex, *lpINS*; left posterior insula, *STG*; superior temporal gyrus, *IFG*; inferior frontal gyrus. The upper bar (red) represents F-scores whereas the lower bar represents (Z-scores). Solid regression lines correspond to Spearman's regression slope, dashed regression lines correspond to Robust regression slopes.

3.3 Neural correlates of heat-induced pain stimulation

To test hypotheses on early and late pain periods, we first performed a manipulation check. This yielded clear pain matrices (activation in *pINS/aINS*, and *aMCC*) when combining pain stimulations across groups, states and trial types. Clear pain matrices were also observed when analyzing novices and experts separately. However, when we inspected the early phase of long pain stimuli (first 8s of 16s long stimuli) pain matrices were only observed for experts but not for novices (averaging across states). Specifically, experts showed activation in bilateral operculoinsula (*S2/pINS*), *aINS* and *aMCC*. Novices on the other hand, did not show activity in operculoinsula (*S2/pINS*) or *aMCC*, but only in *S1*, bilateral *aINS* and several prefrontal regions (see Figure 3 and Supplementary information 3). As we previously encountered physiological noise-related problems (see discussion), we did not further analyze pain contrasts.

Table 1. Pain anticipation

Brain regions	k	Peak MNI Coordinates			Z	p
		X	Y	Z		
SVC						
L Insula anterior inferior cortex (AAIC, MI)	44	-38	16	-10	4.6	0.034
Whole brain analysis						
L Middle frontal gyrus (Area 9-46d, 9m, 9a, a32pr, d32, p24) ^a	3209	-24	44	14	5.3	<0.001
R Middle frontal gyrus (Area 9-46d)*	-	22	46	16	5.1	0.005
R Superior frontal gyrus (p10p/9a)*	-	18	60	6	4.9	0.012
Whole-brain correlation (uncoupling scores)						
L Superior temporal gyrus middle (po11-2, Mbelt, A1, OP1,2-3, MI, Area 43-44,52, FOP1-2,4)	689	-44	-16	4	-4.3	0.047
L Inferior frontal gyrus (FOP4)	-	-48	12	4	3.5	-
L Supramarginal gyrus (OP1/SII)	-	-44	-22	26	3.3	-

Peak activations were classified according to the Hammersmith atlas [Hammers et al., 2003; Faillenot et al., 2017]. Other regions included in the clusters are denoted (inside brackets) according to the abbreviation system of the Human Connectome Project atlas (HCP MMP 1.0) [Glasser et al., 2016]. X, y, z coordinates (MNI) and statistical information (Z-statistic and p-value) refer to peak voxels in the identified clusters. P-values are adjusted for family-wise error correction for multiple comparisons across the whole brain and across the combined masks of the right and left AIC and left amygdala using small volume correction (SVC). ^aBecause of the large cluster size only bilateral activation foci are denoted. For large clusters, the main peak plus subpeaks as provided by SPM are listed. Asterisks (*) indicate subpeaks where the peak-value also survived FWE-correction ($p < .05$) at the voxel level. Associated p-value corresponds to peak-level statistics.

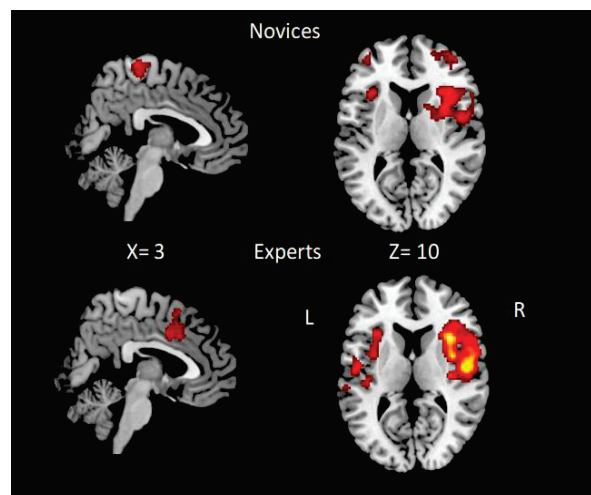


Figure 3. Early pain activation. (A) Novices showed activation in ipsilateral S1 and bilateral aINS but not in the operculoinsular complex (S2/pINS) or aMCC. **(B)** Experts showed activation in bilateral operculoinsula (S2/pINS), aINS and aMCC. S1, primary somatosensory cortex; S2 secondary somatosensory cortex; pINS, posterior insula; aINS, anterior insula; aMCC, anterior midcingulate cortex.

4. Discussion

The present work aimed to test the hypothesis that the chronometry of the anterior insula is a sensitive marker of present-centeredness vs conceptually driven top-down processing, which could be related to sensory-affective uncoupling and pain catastrophizing scores. Hypotheses were only partly confirmed at this stage. Specifically, regarding the first hypothesis that mindfulness meditation downregulates representations of anticipatory brain activity, we found that experts had reduced activity in the left aINS compared to novices during pain anticipation and that the degree of anticipatory activity in this brain region negatively predicted self-reported sensory-affective uncoupling of pain across participants, in line with our hypotheses. However, contrary to our hypotheses we did not find evidence for a modulation of state on anticipatory brain activity or for an association between anticipatory aINS-activity and pain catastrophizing scores. We were not able at this stage to test our second hypothesis that mindfulness meditation would be associated with an increased aINS-response during early pain -putatively reflecting increased bottom-up salience processing, nor our third hypothesis that mindfulness meditation would be associated with reduced aINS-activity during late pain -putatively reflecting decreased top-down salience processing. Each of these results and lack of finding will be further discussed below.

4.1 Effect of mindfulness meditation on pain anticipation

Our main finding was that experts compared to novices showed reduced activity during pain anticipation in left aINS, in a region that negatively predicted self-reported sensory-affective pain uncoupling across participants. This finding largely replicates the study by Lutz et al., 2013, which found that a sample of expert meditators in the same Tibetan Buddhist meditation tradition as in the present study exhibited reduced anticipatory activity in left aINS, aMCC and amygdala as compared to controls. Similar to that study, experts in the present work, also exhibited reduced anticipatory activity in the aMCC as well as in bilateral DIPFC, which together with the aINS are among the brain regions most frequently activated during pain anticipation (Palermo et al., 2015), and whose activity is known to scale with the expected magnitude of pain (Koyama et al., 2005). The present findings also extends the previous work by Lutz and colleagues, by explicitly manipulation anticipatory processes in our design, and by showing that anticipatory aINS-activity negatively predicted self-reported sensory-affective pain uncoupling across participants. This finding is consistent with several other studies that found that the degree of pre-stimulus aINS-activation to modulates the perception of subsequent pain stimuli (Whiech et al., 2010; Atlas et al., 2010; Ploner et al., 2010). However, in the present work, left aINS-activity specifically predicted sensory-affective uncoupling of pain and not pain intensity or unpleasantness scores. Whether this merely reflects different participant's behavior by the implementation of both intensity and unpleasantness ratings or a functionally significant difference remains to be explored. Nevertheless, our findings show that

mindfulness expertise is associated with decreased pain anticipation which predicts increased sensory-affective uncoupling of pain.

Several other findings are worth discussing. First, contrary to our hypotheses, we did not observe lower amygdala in experts compared to novices, which might be related to the fact that the present study employed certain anticipation (i.e. veridical cues about the temperature of the upcoming stimulation) in contrast to the previous study that employed uncertain anticipation (participants did not know whether upcoming stimuli would be nonpainful warm or painful hot) (Lutz et al., 2013). Uncertain anticipation of aversive events is known to lead to higher recruitment of ACC, insula, and amygdala (Sarinopoulos et al., 2010; Critchley et al., 2001). Furthermore, also contrary to our hypotheses, we found no evidence for a modulation of pre-stimulus activity by mindfulness state. This could have several possible explanations. First, as mentioned before, the fact that we employed certain expectation may have decreased overall anticipatory activity and thus our sensitivity to detect potentially subtle state differences. Second, it is possible that the control state did not have the intended effect. This condition consisted of a relatively simple addition task, which was meant to prevent participants from allocating mindfulness-related monitoring resources to pain, while still keeping working memory load so low as to allow room for pain elaborative processes to occur. It is possible that several of these assumptions have not been met. For example, working memory load could have unintentionally be higher than expected, which is known to suppress pain-related activity (Sprenger et al., 2012). However, given the overall lack of state differences in this experiment, perhaps a more likely explanation is that we lacked power to detect state differences, or that state effects are related to neuronal mechanisms not detected with our approach.

Another finding worth mentioning is that during exploratory whole-brain analyses we identified a large left-lateralized cluster in which pre-stimulus activity predicted self-reported sensory-affective uncoupling of pain across participants. This cluster extended from the parietal operculum (pINS/S2) anteriorly to mid-insula and further into the IFG. Activity in these regions during pain anticipation has also been formally shown to scale with the magnitude of expected pain (Koyama et al., 2005). Furthermore, the pINS and S2 are known to activate during the mental simulation of pain (Wilson-Mendenhall et al., 2019; Ogino et al., 2007; Meyer et al., 2015). As such, decreased pre-stimulus activity in these regions likely reflects other aspect of decreased pain anticipation. Interestingly, decreased pre-stimulus activity in these regions predicted increased sensory-affective uncoupling of pain across participants. Experts as a group reported larger sensory-affective uncoupling of pain but did not show lower pre-stimulus activity in these regions compared to novices. As such the relevance of this finding to mindfulness-based pain regulation still needs to be demonstrated. Finally, contrary to our hypotheses, we did not find evidence for a modulation of anticipation-related brain activity, including in left aINS by pain catastrophizing. We had not expected this to be the case as we had previously reported that experts reported markedly reduced pain catastrophizing compared to novices (Zorn et al., 2020), and because there are strong theoretical

reasons to think that pain catastrophizing should be linked to altered pain anticipation that subsequently influences pain reports (Sullivan et al., 2001). Nevertheless, our null findings corroborate other studies that did not find evidence for a relation between prestimulus aINS-activity and pain catastrophizing scores in clinical samples (Brown et al., 2013; Loggia et al., 2015).

4.2 Effect of mindfulness meditation on pain processing

We could not confirm our hypotheses on pain periods due to methodological issues. Specifically, during a manipulation check for novices we did not observe activation in parts of the pain matrix (i.e. pINS/S2, mACC), regions that are generally considered to reflect sufficient nociceptive processing to generate a conscious pain percept (Tracey et al., 2005). As to what caused this problem, we think it is unlikely that findings reflect insufficient nociceptive stimulation considering that novices generally provided equal if not higher pain ratings as compared to experts. Rather, we think that the lack of clear pain matrices for some contrast for novices is related to physiological noise-related problems.

We implemented a novel fMRI-imaging technique called simultaneous-multi-slice imaging (SMS-EPI), which has the advantage that it allows for a faster sampling resolution (which we deemed useful since we were interested in chronometry of aINS), however, this technique is recent and it has been associated with more inference by physiological noise artifacts. Specifically, the higher sampling resolution causes more frequencies, including those corresponding to physiological noise to be sampled directly, giving rise to many new effects. Accordingly, studies suggest that with SMS-EPI, residuals of noise can be clearly detected in non-noise components if not accounted for (Scheel et al., 2014; Agrawal et al., 2020). Furthermore, it has been reported that physiological noise scales with the sensitivity of fMRI measurements (Agrawal et al., 2020; see (Hutton et al., 2011; Krüger and Glover, 2001; Triantafyllou et al., 2005). For these reasons, appropriate physiological noise removal is deemed critical with SMS-EPI during task-related fMRI (Scheel et al., 2014; Agrawal et al., 2020).

A generally accepted and effective physiological noise removal technique is RETROICOR (Glover et al., 2000; see Caballero-Gaudes and Reynolds 2017 for a review on fMRI cleaning methods), which creates physiological noise regressors based on cardiac and respiratory signal which can then be added to the GLM. In this work, we recorded cardiac and respiratory signals. However, closer inspection revealed that the cardiac recordings were corrupted by interference of the fMRI-related signal corresponding to the multiband-sequence (~1 Hz) in the same range of the heart-beat frequency of the heart (~1 HZ), which left it impossible to separate both signals as would have normally been possible. Therefore, we opted for to use aCompCor which is a method that infers noise-related signals directly on the brain which can then be used to create physiological regressors (Behzadi et al. 2017). A disadvantage of this method, is that it

also detects movement-related components which can be task-correlated, especially in the contexts of pain-related paradigms (Caballero-Gaudes and Reynolds 2017). For this reason, we included an additional intermediate step, which consisted of first-removing task-related voxels (see methods). However, this might have made the cleaning overall less effective as the aim is to clean noise-related components that confound task-related periods (used to estimate beta-estimates). RETROICOR is able to effectively separate noise- and task related signals due to the different harmonics of physiological signals (Scheel et al., 2014; Birn et al., 2006). As such, we propose that the issue might be resolved using RETROICOR limited to respiratory artefacts.

4.5 Limitations

The present study had several limitations. First, even though the results on the pain anticipation period are in line with previous reports on mindfulness-based pain regulation as well as a larger literature on pain anticipation, at this stage, they should be interpreted with caution, given the methodological issues we encountered when analyzing the pain periods and putatively pertaining to physiological noise artifacts. Furthermore, the presentation of the relief cue overlapped with the early pain period. As such it was not modeled, but its associated response could still have influenced the pain-related regressor. However, we contend that this is unlikely to have influenced results, since we primarily examined state and group differences, and the contribution of the relief cue would thus have been canceled out. Similarly, the temperature of long painful stimuli was dropped slightly by 1° C two seconds in the stimulation, as initial pilots revealed that long painful stimuli would otherwise be unsustainable. This risked inducing offset analgesia. However, here also we contend that the examination of state and group differences would have largely canceled out such effects. Third, due to time constraints, the study lacked a baseline condition. This could have helped us to better understand the reason of the absence of state effects in this study.

5. Conclusion

The present work shows that mindfulness expertise is associated with decreased pain anticipation, including in left aINS, whose lower pre-stimulus activity positively predicted increased sensory-affective uncoupling of pain across participants. Nevertheless, methodological limitations prevented us to test our prediction that the aINS is a sensitive marker of present-centeredness vs conceptually driven top-down processing. Therefore, regressing explicitly respiratory artefact could improve our approach.

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References

Abdoun O, Zorn J, Fucci E, Perraud E, Aarts K, Lutz, A. Brain & Mindfulness Project Manual. 2018. OSF. <https://osf.io/dbwch/>

Abdoun O, Zorn J, Poletti S, Fucci E, Lutz A, Training novice practitioners to reliably report their meditation experience using shared phenomenological dimensions. *Consciousness and Cognition*. 2019. Feb 68: 57-72. <https://doi.org/10.1016/j.concog.2019.01.004>

Agrawal U, Brown EN, Lewis LD . Model-based physiological noise removal in fast fMRI. 2020. Volume 205, 15, 116231. <https://doi.org/10.1016/j.neuroimage.2019.116231>

Atlas LY., Bolger N., Lindquist MA, Wager TD, 2010. Brain mediators of predictive cue effects on perceived pain. *J. Neurosci*. 30, 12964–12977.

Behzadi Y, Restom K, Liao J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage* 37 (2007) 90–101.

Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, Segal ZV, Abbey S, Speca M, Velting D, Devins G. Mindfulness: A proposed operational definition. *Clin Psychol Sci Prac*. 2004. 11: 230–241. <https://doi.org/10.1093/clipsy.bph077>

Birn RM, Diamond JB, Smith MA, Bandettini PA. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in FMRI. *Neuroimage*, 31 (4) (2006), pp. 1536-1548, [10.1016/j.neuroimage.2006.02.048](https://doi.org/10.1016/j.neuroimage.2006.02.048).

Bornemann B, Singer T. Taking time to feel our body: Steady increases in heartbeat perception accuracy and decreases in alexithymia over 9 months of contemplative mental training.. *Psychophysiology*, 2016., 00–00.

Brown CA, El-Deredy W, Jones AKP, When the brain expects pain: common neural responses to pain anticipation are related to clinical pain and distress in fibromyalgia and osteoarthritis. *European Journal of Neuroscience*, pp. 1–10, 2013. doi:10.1111/ejn.12420

Brown CA, Jones AK. Meditation experience predicts less negative appraisal of pain: electrophysiological evidence for the involvement of anticipatory neural responses. *Pain*. 2010. 150(3): 428–438. <https://doi.org/10.1016/j.pain.2010.04.017>

Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B. Pain perception: Is there a role for primary somatosensory cortex? *PNAS*. 1999. 96 (14) 7705-7709; <https://doi.org/10.1073/pnas.96.14.7705>.

Chambers R, Gullone E, Allen NB, Mindful emotion regulation: an integrative review. *Clin Psychol Rev*. 2009. 29, 560–572. <https://doi.org/10.1016/j.cpr.2009.06.005>

Coghill RC, Gilron I, Iadarola MJ (2001): Hemispheric lateralization of somatosensory processing. *J Neurophysiol* 85:2602–2612.

Coghill RC, McHaffie JG, Yen YF (2003): Neural correlates of interindividual differences in the subjective experience of pain. *Proc Natl Acad Sci U S A* 100:8538–854

Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. *Neuron*. 2008;58:306–24.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci*. 2002;3:201–15.

Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. 2000. *Nat Neurosci* 3:184

Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci.* 2002;3(8):655–666.

Craig AD. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol.* 2003;13(4):500–505.

Craig AD. How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci.* 2009;10(1):59–70.

Craig AD. The sentient self. *Brain Struct Funct.* 2010;214(5–6) doi: 10.1007/s00429-010-0248-y.

Critchley HD, Mathias CJ, Dolan RJ. 2001. Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron.* 29:537--545.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neuro-sci.* 2004;7(2):189–195.

Davis DA, Seminowicz KD. Cortical responses to pain in healthy individuals depends on pain catastrophizing. 2006. *Pain* 120 (2006) 297–306.

Dahl CJ, Lutz A, Davidson RJ, 2015. Reconstructing and deconstructing the self: cognitive mechanisms in meditation practice. *Trends Cogn. Sci.* <https://doi.org/10.1016/j.tics.2015.07.001>.

Downar J, Mikulis DJ, Davis KD. Neural correlates of the prolonged salience of painful stimulation. *Neuroimage.* 2003. 20(3):1540-51.

Duerden,EG, Albanese M-C, Localization of Pain-Related Brain Activation: A Meta-Analysis of Neuroimaging Data. *Human Brain Mapping.* 2013. 34:109–149

Dunne J. Toward an understanding of non-dual mindfulness. *Contemp. Buddhism.* 2011. 12, 71–88. doi: 10.1080/14639947.2011.564820

Faillenot, I., Heckemann, R. A., Frot, M. & Hammers, A. Macroanatomy and 3D probabilistic atlas of the human insula. *Neuroimage.* 2017.150, 88–98.

Farb, NAS., Segal, ZV, Mayberg, H, Bean, J, Mckeon, D, Fatima, Z, Anderson, AK. Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *Soc. Cogn. Affect. Neurosci.* 2007. 2, 313–322

Fazeli S, Büchel C, Pain-Related Expectation and Prediction Error Signals in the Anterior Insula Are Not Related to Aversiveness. *Journal of Neuroscience.* 2018, 38 (29) 6461-6474; DOI: <https://doi.org/10.1523/JNEUROSCI.0671-18.2018>.

Fruhstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry.* 1976. 39: 1071–1075. doi: 10.1136/jnnp.39.11.1071

Garcia-Larrea L, Peyron R. Pain matrices and neuropathic pain matrices: A review. *PAIN.* 2013.154: S29–S43

Grant JA, Courtemanche J, Rainville P. A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain.* 2011. 152:150–156. <https://doi.org/10.1016/j.pain.2010.10.006>

Geuter S, Boll S, Eippert F, Büchel C. Functional dissociation of stimulus intensity encoding and predictive coding of pain in the insula. 2017. *eLife*6:e24770. 10.7554/eLife.24770

Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, Xu J, Jbabdi S, Webster M, Polimeni JR, Van Essen DC, Jenkinson M, for the WU-Minn HCP Consortium. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage.* 2013. Volume 80, 15 October 2013, Pages 105-124.

Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, Ugurbil K, Andersson J, Beckmann CF, Jenkinson M, Smith SM, Van Essen DC. A multi-modal parcellation of human cerebral cortex. *Nature.* 2016. 536, 171–178.

Gorgolewski, Krzysztof et al. "Nipype: A Flexible, Lightweight and Extensible Neuroimaging Data Processing Framework in Python." *Frontiers in Neuroinformatics.* 2011.

Gracely RH, Geisser ME, Giesecke T, Grant MAB, Petzke F, Williams DA, Clauw DJ, Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain*, Volume 127, Issue 4, April 2004, Pages 835–843, <https://doi.org/10.1093/brain/awh098>

Hammers A, Allom R, Koepp MJ, Free SL, Myers R, Lemieux L, Mitchell TN, Brooks DJ, Duncan JS. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Hum. Brain Mapp.* 2003.19, 224–247.

Hayes S, Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies. *Behavior Therapy.* 2004. 35, 639–665. [https://doi.org/10.1016/S0005-7894\(04\)80013-3](https://doi.org/10.1016/S0005-7894(04)80013-3)

Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, Colaiaco B, Maher AR, Shanman RM, Sorbero ME, Maglione MA, Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis, *Annals of Behavioral Medicine.* 2017. 51(2); 199-213. <https://doi.org/10.1007/s12160-016-9844-2>

Hutton C, Josephs O, Stadler J, Featherstone E, Reid A, Speck O, Bernarding J, Weiskopf N. The impact of physiological noise correction on fMRI at 7T. *Neuroimage*, 57 (1) (2011), pp. 101-112, [10.1016/j.neuroimage.2011.04.018](https://doi.org/10.1016/j.neuroimage.2011.04.018)

Hofbauer RK, Rainville P, Duncan GH, Bushnell MC. Cortical Representation of the Sensory Dimension of Pain. *Journal of neurophysiology.* 2001. 86:1 402-411.

Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen. Hosp. Psychiatry.* 1982. 4, 33–47. [https://doi.org/10.1016/0163-8343\(82\)90026-3](https://doi.org/10.1016/0163-8343(82)90026-3)

Kong, J. et al. Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. *Hum. Brain Mapp.* 2006. 27, 715–721.

Koyama T, McHaffie JG, Laurienti PJ, Coghill RC (2005): The subjective experience of pain: Where expectations become reality. *Proc Natl Acad Sci USA* 102:12950–12955.

Gunnar Krüger, Gary H. Glover. Physiological noise in oxygenation-sensitive magnetic resonance imaging. *Magn. Reson. Med.* 2001. 46 (4) pp. 631-637, 10.1002/mrm.1240

Loggia ML, Berna C, Kim J, Cahalan CM, Martel M, Gollub RL, Wasan AD, Napadow V, Edwards RR. The lateral prefrontal cortex mediates the hyperalgesic effects of negative cognitions in chronic pain patients. *Journal of Pain.* 2015. Volume 16, Issue 8, August 2015, Pages 692-699. <https://doi.org/10.1016/j.jpain.2015.04.003>

Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain.* 2003 May;126(Pt 5):1079-91.

Lutz A, Dunne J, Davidson R. Meditation and the neuroscience of consciousness: an introduction. *The Cambridge Handbook of Consciousness*, 2006. 19.

Lutz A, Slagter HA, Dunne JD, Davidson RJ. Attention regulation and monitoring in meditation. *Trends Cogn Sci.* 2008. 12, 163–169. <https://doi.org/10.1016/j.tics.2008.01.005>

Lutz A, McFarlin DR, Perlman DM, Salomons TV, Davidson RJ. Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *Neuroimage.* 2013. 1;64:538-46. <https://doi.org/10.1016/j.neuroimage.2012.09.030>

Lutz A, Jha AP, Dunne JD, Saron CD, Investigating the phenomenological matrix of mindfulness-related practices from a neurocognitive perspective. *Am Psychol.* 2015. 70(7): 632–658. doi: 10.1037/a0039585

Maechler M, Rousseeuw P, Croux C, Todorov V, Ruckstuhl A, Salibián-Barrera M, Verbeke T, Koller M, Conceicao EL, Anna di Palma M. *robustbase: Basic Robust Statistics*. 2020. R package version 0.93-6, <http://robustbase.r-forge.r-project.org/>.

Maihofner C, Herzner B, Handwerker H. Secondary somatosensory cortex is important for the sensory-discriminative dimension of pain: a functional MRI study. *European Journal of Neuroscience*, Vol. 23, pp. 1377–1383, 2006

Maihofner C, Herzner B, Handwerker H. Secondary somatosensory cortex is important for the sensory-discriminative dimension of pain: a functional MRI study. *Eur J Neurosci.* 2006; 23: 1377-1383

Mazzola L, Faillenot I, Barral F-B, Mauguier F, Peyron R. , Spatial segregation of somato-sensory and pain activations in the human operculo-insular cortex. *NeuroImage*. 2012. Volume 60, Issue 1, Pages 409-418

Menon, V, Uddin, LQ, Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* 2010. 214, 655–667.

Meyer ML, Williams KD, Eisenberger NI. Why social pain can live on: Different neural mechanisms are associated with reliving social and physical pain. *PLoS One*. 2015. 10, e0128294

Ogino Y, Nemoto H, Inui K, Saito S, Kakigi R, Goto F. Inner experience of pain: Imagination of pain while viewing images showing painful events forms subjective pain representation in human brain. *Cerebral Cortex*. 2007. 17, 1139–1146.

Palermo S, Benedetti F, Costa T, Amanzio M. Pain Anticipation: An Activation Likelihood Estimation Meta-Analysis of Brain Imaging Studies. *Human Brain Mapping*. 2015. 36:1648–1661.

Paulus MP, Stein MB. Interoception in anxiety and depression. *Brain Struct. Funct.* 2010. 214, 451–463.

Peirce JW. Generating stimuli for neuroscience using PsychoPy. *Frontiers in Neuroinformatics*. 2009.2 (10), 1-8. doi: 10.3389/neuro.11.010.2008

Perlman DM, Salomons TV, Davidson RJ, Lutz A. Differential effects on pain intensity and unpleasantness of two meditation practices. *Emotion*. 2010. 10, 65–71

Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN. Dissociating pain from its anticipation in the human brain. *Science*. 1999. 284(5422):1979-81.

Ploner M, Lee MC, Wiech K, Bingel U, Traey I. Prestimulus functional connectivity determines pain perception in humans. *PNAS*. 2010. 107;355-360. <https://doi.org/10.1073/pnas.0906186106>

Poisnel G, Arenaza-Urquijo E, Collette F, Klimecki OM, Marchant NL, Wirth M, de La Sayette V, Rauchs G, Salmon E, Vuilleumier P, Frison E, Maillard A, Vivien D, Lutz A, Chételat G, and Medit-Ageing Research Group. The Age-Well randomized controlled trial of the Medit-Ageing European project: Effect of meditation or foreign language training on brain and mental health in older adults. *AlzheimersDement* (N Y). 2018; 4: 714–723. doi: 10.1016/j.trci.2018.10.011

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in the human anterior cingulate but not in somatosensory cortex. *Science*. 1997. 277, 968– 971.

Rousselet GA, Pernet CR. Improving standards in brain-behavior correlation analyses. *Front. Hum. Neurosci*. 2012. 6:119. doi: 10.3389/fnhum.2012.00119

Rudorf S, Schmelz K, Baumgartner T, Wiest R, Fischbacher U, Knoch D. Neural Mechanisms Underlying Individual Differences in Control-Averse Behavior. *Journal of Neuroscience* 30 May 2018, 38 (22) 5196-5208; DOI: <https://doi.org/10.1523/JNEUROSCI.0047-18.2018>

Sarinopoulos I, Grupe DW, Mackiewicz KL, Herrington JD, Lor M, Steege EE, Nitschke JB. Uncertainty during Anticipation Modulates Neural Responses to Aversion in Human Insula and Amygdala. *Cerebral Cortex*, Volume 20, Issue 4, 2010, Pages 929–940, <https://doi.org/10.1093>

Scheel N, Chang C, Mamlouk AM. The Importance of Physiological Noise Regression in High Temporal Resolution fMRI. *Lecture Notes in Computer Science*, 829–836. doi:10.1007/978-3-319-11179-7_104.

Schreckenberger M, Siessmeier T, Viertmann A, Landvogt C, Buchholz HG, Rolke R, Treede RD, Bartenstein P, Birklein F. The unpleasantness of tonic pain is encoded by the insular cortex. *Neurology*. 2005; 64 (7).

Sege CT, Bradley MM, Weymar M, Lang PJ. A direct comparison of appetitive and aversive anticipation: Overlapping and distinct neural activation. *Behavioural Brain Research* Volume 326, 2017. Pages 96-102

Singer, T., Critchley, H.D., Preuschoff, K. A common role of insula in feelings, empathy and uncertainty. *Trends Cogn. Sci*. 2009. 13, 334–340.

Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*. 2001. 17:52-64. doi: 10.1097/00002508-200103000-00008.

Timmermann L, Ploner M, Haucke K, Schmitz F, Baltissen R, Schnitzler A, Differential Coding of Pain Intensity in the Human Primary and Secondary Somatosensory Cortex. *Journal of Neurophysiology*. 2001. 86(3):1499-503. DOI: 10.1152/jn.2001.86.3.1499

Tolle TR, Kaufmann T, Siessmeier T, Lautenbacher S, Berthele A, Munz F, Zieglgansberger W, Willoch F, Schwaiger M, Conrad B, Bartenstein P. Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. *Ann Neurol*. 1999. Jan;45(1):40-7. doi: 10.1002/1531-8249(199901)45:1<40::aid-art8>3.0.co;2-l.

Tracey I. Nociceptive processing in the human brain. *Current Opinion in Neurobiology*. 2005,15:478–487.

Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron*. 2007. 2;55(3):377-91.

Treede RD, Kenshalo DR, Gracely RH, Jones AK. The cortical representation of pain. *Pain*. 1999 Feb;79(2-3):105-11.

Villain N, Landeau B, Groussard M, Mevel K, Fouquet M, Dayan J, Eustache F, Desgranges B, Chételat G. A Simple Way to Improve Anatomical Mapping of Functional Brain Imaging. *J Neuroimaging*. 2010. 20(4):324-33.

Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*. 2004. 20;303(5661):1162-7.

Wager TD, Keller MC, Lacey SC, Jonides J. Increased sensitivity in neuroimaging analyses using robust regression. *Neuroimage*. 2005;26:99–113

Wager TD, Atlas LY, Ph.D., Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-Based Neurologic Signature of Physical Pain. 2013. *N Engl J Med*. 11; 368(15): 1388–1397. doi: 10.1056/NEJMoa1204471

Wiech, K., Farias, M., Kahane, G., Shackel, N., Tiede, W., Tracey, I., 2008a. An fMRI study measuring analgesia enhanced by religion as a belief system. *Pain* 139, 467–476.

Wiech, K., Lin, C., Brodersen, K.H., Bingel, U., Ploner, M., Tracey, I., 2010. Anterior insula integrates information about salience into perceptual decisions about pain. *J. Neurosci.* 30, 16324–16331

Wiech, K. Deconstructing the sensation of pain: The influence of cognitive processes on pain perception. *Science*. 2016. 354(6312), 584–587. doi:10.1126/science.aaf8934

Wilson-Mendenhall CD, Henriques A, Barsalou LW, Barrett LS., Primary Interoceptive Cortex Activity during Simulated Experiences of the Body. *J Cogn Neurosci*. 2019. Feb; 31(2): 221–235. doi: 10.1162/jocn_a_01346.

Zeidan F, MartucciKT, Kraft RA , Gordon NS , McHaffie JG , Coghill RC. Brain mechanisms supporting the modulation of pain by mindfulness meditation. *J. Neurosci*. 2011. 31:5540–5548. doi: 10.1523/JNEUROSCI.5791-10.2011

Zeidan F, Emersion NM, Farris SR, Ray JN, Jung Y, McHaffie JG, Coghill RC. Mindfulness-meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness-meditation induced analgesia. *The Journal of Neuroscience*. 2015. 35(46):15307–15325. doi: 10.1523/JNEUROSCI.2542-15.2015

Zorn J, Abdoun O, Bouet R, Lutz A. Mindfulness meditation is related to sensory-affective uncoupling of pain in trained novice and expert practitioners. *European Journal of Pain*. 2020.

Supplementary information

1. Task instructions

Written instructions

Distraction condition: Concentrate your mind on the numbers and visual cues on the screen. Whenever a new number appears, mentally add it to the total sum of the previous number(s). You should focus your attention only on the numbers and the cues. Block all other emotions, sensations, or thoughts that may arise during the calculation task. Be very focused so that you don't miss any number or cue.

OM condition: Start to anchor your attention in your body. Simply rest your body. Relax your muscles. Rest your mind without blocking anything. Allow everything to arise in the field of awareness as it is in the present moment. The body and the mind rest in unity. Gently watch the numbers and the cues appear on the screen. Pay attention to cues, while not doing anything in particular with the numbers. When the thermal stimulus arises, gently let it be a support for your attention. You know that you are feeling the sensation; you recognize it, while resting the mind on this support. While resting your attention on the thermal sensation, thoughts, or emotions may arise. Just let them be in the vast field of your awareness while remaining at ease in the present moment.

Auditory instructions

Distraction condition: Concentrate your mind on the number and the visual cues on the screen. You should focus your attention completely on the screen and the counting task. Block all the emotions, sensations and thought that arise during this task. Be very concentrated so that you don't miss any number or visual cue.

OM condition: Relax your body and your mind, there is no need to block anything. When the heat stimulation starts, gently be aware of it. Be aware of your experience of this sensation and let your mind relax with it. When any thoughts or emotions arise, let them be there in the vast space of your awareness.

2. Self-reports

Different self-report questions:

'Intensity: How hot was the stimulation?'

Labels: 1 = Not at all, 9: Extremely hot

'Unpleasantness: How much did the stimulation bother you?'

Labels: 1 = Not at all, 9: Extremely

'Relief': How relieved were you by the end of the stimulation?'

Labels: 1 = Not at all, 9: Extremely

'Meditation Instruction': To what degree were you able to follow the instruction?'

Labels: 1 = Not at all, 9: Completely

'Addition': What is the total sum of the numbers that were presented?'

5 different two digit-numbers were presented, one of which was the correct answer.

Presentation frequency:

<u>OM condition:</u>		
10 x Warm Long	10 x Hot Long	10 x Short Long
6 x Unpleasantness	6 x Unpleasantness	6 x Unpleasantness
6 x Relief	6 x Relief	6 x Relief
4 x Intensity	4 x Intensity	4 x Intensity
4 x Meditation	4 x Meditation	4 x Meditation
<u>Distraction condition:</u>		
10 x Warm Long	10 x Hot Long	10 x Short Long
6 x Unpleasantness	6 x Unpleasantness	6 x Unpleasantness
6 x Relief	6 x Relief	6 x Relief
4 x Intensity	4 x Intensity	4 x Intensity
4 x Addition	4 x Addition	4 x Addition

3. Brain activity during early pain for novices and experts

Brain regions	k	Peak MNI Coordinates			Z	p
		X	Y	Z		
Novices						
R Middle frontal gyrus	1767	34	10	14	5.4	<0.001
R Inferior frontal gyrus	-	38	20	6	4.7	-
R Middle frontal gyrus	-	32	22	14	4.7	-
R Middle frontal gyrus	1343	32	44	18	4.4	<0.001
R Superior frontal gyrus	-	22	48	22	4.3	-
R Middle frontal gyrus	-	42	52	8	3.9	-
L Precentral gyrus	334	0	-32	68	4.3	<0.001
R Precentral gyrus	-	8	-28	78	3.7	-
L Lateral orbital gyrus	637	-36	48	-10	4.1	<0.001
L Middle frontal gyrus	-	-20	42	24	3.9	-
L Middle frontal gyrus	-	-38	30	40	3.3	-
L Inferior frontal gyrus	225	-	20	8	4.1	<0.001
L Inferior frontal gyrus	-	36	18	2	3.8	-
L Anterior insula short gyrus	-	-	20	-6	3.3	-
		42				
		-				
		34				
R supramarginal gyrus	354	58	-26	30	3.9	<0.001
R supramarginal gyrus	-	48	-20	26	3.8	-
R supramarginal gyrus	-	56	-18	20	3.5	-
Experts						
R Inferior frontal gyrus	5606	34	16	12	5.6	<0.001
R Postcentral gyrus	-	34	-18	20	5.5	-
R Insula posterior long gyrus	-	38	0	8	5.4	-
L Supramarginal gyrus		-60	-26	18	4.7	<0.001
L Pallidum	2092	-14	6	-6	4.4	-
L Inferior frontal gyrus	-	-34	22	6	4.3	-
		-				
L Middle superior temporal gyrus	240	-40	-24	6	4.1	<0.024
L Insula posterior long gyrus	-	-38	-14	-6	3.9	-
L Middle superior temporal gyrus	-	-40	-18	12	3.5	-
R Superior frontal gyrus	358	6	18	42	4.0	<0.001
R Anterior cingulate gyrus	-	4	8	38	3.8	-
R Superior frontal gyrus	-	4	14	56	3.4	-

Activations were classified according to the Hammersmith atlas [Hammers et al., 2003; Faillenot et al., 2017]. X, y, z coordinates (MNI) and statistical information (Z-statistic and p-value) refer to peak voxels in the identified clusters. P-values are adjusted for family-wise error correction for multiple comparisons across the whole brain. Subpeaks as provided by SPM are listed.

DISCUSSION AND CONCLUSION

General discussion

General summary

This work aimed to examine the cognitive, phenomenological and neuronal mechanisms underlying mindfulness-based pain regulation. Methodologically, defining and novel features of the present work were: i) the recruitment of a carefully recruited sample of expert meditators from the Kagyu or Nyingma school of Tibetan Buddhism, ii) a rigorously trained novice control group that was extensively trained in mindfulness meditation and familiarized with related phenomenological dimensions during a formal meditation training weekend, and iii) a novel fMRI-scanner acute pain paradigm that was designed to amplify the cognitive-affective aspects of pain. The overarching guiding hypothesis was that the specific meta-cognitive stance labeled cognitive defusion underlies sensory-affective uncoupling of pain during mindfulness meditation by its opposing effects on pain catastrophizing-related processes. More broadly, this research was embedded in an overarching research project that attempted to identify biomarkers of metacognitive states in opposition to those of maladaptive mental states characterized by cognitive and emotional reactivity.

We hypothesized that a mindfulness state and expertise would both be associated with increased sensory-affective uncoupling of pain experience. Additionally, we predicted that this uncoupling would be predicted by trait pain catastrophizing, which would be lower in expert meditators (Study 1).

Furthermore, in line with the hypothesized important of cognitive defusion in mindfulness-based pain regulation, and its theoretical conceptualization as a process opposite to and at the root of what causes pain catastrophizing (i.e. the believability of thoughts), we expected that the construct of cognitive defusion, as measured by the DDS, would be specifically and inversely related to the construct of pain catastrophizing, as measured by the PCS. We additionally examined the respective relationship of cognitive defusion and pain catastrophizing to subjective pain reports (Study 2).

Finally, we hypothesized that the aINS is a sensitive marker of present-centeredness versus top-down conceptual processing, which would be reflected in lower mindfulness-related activity during pain anticipation and late pain respectively reflecting decreased anxious pain anticipation and reduced ruminative processing; consistent with decreased top-down salience processing, but increased activation during early pain reflecting increased bottom-up salience processing. We additionally, aimed to explore the relation of aINS-chronometry to pain catastrophizing and sensory-affective uncoupling of pain experience (Study 3).

In study 1, we found that OM meditation compared to attentional distraction, reduced ratings of unpleasantness but not intensity for novice and expert practitioners. Experts reported higher sensory-affective uncoupling of pain, during short, but particularly during long pain stimuli. In experts, this meditation-induced uncoupling spilled over to the control condition. Experts reported lower trait pain catastrophizing compared to novices, and lower pain catastrophizing positively predicted higher sensory-affective uncoupling of pain across groups and task conditions.

In study 2, we found that the DDS and PCS were negatively correlated and shared unique variance that survived controlling for variance shared with other cognitive-emotional constructs, including anxiety (STAI), depression (BDI) and worry (PSWQ), as well as other mindfulness-related dimensions, including the mindfulness dimensions of the FFMQ and interoceptive awareness (MAIA). In addition, we found that relationships between PCS and every other construct were no longer significant when controlling for DDS, questioning the specificity of the relationship of these constructs to PCS. As expected, both PCS and DDS specifically predicted pain unpleasantness as opposed to pain intensity but in the opposite direction, positively and negatively respectively.

In study 3, we found that mindfulness expertise lowers representations of pain anticipation including in the dlPFC, ACC and left aINS, all regions known to be implicated in conscious pain expectation. Furthermore, prestimulus activity in the left aINS positively predicted sensory-affective uncoupling of pain across participants. No state-effects were observed during pain anticipation. Due to methodological issues we were not able to test hypotheses on early and late pain periods.

Collectively, these findings suggest that the novel experimental pain paradigm and novice training protocol delivered their intended effects. The findings replicate previous work, extend this research in several ways, and open up new avenues for exploration, as will be discussed more extensively below.

The relation of mindfulness meditation to sensory-affective uncoupling of pain and pain catastrophizing

Using a novel fMRI-scanner acute pain paradigm that was designed to amplify the cognitive-aspects of pain experience we found evidence for the longstanding claim that mindfulness meditation leads to sensory-affective uncoupling of pain by counteracting pain-catastrophizing related processes. We observed clinically relevant trait-like and state effects.

With respect to trait-like effects (across task conditions) we observed that experts reported lower pain amplification as compared to novices (lower increase in pain unpleasantness but equal increase in pain intensity between short and long trial types), as well as larger sensory-affective uncoupling of pain, particularly during long trial types, which could be explained by lower trait pain catastrophizing for experts as compared to novices. These findings suggest that reduced pain catastrophizing is an important mechanism underlying mindfulness-related sensory-affective uncoupling of pain and reduced pain amplification. This finding is clinically important as pain catastrophizing is a key factor aggravating pain, and has been implicated in the maintenance and exacerbation of chronic pain (Edwards et al., 2016; Gatchel et al., 2007). Our results suggest that pain catastrophizing is a malleable trait that can be altered with mindfulness meditation. In an attempt to gain further insight into dosage-effects, we tested whether experts' lifetime meditation experience could predict pain catastrophizing scores. This was not the case, which was possibly due to the very high level of meditation experience for experts (~ 40.000 h on average) inducing a ceiling effect. As such, it remains unclear how much meditation practice is needed to effectuate trait changes, or indeed whether mindfulness meditation was the causal factor of lower pain catastrophizing scores in experts at all. Future longitudinal studies or studies including intermediate to advanced meditators could shed light on this issue.

Arguing for clinically feasible dosage-effects is the observation of state sensory-affective uncoupling of pain, following brief formal mindfulness training in novices. Specifically, OM compared to attentional distraction reduced ratings of unpleasantness but not intensity across groups. For experts, this finding replicated a previous study reporting sensory-affective uncoupling of pain in a comparable sample during OM (Perlman et al., 2010). For novices, this is the first time such a finding is observed as earlier studies on OM-like techniques did not observe effects for control participants possibly due to a lack of formal meditation training in these studies (Perlman et al., 2010; Gard et al., 2012). Our study differed from this previous work in that novices underwent a highly novel formal meditation protocol in which they were acquainted with different meditation techniques as well as familiarized with several phenomenological dimensions relevant to mindfulness meditation, followed by several weeks of home practice (~ 20 h on average). Surprisingly, practice metrics for novices could not predict the state effect (reduced unpleasantness with OM). Instead, time elapsed since the meditation weekend emerged as the only significant predictor, such that novices who participated closer to the meditation weekend reported larger state effects. Further inspection revealed that this could potentially be explained by motivation effects.

Specifically, we had reported before that novices who enrolled in the training protocol initially showed high motivation, but that the intensity of practice linearly decreased over weeks (Abdoun et al. 2019), paralleling the decrease in state effect. If indeed true, this finding has several important clinical implications. First, it suggests that, for beginner meditators, a continuous and disciplined effort may be required to achieve sustained effects on pain regulation. In this light brief and intense formal meditation booster sessions might be an outcome. Second, the finding points to the importance of taking into account sustainability of effects as initial results may be overly optimistic. Lastly, the results beg the question of how much effort is required to maintain effects and whether the capacity to non-judgmentally monitor pain can become learned and effortless (as the findings on experts suggest), and if so, at which stage. These are interesting avenues for future research.

The role of cognitive defusion in mindfulness-based pain regulation

Another novelty of the present work was that it aimed to bridge two literatures: one extensive and established literature of the negative role of pain catastrophizing in pain experience (e.g. Sullivan et al., 2001; Edwards et al., 2006; Gatchel et al., 2007; Crombez, 2013; Edwards et al., 2016), and another emerging literature on the capacity for metacognitive processes such as meta-awareness and dereification, commonly collapsed into the single construct of cognitive defusion, to counteract maladaptive cognitive and emotional states and to cultivate well-being (Chambers et al., 2009; Lutz et al., 2015; Dahl et al., 2015; McCracken et al., 2013a). We were specifically guided in our investigations by a new phenomenological model of meditation practices grounded on clinical and traditional Buddhist contemplative accounts. Based on this and other work (Kabat-Zinn, 1982; McCracken et al., 2013a), we hypothesized that the lack of cognitive defusion or cognitive fusion is the process at the basis of what causes one to catastrophize about pain (i.e. the believability of thoughts). Therefore, cognitive defusion, a process cultivated with mindfulness meditation should counteract pain-catastrophizing related processes and show an inverse relation to pain.

In support of the central role of cognitive defusion in mindfulness-based pain regulation, we found that the DDS, showed a highly specific inverse relationship to the PCS. Our finding that this relationship survived controlling for several other more general cognitive-emotional constructs including the PSWQ (worry) and the different mindfulness dimensions is an important advance over the current literature as virtually all psychometric investigations on the relationship between pain catastrophizing and mindfulness have focused on and reported relationships between the PCS and FFMQ-scales that have recently been reported to be non-specific as they could be fully explained away by the PSWQ (worry) a general anxiety-related construct (Day et al., 2015). Our findings show that the PCS, as well as several other cognitive-emotional and mindfulness-related constructs, are better explained by the DDS, providing compelling support for the centrality of this construct in relation to other psychological constructs. Further showing its importance to mindfulness-based pain regulation, DDS was significantly higher in experts (in accordance

with its inverse relationship to PCS), and showed an inverse relationship to pain experience, with both constructs specifically predicting pain unpleasantness as opposed to pain intensity. The relationship of DDS to pain unpleasantness survived controlling for PCS in the control state, but not vice versa, in line with the hypothesized primacy of DDS, although this finding warrants replication with more general and perhaps clinical samples. Nevertheless, our results are promising and highlight DDS as a potential mediator of change following mindfulness-based interventions for the management of chronic pain. A finding in line with the mediating role of cognitive defusion-related constructs on reductions in depression symptomatology following mindfulness-based interventions (Bieling et al., 2012; Farb et al., 2018), and reported positive associations between decentering-related constructs and pain-related outcomes (McCracken et al., 2013a,b, 2014).

Neuronal correlates underlying mindfulness-based sensory-affective uncoupling of pain

In this work, we aimed to explore the tentative hypothesis that the chronometry of the anterior insula (aINS) is a sensitive marker of present-centeredness vs top-down-conceptual processing (as reflected in decreased activity during pain anticipation and late pain reflecting decreased anxious anticipation and pain rumination respectively, but increased activation during early pain, reflecting increased bottom-up salience processing). We could confirm our hypothesis that mindfulness expertise is associated with a downregulation of neuronal representations of pain anticipation, including in the left aINS, whose pre-stimulus activity negatively predicted sensory-affective uncoupling of pain across participants. This finding replicates previous work by Lutz and colleagues who showed that mindfulness meditation is associated with decreased left aINS activation during pain anticipation (Lutz et al., 2013). The present work made an important contribution to this previous work by showing that lower pre-stimulus activity predicts mindfulness-related sensory-affective uncoupling of pain. Nevertheless, contrary to our hypotheses, we were not able to show any relationship of pre-stimulus aINS-activity to pain catastrophizing scores, or evidence for a modulation by state. Furthermore, we were not able to test our hypotheses on pain periods due to persisting methodological issues. As such the testing of several hypotheses and the corroboration of the promising behavioral results on the cognitive and phenomenological mechanisms underlying mindfulness-based pain regulation awaits resolution of this issue. Only then will we be able to tell whether this work can advance our understanding of the neuronal correlates underlying mindfulness-based pain regulation.

Future directions

We see several exciting possible future directions. First, we think that our findings warrant future investigation of the effect of mindfulness meditation on pain catastrophizing and cognitive defusion in

chronic pain samples. In this sense, the present work can be considered an effort to identify markers of mindfulness-based pain regulation which can then be used to guide longitudinal and mechanistic investigations on the efficacy of mindfulness-based interventions for the treatment of chronic pain. Ultimately, the utility of the findings of the present work and similar others depend largely on their extendibility to clinical samples. As such it is timely that such investigations start.

Furthermore, although not mentioned in the primary thesis, we additionally implemented a qualitative approach that allowed us to identify phenomenological clusters in participants relating to pain-related coping styles. Identified clusters were then used to predict several measures relating to the pain task of the present work, including participants' pain sensitivity, subjective pain reports and reported phenomenological dimensions. It was shown that the phenomenological clusters each relate to a specific pain-related phenomenological profile in ways congruent with known features of each coping style (see Annex III). As such, it seems warranted to let some of the behavioral and neuronal explorations be guided by the phenomenological dimensions or alternatively the phenomenological clusters identified in this work.

Finally, we hope to be soon able to continue the exploration of the neuronal correlates underlying mindfulness-based sensory-affective uncoupling of pain and hope that this yields results as exciting as the ones we found in the behavioral analyses. Regressing respiration artefacts could potentially solve the methodological issues relating to the fMRI.

Conclusion

This work identified pain catastrophizing and cognitive defusion as two interrelated cognitive mechanism underlying the effects of mindfulness-based sensory-affective uncoupling of pain. It also demonstrates the value of using a first-person approach in identifying novel aspects of mindfulness-based pain regulation. Finally, it made a start at unraveling the neuronal correlates of mindfulness-based pain regulation by showing that expertise in mindfulness meditation downregulates neuronal representations of pain anticipation in the left anterior insula, whose pre-stimulus activity negatively predicted sensory-affective uncoupling of pain across participants. We hope to be able to complement these finding in the near future with further results on the actual neuronal correlates of mindfulness-based sensory-affective uncoupling of pain.

References

- Almeida TF, Roizenblatt S, Tufik S. Afferent pain pathways: a neuroanatomical review. 2004. *Brain Research* 1000:40 – 56. <https://doi.org/10.1016/j.brainres.2003.10.073>.
- Anheyer D, Haller H, Barth J, Lauche R, Dobos G, Cramer H. Mindfulness-Based Stress Reduction for Treating Low Back Pain: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2017 Jun 6;166(11):799-807. doi: 10.7326/M16-1997. Epub 2017 Apr 25.
- Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005;9:463-484.
- Arnsten AFT. Stress signaling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*. 2009;32:267–287.
- Atlas LY, Bolger N, Lindquist MA, Wager TD, 2010. Brain mediators of predictive cue effects on perceived pain. *J. Neurosci*. 30, 12964–12977.
- Atlas LY, Wager TD How expectations shape pain. *Neuroscience Letters*. 2012. 520(2): p. 140-148.
- Baer RA Mindfulness Training as a Clinical Intervention A Conceptual and Empirical Review. *Clinical Psychology Science and Practice*. 2003. 10, 125-143. <https://doi.org/10.1093/clipsy.bpg015>
- Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment*. 2006; 13(1):27–45.
- Baer RA., Samuel DB., Lykins EL. Differential item functioning on the Five Facet Mindfulness Questionnaire is minimal in demographically matched mediators and non-mediators. *Assessment*. 2011. 18, 3–10.
- Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009. 139(2):267-84. doi: 10.1016/j.cell.2009.09.028.
- Bawa FL, Mercer SW, Atherton RJ, et al. Does mindfulness improve outcomes in patients with chronic pain? Systematic review and meta-analysis. *British Journal of General Practice*. 2015;65:e387–400. doi: 10.3399/bjgp15X685297.

Bernstein A, Hadash Y, Lichtash Y, Tanay G, Shepherd K, Fresco DM. Decentering and Related Constructs: A Critical Review and Metacognitive Processes Model. *Perspect Psychol Sci*. 2015. 10(5): 599–617. doi: 10.1177/1745691615594577

Bieling PJ, Hawley LL, Bloch RT, Corcoran KM, Levitan RD, Young LT, MacQueen GM, Segal ZV. Treatment Specific Changes in Decentering Following Mindfulness-Based Cognitive Therapy Versus Antidepressant Medication or Placebo for Prevention of Depressive Relapse. *J Consult Clin Psychol*. 2012. 80(3): 365–372. doi: 10.1037/a0027483

Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, Segal ZV, Abbey S, Speca M, Velting D, Devins G. Mindfulness: A proposed operational definition. *Clin Psychol Sci Pract*. 2004. 11: 230–241. <https://doi.org/10.1093/clipsy.bph077>

Blackledge JT. Disrupting verbal processes: cognitive defusion in acceptance and commitment therapy and other mindfulness-based psychotherapies. *The Psychological Record*. 2007. 57, 555–576.

Bohdi B. *In the Buddha's words: an anthology of discourses from the pali canon*. Boston: Wisdom Publications; 2005.

Bressler SL, Menon V. Large-scale Brain Networks in Cognition: Emerging Methods and Principles. *Trends Cogn Sci*. 2010 Jun;14(6):277-90. doi: 10.1016/j.tics.2010.04.004.

Brooks JCW, Zambreanu L, Godinez A, Craig ADB, Tracey I. Somatotopic Organisation of the Human Insula to Painful Heat Studied With High Resolution Functional Imaging. *Neuroimage*. 2005. 1;27(1):201-9. doi: 10.1016/j.neuroimage.2005.03.041

Brown CA, Jones AK. Meditation experience predicts less negative appraisal of pain: electrophysiological evidence for the involvement of anticipatory neural responses. *Pain*. 2010. 150(3): 428–438. <https://doi.org/10.1016/j.pain.2010.04.017>

Bushnell MC, Ceko M, Low LA. Cognitive and Emotional Control of Pain and Its Disruption in Chronic Pain. *Nat Rev Neurosci*. 2013 Jul;14(7):502-11. doi: 10.1038/nrn3516.

Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B. Pain perception: Is there a role for primary somatosensory cortex? *PNAS*. 1999. 96 (14) 7705-7709; <https://doi.org/10.1073/pnas.96.14.7705>.

Chambers R, Gullone E, Allen NB, Mindful emotion regulation: an integrative review. *Clin Psychol Rev*. 2009. 29, 560–572. <https://doi.org/10.1016/j.cpr.2009.06.005>

Chang LJ, Yarkoni T, Khaw MW, Sanfey AG . Decoding the Role of the Insula in Human Cognition: Functional Parcellation and Large-Scale Reverse Inference. *Cereb Cortex* . 2013 Mar;23(3):739-49. doi: 10.1093/cercor/bhs065

Chaves JF, Brown JM. Spontaneous cognitive strategies for the control of clinical pain and stress. *J Behav Med*. 1987;10:263–76. Epub 1987/06/01. PubMed PMID: 3612783.

Chiesa A, Serretti A. Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *Journal of Alternative and Complementary Medicine*. 2011;17:83–93. doi: 10.1089/acm.2009.0546

Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol*. 1999;82:1934–1943.

Robert C. Coghill, John G. McHaffie, and Yi-Fen Yen. Neural correlates of interindividual differences in the subjective experience of pain. *PNAS* July 8, 2003 100 (14) 8538-8542; first published June 24, 2003 <https://doi.org/10.1073/pnas.1430684100>

Coghill RC, Gilron I, Iadarola MJ (2001): Hemispheric lateralization of somatosensory processing. *J Neurophysiol* 85:2602–2612.

Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. *Neuron*. 2008;58:306–24.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci*. 2002;3:201–15.

Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. 2000. *Nat Neurosci* 3:184.

Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*. 2002;3(8):655–666.

Craig AD Blomqvist A, Is There a Specific Lamina I Spinothalamocortical pathway for pain and temperature sensations in primates? *The Journal of Pain*, 2002. 3(2):95-101. DOI: 10.1054/jpai.2002.122953.

Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*. 2002. 3:655–666.

Craig B. A new view of pain as a homeostatic emotion. *Trends in Neurosciences*. 2003. 26:6, 303-307.

Craig AD., Pain mechanisms: Labeled Lines Versus Convergence in Central Processing. *Annu. Rev. Neurosci.* 2003a. 26:1–30. doi: 10.1146/annurev.neuro.26.041002.131022.Craig AD. A new view of pain as a homeostatic emotion. *Trends Neurosci.* 2003b Jun;26(6):303-7. Review. DOI: 10.1016/s0166-2236(03)00123-1.

Craig AD. How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci.* 2009;10(1):59–70.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neuro-sci.* 2004;7(2):189–195.

Crombez G, Eccleston C, Van Damme S, Vlaeyen JW, Karoyl P. Fear-avoidance model of chronic pain: the next generation. *Clin J Pain.* 2013. 28(6): 475-483. doi: 10.1097/AJP.0b013e3182385392

Crottaz-Herbette S, Menon V. Where and when the anterior cingulate cortex modulates attentional response: combined fMRI and ERP evidence. *J Cogn Neurosci.* 2006;18(5):766–780.

Dahl CJ, Lutz A, Davidson RJ, 2015. Reconstructing and deconstructing the self: cognitive mechanisms in meditation practice. *Trends Cogn. Sci.* <https://doi.org/10.1016/j.tics.2015.07.001>.

Davidson, RJ, Kaszniak AW. Conceptual and methodological issues in research on mindfulness and meditation. *American Psychologist.* 2015. 70(7), 581–592. <https://doi.org/10.1037/a0039512>

Day MA, Smitherman A, Ward LC, Thorn BE. An investigation of the associations between measures of mindfulness and pain catastrophizing. *Clin J Pain.* 2015. 31:222–8. doi: 10.1097/AJP.000000000000102

Deen B, Pitskel NB, Pelphrey KA. Three Systems of Insular Functional Connectivity Identified with Cluster Analysis. *Cerebral Cortex*, Volume 21, Issue 7, July 2011, Pages 1498–1506, <https://doi.org/10.1093/cercor/bhq186>

Downar J, Crawley AP, Mikulis DJ, Davis KD. A multimodal cortical network for the detection of changes in the sensory environment. *Nat Neurosci*. 2000;3(3):277–283.

Downar J, Crawley AP, Mikulis DJ, Davis KD. The effect of task relevance on the cortical response to changes in visual and auditory stimuli: an event-related fMRI study. *Neuroimage*. 2001;14(6):1256–1267.

Downar J, Crawley AP, Mikulis DJ, Davis KD. A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *J Neurophysiol*. 2002;87(1):615–620.

Downar J, Mikulis DJ, Davis KD. Neural correlates of the prolonged salience of painful stimulation. *Neuroimage*. 2003. 20(3):1540-51.

Duerden EG, Albanese M-C. Localization of Pain-Related Brain Activation: A Meta-Analysis of Neuroimaging Data. *Hum Brain Mapp* . 2013. 34(1):109-49. doi: 10.1002/hbm.21416.

Dunne JD. Toward an understanding of non-dual mindfulness. *Contemporary Buddhism*. 2011. 12(1): 71–88. <http://doi.org/10.1080/14639947.2011.564820>.

Dunne JD, Thompson E, Schooler J Mindful meta-awareness: sustained and non-propositional. *Current Opinion in Psychology*. 2019. Volume 28, August 2019, Pages 307-311

Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The role of psychosocial processes in the development and maintenance of chronic pain. *The Journal of Pain*. 2016.17(9):T70-T92. <https://doi.org/10.1016/j.jpain.2016.01.001>

Edwards RR, Smith MT, Stonerock G, Haythornthwaite JA. Pain-related catastrophizing in healthy women is associated with greater temporal summation of an reduced habituation to thermal pain. *Clin J Pain* 2006;22:730–737.

Elvery N, Jensen MP, Ehde DM, Day MA. Pain catastrophizing, mindfulness, and pain acceptance: What's the difference? *The Clinical Journal of Pain*. 2017. 33: 485–495. doi: 10.1097/AJP.0000000000000430

Fazeli S, Büchel C, Pain-Related Expectation and Prediction Error Signals in the Anterior Insula Are Not Related to Aversiveness. *Journal of Neuroscience*. 2018, 38 (29) 6461-6474; DOI: <https://doi.org/10.1523/JNEUROSCI.0671-18.2018>.

Forman EM, Herbert JD, Juarascio AS, Yeomans PD, Zebell JA, Goetter EM, Moitra E. The Drexel defusion scale: A new measure of experiential distancing. *Journal of Contextual Behavioral Science*. 2012. 1(s 1-2):55-65. doi: 10.1016/j.jcbs.2012.09.001

Fruhstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry*. 1976. 39: 1071–1075. doi: 10.1136/jnnp.39.11.1071

Garcia-Larrea L, Peyron R. Pain matrices and neuropathic pain matrices: A review. *PAIN*. 2013.154: S29–S43

Garcia-Larrea. The Posterior Insular-Opercular Region and the Search of a Primary Cortex for Pain. *Neurophysiol Clin* . 2012 Oct;42(5):299-313. doi: 10.1016/j.neucli.2012.06.001.

Garcia-Larrea L, Bastuji H. Pain and consciousness. *Progress in Neuropsychopharmacology & Biological Psychiatry*. Volume 87, Part B, 20 December 2018, Pages 193-199.

Gard T, Hölzel BK, Sack AT, Hempel H, Lazar SW, Vaitl D, Ott U. Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. *Cereb. Cortex*. 2012. 11: 2692–2702. doi: 10.1093/cercor/bhr352

Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. 2007. 133(4):581-624. doi: 10.1037/0033-2909.133.4.581

Gillanders, D. T., Boderston, H., Bond, F. W., Dempster, M., Flaxman, P. E., Campbell, L., Kerr, S., Tansey, L., Noel, P., Ferenbach, C., Masley, S., Roach, L., Lloyd, J., May, L., Clarke, S., & Remington, B. (2014). The development and initial validation of the Cognitive Fusion Questionnaire. *Behavior Therapy*, 45, 83-101.

Goleman D. *The meditative mind: The varieties of meditative experience*. New York: Tarcher; 1988.

Grant JA, Courtemanche J, Rainville P. A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain*. 2011. 152:150–156. <https://doi.org/10.1016/j.pain.2010.10.006>

Grant JA, Rainville P. Pain sensitivity and analgesic effects of mindful states in Zen meditators: a cross-sectional study. *Psychosomatic Medicine*. 2009. 71:106–114. doi: 10.1097/PSY.0b013e31818f52ee

Grossman P. Mindfulness for psychologists: Paying kind attention to the perceptible. *Mindfulness*. 2010. 1:87–97. DOI: 10.1007/s12671-010-0012-7

Grossman P. Defining mindfulness by how poorly I think I pay attention during everyday awareness and other intractable problems for psychology's (re)invention of mindfulness: Comment on Brown et al. (2011). *Psychological Assessment*. 2011; 23(4):1034–1040. <http://doi.org/10.1037/a0022713>.

Gu Q, Hou JC, Fang XM. Mindfulness Meditation for Primary Headache Pain: A Meta-Analysis. *Chin Med J (Engl)*. 2018 Apr 5;131(7):829-838. doi: 10.4103/0366-6999.228242.

Geuter S, Boll S, Eippert F, Büchel C (2017) Functional dissociation of stimulus intensity encoding and predictive coding of pain in the insula. *eLife*6:e24770. 10.7554/eLife.24770

Hayes SC, Strosahl K, Wilson KG. *Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change*. New York: Guilford Press; 1999.

Hayes SC Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies. 2004. *Behav. Ther.* 35, 639–665

Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behav Res Ther.* 2006. 4:1–25. doi: 10.1016/j.brat.2005.06.006

Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, Colaiaco B, Maher AR, Shanman RM, Sorbero ME, Maglione MA, Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis, *Annals of Behavioral Medicine*. 2017. 51(2); 199-213. <https://doi.org/10.1007/s12160-016-9844-2>

Hofbauer RK, Rainville P, Duncan GH, Bushnell MC. Cortical Representation of the Sensory Dimension of Pain. *Journal of neurophysiology*. 2001. 86:1 402-411.

Hoge, E.a. et al. (2014) Change in decentering mediates improvement in anxiety in mindfulness-based stress reduction for generalized anxiety disorder. *Cognit. Ther. Res.* 39, 228–235.

Hu L, Iannetti GD. Neural indicators of perceptual variability of pain across species. *PNAS.* 2019. 29, 116 (5) 1782-1791.

Jensen KB, Regenbogen C, Ohse MC, Frasnelli J, Freiherr J, Lundström JN. Brain Activations During Pain: A Neuroimaging Meta-Analysis of Patients With Pain and Healthy Controls. *Pain.* 2016 Jun;157(6):1279-86. doi: 10.1097/j.pain.0000000000000517.

Julius D, Basbaum A. Molecular mechanisms of nociception. *Nature.* 2001. 413:203–210.

Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen. Hosp. Psychiatry.* 1982. 4, 33–47. [https://doi.org/10.1016/0163-8343\(82\)90026-3](https://doi.org/10.1016/0163-8343(82)90026-3).

Kabat-Zinn J. Full catastrophe living: The program of the Stress Reduction Clinic at the University of Massachusetts Medical Center. Dell Publishing; 1990.

Kabat-Zinn J. Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness. 2014. Bantam Ann Behav Med. 2007 Apr;33(2):179-88.

Kabat-Zinn J. Some reflections on the origins of MBSR, skillful means, and the trouble with maps. *Contemp. Buddhism.* 2011. 12, 281–306. <https://doi.org/10.1080/14639947.2011.564844>

Kong, J. et al. Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. *Hum. Brain Mapp.* 2006. 27, 715–721.

Kosaza EH, Tanaka LH, Monson C, Little S, Leap FC, Peres MP, The Effects of Meditation-Based Interventions on the Treatment of Fibromyalgia. *Current Pain and Headache Reports.* 2012. volume 16, 383–387

Koyama T, McHaffie JG, Laurienti PJ, Coghill RC (2005): The subjective experience of pain: Where expectations become reality. *Proc Natl Acad Sci USA* 102:12950–12955.

Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded. A salience detection system for the body. *Progress in Neurobiology.* 2011. Volume 93, Issue 1, January 2011, Pages 111-124

Leknes S, Berna C, Lee MC, Snyder GD, Biele G, Tracey I. The Importance of Context: When Relative Relief Renders Pain Pleasant . *Pain* . 2013 Mar;154(3):402-10. doi: 10.1016/j.pain.2012.11.018.

Lenz FA, Casey KL, Jones EG, Willis WD. *The Human Pain System. Experimental and Clinical Perspectives*. Cambridge University Press, <https://doi.org/10.1017/CBO9780511770579>.

Lo CSL, Ho SMY, Yu NKK, Siu BPI. Decentering mediates the effect of ruminative and experiential self-focus on negative thinking in depression. *Cognit. Ther. Res.* 2014. 38, 389–396

Lutz A, Dunne J, Davidson R. *Meditation and the neuroscience of consciousness: an introduction*. The Cambridge Handbook of Consciousness, 2006. 19.

Lutz A, Jha, AP, Dunne JD, Saron CD. Investigating the phenomenological matrix of mindfulness-related practices from a neurocognitive perspective. 2015. *Am. Psychol.* 70, 632–658. <https://doi.org/10.1037/a0039585>

Lutz A, McFarlin DR, Perlman DM, Salomons TV, Davidson RJ. Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *Neuroimage*. 2013. 1;64:538-46. <https://doi.org/10.1016/j.neuroimage.2012.09.030>

Lutz A, Slagter HA, Dunne JD, Davidson RJ. Attention regulation and monitoring in meditation. *Trends Cogn Sci.* 2008. 12, 163–169. <https://doi.org/10.1016/j.tics.2008.01.005>

Maihofner C, Herzner B, Handwerker H. Secondary somatosensory cortex is important for the sensory-discriminative dimension of pain: a functional MRI study. *Eur J Neurosci.* 2006; 23: 1377-1383

Masuda A, Hayes SC, Sackett CF, Twohig MP. Cognitive defusion and self-relevant negative thoughts: examining the impact of a ninety year old technique. *Behaviour Research and Therapy.* 2004. 42(4), 477–485.

Mazzola L, Faillenot, I, Barral, F-B., Mauguière, F., Peyron R. , Spatial segregation of somato-sensory and pain activations in the human operculo-insular cortex. *NeuroImage* Volume 60, Issue 1, 2012, Pages 409-418.

McCracken LM, DaSilva P, Skillicorn B, Doherty R. The Cognitive Fusion Questionnaire: A preliminary study of psychometric properties and prediction of functioning in chronic pain. *The Clinical Journal of Pain.* 2013a. doi:10.1097/AJP. 0000000000000047

McCracken L, Estelle B, Joseph C, Decentering, rumination, cognitive defusion, and psychological flexibility in people with chronic pain. *Journal of Behavioral Medicine*. 2014. 37(6). doi: 10.1007/s10865-014-9570-9.

McCracken LM, Gutierrez-Martinez O, Smyth C. “Decentering” reflects psychological flexibility in people with chronic pain and correlates with their quality of functioning. *Health Psychology*. 2013b. 32, 820–823. doi: 10.1037/a0028093

McCracken LM, Barker E, Chilcot J. Decentering, rumination, cognitive defusion, and psychological flexibility in people with chronic pain. *J. Behav. Med.* 2014. 37, 1215–1225

Melzack R, Casey KL. Sensory, motivational and central control determinants of chronic pain: A new conceptual model. In: Kenshalo DR. *The skin senses: Proceedings of the first International Symposium on the Skin Senses*, held at the Florida State University in Tallahassee, Florida. 1968. P432-439.

Melzack R, 1989. Phantom limbs, the self and the brain. *Can. Psychol.* 30, 1–16.

Melzack R, 2001. Pain and the neuromatrix in the brain. *J. Dent. Educ.* 65, 1378–1382

Menon V, Uddin LQ., Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* 2010. 214, 655–667

Merskey H, Bogduk N. *Classification of chronic pain, IASP Task Force on Taxonomy*. IASP Press; Seattle: 1994.

Miron D, Duncan GH, Bushnell MC. Effects of attention on the intensity and unpleasantness of thermal pain. *Pain*. 1989. 39(3):345-52. [https://doi.org/10.1016/0304-3959\(89\)90048-1](https://doi.org/10.1016/0304-3959(89)90048-1)

Morone NE, Greco CM, Weiner DK. Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study. *Pain*. 2008 Feb;134(3):310-9. Epub 2007 Jun 1. DOI: 10.1016/j.pain.2007.04.038.

Nomi JS, Farrant K, Damaraju E, Rachakonda S, Calhoun VD , Uddin LQ: Dynamic Functional Network Connectivity Reveals Unique and Overlapping Profiles of Insula Subdivisions. *Hum Brain Mapp* . 2016 May;37(5):1770-87. doi: 10.1002/hbm.23135.

Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med* 1997, 20: 589 - 605

Osman A, Barrios FX, Gutierrez PM, Kopper BA, Merrifield T, & Grittmann L (2000). The Pain Catastrophizing Scale: Further psychometric evaluation with adult samples. *Journal of Behavioral Medicine*, 23(4), 351–365.

Palermo S, Benedetti F, Costa T, Amanzio M. Pain Anticipation: An Activation Likelihood Estimation Meta-Analysis of Brain Imaging Studies. *Human Brain Mapping* 36:1648–1661 (2015)

Peirs C, Seal RP. Neural circuits for pain: Recent advances and current views. *Science* 2016. 354:578-584. DOI: 10.1126/science.aaf8933 Price DD, Greenspan JD, Dubner R., Neurons involved in the exteroceptive function of pain, *Pain*. 2003. 106(3):215-9. DOI: 10.1016/j.pain.2003.10.016.

Peltz E, Seifert F, DeCol R, Dörfler A, Schwab S, Maihöfner C. Functional connectivity of the human insular cortex during noxious and innocuous thermal stimulation. *Volume 54, Issue 2, 15 January 2011, Pages 1324-1335.*

Perlman DM, Salomons TV, Davidson RJ, Lutz A. Differential effects on pain intensity and unpleasantness of two meditation practices. *Emotion*. 2010. 10:65–71. doi: 10.1037/a0018440

Peyron R, Laurent B, Garcia-Larrea L: Functional imaging of brain responses to pain. A review and meta-analysis. *Neurophysiol Clin* 2000, 30:263-288.

Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN. Dissociating pain from its anticipation in the human brain. *Science*. 1999. 284(5422):1979-81.

Ploner M, Lee MC, Wiech K, Bingel U, Traey I. Prestimulus functional connectivity determines pain perception in humans. *PNAS*. 2010. 107:355-360. <https://doi.org/10.1073/pnas.0906186106>.

Price D. Spinothalamic Tract Neurons, in Deep Dorsal Horn. *Encyclopedia of Pain*. 2007 edition. doi: https://doi.org/10.1007/978-3-540-29805-2_4173.

Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia AS, McNamara JO, Williams SM. Sunderland, MA, Sinauer Associates, Neuroscience, 3rd Edition. Inc., 2004. 9: 209-214.

Quartana PJ, Campbell CM, Edwards RR, Pain catastrophizing: a critical review. *Expert Rev Neurother*. 2009. 9(5): 745–758. DOI: 10.1586/ern.09.34

Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception – Part 1: Are there really differences between women and men? *PAIN*. 2012. 153; 602–618.
<https://doi.org/10.1016/j.pain.2011.11.025>

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in the human anterior cingulate but not in somatosensory cortex. *Science*. 1997. 277, 968– 971.

Rainville P. Brain mechanisms of pain affect and pain modulation. *Curr Opin Neurobiol*. 2002. 12:195–204.

Rinpoche YM, Swanson E. *The joy of living: Unlocking the secret and science of happiness*. New York: Harmony Books.

Rolls ET, Grabenhorst F. The orbitofrontal cortex and beyond: from affect to decision-making. *Prog Neurobiol*. 2008;86:216–244.

Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: Relationship to patient characteristics and current adjustment. *Pain*. 1983;17:33–44. Epub 1983/09/01. PubMed PMID: 6226916.

Roy M, Shohamy D, Wager TF. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn Sci*. 2012 Mar; 16(3): 147–156.

Sarinopoulos I, Grupe DW, Mackiewicz KL, Herrington JD, Lor M, Steege EE, Nitschke JB. Uncertainty during Anticipation Modulates Neural Responses to Aversion in Human Insula and Amygdala. *Cerebral Cortex*, Volume 20, Issue 4, April 2010, Pages 929–940, <https://doi.org/10.1093>

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., and Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat. Rev. Neurosci*. 12, 154–167.

Schutze R, Rees C, Preece M, Schutze M. Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. *Pain*. 148: 120–127. <https://doi.org/10.1016/j.pain.2009.10.030>.

Segal, Z.V. et al. (2012) *Mindfulness-based Cognitive Therapy for Depression*, Guilford Press

Sege CT, Bradley MM, Weymar M, Lang PJ. A direct comparison of appetitive and aversive anticipation: Overlapping and distinct neural activation. *Behavioural Brain Research* Volume 326, 30 May 2017, Pages 96-102

Shapiro SL, Carlson LE, Astin JA, Freedman B. Mechanisms of mindfulness. *Journal of Clinical Psychology*. 2006. 62(3):373–386. <http://doi.org/10.1002/jclp.20237>.

Silananda U. *The four foundations of mindfulness*. 1990. Boston: Wisdom Publications.

Smallwood J, Schooler JW. The science of mind wandering: Empirically navigating the stream of consciousness. *Annual Review of Psychology*. 2015. 66:487–518. <http://doi.org/10.1146/annurev-psych-010814-015331>.

Spanos NP, Radtke-Bodorik HL, Ferguson JD, Jones B. The effects of hypnotic susceptibility, suggestions for analgesia, and the utilization of cognitive strategies on the reduction of pain. *J Abnorm Psychol*. 1979;88:282–92. Epub 1979/06/01. PubMed PMID: 500957.

Sprenger C, Eippert F, Finsterbusch J, Bingel U, Rose M, Büchel C. Attention Modulates Spinal Cord Responses to Pain. *Current Biology*. 2012. 22; 1019–1022. <https://doi.org/10.1016/j.cub.2012.04.006>

Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*. 1995. 7(4), 524-532. doi:10.1037//1040-3590.7.4.524

Sullivan MJL, Tripp DA, Santor D. Gender differences in pain and pain behavior: The role of catastrophizing. *Cog Ther Res* 2000, 21: 555 -568.

Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*. 2001. 17:52-64. doi: 10.1097/00002508-200103000-00008.

Teasdale JD, Scott J, Moore RG, Hayhurst H, Pope M, Paykel ES. How does cognitive therapy prevent relapse in residual depression? Evidence from a controlled trial. *Journal of Consulting and Clinical Psychology*. 2001. 69(3), 347–357. doi: 10.1037//0022-006x.69.3.347

Tergar (n.d.). What is the joy of living? Retrieved July 21, 2018, from <https://tergar.org/programs/what-is-the-joy-of-living/>.

Thera N. The heart of Buddhist meditation: A handbook of mental training based on the Buddha's way of mindfulness. 1962. London: Rider and Company.

Timmermann L, Ploner M, Haucke K, Schmitz F, Baltissen R, Schnitzler A, Differential Coding of Pain Intensity in the Human Primary and Secondary Somatosensory Cortex. *Journal of Neurophysiology*. 2001. 86(3):1499-503. DOI: 10.1152/jn.2001.86.3.1499.

Tracey I. Nociceptive processing in the human brain. *Current Opinion in Neurobiology*. 2005,15:478–487

Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron*. 2007. 2;55(3):377-91.

Treede RD, Kenshalo DR, Gracely RH, Jones AKP: The cortical representation of pain. *Pain* 79:105-111, 1999

Treede RD. Spinothalamic and thalamocortical nociceptive pathways. *J Pain*. 2002 3(2):109-12; discussion 113-4.

Treede RD, Apkarian AV, Bromm B, Greenspan JD, Lenz FA. Cortical representation of pain: functional characterization of nociceptive areas near the lateral sulcus. *Pain* 87 (2000) 113±119

Turner JA, Anderson ML, Balderson BH, Cook AJ, Sherman KJ, Cherkin DC. Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain: similar effects on mindfulness, catastrophizing, self-efficacy, and acceptance in a randomized controlled trial. *PAIN*. 2016. 157:2434–44. doi: 10.1097/j.pain.0000000000000696

Uddin LQ, Kinnison J, Pessoa L, Anderson ML. Beyond the Tripartite Cognition-Emotion-Interoception Model of the Human Insular Cortex. *J Cogn Neurosci* . 2014 Jan;26(1):16-27. doi: 10.1162/jocn_a_00462.

Van Dam, N. T., Earleywine, M., & Danoff-Burg, S. (2009). Differential item functioning across meditators and non-meditators on the Five Facet Mindfulness Questionnaire. *Personality and Individual Differences*, 47, 516–521.

Van Dam NT, van Vugt MK, Vago DR, Schmalzl L, Saron CD, Olendzki A, ... Meyer DE. Mind your words: Positive and negative items create method effects on the five facet mindfulness questionnaire. *Assessment*. 2012. 19(2), 198-204. <https://doi.org/10.1177/1073191112438743>.

Van Dam NT, van Vugt MK, Vago DR, Schmalzl L, Saron CD, Olendzki A, Meissner T, Lazar SW, Kerr CE, Gorchov J, Fox KCR, Field BA, Britton WB, Brefczynski-Lewis JA, Meyer DE, 2017. Mind the Hype: A Critical Evaluation and Prescriptive Agenda for Research on Mindfulness and Meditation. *Perspect. Psychol. Sci.* 1745691617709589. <https://doi.org/10.1177/1745691617709589>

Van Damme, S., Crombez, G., Eccleston, C. Retarded disengagement from pain cues: the effects of pain catastrophizing and pain expectancy. *Pain* 2002, 100: 111 - 118

Vlaeyen JW, Kole-Snijders AM, Rotteveel AM, Ruesink R, Heuts PH. The role of fear of movement/(re)injury in pain disability.. *J Occup Rehabil.* 1995 Dec;5(4):235-52. doi: 10.1007/BF02109988.

Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000. 85:317–332. doi: 10.1016/s0304-3959(99)00242-0

Vogt, BA, Sikes RW, Vogt LJ. Anterior Cingulate Cortex and the Medial Pain System. *Neurobiology of Cingulate Cortex and Limbic Thalamus*, 1993. 313–344. doi:10.1007/978-1-4899-6704-6_11

Wager TD, Atlas LY, Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-Based Neurologic Signature of Physical Pain. *N Engl J Med* 2013; 368:1388-1397 DOI: 10.1056/NEJMoa1204471.

Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science*. 2004. 20;303(5661):1162-7.

Werberger R, Basbaum AI, Spinal cord projection neurons: a superficial, and also deep analysis. 2019. 11:109-115. <https://doi.org/10.1016/j.cophys.2019.10.002>

Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. *Trends Cogn Sci.* 2008 Aug;12(8):306-13. doi: 10.1016/j.tics.2008.05.005.

Wiech K, Lin C, Brodersen KH, Bingel U, Ploner M, Tracey I, 2010. Anterior insula integrates information about salience into perceptual decisions about pain. *J. Neurosci.*30, 16324–16331.

Zeidan F, Adler-Neal AL, Wells RE, Stagnaro E, May LM, Eisenach JC, McHaffie JG, Coghill RC. Mindfulness-meditation-based pain relief is not mediated by endogenous opioids. *J. Neurosci.*, 2016. 36(11):3391–3397. doi: 10.1523/JNEUROSCI.4328-15.2016

Zeidan F, Emersion NM, Farris SR, Ray JN, Jung Y, McHaffie JG, Coghill RC. Mindfulness-meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness-meditation induced analgesia. *The Journal of Neuroscience*. 2015. 35(46):15307–15325. doi: 10.1523/JNEUROSCI.2542-15.2015

Zeidan F, Grant JA, Brown CA, McHaffie JG, Coghill RC, The neural mechanisms of mindfulness-based pain relief: a functional magnetic resonance imaging-based review and primer. *PAIN Reports*. 2019. 7;4(4):e759. Volume 4 - Issue 4 - p e759. doi: 10.1097/PR9.0000000000000759

Zeidan F, Martucci KT, Kraft RA, Gordon NS, McHaffie JG, Coghill RC. Brain mechanisms supporting the modulation of pain by mindfulness meditation. *J. Neurosci.* 2011. 31:5540–5548. doi: 10.1523/JNEUROSCI.5791-10.2011

Zeidan F, Baumgartner JN, Coghill RC. The Neural Mechanisms of Mindfulness-Based Pain Relief: A Functional Magnetic Resonance Imaging-Based Review and Primer. *Pain Rep*. 2019 Aug 7;4(4):e759. doi: 10.1097/PR9.0000000000000759.

ANNEXES

ANNEX I

Brain & Mindfulness

Manual

Principal investigator

LUTZ Antoine



Foreword

Brain & Mindfulness is an ERC-funded research project led by Antoine LUTZ, carried out in Lyon (France) from 2015 to 2019. The main aim of this project is to investigate the phenomenological, behavioral, neural and physiological correlates of meditation in cognitive and emotion regulation processes. It is embedded in the more general exploration of processes and biomarkers of mental health and wellbeing.

This document presents the scientific context and the overarching goals of the study, its general methodology, and the experiments that compose it.

Authors of the present manual

Coordinator

ABDOUN Oussama

Contributors

AARTS Kristien

FUCCI Enrico

PERRAUD Eléa

ZORN Jelle

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Context and goals

Over the last decades, the scientific study of meditation, especially the so-called *mindfulness* meditation, has received increasing attention in the fields of medicine, psychology and cognitive neurosciences. The growing interest for the practice of meditation is also supported by its widespread implementation in cognitive therapy. Mindfulness-based therapies are successfully applied in contexts such as stress management, depression relapse and chronic pain, among others.

Nevertheless, the understanding of the neurocognitive mechanisms underlying meditation is still quite limited. Whereas an increasing number of studies have described how meditation training impacts several cognitive and affective processes in terms of observed behaviour and related neural correlates, this field of research is still facing a number of shortcomings. Neuroimaging studies of meditation, pain and emotion regulation, as well as of specific meditation states, has not reached a consensus on the neural networks implicated in the practice. The actual neurophysiological mechanisms underlying the observed modulation of behavioural and neuroimaging markers are also poorly understood. Moreover, this field of research often lacks a precise characterisation of subjective accounts of meditation experience and their correlation with neurophysiological and neuroanatomical measures. Finally, previous cross-sectional studies have been limited by a lack of rigorous selection of expert meditation practitioners and have often not provided an in-depth introduction to the practice for control participants.

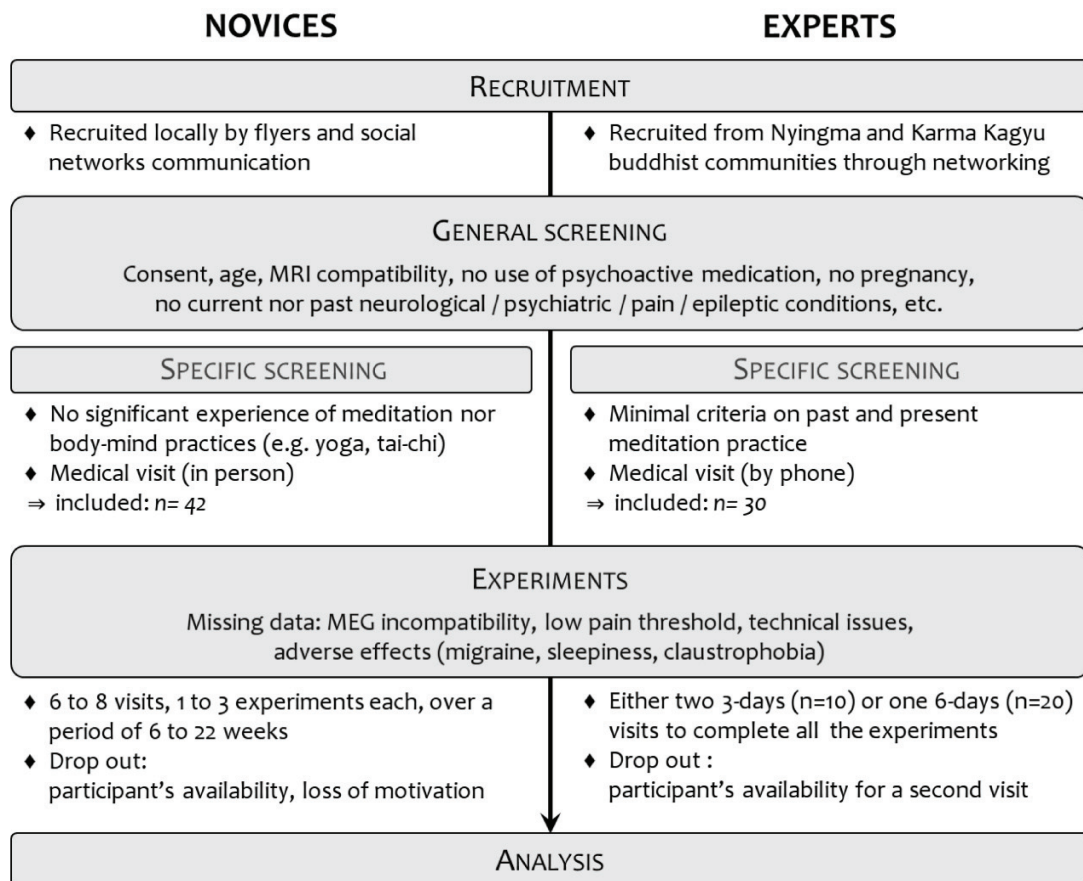
This project tries to address these limitations by proposing a methodological approach that 1) takes into account the variety of meditation practices such as Focused Attention (FA), Open Monitoring (OM) and Compassion, 2) provides a detailed meditation introduction to novice practitioners through experiential exercises and home practice, and 3) brings together a group of expert practitioners that followed a similar path of extensive practice in the same tradition. Within this general framework, we attempt to bridge the gap between third and first-person methods by implementing measures of neural activity (fMRI, EEG, MEG) and bodily physiology (e.g. heart rate, respiration, etc.) together with subjective accounts of the experimental conditions provided by self-report scales and extensive interviews.

The aim of this *manual* is to provide the scientific community with an overview of the core methodological aspects of this project. In the [first section](#), the reader will find detailed information on the recruitment process of novice and expert meditators, along with a short presentation of their training. In the [second section](#), we provide a brief description of the experimental aspects of the project, including a list of the tasks, the implemented paradigms, and primary outcome measures. For background information on the paradigms used in the tasks, the reader is referred to relevant sources in the existing literature. Specific methodological information pertaining to each task will be available in forthcoming publications, [listed at the end of the manual](#).

Participants

Recruitment

Meditation naive participants were recruited locally from January 2016 to January 2018 through flyers and posters in public places, on mailing lists, Facebook and notifications to research participant databases. Long term practitioners (hereafter referred to as *LTPs* or *experts*) were recruited by a long term practitioner (with extensive contacts within the Nyingma community) from multiple meditation centers, predominantly in France but also internationally. Interested candidates received a detailed study information sheet, informed consent, and initial screening questionnaire for general inclusion and exclusion criteria.



Inclusion and exclusion criteria

General

- Aged between 35 and 65 years
- No use of medication affecting the central nervous system (e.g. anti-depressants, opioids) or the pain system (e.g. nonsteroidal anti-inflammatory drugs)
- No neurological and/or psychiatric illnesses (e.g. epilepsy, depression) and/or condition involving sensitization to pain (e.g. chronic pain, fibromyalgia)
- No family history of epilepsy
- A score to the Beck Depression Inventory (BDI) below 20
- No severe hearing loss
- For women: not pregnant, breastfeeding or having given birth in the last 6 months
- MRI compatibility (no claustrophobia or metal implants, not including dental prostheses)
- Affiliation to the social security system
- Motivation to participate in the project in an effective manner
- Willing to sign the informed consent

Specific to novices

For novices, there was an additional inclusion criteria in the screening questionnaire:

- No significant experience with meditation or other mind-body techniques (e.g. yoga, tai-chi, chi-gong, sophrology, neuro linguistic programming)

Potential novices who satisfied the general criteria had a medical check by a physician who also collected their informed consent, before being formally included in the study. As recruitment of novice and expert practitioners progressed simultaneously, a selection of candidates for the novice group was sometimes made to improve the matching between the two groups in terms of age, gender, hand laterality and education level.

Specific to experts

Potential LTPs who satisfied the general inclusion criteria then entered a second screening phase. They were contacted to check the following additional inclusion criteria:

- having followed at least one 3 year meditation retreat
- having a minimum of 10 000 hours of meditation practice
- sustaining a daily practice of a minimum of 45 minutes over the past year
- being familiar with either Mahamudra or Dzogchen teachings and practices

Finally, they had an interview by phone with a medical doctor who gave his agreement for the inclusion of the participant in the study.

One expert had a BDI score above our criterion threshold. However, considering that he has never been clinically diagnosed for depression and the difficulty of recruiting LTPs satisfying our practice criteria, we decided to include him in the study.

Task-specific

For novices, participation to the task PAR (see below, [Outcome measures](#)) was conditioned on a pain threshold above 47 C°. A standard pain calibration procedure (method of limits) was performed using a Medoc TSA-II stimulator with a 30 x 30 mm flat thermode. This was done to ensure better matching with LTPs, as LTPs showed elevated pain thresholds in a previous study by the principal investigator (Lutz et al. 2013, data not reported in the original paper).

For both novice and expert participants, participation to the experiments in magnetoencephalography (MEG) was conditioned on sufficient signal quality. Signal quality was potentially impaired in participants with dental restoration. Assessment of signal quality was performed on a few minutes of resting-state recording, based on the nature of the planned analyses and on the expertise of the MEG engineer.

Meditation training

Novices

Included meditation naïve participants participated in a training weekend. The training protocol was based on 'Joy of Living', a secular meditation program authored by Yongey Mingyur Rinpoche and rooted in Tibetan Buddhism, and included teachings on, and practices with three different styles of meditation (focus attention, FA; open monitoring, OM; and compassion, CO). The program was modified to also accommodate various experiential exercises designed to familiarize participants with different phenomenological categories of interest to the research program (Lutz et al. 2015), in order to ensure they accurately understood these different constructs. The training was provided by a qualified instructor with 13 of years of practice in the Karma Kagyu and Nyingma traditions and 8 years of teaching experience with the *Joy of Living* program. A total of five meditation weekends were hosted in the Lyon Neuroscience Research Center from March 2015 until September 2018 (fig. 1). More details on the aims, contents and structure of the meditation weekend will be described elsewhere (submitted paper).



Figure 1. Timeline of the 5 meditation weekends

Experts

We included 30 long-term practitioners within French and European Tibetan buddhist communities. 17 participants were trained in the Nyingma school (Mahamudra), 11 in the Karma Kagyü school (Dzogchen), and 2 in both. Two participants received additional training from Theravadin monks, and one from the Gelug Tibetan school.

Core practices shared by all participants included “calm abiding” (shamatha, Skt. *śamatha*; Tib. *shyiné*), “insight” meditation (Skt. *vipaśyanā*, Pāli *vipassanā*), Vajrayana practices, and at least one open presence style of practice aiming at the recognition and sustaining of the “nature of the mind” (Tib. Wylie, *sems nyid* or *sems kyi rang bzhin*) or one’s “fundamental awareness” (Tib. Wylie, *rig pa*).

Outcome measures

Self-administered questionnaires

All participants were invited to fill a series of 13 questionnaires (see table below). Answers were saved anonymously and participants were informed of this.

Novice participants filled the questionnaires prior to the meditation week-end, in the lab, on a computer. Because of technical issues, 10 participants had to fill 8 questionnaires at home, after the meditation training.

Expert practitioners filled the questionnaires either on a computer in the lab, during their visit, or from home afterwards.

Acronym	Full name	Reference
BDI	Beck Depression Inventory	Beck et al. 1961
BDIR	Balanced Inventory of Desirable Responding	Paulhus 1991
CFQ	Cognitive Fusion Questionnaire	Gillanders et al. 2014
DDS	Drexel Defusion Scale	Forman et al. 2012
FFMQ	Five Facet Mindfulness Questionnaire	Baer et al. 2006
FLANDERS	Flinders Handedness Survey	Nicholls et al. 2013
IRI	Interpersonal Reactivity Index	Davis 1980
LHQ	Language History Questionnaire	Li et al. 2006
MAIA	Multidimensional Assessment of Interoceptive Awareness	Mehling et al. 2012
PCS	Pain Catastrophizing Scale	Sullivan et al. 1995
PNCS	Pommier and Neff Compassion Scale	Pommier 2010
PSWQ	The Penn State Worry Questionnaire	Meyer et al. 1990
STAI	State Trait Anxiety Inventory	Spielberger 1970

Behavioral, neurophysiological and phenomenological measures

Subjects participated to up to 16 experiments/tasks, spread over 8 sessions, for a total of 5 to 7 days. Experts' participation was spread either over 2 visits (4 days + 2 or 3 days) or 1 single visit lasting 6 days. Novices came 5-7 times to the lab during a period ranging from 1 to 4 months. For novices, two experimental sessions were sometimes combined in a single visit. Some subjects did not participate to all experimental sessions. In particular, some tasks had specific inclusion criteria (see [Task-specific inclusion criteria](#)):

- for novices, the participation to experimental session 2 was conditional on a sufficiently high pain threshold
- only MEG-compatible participants (from both groups) did experimental session 3

Experimental session 1

Modalities: MRI, behavior

Duration: half a day

CODE	MEASURES	PARADIGM	REFERENCES
ANAT	- structural anatomy	- T1, T2, T2* - FLAIR - DWI - Hippocampal scan	Villain et al. 2010 La Joie et al. 2010
PERC	- BOLD MRI - ECG, respiration	- Multisensory stimulation	López-Solà et al. 2014
SMRI	- BOLD MRI - ECG, respiration	- Resting-state	
BLAST	- behavior	- Delayed visual discrimination	
FLANC	- behavior - Likert scales	- Posner cueing - Eriksen flanker	Trautwein et al. 2016

Experimental session 2

Modalities: MRI

Duration: half a day

CODE	MEASURES	PARADIGM	REFERENCES
PAR	- BOLD MRI - ECG, respiration - behavior - Likert scales - semi-structured interview	- Anticipation and relief in thermal nociception - Regulation of pain through mindfulness	Atlas et al. 2010 Leknes et al. 2012 Lutz et al. 2013

Experimental session 3

Modalities: MEG

Duration: half a day

CODE	MEASURES	PARADIGM	REFERENCES
MIMOSA	<ul style="list-style-type: none"> - MEG - ECG, EGG, respiration - behavior - Likert ITEMS - semi-structured interview 	<ul style="list-style-type: none"> - Visual passive oddball - Visual consciousness report 	<ul style="list-style-type: none"> Stefanics et al. 2014 Park et al. 2014 Richter et al. 2016
SMEG	<ul style="list-style-type: none"> - MEG - ECG, respiration - Likert scales - semi-structured interview 	<ul style="list-style-type: none"> - Resting-state 	

Experimental session 4

Modalities: EEG

Duration: one full day

CODE	MEASURES	PARADIGM	REFERENCES
MMN	<ul style="list-style-type: none"> - EEG - Likert scales - semi-structured interview 	<ul style="list-style-type: none"> - Auditory passive oddball - Stress induction 	<ul style="list-style-type: none"> Cornwell et al. 2007
PEC	<ul style="list-style-type: none"> - EEG - Likert scales - ECG, respiration 	<ul style="list-style-type: none"> - Electrical stimulation - Emotional images 	<ul style="list-style-type: none"> Ring et al. 2013

Experimental session 5

Modalities: EEG

Duration: half a day

CODE	MEASURES	PARADIGM	REFERENCES
CAAT	<ul style="list-style-type: none"> - behavior - ECG, respiration - skin conductance - Likert scales - semi-structured interview 	<ul style="list-style-type: none"> - Approach-avoidance - Emotional videos 	<ul style="list-style-type: none"> Baquedano et al. 2017 Klimecki et al. 2013

Experimental session 6

Modalities: EEG

Duration: half a day

CODE	MEASURES	PARADIGM	REFERENCES
RIV	- EEG - behavior - Likert scales	- Binocular rivalry - Affordance	Riddoch et al. 2002 Pace & Saracini 2014

Experimental session 7

Modalities: behavior, interview

Duration: one full day

CODE	MEASURES	PARADIGM	REFERENCES
FBI	- behavior - Likert scales	- Full body illusion	Lenggenhager et al. 2007
HBA	- behavior	- Heartbeat counting	Khalsa et al. 2008
PPS	- behavior - Likert scales	- Peripersonal space	Canzoneri et al. 2012

In addition, this experimental session included a 1h semi-structured in-depth interview to explore participants' backgrounds, motivations and worldviews.

Experimental session 8

Modalities: behavior

Duration: half a day

CODE	MEASURES	PARADIGM	REFERENCES
WIM	- behavior	- Visual short-term memory	Vandenbroucke et al. 2011 Rerko et al. 2014

Contributions

Principal investigator	LUTZ	Antoine	<i>PhD</i>
Medical investigators	JUNG SONIÉ	Julien Sandrine	<i>MD, PhD</i> <i>MD</i>
Ethics Coordination Data management	AARTS ABDOUN	Kristien Oussama	<i>post-doctoral fellow</i> <i>post-doctoral fellow</i>
Experts recruitment	BENSON	Clara	<i>research assistant</i>
Novices recruitment	AARTS	Kristien	<i>post-doctoral fellow</i>
Novices training	TRAN	Titi	<i>meditation instructor</i>
Design	AARTS ABDOUN	Kristien Oussama	<i>post-doctoral fellow</i> <i>post-doctoral fellow</i>
Data collection	BAQUEDANO FUCCI	Constanza Enrico	<i>PhD student</i> <i>PhD student</i>
Data analysis	KATYAL POLETTI ZORN	Sucharit Stefano Jelle	<i>post-doctoral fellow</i> <i>PhD student</i> <i>PhD student</i>
Data collection	ASSOULY BENSON BOYER DALIGAULT FAKCHE MONDRAGON LAMBERTON LEFÉVÈRE PERRAUD SAVEROT	Kelly Clara Damien Sébastien Camille Liliana Franck Aindrias Eléa Arthur	<i>L3 student</i> <i>research assistant</i> <i>L3 student</i> <i>engineer</i> <i>research assistant</i> <i>M2 student</i> <i>engineer</i> <i>L3 student</i> <i>research assistant</i> <i>L3 student</i>
Data analysis	ADOR ARNAS BOYER FAKCHE GARNIER LEFÉVÈRE MONDRAGON NISSOU PASMANTIER POUBLAN VOGEL	Benjamin Alix Damien Camille Manon Aindrias Liliana Manon Alexandre Arnaud Gabriel	<i>M2 student</i> <i>M1 student</i> <i>L3 student</i> <i>research assistant</i> <i>M1 student</i> <i>L3 student</i> <i>M2 student</i> <i>L2 student</i> <i>M1 student</i> <i>M2 student</i> <i>L3 student</i>
Collaborators	BLANKE BOUET LECAIGNARD MATTOU MEUNIER	Olaf Romain Françoise Jérémie David	<i>PhD</i> <i>PhD</i> <i>PhD</i> <i>PhD</i> <i>PhD</i>

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References

- Atlas, L. Y., Bolger, N., Lindquist, M. A., & Wager, T. D. (2010). Brain Mediators of Predictive Cue Effects on Perceived Pain. *Journal of Neuroscience*, 30(39), 12964–12977. <https://doi.org/10.1523/JNEUROSCI.0057-10.2010>
- Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. *Assessment*, 13, 27-45.
- Baquedano, C., Vergara, R., Lopez, V., Fabar, C., Cosmelli, D., & Lutz, A. (2017). Compared to self-immersion, mindful attention reduces salivation and automatic food bias. *Scientific Reports*, 7(1), 13839. <https://doi.org/10.1038/s41598-017-13662-z>
- Beck, A.T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961) An inventory for measuring depression. *Archives of General Psychiatry*, 4, 561-571.
- Canzoneri, E., Magosso, E., & Serino, A. (2012). Dynamic Sounds Capture the Boundaries of Peripersonal Space Representation in Humans. *PLOS ONE*, 7(9), e44306. <https://doi.org/10.1371/journal.pone.0044306>
- Cornwell, B. R., Baas, J. M. P., Johnson, L., Holroyd, T., Carver, F. W., Lissek, S., & Grillon, C. (2007). Neural responses to auditory stimulus deviance under threat of electric shock revealed by spatially-filtered magnetoencephalography. *NeuroImage*, 37(1), 282–289. <https://doi.org/10.1016/j.neuroimage.2007.04.055>
- Davis, M. H. (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology*, 44(1), 113–126. <https://doi.org/10.1037/0022-3514.44.1.113>
- Forman, E. M., Herbert, J. D., Juarascio, A. S., Yeomans, P. D., Zebell, J. A., Goetter, E. M., & Moitra, E. (2012). The Drexel defusion scale: A new measure of experiential distancing. *Journal of Contextual Behavioral Science*, 1(1-2), 55-65.
- Gillanders, D. T., Bolderston, H., Bond, F. W., Dempster, M., Flaxman, P. E., Campbell, L., ... Remington, B. (2014). The Development and Initial Validation of the Cognitive Fusion Questionnaire. *Behavior Therapy*, 45(1), 83–101. <https://doi.org/10.1016/j.beth.2013.09.001>
- Khalsa, S. S., Rudrauf, D., Damasio, A. R., Davidson, R. J., Lutz, A., & Tranel, D. (2008). Interoceptive awareness in experienced meditators. *Psychophysiology*, 45(4), 671–677. <https://doi.org/10.1111/j.1469-8986.2008.00666.x>
- Klimecki, O. M., Leiberg, S., Ricard, M., & Singer, T. (2014). Differential pattern of functional brain plasticity after compassion and empathy training. *Social Cognitive and Affective Neuroscience*, 9(6), 873–879. <https://doi.org/10.1093/scan/nst060>
- La Joie, R., Fouquet, M., Mézence, F., Landeau, B., Villain, N., Mevel, K., ... Chételat, G. (2010). Differential effect of age on hippocampal subfields assessed using a new high-resolution 3T MR sequence. *NeuroImage*, 53(2), 506–514. <https://doi.org/10.1016/j.neuroimage.2010.06.024>

- Leknes, S., Berna, C., Lee, M. C., Snyder, G. D., Biele, G., & Tracey, I. (2013). The importance of context: When relative relief renders pain pleasant. *PAIN*, 154(3), 402–410. <https://doi.org/10.1016/j.pain.2012.11.018>
- Lenggenhager, B., Tadi, T., Metzinger, T., & Blanke, O. (2007). Video Ergo Sum: Manipulating Bodily Self-Consciousness. *Science*, 317(5841), 1096–1099. <https://doi.org/10.1126/science.1143439>
- Li, P., Sepanski, S., & Zhao, X. (2006). Language history questionnaire: A web-based interface for bilingual research. *Behavior research methods*, 38(2), 202-210.
- López-Solà, M., Pujol, J., Wager, T. D., Garcia-Fontanals, A., Blanco-Hinojo, L., Garcia-Blanco, S., ... Deus, J. (2014). Altered Functional Magnetic Resonance Imaging Responses to Nonpainful Sensory Stimulation in Fibromyalgia Patients. *Arthritis & Rheumatology*, 66(11), 3200–3209. <https://doi.org/10.1002/art.38781>
- Lutz, A., McFarlin, D. R., Perlman, D. M., Salomons, T. V., & Davidson, R. J. (2013). Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2012.09.030>
- Lutz, A., Jha, A. P., Dunne, J. D., & Saron, C. D. (2015). Investigating the phenomenological matrix of mindfulness-related practices from a neurocognitive perspective. *American Psychologist*, 70(7), 632–658. <https://doi.org/10.1037/a0039585>
- Mehling, W. E., Price, C., Daubenmier, J. J., Acree, M., Bartmess, E., & Stewart, A. (2012). The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLOS ONE*, 7(11), e48230. <https://doi.org/10.1371/journal.pone.0048230>
- Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy*, 28(6), 487–495. [https://doi.org/10.1016/0005-7967\(90\)90135-6](https://doi.org/10.1016/0005-7967(90)90135-6)
- Nicholls, M. E., Thomas, N. A., Loetscher, T., & Grimshaw, G. M. (2013). The Flinders Handedness survey (FLANDERS): a brief measure of skilled hand preference. *Cortex*, 49(10), 2914-2926.
- Pace, E. D., & Saracini, C. (2014). Action Imitation Changes Perceptual Alternations in Binocular Rivalry. *PLOS ONE*, 9(5), e98305. <https://doi.org/10.1371/journal.pone.0098305>
- Paulhus, D.L. (1991). Measurement and control of response bias. In J.P. Robinson, P.R. Shaver, & L.S. Wrightsman (Eds.), *Measures of personality and social psychological attitudes* (pp.17-59). San Diego: Academic Press
- Park, H.-D., Correia, S., Ducorps, A., & Tallon-Baudry, C. (2014). Spontaneous fluctuations in neural responses to heartbeats predict visual detection. *Nature Neuroscience*, 17(4), 612–618. <https://doi.org/10.1038/nn.3671>
- Pommier, E. A. (2010). *The Compassion Scale* (thesis). Retrieved from <https://repositories.lib.utexas.edu/handle/2152/ETD-UT-2010-12-2213>
- Rerko, L., Souza, A. S., & Oberauer, K. (2014). Retro-cue benefits in working memory without sustained focal attention. *Memory & Cognition*, 42(5), 712–728. <https://doi.org/10.3758/s13421-013-0392-8>

- Richter, C. G., Babo-Rebelo, M., Schwartz, D., & Tallon-Baudry, C. (2016). Phase-amplitude coupling at the organism level: The amplitude of spontaneous alpha rhythm fluctuations varies with the phase of the infra-slow gastric basal rhythm. *NeuroImage*.
<https://doi.org/10.1016/j.neuroimage.2016.08.043>
- Riddoch, M. J., Humphreys, G. W., Edwards, S., Baker, T., & Willson, K. (2003). Seeing the action: neuropsychological evidence for action-based effects on object selection. *Nature Neuroscience*, 6(1), 82–89. <https://doi.org/10.1038/nn984>
- Ring, C., Kavussanu, M., & Willoughby, A. R. (2013). Emotional modulation of pain-related evoked potentials. *Biological Psychology*, 93(3), 373–376. <https://doi.org/10.1016/j.biopsycho.2013.04.006>
- Sligte, I. G., Scholte, H. S., & Lamme, V. A. F. (2008). Are There Multiple Visual Short-Term Memory Stores? *PLoS ONE*, 3(2), e1699. <https://doi.org/10.1371/journal.pone.0001699>
- Souza, A. S., Rerko, L., & Oberauer, K. (2016). Getting more from visual working memory: Retro-cues enhance retrieval and protect from visual interference. *Journal of Experimental Psychology. Human Perception and Performance*, 42(6), 890–910. <https://doi.org/10.1037/xhp0000192>
- Spielberger, C. D. (1970). STAI manual for the state-trait anxiety inventory. *Self-Evaluation Questionnaire*, 1–24.
- Stefanics, G., Kremláček, J., & Czigler, I. (2014). Visual mismatch negativity: a predictive coding view. *Frontiers in Human Neuroscience*, 8. <https://doi.org/10.3389/fnhum.2014.00666>
- Sullivan, M. J., Bishop, S. R., & Pivik, J. (1995). The pain catastrophizing scale: development and validation. *Psychological Assessment*, 7(4), 524.
- Trautwein, F.-M., Singer, T., & Kanske, P. (2016). Stimulus-Driven Reorienting Impairs Executive Control of Attention: Evidence for a Common Bottleneck in Anterior Insula. *Cerebral Cortex*, 26(11), 4136–4147. <https://doi.org/10.1093/cercor/bhw225>
- Vandenbroucke, A. R. E., Sligte, I. G., & Lamme, V. A. F. (2011). Manipulations of attention dissociate fragile visual short-term memory from visual working memory. *Neuropsychologia*, 49(6), 1559–1568. <https://doi.org/10.1016/j.neuropsychologia.2010.12.044>
- Villain, N., Landeau, B., Groussard, M., Mevel, K., Fouquet, M., Dayan, J., ... Chételat, G. (2010). A Simple Way to Improve Anatomical Mapping of Functional Brain Imaging. *Journal of Neuroimaging*, 20(4), 324–333. <https://doi.org/10.1111/j.1552-6569.2010.00470.x>

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ANNEX II



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Training novice practitioners to reliably report their meditation experience using shared phenomenological dimensions



Oussama Abdoun, Jelle Zorn, Stefano Poletti, Enrico Fucci, Antoine Lutz*

Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR5292, Lyon 1 University, Lyon, France

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ABSTRACT

Empirical descriptions of the phenomenology of meditation states rely on practitioners' ability to provide accurate information on their experience. We present a meditation training protocol that was designed to equip naive participants with a theoretical background and experiential knowledge that would enable them to share their experience. Subsequently, novices carried on with daily practice during several weeks before participating in experiments. Using a neurophenomenological experiment designed to explore two different meditation states (focused attention and open monitoring), we found that self-reported phenomenological ratings (i) were sensitive to meditation states, (ii) reflected meditation dose and fatigue effects, and (iii) correlated with behavioral measures (variability of response time). Each of these effects was better predicted by features of participants' daily practice than by desirable responding. Our results provide evidence that novice practitioners can reliably report their experience along phenomenological dimensions and warrant the future investigation of this training protocol with a longitudinal design.

1. Introduction

This article aims to describe a meditation training protocol developed in the context of an empirical brain imaging, cross-sectional study that investigates the mechanisms of mindfulness and compassion meditations. The novelty of this protocol is to obtain a meditation active control group by training healthy, naive participants to verbally express their subjective experience of meditation practice using a multidimensional phenomenological space (Lutz, Jha, Dunne, & Saron, 2015). Phenomenological space refers here to the description of features of the field of experience, as it is lived and verbally expressed in the first person (e.g., Husserl, 1991). This phenomenological matrix has been recently proposed as a framework to map different styles and levels of training in mindfulness, as well as heuristic tool to generate hypotheses for empirical research.

The *Brain & Mindfulness* project attempts to practically apply this theoretical framework (for the study manual, see Abdoun, Zorn, Fucci, Perraud, Aarts, & Lutz, 2018). During the training participants were introduced to various styles of meditation practices and acquainted with phenomenological categories through various experiential exercises. These phenomenological dimensions were then investigated at neural, behavioral and physiological levels during the various cognitive and affective experimental paradigms. Such explicit use of first-person data to guide the analysis of third-person data is inspired by Francisco Varela's research program of neurophenomenology (Lutz & Thompson, 2003; Varela, 1996).

The current training protocol attempts to pragmatically tackle three methodological and conceptual challenges. The first one is concerned with issues regarding the definition of mindfulness meditation in psychology and cognitive neuroscience. The second one

* Corresponding author.

E-mail address: antoine.lutz@inserm.fr (A. Lutz).

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pertains to epistemological and methodological issues related to the integration of first-person reports in an experimental protocol. The third one is related to the quality of control groups for cross-sectional studies of meditation expertise.

1.1. Theoretical context: mindfulness as a dimensional, phenomenological state

In experimental and clinical psychology, the construct of mindfulness is generally used with three different meanings that refer either to: (a) a mental trait or a dispositional inclination (e.g. the Five Facet of Mindfulness proposed by Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006), (b) a soteriological or spiritual path conceived in therapeutic and health-promotion terms (e.g. in the Mindfulness-Based-Stress-Reduction program; Kabat-Zinn, 1982), and (c) a single cognitive process trained and potentially brought to various human activities (e.g. like in “paying attention in a particular way: on purpose, in the present moment, and non-judgmentally”, Kabat-Zinn, 1994, p.4; or “the optimal interaction between attention and peripheral awareness”, Culadasa et al., 2015, p.30). While these meanings remain useful for many contexts, they are also problematic. Self-report questionnaires to study mindfulness as a trait lack specificity (Goldberg et al., 2016) and may even yield contradictory findings. For instance, Leigh, Bowen, and Marlatt (2005) found that binge drinkers’ mindfulness scores were higher than those of participants in a mindfulness retreat. In addition, findings may be biased by social desirability, consistency effects, or shared language between intervention instructions and scales (see Sauer et al., 2013, Van Dam, Hobkirk, Danoff-Burg, & Earleywine, 2012). Interpreting mindfulness as a soteriological process (meaning [b]) is often too broad to guide empirical research. Up to this point, discussions of mindfulness as a cognitive process (meaning [c]) make it difficult to account for differences in practice styles and levels of expertise, while also lacking the specificity required to formulate mechanistic hypotheses. Because these meanings are too restrictive, with C. Saron, A. Jha and J Dunne, we have argued against formulating a single, universally applicable consensus definition of mindfulness (Lutz et al., 2015).

Instead we favor reconceiving mindfulness through a family resemblance approach whereby it can be conceptualized as “a variety of cognitive processes embedded in a complex postural, aspirational, and motivational context that contribute to states that resemble one another along well-defined phenomenological dimensions” (Lutz et al., 2015, p.633). This approach draws on previous efforts to conceptualize mindfulness (Chambers, Gullone, & Allen, 2009; Hölzel et al., 2011; Lutz, Slagter, Dunne, & Davidson, 2008) and the phenomenology of mindfulness practice. It is compatible with multiple explanatory and analytical frameworks from different sub-disciplines, including contemplative theories, clinical frameworks and psychological and neuroscientific models. This approach is guided by a pragmatic inquiry: when one is formally practicing mindfulness, what observable and manipulable features of consciousness are most relevant to report in an experimental setting? We identified seven features proposed in a bipartite phenomenological model (detailed in Lutz et al., 2015 and resumed here in Table 1).

The model assumes that these dimensions of experience are dynamic and manipulable in that they are affected—directly or indirectly—by different instructions of practice and/or by the level of expertise. This model was used to plot the hypothetical phenomenological characteristics of two styles of mindfulness, Focused attention (FA) and Open monitoring (OM) meditations, for both novice and expert meditators (Lutz et al., 2015). These plots have been created based on various instruction sets and descriptions. They should not be taken as actual plots of any individual’s phenomenology. The same set of mindfulness instructions could be mapped to different points in the phenomenological space. This is due to individual differences between practitioners in the manner in which they interpret and instantiate instructions.

One aim of the Brain & Mindfulness project is to implement this heuristic model and to empirically test some of its assumptions. For instance, can we use self-report scales to reliably measure and monitor consistent changes in these features in response to

Table 1

The seven phenomenological dimensions proposed in Lutz et al. (2015). Although primary dimensions are presented in an orthogonal Euclidean space, they can vary independently from one another. Within this multidimensional space, secondary dimensions represent features dependent on specific mental states and level of expertise. In addition, the model assumes four general features that are common across the family of practices associated to mindfulness, that are physical posture, non-aversive affect, axiological framework, and task-set maintenance. These common general features are necessary elements of mindfulness practice, but they are not explicitly depicted in the model because they are less significant in distinguishing styles of practice. In the present manuscript, these general features will not be explicitly discussed, even if they were measured during the experimental settings. For instance, we measure non-aversive affect dimension during a nociceptive paradigm, and we interviewed after this paradigm the participants about the relationship between pain and their worldview.

Primary dimensions	Secondary dimensions
Object orientation Sense that a mental state is oriented towards some object or class of objects (e.g. perceptions, emotions)	Aperture Broadness of the scope of attention
Dereification Degree to which mental phenomena are experienced as mental processes rather than accurate depictions of reality	Clarity Degree of vividness of the experience
Meta-Awareness Extent to which the experience is under monitoring	Stability Degree to which experience presents itself as enduring over time
	Effort Impression that one’s present mental state is easy or difficult to maintain

different meditation instructions and training, congruent with the hypothetical plots previously published?

1.2. Epistemological limitations: Reliability of self-report data

A second methodological aim arises from the first one: are the empirically-obtained plots of the different styles and levels of expertise reliable in this phenomenological space?

1.2.1. The reliability of self-reports

The perceived demise of early twentieth century introspectionism (Costall, 2006) and the seminal review by Nisbett and Wilson (1977) questioned the ability of the participants to report the real causes of their behavior. Since then, introspective-like methods have been looked upon with distrust by many in the fields of psychology and cognitive science. Contrastingly, others have warned against drawing general conclusions from these failures. For example, Hurlburt and Heavey (2001) have criticized how Nisbett and Wilson's work has been carelessly taken as “an unconditional refutation of introspection in general, not merely of the attribution of causation”, thus ignoring that “even Nisbett and Wilson recognized the possibility of accurate reports about inner experience” (Hurlburt & Heavey, 2001, p.401).

Devising ways to detect and/or limit the diverse types of self-reports distortions is an active field of methodological research. For example, self-administered questionnaires have long included validity scales designed to this effect (Baer, Rinaldo, & Berry, 2003). More recently, there has been a renewed interest for ‘first-person methods’ to study consciousness (see the three special issues of the *Journal of Consciousness Studies* on this question: Jack and Roepstorff, 2003, 2004; Hasenkamp & Thompson, 2013). First-person methods refer to methods that allow an investigator to bring a participant close to their subjective experience¹ (Petitmengin, 2006), as well as to practices that subjects themselves can use to increase their sensitivity to their own experiences (Bitbol & Petitmengin, 2013; Depraz, Varela, & Vermersch, 2003; Petitmengin, Remillieux, Cahour, & Carter-Thomas, 2013; Varela & Shear, 1999).

Meditation training has been proposed as a pragmatic response to this challenge due to its disciplined approach to examining experience. Approaching experience from this perspective allows for the refinement of first person categories' repertoire and strengthen the robustness of the relationship between first and third-person data (Varela, 1996). However, this hypothesis remains to be thoroughly tested. Current available evidence includes the improvement of the congruence between implicit and explicit measures of self-views after brief mindfulness exercises (see Strick & Papiés, 2017 for a study on affiliation motives and goals, and Koole, Govorun, Cheng, & Gallucci, 2009 for a study on self-esteem). In contrast, measures of interoceptive awareness based on heartbeat perception in experienced meditators have yielded mixed and contradictory results (Bornemann & Singer, 2017; Khalsa et al., 2008; Melloni et al., 2013). The inconclusiveness of these studies may be due to a lack of methodological validity (Zamariola, Maurage, Luminet, & Corneille, 2018), discrepancies in the experimental designs and/or in the extent of bodily focus in participants' meditation practice.

1.2.2. Demand characteristics and desirable responding

In the context of phenomenological research on self-induced mental states (such as in meditation research), demand characteristics is a major source of confound that undermines the credibility of self-reports. *Demand characteristics* refer to “the totality of cues which convey an experimental hypothesis to the subject[s]” and which consequently “become significant determinants of subjects' behavior” (Orne, 1962, p.779). Participants volunteering for scientific experiments have various motivations that may, consciously or unconsciously, incite them to play the role of the good participant and try to serve the experiment by producing the data that they think will confirm the (presumed) research hypothesis. To attenuate the confounding effects of demand characteristics, researchers commonly resort to the concealment of – if not the deception about – hypotheses, manipulations, dependent measures and independent variables. Another source of distortion of a participant's behavior is his/her wish to present herself favorably to the experimenter, who may be perceived as an evaluator. This so-called *social desirability* bias is related to the effect of demand characteristics, but not identical to it (Weber & Cook, 1972). To eliminate this confound, some researchers advocate the use of scales developed to capture individuals' inclination to self-enhancement (Crowne & Marlowe, 1960; Paulhus, 1984), as covariates in the models assessing the effects of interest.

In the phenomenological study of meditation, demand characteristics lurk in the large overlap between the semantics of meditation instructions taught or familiar to the participants, and the phrasing of self-report scales aimed at measuring the phenomenological dimensions of interest (e.g. terms such as present-centered and nonjudgmental, see Van Dam et al., 2012). Consequently, the magnitude of self-reported phenomenological features of meditation remain overshadowed by doubt, even when shown to be highly specific (see for example Kok & Singer, 2017). Unfortunately, the usual concealment strategies can hardly be applied in this context, considering that participants are necessarily aware of the manipulation in so far as they are asked to implement it through the practice of meditation.

This is not to say that all self-report results from meditation studies are inexorably confounded by the effect of demand characteristics. Even when demand characteristics are difficult to attenuate, one can look for evidence that supports an interpretation of the effect beyond their impact. In this study, we adopt a strategy of comparing certain factors (which are unaffected by demand characteristics or desirable responding) with self-reporting effects. We will illustrate this general approach in two ways: (i) within-subject, by testing whether fluctuations of phenomenological self-reports correlate with relevant behavioral measures, and (ii) across

¹ Such techniques were sometimes dubbed ‘second person’ methods, because they rely on the critical interventions of an interviewer.

subjects, by testing whether participants' amount and structure of daily practice predict the self-reported effects on phenomenological dimensions.

1.3. Methodological issue: quality active control group

A critical effort of the *Brain & Mindfulness* project was to refine the matching between the control group and expert meditators. This was done primarily by training novices in different styles of meditation practice and by familiarizing them to different phenomenological categories of interest. A prominent issue in the field of neuroscientific studies on mindfulness meditation is the relative paucity of high quality active control (Goldberg et al., 2017). This issue has been repeatedly raised and suggestions of improvement have been discussed in the context of longitudinal studies (Davidson & Kaszniak, 2015; Kuyken et al., 2016). However, cross-sectional studies with long term practitioners have received less methodological attention. In such studies, an active control group is often lacking or too basic when present. Of the nineteen independent cross-sectional studies on the neurofunctional effects of long term meditation in a recent meta-analysis (Fox et al., 2016), only seven included an active control.² In six of these studies, meditation-naive participants received written and/or oral instructions and were encouraged to sustain a daily practice for 7 to 10 days until the moment of the experiment. In the remaining study, participants received a brief training session by an experienced teacher on the day of the experiment (Kalyani et al., 2011). These approaches, while clearly better than not including an active control group, have several limitations. First, limited possibility for feedback or the lack of guidance by an experienced and qualified instructor induces a high risk of misinterpretations and inadequate implementations of the practices. Second, the short duration of the training limits the opportunities to engage with the practice. Here we addresses some of these issues by: (1) formally training meditation-naive participants in practices from the same meditation background as the long-term practitioners, (2) letting this training be provided by a qualified instructor in a context with attention to sufficient opportunity for guided practice and feedback, and (3) encouraging participants to maintain a daily practice at home for a minimum of 20 min a day for an extended duration (6–22 weeks depending on the availability of participants and experimental resources). We contend that these adaptations make it more likely for participants to reach a refined understanding of the various practices and experiential dimensions at hand. This training has the potential of reducing the risk that any group differences are merely driven by confounding factors (e.g. misunderstanding practices and/or unfamiliarity with meditation terminology for novices but not experts), instead of reflecting the true effect of interest, i.e. meditation expertise.

We will first report the specifics of our meditation training protocol. Then we will provide empirical evidence for its effectiveness in teaching meditation-naive participants to use first-person categories to describe their conscious experience and discriminate between phenomenological dimensions.

2. Methods

2.1. Participants

The first stage of the research included a meditation training weekend comprising of 42 healthy participants naive to meditation. These individuals were recruited for their interest to learn meditation and their willingness to sustain a regular practice for several months. After a preliminary inclusion procedure (see study manual for details, Abdoun et al., 2018), participants were invited to attend a weekend-long training program in the Lyon Neuroscience Research Center. The program looked to support participants in developing a refined understanding of the states of consciousness involved in the following experimental study.

The expert group was comprised of 30 healthy long-term practitioners with more than 10,000 h of formal meditation in their life and trained in the Kagyü and Nyingma schools of Tibetan Buddhism.

Both novices and experts participated in up to 8 experimental sessions (see study manual for details, Abdoun et al., 2018). For expert participants, these experimental sessions were gathered in 2 visits of 3 days, or a single visit of 6 days. For novice participants, each visit comprised 1 or 2 experimental sessions, and the visits were spread over a period spanning from 2 to 23 weeks after the training weekend. Visits were scheduled according to participants' and equipment (MRI, MEG, EEG) availabilities, leading to a large but quasi-random variability across the novice group in time elapsed between the training and the experiment.

Among all participants, 25 trained novice practitioners and 25 expert practitioners participated in the MEG experiment described below. The remaining participants included in the larger study were excluded for the MEG experiment because of excessive signal artifacts caused by dental prostheses. The novice and expert groups for the MEG experiment did not differ in gender (16 and 15 males, respectively; $\chi^2(1) = 0.08$), age (53.9 ± 7.1 and 51.6 ± 8.0 years, respectively; independent t -tests $t = 0.84$) and education (3.88 ± 2.15 and 3.20 ± 2.16 years of higher education, respectively; independent t -tests $t = 0.46$).

2.2. Meditation training protocol

2.2.1. General outline

The training protocol was based on *Joy of Living* (Rinpoche & Swanson, 2007; Tergar, 2018), a secular meditation program aimed at Western audiences authored by Yongey Mingyur Rinpoche, a renowned master of Karma Kagyü and Nyingma schools of Tibetan

² One study by Lutz et al. (2009) included samples from two other studies in the meta-analysis and was not taken into account. We excluded studies on yoga and chanting.

Table 2
Program of the training weekend.

DAY 1	DAY 2
11:00 – 12:00 Effort in perception and attention (<i>on a sound</i>) Absorption vs. Meditative awareness (<i>introduction</i>)	9:30 – 10:30 Meditative awareness BREAK
12:00 – 13:00 Absorption vs. Meditative awareness (<i>on the breath</i>) BREAK	10:45 – 12:30 Group discussion Empathy vs. Compassion (<i>introduction</i>) BREAK
14:30 – 15:30 Absorption vs. Meditative awareness (<i>on the breath</i>) BREAK	14:00 – 15:45 Focused Attention & Open Monitoring (<i>on pain</i>) Empathy vs. Compassion (<i>images</i>) BREAK
16:30 – 17:30 Focused Attention & Open Monitoring Object orientation & Aperture Background & Foreground	16:00 – 17:00 Closing meditation (intention to practice) Presentation of the research project Instructions for home practice

Buddhism. This program was selected for its shared background with experts' training. In its original format, the program is divided into three stages, each lasting two days; in addition, there are minimal practice requirements to attend stages 2 and 3. For our training protocol, we drew from the material of stages 1 and 2, condensing them in a two-day format, and included adaptations to emphasize the specific dimensions of experience of interest to the research program.

The training was provided by a qualified instructor with thirteen years of practice under the guidance of Mingyur Rinpoche, and eight years of teaching experience with the *Joy of Living* program. The training included teachings with the support of instruction videos, guided meditations and experiential exercises, question and answer sessions, as well as sufficient time to reflect and share within the group.

The training allowed a basic understanding of a few selected phenomenological dimensions eligible for an active comparison with expert practitioners. In particular, the program introduced participants to the following dimensions: effort, aperture, absorption vs. meditative awareness, foreground vs. background awareness, equanimity, clarity (see [Table 1](#) and [supplementary materials](#)). The discernment of these dimensions was implemented by introducing the lived phenomenology of these states and creating occasions for a direct exploration of them. To access both the experience and the meaning of meditation the teacher devised specific exercises with connected theoretical principles. As a sommelier apprentice does in tasting, savoring, comparing and sampling different wines under the guidance of a sommelier, participants were invited to learn, practice and distinguish few states of consciousness under the guidance of a meditation teacher in order to become progressively familiar with some meditative phenomenological dimensions commonly described in contemplative traditions.

The training followed a specific day program ([Table 2](#)) which will be briefly described here.

In **day 1**, participants were first introduced to the notion of mental '*effort*' in meditation through an experiential exercise that involved listening to sounds. The rest of the day was spent exploring the concepts of '*absorption and meditative awareness*'. This exercise was done first by using the breath as an anchor for meditative awareness. Participants were asked to restrict their attention to the breath, to notice when their mind had wandered, and to return their attention to the breath when this happened. Later during the day, they were also asked to gradually explore more open forms of awareness, by opening up to sense experiences from the environment (e.g. sounds and vision). While doing so, participants also engaged in two other experiential exercises that introduced the concepts of '*object orientation and aperture*' and '*foreground and background awareness*'.

At the beginning of **day 2**, participants continued to explore meditative awareness of the environment with various exercises including a walking meditation in open awareness. Then the instructor asked participants to form small groups and share their personal experience of the weekend. After some time, the small groups gathered to share collectively the problems and difficulties which had emerged, so that the teacher could provide adequate feedback. Then the concepts of '*empathy and compassion*' were introduced and the teacher asked participants to briefly cultivate feelings of self-compassion. After lunch, participants engaged in an exercise that involved switching between focused attention on, and open monitoring of, pain. The rest of the afternoon was spent further elucidating concepts of empathy and compassion, including an experiential exercise that presented images of people's suffering to participants. Finally, during the closing meditation session, the importance of the intention to practice was discussed and emphasized. Participants were asked to fully engage in their own practice.

2.2.2. Experiential exercises

Throughout the training weekend, subjects were prompted to familiarize themselves with the dimensions of subjective experience that were going to be of interest in the neuroscientific experiments. This familiarization was carried out by using experiential exercises. During each exercise, a dimension or process was introduced in a more or less explicit form. Some dimensions were experienced and described in the context of guided meditation sessions and teachings, while other exercises were implemented with

the specific aim of familiarizing subjects with a phenomenological dimension. We refer the reader to the [Supplementary Materials](#) for a full description of these exercises.

At the end of the weekend, subjects received a document that briefly described each phenomenological dimension and reminded them how it was introduced by corresponding exercises during the weekend.

2.2.3. Compliance and engagement with practice

The minimal goal of the training weekend was to give novice participants sufficient understanding and confidence to carry on practice autonomously, thus deepening their familiarity with the practices under study.

At the end of the weekend, participants received an explanation of what was expected of them in terms of homework practice. Participants were advised to practice for 20–30 min on a daily basis and to give equal importance to each of the three practices they had learned. In addition, they were asked to report the type and amount of practice in a practice logbook that was provided at the end of the meditation training weekend. In order to ensure truthful reports, participants were assured that non-compliance to these recommendations would not call into question their participation to the study.

Participants were provided with three 15 min-long audio recordings of guided meditations by their instructor to aid their practice (one recording for each of the three meditative practices). However, they were strongly encouraged to avoid relying exclusively on them and to get used to meditating unguided. Participants were also given excerpts from the book *Joy of Living*, summarizing most of the teachings received during the weekend: the physical posture, the mental attitude, as well as various meditative and experiential exercises examined during the weekend (Rinpoche & Swanson, 2007).

2.3. Practice metrics

Four metrics were used to assess participants' home practice and degree of engagement: the proportion of days involving practice (hereafter referred to as *Frequency of practice* or simply *Frequency*); the average amount of practice during days with practice (hereafter, *Session length*); the daily average amount of practice, all days included (*Intensity of practice* or simply *Intensity*); and the total amount of practice (*Experience*).³ Fig. 1 describes how these four metrics relate to each other and how they were derived from the data contained in the practice logbooks. These metrics were also explored in relation to phenomenological ratings and behavioral measures from the experiments.

In addition, we calculated an index of balance between focus and open styles of practice, the Focus/Open Balance Index (hereafter referred to as FOB) for each participant. FOB is defined as the absolute difference between OM practice and FA practice, normalized by the sum of the two⁴:

$$1 - \frac{|practice(FA) - practice(OM)|}{practice(FA + OM)}$$

2.4. Protocol of the MEG experiment

One major purpose of the meditation course undertaken by novice participants was to train them in using phenomenological categories of interest in the study. In order to validate that they understood these categories as intended and used them appropriately, we analyzed the self-report data from a magnetoencephalographic (MEG) experiment with a hierarchical repeated measure design that included several periods of FA and OM meditations, along with a control (resting-state, RS) period (Fig. 2).

The experiment started with a staircase visual threshold calibration for a visual task whose detailed procedure and results are irrelevant for the present article but will be described in another publication. Following the calibration, we recorded a 7 min baseline period. Then, participants practiced FA and OM twice each, in sequences of approximately 24 min (Fig. 2a). Each sequence opened with a 7 min-long block of meditation only, during which participants were presented with a 1.5°-wide white dot in the middle of a black screen (Fig. 2b). The instruction was to keep the gaze steady on the white dot; in FA, participants were additionally instructed to use that disk as a support for the attention. This first block was followed by three blocks lasting approximately 5.5 min each, during which participants were instructed to maintain the meditative state while performing a simple visual conscious report task using a threshold stimulus embedded in a passive visual oddball paradigm (Fig. 2c). After each block, participants were invited to rate their experience over 6 different dimensions, using a 7-point Likert-type item (Fig. 2d): *Capacity* to apply the meditation instructions, *Stability* of the mind, *Clarity* of the mind, *Aperture* of the field of awareness (see table 1 for definitions), *Awareness of bodily sensations*, and *Wakefulness*. Here we will limit our analysis to the dimensions featured in the phenomenological matrix: *Stability*, *Clarity* and *Aperture*.⁵ Rating scales were thus introduced: “Compared to your usual experience, how would you rate the last block in terms of *Stability/Clarity/Aperture*?”

³ Capitals are used to distinguish these terms from their common definitions.

⁴ Note that for the calculation of FOB, using *Intensity* or *Experience* as measures of practice produce exactly the same result because, for each participant, *Intensity* is equal to *Experience* divided by a time factor (the number of days between the training week-end and the experiment). This factor would be cancelled out in the ratio present in the formula of FOB.

⁵ Just like for practice metrics, capitals are used for phenomenological dimensions to distinguish the terms from their common definitions.

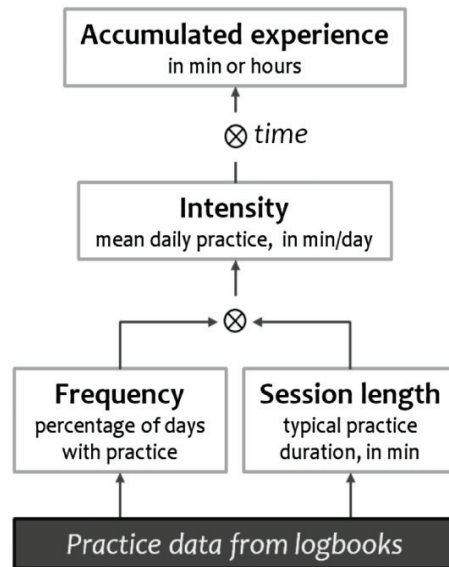


Fig. 1. Four interrelated metrics were used to assess commitment to home practice.

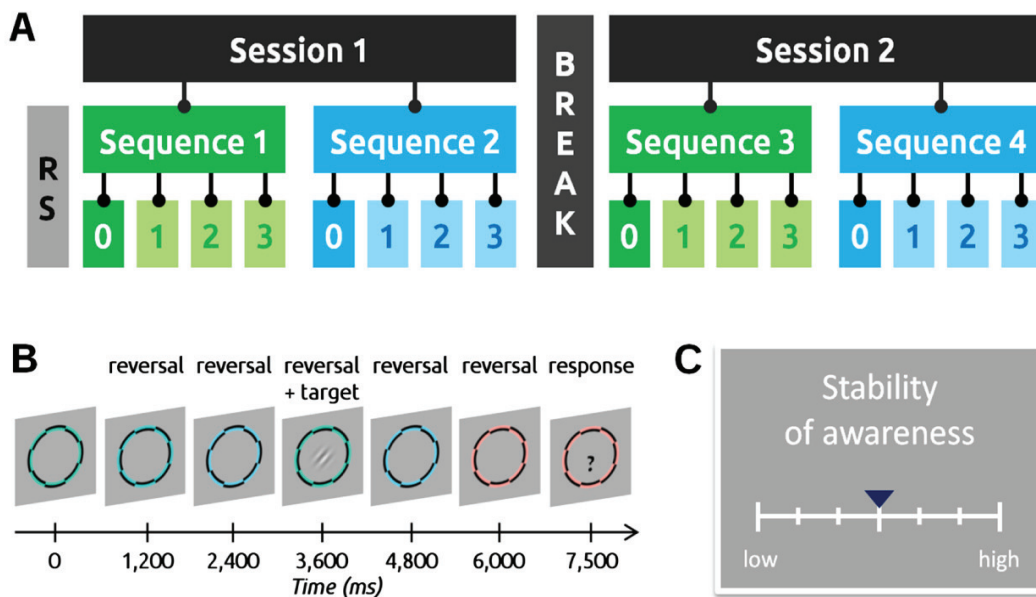


Fig. 2. The neurophenomenological experiment MIMOSA, the self-report data of which is used in the current article. **A.** Hierarchical structure of the experiment. After an initial resting state period (RS), the experiment was divided into 2 sessions, with a 5–20 min break in between. Each session was divided into 2 sequences: one of FA (focused attention) and one of OM (open monitoring), presented in a randomized order. Therefore, there were 4 different combinations for the state order across the experiment: FA-OM-FA-OM (illustrated here), OM-FA-OM-FA, FA-OM-OM-FA, OM-FA-FA-OM; state order was counterbalanced across each group of participants. Each sequence consisted of 4 blocks: a first 7 min block of “meditation only” (block 0) followed by three ~6 min long blocks of “meditation + task” with dynamic stimuli (blocks 1-2-3). During the “meditation only”, a white disk was displayed on a black background and participants were instructed to either use it as a support of their attention (in the case of FA) or to maintain their gaze on it (in OM blocks). During subsequent blocks, participants had to maintain the state induced in block 0, while going through 41 trials of a visual conscious report task. **B.** One trial of the task. During the task, a black-and-colored checkerboard was continuously displayed at the center of the screen. Each trial consisted of a series of checkerboard reversals, the last color of which was systematically deviant from the previous ones of the series (passive color oddball paradigm). A trial lasted 3–7 reversals. In 36 of the 41 trials, a Gabor patch set at threshold contrast was flashed for 50 ms, any time between the second and the last reversal. At the end of the trial, a question mark prompted the participant to report whether they had consciously seen it or not. **C.** After each of the 17 blocks of the experiment, participants rated 6 different dimensions of their experience using a Likert item.

2.5. Statistical analyses

Statistical modeling and inference. ANOVAs were of type 2. Post hoc tests were performed using one- or two-sample *t*-tests, adjusted for family-wise multiple comparison using Tukey's honestly significant difference (HSD) method. One-sample and paired two-sample tests were performed using the non-parametric Wilcoxon signed rank test. Linear mixed models were fitted using maximum likelihood and significance of fixed effects were evaluated using the likelihood ratio test. All linear regressions were ordinary least square (OLS) regressions.

Correlation between scale ratings and variability of response times. Outlier trials were defined as trials for which response times were not within 3 standard deviations from the mean value, for each participant, state and response type (*yes/no*), and excluded. An index of RT variability was defined for each block as the standard deviation of RTs. Finally, we computed for each participant the Pearson correlation coefficient between Stability ratings and RT variability. We did the same with Clarity. Correlation coefficients were *z*-transformed for the purpose of statistical modeling and are noted *z* hereafter. The data from one subject was removed because it had no variance in the Clarity scale (the subject responded 6 in all blocks).

Model selection for multiple regression analyses. For each of the effects related to phenomenological rating scores, we considered several potential predictors: metrics of home practice (*Intensity*, *Experience* and the *balance* between focus and open styles of practice), and an index of desirable responding (the score to the Balanced Inventory of Desirable Responding, *BIDR*). Practice data was missing for one participant, who was therefore excluded from subsequent analyses. We used an information-based model selection to determine the most important predictors for our data (Burnham & Anderson, 2002). Model selection is well suited to multiple regression analysis when the number of predictors is high compared to the number of data points; in addition, it virtually guarantees that no potential effect of interest is missed, as long as it is included in the variable set. We performed model selection in 2 steps, using *glmulti* for R (Calcagno & de Mazancourt, 2010). Firstly, we fitted all possible models that contained a subset of the predictors mentioned above and their two-way interactions, and that satisfied the marginality constraint (i.e. included all interaction terms as main effects). We used the corrected Akaike information criteria (AICc) as a measure of the quality of fit, because it is well adapted to small sample sizes (Hurvich & Tsai, 1989). Secondly, we selected models that were within 2 information criteria (IC) units of the best fitting model (Burnham & Anderson, 2002) for further consideration. Detailed results of the model selection output are presented in the [Supplementary Materials](#). These include the *relative evidence weight*, a measure of relative importance of each term across the entire model space (Calcagno & de Mazancourt, 2010), comprised between 0 and 1.

3. Results

3.1. Structure of home practice

The total duration of participation to the entire study ranged from 41 to 163 days (99.4 ± 31.4 days) after the training weekend. Average daily practice (=Intensity) ranged from 1.3 to 30.5 min (15.9 ± 7.3 min; [supplementary Fig. 1a](#), top left), suggesting that many participants fell short of the recommended amount of practice (20 to 30 min a day). However, when average daily practice was calculated over the number of days with at least *some* practice (rather than *all* days), the obtained Session length was found to range from 14.0 to 33.1 min (21.2 ± 5.5 min; [supplementary Fig. 1a](#), bottom right). Participants dedicated $45.2 \pm 16.8\%$ of their practice time to OM (Open Monitoring), $33.4 \pm 17.5\%$ to FA (Focused Attention) and $21.4 \pm 9.8\%$ to CO (Compassion). A one-way repeated measure ANOVA revealed a significant difference between the proportion of time dedicated to the different practices ($F(2,80) = 16.95$, $p < .0001$, $\eta^2 = 0.30$). Post hoc paired *t*-tests revealed that all comparisons of pairs of practices were significant ([supplementary Fig. 1b](#)).

Intensity of practice decreased linearly over weeks ([supplementary Fig. 2a](#); $R_{\text{adj}}^2 = 0.87$, $p < .001$, $\beta = -0.44$, 95% CI $[-0.53, -0.35]$). A large portion of this drop (80.9%) is imputable to a sharp decline of Frequency of practice over weeks ([supplementary Fig. 2b](#); $R_{\text{adj}}^2 = 0.92$, $p < .001$, $\beta = -0.14$, 95% CI $[-0.16, -0.12]$). The remaining 19.1% is due to a slight shortening of practice sessions ([supplementary Fig. 2c](#); $R_{\text{adj}}^2 = 0.22$, $\beta = -0.10$, 95% CI $[-0.18, -0.01]$). Taken together, these results show that participants managed to follow the recommendation of 20-to-30 min-long practice sessions throughout the study, but failed to practice on a daily basis and were increasingly inclined to skip days.

3.2. Patterns in self-reports and relationships to practice

We tested three predictions that should be verified if the phenomenological self-reports are reliable. We examined whether the responses of the novices to the rating scales in the MEG experiment (i) were sensitive to the meditation state, in a way consistent with the known phenomenology of mindfulness practices (Lutz et al., 2015), (ii) exhibited classic temporal dynamics such as dose and fatigue effects, and (iii) were functionally informative, as would be suggested by correlations with behavioral measures.

In each instance, we tested whether desirable responding and/or features of participants' home practice predicted the effects observed on self-reports. The results are summarized in [Table 3](#).

3.2.1. Effect of states on self-reports

In the phenomenological model introduced in Lutz et al., 2015, Stability and Clarity are described as secondary qualities that are both increased when practicing either FA and OM (compared to mind-wandering), and even more so with expertise. In contrast, Aperture is hypothesized to increase specifically during the practice of OM.

Table 3

Summary of experimental results on self-reports of phenomenological dimensions during meditation states. All reported effects (discrimination of states, fatigue and discrimination of phenomenological dimensions) were associated to specific aspects of participants' home practice. The importance of desirable responding score as a predictor was never higher than practice. DV: dependent variable; DC: demand characteristics; BIDR: Balanced Inventory of Desirable Responding; FA: focused attention; OM: open monitoring; FOB: focus/open practice balance index; Stb: Stability; Clr: Clarity; Apr: Aperture; RTV: response time variability.

DV	Interpretation	Level of DC	Predictors' evidence across model space		
			BIDR	Practice	
$ap_{OM} - ap_{FA}$	Discrimination of states	strong	0.31	0.55	FOB × Experience
$\frac{stb_3 - stb_1}{2} + \frac{clr - clr_1}{2}$	Fatigue	moderate	0.40	0.74	Intensity _{focus}
$z_{RTV, stb} - z_{RTV, clr}$	Discrimination of phenomenological dimensions	none	0.23	0.84	Experience

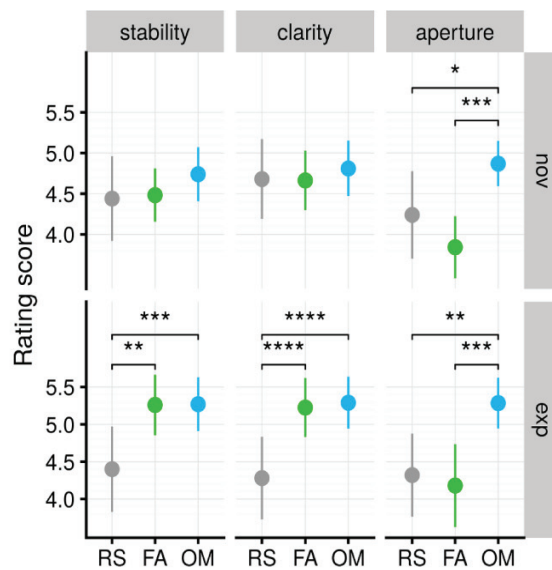


Fig. 3. Effects of meditation states on three dimensions of experience reported by the participants. Both novice and expert groups reported greater Aperture of the attentional field during OM compared to RS and FA. Experts also reported greater Stability and Clarity during meditation compared to RS, but not novices. All ratings were given on a scale ranging from 1 to 7. RS: resting-state; FA: focused attention; OM: open monitoring. Errors bars are 95% confidence intervals. Significance levels: *: $p < .05$; **: $p < .01$; ***: $p < .001$; ****: $p < .0001$.

In order to test this prediction, we modeled the ratings per scale using a two-way ANOVA model with *state* (RS, FA, OM) as a within-subject factor and *group* (novices, experts) as a between-subjects factor (Fig. 3). For Aperture, we found a main effect of state ($F(2,96) = 19.54, p < 0.001, \eta_G^2 = 0.15$). Post-hoc *t*-tests showed that there was no significant difference between RS and FA ($p > .32$), while Aperture was reported significantly higher in OM than in FA and RS ($p < .0001$). For both Stability and Clarity, a small-to-medium state-by-group interaction was found ($F(2,96) = 5.19, p = .007, \eta_G^2 = 0.027$, and $F(2,96) = 10.22, p < .001, \eta_G^2 = 0.045$, respectively). Further post-hoc *t*-tests showed that experts' ratings differed significantly in both dimensions between the control condition and each of the two meditation states (all $p < .0001$), but not between FA and OM (both $p > .92$). In contrast, there was no difference in neither Stability nor Clarity, across the 3 conditions, in the novice group (all $p > .24$). To summarize, participants' ratings corroborated the hypothesized phenomenological pattern in the expert group for all three secondary dimensions tested, but only for Aperture in novices.

3.2.2. Predictors of the state effect on Aperture

When participants are asked to rate the broadness of their attentional scope (i.e. Aperture) in two different meditation states referred to as “focus attention” and “open presence”, the fact that the expected response lies in the very names of the state conditions can hardly remain unnoticed. Thus, we cannot exclude the possibility that participants' responses were influenced by their willingness to please the experimenter, and/or to show that they have correctly understood the meditation instructions.

Another, non-trivial hypothesis is that novice participants develop the ability to differentiate a state of focus attention and a state of broader awareness by getting equally familiar with both attentional styles. Said otherwise, we expect participants who have had more practice in OM than in FA to have more ease opening (or more difficulty narrowing) their attentional scope than participants who have developed an equal familiarity of the two styles of practice. As a result, we would expect the latter to better differentiate FA and OM on the Aperture scale than the former. The same reasoning can be straightforwardly applied, *mutatis mutandis*, to participants

who favored FA over OM. We explored the plausibility of this hypothesis by testing whether our data were coherent with the ensuing predictions. We included an index of balance between FA and OM (FOB), along with other practice metrics (Intensity and Experience) and an index of desirable responding (BIDR) in the set of variables tested for model selection (see [Section Methods, Statistical analyses](#)).

Three models survived the model selection procedure: the best one included a significant FOB-by-Experience interaction (model A1), while the other two contained a significant FOB-by-Intensity interaction (models A2 and A3; see details in [supplementary Table 1](#)). BIDR was not present in any of these models, and its evidence across all models was found relatively low (0.31). The FOB-by-Experience interaction had a higher evidence across model space than the FOB-by-Intensity interaction (0.55 and 0.31, respectively). To illustrate how the balance between focus and open styles of practice interacts with the amount of practice, we performed a Johnson-Neyman post-hoc analysis of the interaction in model A1, using FOB as a predictor and Experience as a moderator. We found that for participants who had accumulated more than 23.9 h of practice, the FOB index positively predicts ($p < .05$) the self-reported difference in Aperture between FA and OM during the MEG experiment (see [supplementary Fig. 3](#)).

Considering that all our participants except one practiced OM more than FA at home, a higher FOB could have been entirely driven by FA practice in our dataset. Thus, the FOB-by-Experience interaction could actually hide an effect of Experience in FA only, which would lead to a very different interpretation of our results⁶. To test this alternative explanation, we fitted a model with Experience in FA as a single regressor, as well as a model that also included Intensity as a regressor. None of them was found significant ($p > .98$ and $p > .16$ respectively). We repeated this analysis with Experience in OM instead of FA – again, neither model was significant ($p > .84$ and $p > .22$, respectively).

To summarize, the results of our model selection analysis and post hoc tests are consistent with the hypothesis that equal familiarity with focus and open attentional states, rather than experience in any specific practice, drives the ability to differentiate between states.

3.2.3. Temporal dynamics

The absence of effect on self-reported Stability and Clarity in novices over the experiment does not necessarily rule out the possibility that novice participants used these categories appropriately and informatively. For example, averaging ratings over the entire experiment could have occluded temporal effects. This is indeed what we have observed in our data ([supplementary Fig. 4](#)). We used linear mixed models to account for the nested nature of the MEG experiment structure (blocks within sequences within sessions). The models included all possible interactions in fixed effects, as well as random subjects' intercepts and by-subject random slopes across blocks, sequences and sessions. We used two models: one for Stability ratings and one for Clarity ratings. In both models, we found an effect of block on ratings only for the first sequence of each session (i.e. sequences 1 and 3; cf. [Fig. 2](#); Stability: $\chi^2(3) = 8.58$, $p = .035$; Clarity: $\chi^2(3) = 7.85$, $p = .049$), suggesting that the middle break had some sort of resetting effect. Post-hoc pairwise *t*-tests revealed a significant decrease of ratings from blocks 1 to 3 in sequences 3 and 4 (Stability: $\Delta = 0.62$, 95% CI [0.19, 1.05], $p < .002$; Clarity: $\Delta = 0.43$, 95% CI [0.09, 0.77], $p < .007$; all other $p > .1$), but no pairwise differences in other sequences (all $p > .5$).

3.2.4. Predictors of the fatigue effect

The decrease of self-reported Stability and Clarity in novices after four blocks (~24 min) of meditation may reflect fatigue. This is not surprising considering that most novices were not used to meditating for more than approximately 20 min during their daily home practice (see [supplementary Fig. 1a](#)). A corollary of this interpretation is that the longer and more frequently the participants were used to meditate, the less likely they should be to experience fatigue in the context of the experiment. We tested this prediction by modeling a fatigue index, defined for each participant as the difference between their ratings in block 3 and block 1 of sequence 1,⁷ averaged over the dimensions of Stability and Clarity. Five models were selected ([supplementary Table 2](#)). Intensity was present in 2 of them as a main effect, and in 2 others in interaction with BIDR. Surprisingly, FOB was present as a main effect in 4 out of the 5 selected models. Across all models, FOB and Intensity had the highest relative weighted evidence (0.74 and 0.66, respectively) closely followed by BIDR (0.60).

The fact that FOB was found as important as Intensity suggests that the mitigating effect of practice Intensity on Fatigue is driven by the level of engagement in a specific style of practice. To explore this idea, we performed a second model selection where we replaced Intensity and FOB by the two subcomponents of Intensity: Intensity_{FA} and Intensity_{OM}, corresponding to the two styles of practice. For the sake of parsimony, we also removed Experience, which was already found to be of low importance. The only selected model from this new variable space had a single regressor, Intensity_{FA} ($p = .034$, $\beta = 0.085$, 95% CI [0.007, 0.162]; [supplementary Table 3](#)).

3.2.5. Correlation with behavioral measures

Previous studies have reported intra-individual variability of performance (most notably response times) as a good predictor of whether the participant is on-task at a given moment or not ([Bastian & Sackur, 2013](#); [Seli, Cheyne, & Smilek, 2013](#)). Based on this literature, we predicted that self-reported Stability, but not other dimensions, would be significantly correlated to variability of response times at the level of individual participants. We chose Clarity as a control dimension, for its similar pattern of sensitivity to

⁶ We thank an anonymous reviewer for suggesting this alternative interpretation.

⁷ The same analysis based on combined data from sequences 1 and 3 leads to the same conclusions.

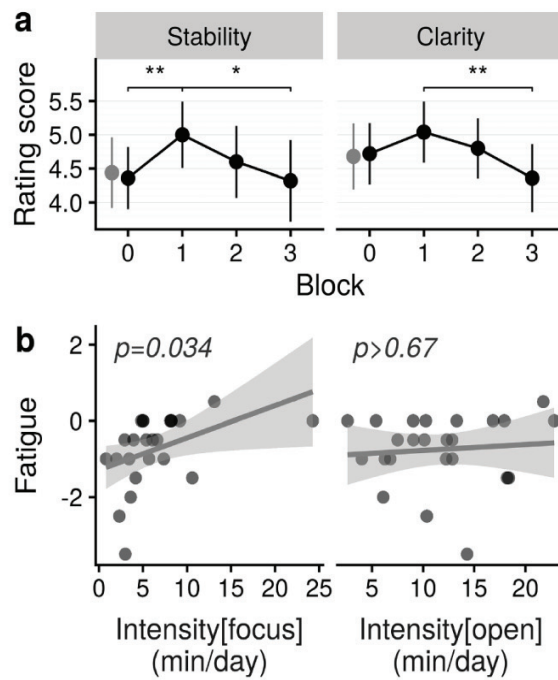


Fig. 4. Evolution of self-reported Stability and Clarity in novices during the four blocks of the first meditation sequence. (a) There was a two-stage temporal pattern; namely, a boost of Stability from block 0 to block 1 ($\Delta = 0.64$, 95% CI [0.03, 1.25], $p = .036$), followed by fatigue in subsequent blocks (Stability: $\Delta = -0.68$, 95% CI [-1.29, -0.07], $p = .023$; Clarity: $\Delta = -0.68$, 95% CI [-1.20, -0.16], $p = .005$). Ratings of the RS block are indicated in grey next to block 0. (b) This fatigue effect was reduced in those novices who engaged the most in focus (left) but not in open (right) styles of meditation. Errors bars are 95% confidence intervals. Significance levels: *: $p < .05$; **: $p < .01$.

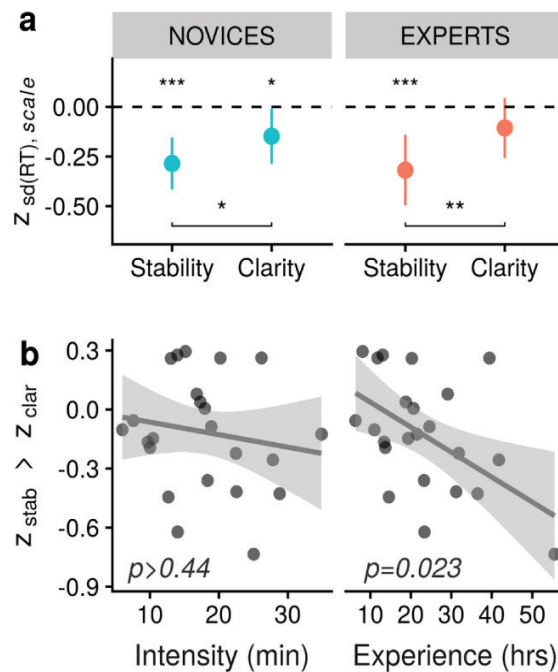


Fig. 5. Self-reports from novices appear to be functionally relevant. (a) The variability of response time correlates negatively with self-reported stability. In novice participants, it also correlates negatively with clarity, but significantly less so, indicating that these two dimensions are properly differentiated by novices. (b) Functional differentiation of stability and clarity was higher in those novice participants with the highest amount of practice (right), while intensity of practice was not a reliable predictor (left). Errors bars are 95% confidence intervals. Significance levels: *: $p < .05$; **: $p < .01$; ***: $p < .001$.

state and group (see Fig. 3).

One sample Wilcoxon signed rank tests of z-transformed within-subject Pearson correlation coefficients against zero show that the RT variability correlated negatively with Stability ($z = -0.26$, 95% CI $[-0.40, -0.12]$, $p < .0003$) as expected, but also with Clarity ($z = -0.14$, 95% CI $[-0.28, -0.003]$, $p = .046$) (Fig. 5a, left). However, a two-sample paired test between $z_{\text{stability}}$ and z_{clarity} was found significant ($p = 0.041$). Thus, even though self-reported ratings of Stability and Clarity were strongly correlated within subjects (Wilcoxon signed rank test on z-transformed correlation coefficients: $z = 0.77$, 95%CI $[0.62, 0.94]$, $p < .0001$), the association with RT variability was significantly stronger for Stability than for Clarity. This suggests that although the phenomenological dimensions of Stability and Clarity tend to fluctuate naturally together, novices are able to differentiate them functionally in their reports, just like experts (Fig. 5a, right). In order to further assess the specificity of these findings, we repeated the same analysis using mean RT (instead of RT variability). We found that neither Stability nor Clarity correlated significantly with mean RT (both $p > 0.1$).

3.2.6. Predictors of the phenomenological specificity

Based on these results, we further hypothesized that this fine differentiation could have been implicitly trained in our novice group through the practice of meditation. Indeed, the reflexive quality cultivated in contemplative practices is expected to improve one's familiarity with the specific phenomenal characteristics of different experiential dimensions. To test this prediction, we defined an index of phenomenological specificity as the difference between z_{stab} , the z-transformed Pearson correlation coefficient between Stability ratings and RT variability, and z_{clar} , the analogue measure for Clarity ratings. Only one model survived selection (supplementary Table 4), and it contained a single regressor, Experience ($p = .023$, $\beta = -0.011$, 95% CI $[-0.021, -0.002]$; Fig. 5b). Across all models, Experience had by far the highest evidence weight (0.84).

Following the suggestion of a reviewer, we further explored whether Experience in *particular practices* drove phenomenological specificity. We performed a second model selection using the amount of Experience in each practice (FA, OM and CO) and the 2-way interactions between these 3 variables (to model for potential synergies between practices). Three models were selected from this new variable space (supplementary Table 5). All of them included Experience_{OM} as a regressor but no interactions whatsoever. Experience_{OM} had by far the highest evidence weight (0.91), while Experience_{FA} and Experience_{CO} were on par (0.44 and 0.49 respectively).

4. Discussion

We described a meditation training protocol intended for naive candidates with no prior experience of meditation. We designed this protocol out of the need for a high-quality control group for a neurophenomenological study on the effects of meditation state and expertise in meditation on brain, behavior and physiology. The aim of the training was twofold: (1) to provide participants with sufficient background knowledge and direct experience with three types of meditations so that they could sustain a regular practice for an extended period of time, and be comfortable to practice in the laboratory context for the experimental tasks of the study; (2) to establish a common ground of relevant phenomenological categories with the participants, in order to allow them to report their experience during meditation states reliably.

Overall we found evidence that the phenomenological training was successful in the sense that participants' self-reports: (i) were reliable and sensitive to the meditation state manipulation, (ii) exhibited expected temporal dynamics such as dose and fatigue effects, and (iii) were functionally informative; in addition each of these effects was more strongly predicted by the amount and structure of participants' practice than by desirable responding as indexed by the BIDR questionnaire.

4.1. Motivation and compliance

In meditation research, motivation is often discussed for its potential confounding effect that limits the interpretability of longitudinal studies (Eberth & Sedlmeier, 2012). On the other hand, motivation of novice control participants can be considered a strength for the cross-sectional study of expertise as expert meditators, in so far as they dedicate a large amount of time and resources to their training and practice, are expected to have strong motivation. Our study was highly demanding for the novices, as they had to engage in daily practice and participate in 6 to 8 experimental sessions over the course of several months. This, along with the multi-step recruitment procedure, acted as a filter for motivation.

The high level of motivation of the novice participants was reflected in the satisfactory level of commitment to the practice maintained throughout their participation to the study. Three months after their training, they were still accomplishing more than half of the prescribed amount of practice, in the absence of any reminders or booster sessions. This even though they were assured that dropping the practice would remain without consequences for their participation to the study and financial compensation. This laxity given to participants, while having the effect of revealing their intrinsic motivation, is not without shortcomings. Compassion meditation, for example, was largely neglected. This might be related to the dense set-up of our initiation program, which attempted to train the participants in three different forms of meditation in just two consecutive days. In contrast, the original *Joy of living* program on which the training was based requires that practitioners first engage in 6 months of regular practice before they can receive teachings on compassion. However, this shortcoming has limited consequences for our study as the goal was primarily to get participants accustomed to the concept and practice of compassion and sensitize them to its difference with empathic resonance.

A large majority (75%) of participants favored the practice of OM at home. This may come as a surprise considering that in many Buddhist contemplative traditions, OM practices are considered more advanced and are approached only after some training in FA (Lutz et al., 2008). However, this bias towards OM is consistent with the deliberate stance adopted by Mingyur Rinpoche, author of

the *Joy of living* program, whereby one is invited to enter the field of open awareness from the outset.

4.2. Phenomenological proficiency

During their training, novice participants were introduced to phenomenological categories with the help of practical, experiential exercises. Using rating scales and behavioral data from one of the experiments to which they later participated, we have described three effects that can be interpreted as reflecting an effect of practice, phenomenal training, or both. Based on both *a priori* considerations and control for desirable responding, we have systematically assessed the potential confounding effect of demand characteristics and found limited support for it. We review the evidence (see also Table 3) and discuss other potential alternate interpretations below.

First, novice participants reported greater Aperture in OM compared to FA, just like experts, suggesting that they were able to distinguish the two practices. In addition, their responses on the Aperture scale was not driven by their diligence in any specific meditation style, but rather by the overall structure of their practice: the better they balanced focus and open styles of meditation, the larger the divergence in Aperture they reported (at least for participants who practiced the most: more than 24 h in total). This finding suggests that equal familiarity with different states is important for their optimal dissociation, at least at a beginner level. Future studies should test this hypothesis more rigorously using a longitudinal design with measures collected at baseline. Moreover, although we did not find any evidence for desirable responding in this data, we could not rule out the possibility that basic semantic priming inflated the reported dissociation in Aperture. Ideally, future training programs and experiments should try and avoid semantic overlap between meditation instructions and phenomenological dimensions altogether.

Second, self-reported Stability and Clarity had a two-stage dynamic during a series of 4 consecutive six-minute blocks of meditation, with a statistically significant decrease between the second and the last block. We interpret this phenomenon as a fatigue effect, rather than an effect of scale misuse. This is based on the observation that this decrease was negatively and specifically associated to participants' Intensity of practicing focus attention. Interestingly, this specific association is consistent with the role of concentrative practices in Buddhist contemplative traditions. These practices are used as training to stabilize attention and other basic qualities such as clarity and effortlessness, before applying them to more advanced practices. However, this correlation is not necessarily indicative of an effect of training: it may be mediated by an individual trait (e.g. conscientiousness or stamina), present even before the meditation training, that could predict both sustained diligence in the practice of (the relatively effortful) focus attention, and endurance during meditation sessions in the MEG experiment. Regardless, the index of desirable responding was of lesser importance in comparison.

Third, we showed that participants' ratings of the dimension Stability were functionally relevant, as they correlated with the variability of their response times. Using Clarity as a control dimension, we found that this functional relationship was specific. This finding suggests that participants were able to make fine distinctions between two close dimensions (this effect was true for both novice and expert practitioners). Regarding novices, we found that the more Experience they had at the day of the experiment, the sharper their phenomenological acuity. More specifically, we found that Experience in OM, compared to other practices, was the best predictor of this acuity. This is in line with the insight potential commonly attributed to OM-like practices in Buddhist contexts (Dahl, Lutz, & Davidson, 2015).

Here again, in the absence of longitudinal data, the correlation cannot be treated as direct evidence for a causal link involving learning. However, a noteworthy difference with the fatigue effect described above is that the practice metric that predicted phenomenological acuity (accumulated Experience) is not confounded with participants' assiduity, because it depends as much on Intensity of practice as on the time elapsed between the training weekend and the experiment (which was variable and random across the group). Considering that Intensity of practice did *not* predict phenomenological acuity, it appears that a likely explanation of these results is that novice participants became more familiar with the phenomenal richness of their experience throughout the regular practice of meditation, and more proficient in reporting it with specificity and subtlety.

Taken together, our data support the claim that the novices in our study had some phenomenological literacy, and were able to report about qualities of their experience in an appropriate, meaningful and informative way, even though in some cases we could not conclusively rule out the possibility for an *additional* effect of demand characteristics.

4.3. Training and practice

We have introduced several metrics of practice beyond the oft-used *total amount*. Although these metrics are derived from each other, they are not entirely collinear. In particular, our study was able to dissociate Experience (= total amount of practice) from Intensity (= daily average of practice) by having a large variability in the time elapsed between the training and the MEG experiment, across the novice group (from 27 to 133 days; $M = 79$, $SD = 29$). Moreover, we showed that these two metrics could be functionally dissociated when correlated with subjective ratings or behavioral measures. Such dissociations could point to potentially different mechanisms of trait changes brought about by the practice of meditation. This observation is consistent with the finding that intensive retreat practice, but not routine daily practice is associated with reliable differences in resting respiration rate in experienced meditators (Wielgosz, Schuyler, Lutz, & Davidson, 2016). It is also reminiscent of the work of Antonova, Chadwick, and Kumari (2015) who found that intensity of practice was a better predictor of decreased habituation to the acoustic startle reflex than total hours of practice. Future investigation of the mechanisms of meditation would benefit from a systematic exploration of various practice metrics and their relation to experimental outcomes, for both novice and expert practitioners.

What is the minimum amount of practice that should be required from novice participants for the quality of their

phenomenological self-reports to match those of experts', on the dimensions explored here? Based on our experimental results, we can provide tentative, rough estimates. In our samples of participants, 20–40 h were necessary for novices to reach a level of phenomenal specificity comparable to the one of experts; a minimum of 20 min of practice per day on average and a high balance between practices (no more than 40% bias) enabled novice participants to differentiate different styles of meditation as well as expert practitioners. All these criteria are much higher than what most past cross-sectional studies of meditation expertise have required from their control participants (Fox et al., 2016), but are sufficiently low to be practically accessible and implemented in future studies.

4.4. Self-rating scales

We used self-rating scales as tools to help participants translate qualities of their lived experience into quantities that can be manipulated, transformed and statistically analyzed just like any other numerical measure. Such tools raise vexed issues: for example, how can we know that participants use the scales as intended? How can we know that participants, or groups of participants, are not construing a given scale in widely different ways? How can we even be sure that a given participant is consistent in the way he/she uses a scale over time or across experimental conditions, for that matter? To take the example of stability of meditation states, we may argue that stability refers to qualitatively different experiences in FA and OM. In FA, stability reflects the sustained focus on a given object and therefore the stability of mental content. In contrast, OM stability reflects the absence of grasping and as such, should not be affected by variations in content.

Our approach of phenomenological training pragmatically addresses the issue of interpretation by mapping linguistic definitions of categories onto features of lived experience induced and revealed by simple experiential exercises. Performing these exercises in the context of a group, under the guidance of an instructor and with the possibility to share their understanding and reflect collectively, has the potential to attenuate idiosyncratic apprehensions of the phenomenological categories. In addition, concerns related to the subjectiveness and incommensurability of self-reported ratings were pragmatically addressed using within-subject designs and analyses.

Even if our results suggest that our methodological approach was effective in detecting phenomenological fluctuations, it is worth mentioning the low variance of our self-rating data. As an example, 41 out of 50 of our participants used only three values out of the seven available in the Stability and Clarity scales; for Clarity, 18 out of 50 participants used only two values. This suggests a limitation of our experimental design and/or our training program. For instance the relatively short duration of laboratory experiments may not be sufficient to experience large fluctuations in these dimensions. Finer rating scales could be used as a compensation to increase data variance. Another possibility is that our training program was insufficient in developing participants' fine-grained sensitivity to these scales. Further methodological work is needed to address these limitations.

4.5. Future directions

The role of meditation practice for cognitive science was extensively discussed by Varela et al. (1991), becoming a part of their 'enactive' approach and then of Varela's neurophenomenological program (Varela, 1996). We have provided preliminary evidence that meditation experience improves the reliability of self-report data by improving the functional specificity of self-reports, and by shielding them from the effect of demand characteristics. However, several questions remain open and should be addressed by future research.

First, the impact of training on the quality of first-person data should be more rigorously assessed using high-quality, longitudinal, randomized controlled trials. In particular, future work should tackle the open question of whether specific phenomenological training such as the one we implemented through experiential exercises is required to improve the quality of first-person data, or whether meditation practice is sufficient in itself.

In order to evaluate the confounding effect of demand characteristics on our first person-data, we have used an index of desirable responding. Unfortunately, the validity of the questionnaires designed for this purpose, including the one used in this study, has been frequently questioned as they are unable to distinguish between genuine personality traits and self-enhancement (Paulhus, 2002). Special attention should be given to more recent efforts to overcome these limitations using alternative and potentially complementary approaches (Kwan, John, Kenny, Bond, & Robins, 2004; Paulhus, Harms, Bruce, & Lysy, 2003).

We have provided evidence for reliable first person reports of the phenomenology of meditation experience. However, the generalizability of the phenomenal insight provided by meditation practice to other, non-meditation-related applications remains disputed (see Khalsa et al., 2008 for an example of negative result) and warrant more research.

Rather than provide a standardized, validated, ready for use protocol, our intention was to raise methodological concerns pertaining to the quality of control groups used in cross-sectional studies of meditation, and to argue for the possibility of obtaining informative experiential self-reports from adequately trained participants. Although we described in detail the protocol that we designed to address these issues, including the experiential exercises used for the phenomenological training of the participants, our approach is tailored to the specific context of our study, and to a particular phenomenological model of meditation among others (Bodhi, 2011; Lindahl, Fisher, Cooper, Rosen, & Britton, 2017; Van Dam et al., 2018). Still, we hope that the process, rather than the content, will inspire researchers in the field to further explore these critical issues.

Ethics

The entirety of the Brain & Mindfulness project, including the meditation training weekend and the MEG experiment, was approved by the local ethics committee (CPP Sud-Est III, authorization number 2015-A01472-47). All participants signed an informed consent prior to their participation to the meditation training.

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All the authors of the present paper declare no conflicting interests.

Appendix A. Supplementary material

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References

- Abdoun, O., Zorn, J., Fucci, E., Perraud, E., Aarts, K., & Lutz, A. (2018). Brain & Mindfulness project manual. OSF. Retrieved from <https://osf.io/dbwch/>.
- Antonova, E., Chadwick, P., & Kumari, V. (2015). More meditation, less habituation? The effect of mindfulness practice on the acoustic startle reflex. *PLOS ONE*, 10(5), e0123512. <https://doi.org/10.1371/journal.pone.0123512>.
- Baer, R. A., Rinaldo, J. C., & Berry, D. T. R. (2003). Self-report distortions (including faking, lying, malingering, social desirability). *Encyclopedia of Psychological Assessment: Vol. 1–2*, (pp. 862–866). London: SAGE Publications Ltd. <https://doi.org/10.4135/9780857025753>.
- Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. *Assessment*, 13(1), 27–45. <https://doi.org/10.1177/1073191105283504>.
- Bastian, M., & Sackur, J. (2013). Mind wandering at the fingertips: Automatic parsing of subjective states based on response time variability. *Perception Science*, 4, 573. <https://doi.org/10.3389/fpsyg.2013.00573>.
- Bitbol, M., & Petitmengin, C. (2013). On the possibility and reality of introspection. *Kairos. Revista de Filosofia & Ciência*, 6, 173–198.
- Bodhi, B. (2011). What does mindfulness really mean? A canonical perspective. *Contemporary Buddhism*, 12(1), 19–39. <https://doi.org/10.1080/14639947.2011.564813>.
- Bornemann, B., & Singer, T. (2017). Taking time to feel our body: Steady increases in heartbeat perception accuracy and decreases in alexithymia over 9 months of contemplative mental training. *Psychophysiology*, 54(3), 469–482. <https://doi.org/10.1111/psyp.12790>.
- Burnham, K. P., & Anderson, D. R. (2002). *Model selection and multimodel inference: A practical information-theoretic approach* (2nd ed.). New York: Springer-Verlag. www.springer.com/us/book/9780387953649.
- Calcagno, V., & de Mazancourt, C. (2010). glmulti: An R package for easy automated model selection with (generalized) linear models. *Journal of Statistical Software*, 34(12). <https://doi.org/10.18637/jss.v034.i12>.
- Chambers, R., Gullone, E., & Allen, N. B. (2009). Mindful emotion regulation: An integrative review. *Clinical Psychology Review*, 29(6), 560–572. <https://doi.org/10.1016/j.cpr.2009.06.005>.
- Costall, A. (2006). 'Introspectionism' and the mythical origins of scientific psychology. *Consciousness and Cognition*, 15(4), 634–654. <https://doi.org/10.1016/j.concog.2006.09.008>.
- Crowne, D. P., & Marlowe, D. (1960). A new scale of social desirability independent of psychopathology. *Journal of Consulting Psychology*, 24(4), 349–354. <https://doi.org/10.1037/h0047358>.
- Culadasa (Yates, J.), Immergut, M., & Graves, J. (2015). *The mind illuminated: A complete meditation guide integrating Buddhist wisdom and brain science for greater mindfulness*. Hay House.
- Dahl, C. J., Lutz, A., & Davidson, R. J. (2015). Reconstructing and deconstructing the self: Cognitive mechanisms in meditation practice. *Trends in Cognitive Sciences*. <https://doi.org/10.1016/j.tics.2015.07.001>.
- Davidson, R. J., & Kaszniak, A. W. (2015). Conceptual and methodological issues in research on mindfulness and meditation. *American Psychologist*, 70(7), 581–592. <https://doi.org/10.1037/a0039512>.
- Depraz, N., Varela, F., & Vermersch, P. (2003). *On becoming aware: A pragmatics of experiencing*. John Benjamins.
- Eberth, J., & Sedlmeier, P. (2012). The effects of mindfulness meditation: A meta-analysis. *Mindfulness*, 3(3), 174–189. <https://doi.org/10.1007/s12671-012-0101-x>.
- Fox, K. C. R., Dixon, M. L., Nijeboer, S., Girn, M., Floman, J. L., Lifshitz, M., ... Christoff, K. (2016). Functional neuroanatomy of meditation: A review and meta-analysis of 78 functional neuroimaging investigations. *Neuroscience & Biobehavioral Reviews*, 65, 208–228. <https://doi.org/10.1016/j.neubiorev.2016.03.021>.
- Goldberg, Simon B., Tucker, R. P., Greene, P. A., Simpson, T. L., Kearney, D. J., & Davidson, R. J. (2017). Is mindfulness research methodology improving over time? A systematic review. *PLOS ONE*, 12(10), e0187298. <https://doi.org/10.1371/journal.pone.0187298>.
- Goldberg, S. B., Wielgosz, J., Dahl, C., Schuyler, B., MacCoon, D. S., Rosenkranz, M., ... Davidson, R. J. (2016). Does the five facet mindfulness questionnaire measure what we think it does? Construct validity evidence from an active controlled randomized clinical trial. *Psychological Assessment*, 28(8), 1009–1014. <https://doi.org/10.1037/pas0000233>.
- Hasenkamp, W., & Thompson, E. (2013). Examining subjective experience: Advances in neurophenomenology. *Frontiers in Human Neuroscience*.
- Hölzel, B. K., Lazar, S. W., Gard, T., Schuman-Olivier, Z., Vago, D. R., & Ott, U. (2011). How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. *Perspectives on Psychological Science*, 6(6), 537–559. <https://doi.org/10.1177/1745691611419671>.
- Hurlburt, R. T., & Heavey, C. L. (2001). Telling what we know: Describing inner experience. *Trends in Cognitive Sciences*, 5(9), 400–403. [https://doi.org/10.1016/S1364-6613\(00\)01724-1](https://doi.org/10.1016/S1364-6613(00)01724-1).
- Hurvich, C. M., & Tsai, C.-L. (1989). Regression and time series model selection in small samples. *Biometrika*, 76(2), 297–307. <https://doi.org/10.2307/2336663>.
- Husserl, E. (1991). *On the phenomenology of the consciousness of internal time (1893–1917)*, 1991st ed. Kluwer Academic Publishers.
- Jack, A., & Roepstorff, A. (Eds.). (2003). *Journal of Consciousness Studies*.
- Jack, A., & Roepstorff, A. (Eds.). (2004). *Journal of Consciousness Studies*.
- Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical

- considerations and preliminary results. *General Hospital Psychiatry*, 4(1), 33–47. [https://doi.org/10.1016/0163-8343\(82\)90026-3](https://doi.org/10.1016/0163-8343(82)90026-3).
- Kabat-Zinn, J. (1994). *Wherever you go, there you are: Mindfulness meditation in everyday life*. Hyperion.
- Kalyani, B. G., Venkatasubramanian, G., Arasappa, R., Rao, N. P., Kalmady, S. V., Behere, R. V., ... Gangadhar, B. N. (2011). Neurohemodynamic correlates of “OM” chanting: A pilot functional magnetic resonance imaging study. *International Journal of Yoga*, 4(1), 3. <https://doi.org/10.4103/0973-6131.78171>.
- Khalsa, S. S., Rudrauf, D., Damasio, A. R., Davidson, R. J., Lutz, A., & Tranel, D. (2008). Interoceptive awareness in experienced meditators. *Psychophysiology*, 45(4), 671–677. <https://doi.org/10.1111/j.1469-8986.2008.00666.x>.
- Kok, B. E., & Singer, T. (2017). Phenomenological fingerprints of four meditations: Differential state changes in affect, mind-wandering, meta-cognition, and interoception before and after daily practice across 9 months of training. *Mindfulness*, 8(1), 218–231. <https://doi.org/10.1007/s12671-016-0594-9>.
- Koole, S. L., Govorun, O., Cheng, C. M., & Gallucci, M. (2009). Pulling yourself together: Meditation promotes congruence between implicit and explicit self-esteem. *Journal of Experimental Social Psychology*, 45(6), 1220–1226. <https://doi.org/10.1016/j.jesp.2009.05.018>.
- Kuyken, W., Warren, F. C., Taylor, R. S., Whalley, B., Crane, C., Bondolfi, G., ... Dalgleish, T. (2016). Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse: An individual patient data meta-analysis from randomized trials. *JAMA Psychiatry*, 73(6), 565–574. <https://doi.org/10.1001/jamapsychiatry.2016.0076>.
- Kwan, V. S. Y., John, O. P., Kenny, D. A., Bond, M. H., & Robins, R. W. (2004). Reconceptualizing individual differences in self-enhancement bias: An interpersonal approach. *Psychological Review*, 111(1), 94–110. <https://doi.org/10.1037/0033-295X.111.1.94>.
- Leigh, J., Bowen, S., & Marlatt, G. A. (2005). Spirituality, mindfulness and substance abuse. *Addictive Behaviors*, 30(7), 1335–1341. <https://doi.org/10.1016/j.addbeh.2005.01.010>.
- Lindahl, J. R., Fisher, N. E., Cooper, D. J., Rosen, R. K., & Britton, W. B. (2017). The varieties of contemplative experience: A mixed-methods study of meditation-related challenges in Western Buddhists. *PLOS ONE*, 12(5), e0176239. <https://doi.org/10.1371/journal.pone.0176239>.
- Lutz, A., Jha, A. P., Dunne, J. D., & Saron, C. D. (2015). Investigating the phenomenological matrix of mindfulness-related practices from a neurocognitive perspective. *American Psychologist*, 70(7), 632–658. <https://doi.org/10.1037/a0039585>.
- Lutz, A., Slagter, H. A., Dunne, J. D., & Davidson, R. J. (2008). Attention regulation and monitoring in meditation. *Trends in Cognitive Sciences*, 12(4), 163–169. <https://doi.org/10.1016/j.tics.2008.01.005>.
- Lutz, A., & Thompson, E. (2003). Neurophenomenology: Integrating subjective experience and brain dynamics in the neuroscience of consciousness. *Journal of Consciousness Studies*, 10(9–10), 31–52.
- Melloni, M., Sedeño, L., Couto, B., Reynoso, M., Gelormini, C., Favaloro, R., ... Ibanez, A. (2013). Preliminary evidence about the effects of meditation on interoceptive sensitivity and social cognition. *Behavioral and Brain Functions*, 9, 47. <https://doi.org/10.1186/1744-9081-9-47>.
- Nisbett, R. E., & Wilson, T. D. (1977). Telling more than we can know: Verbal reports on mental processes. *Psychological Review*, 84(3), 231–259. <https://doi.org/10.1037/0033-295X.84.3.231>.
- Orne, M. T. (1962). On the social psychology of the psychological experiment: With particular reference to demand characteristics and their implications. *American Psychologist*, 17(11), 776–783. <https://doi.org/10.1037/h0043424>.
- Paulhus, Delroy L. (1984). Two-component models of socially desirable responding. *Journal of Personality and Social Psychology*, 46(3), 598–609. <https://doi.org/10.1037/0022-3514.46.3.598>.
- Paulhus, D. L. (2002). Socially desirable responding: The evolution of a construct. In H. I. Braun, D. N. Jackson, & D. E. Wiley (Eds.). *The role of constructs in psychological and educational measurement* (pp. 61–84). Routledge.
- Paulhus, Delroy L., Harms, P. D., Bruce, M. N., & Lysy, D. C. (2003). The over-claiming technique: Measuring self-enhancement independent of ability. *Journal of Personality and Social Psychology*, 84(4), 890–904. <https://doi.org/10.1037/0022-3514.84.4.890>.
- Petitmengin, C. (2006). Describing one's subjective experience in the second person: An interview method for the science of consciousness. *Phenomenology and the Cognitive Sciences*, 5(3–4), 229–269. <https://doi.org/10.1007/s11097-006-9022-2>.
- Petitmengin, C., Remilieux, A., Cahour, B., & Carter-Thomas, S. (2013). A gap in Nisbett and Wilson's findings? A first-person access to our cognitive processes. *Consciousness and Cognition*, 22(2), 654–669. <https://doi.org/10.1016/j.concog.2013.02.004>.
- Rinpoche, Y. M., & Swanson, E. (2007). *The joy of living: Unlocking the secret and science of happiness*. New York: Harmony Books.
- Sauer, S., Walach, H., Schmidt, S., Hinterberger, T., Lynch, S., Büssing, A., & Kohls, N. (2013). Assessment of mindfulness: Review on state of the art. *Mindfulness*, 4(1), 3–17. <https://doi.org/10.1007/s12671-012-0122-5>.
- Seli, P., Cheyne, J. A., & Smilek, D. (2013). Wandering minds and wavering rhythms: Linking mind wandering and behavioral variability. *Journal of Experimental Psychology: Human Perception and Performance*, 39(1), 1–5. <https://doi.org/10.1037/a0030954>.
- Strick, M., & Papiés, E. K. (2017). A brief mindfulness exercise promotes the correspondence between the implicit affiliation motive and goal setting. *Personality and Social Psychology Bulletin*, 43(5), 623–637. <https://doi.org/10.1177/0146167217693611>.
- Tergar (n.d.). What is the joy of living? Retrieved July 21, 2018, from <https://tergar.org/programs/what-is-the-joy-of-living/>.
- Van Dam, N. T., Hobkirk, A. L., Danoff-Burg, S., & Earleywine, M. (2012). Mind your words: Positive and negative items create method effects on the five facet mindfulness questionnaire. *Assessment*, 19(2), 198–204. <https://doi.org/10.1177/1073191112438743>.
- Van Dam, N. T., van Vugt, M. K., Vago, D. R., Schmalzl, L., Saron, C. D., Olenzki, A., ... Meyer, D. E. (2018). Mind the hype: A critical evaluation and prescriptive agenda for research on mindfulness and meditation. *Perspectives on Psychological Science*, 13(1), 36–61. <https://doi.org/10.1177/1745691617709589>.
- Varela, F. J. (1996). Neurophenomenology: A methodological remedy for the hard problem. *Journal of Consciousness Studies*, 3(4), 330–349.
- Varela, F. J., & Shear, J. (1999). First-person methodologies: What, why, how. *Journal of Consciousness Studies*, 6(2–3), 1–14.
- Weber, S. J., & Cook, T. D. (1972). Subject effects in laboratory research: An examination of subject roles, demand characteristics, and valid inference. *Psychological Bulletin*, 77(4), 273–295. <https://doi.org/10.1037/h0032351>.
- Wielgosz, J., Schuyler, B. S., Lutz, A., & Davidson, R. J. (2016). Long-term mindfulness training is associated with reliable differences in resting respiration rate. *Scientific Reports*, 6, 27533. <https://doi.org/10.1038/srep27533>.
- Zamariola, G., Mauraage, P., Luminet, O., & Corneille, O. (2018). Interoceptive accuracy scores from the heartbeat counting task are problematic: Evidence from simple bivariate correlations. *Biological Psychology*, 137, 12–17. <https://doi.org/10.1016/j.biopsycho.2018.06.006>.

ANNEX III

Qualitative interviews of meditators reveal phenomenological fingerprints of pain regulation which predict self-reports during thermal pain stimulations

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Poletti S., Abdoun O., Zorn J., Lutz A.

Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR5292, Lyon 1 University,
Lyon, France

Abstract

Pain triggers different coping strategies modulated by psychological mechanisms, beliefs and expectations. Mindfulness meditation (MM) has shown to alleviate pain and mental suffering through different mechanisms such as positive reappraisal, attentional and emotional regulation. Yet, subjective experience and meaning of pain in connection with MM are still largely unexplored. The present mixed-methods study combined an interpretative-phenomenological qualitative approach with an experimental thermal pain paradigm to explore and compare the meaning of experiencing pain of 32 novices who received short meditation training and 30 experts in meditation practice (more than 10, 000 hours in life). We collected the qualitative data during in-depth semi-structured interviews where we probed participants' coping strategies. During the pain task, we collected self-reports relative to unpleasantness, avoidance, openness, vividness and blissfulness. Three phenomenological clusters (PhC) emerged from the interviews, which described pain as an unpleasant sensation requesting 1) experiential avoidance-suppression, 2) volitional agency-distancing, 3) or a positive cognitive reappraisal and flexibility. Two additional clusters (4-5), containing mostly expert meditators, thematized pain sensation as an opportunity to gain metacognitive insights about mental processes, and to deconstruct one's suffering through these insights. PhC 5 further integrates these insights with the recognition that suffering is part of the shared human experience and with the aspiration to relieve others from suffering. Each PhC was correlated to a unique profile of self-reports during the pain paradigm. These findings could inform clinical practices of MM. They also warrant the integration of this mixed-method approach with brain imaging data to refine the experiential neuroscience of pain.

PhC1 gathers metacodes characterized by cognitive monitoring and self-evaluative patterns. Participants provide a combination of pain catastrophizing and avoidant strategies. Intense pain is either eliminated or avoided through behavioral diverting activities. Participants in this cluster develop anticipatory worry that hinders the contact with the incoming sensation.

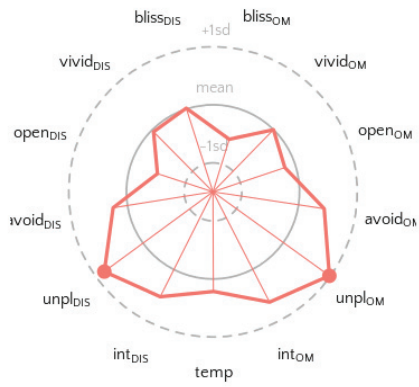
PhC2 gathers metacodes characterized by cognitive control marked by a pronounced sense of agency and self-efficacy towards pain based on self-distancing from the sensory level which immediately becomes peripheral. Cognitive control is reached by suppressing the sensation of pain at the bottom level, nipping it in the bud and cutting it off.

PhC3 gathers different ways to positively reappraise pain through metacognitive knowledge, providing short descriptions based on cognitive and emotional relativation. Without providing experience of intense pain, participants adjust their attitude cultivating cognitive flexibility and bodily awareness.

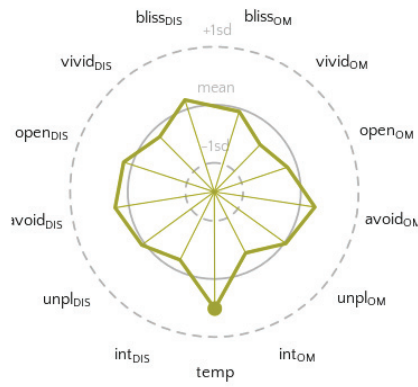
PhC4 deconstructs pain and related suffering through non-preferential metacognitive-awareness. Pain offers the opportunity to gain metacognitive insight about self and mental processes and to deconstruct one's suffering through these insights. Afflictive, reactive patterns are deconstructed, approaching pain with equanimity.

PhC5 integrates the previous deconstructive strategy with altruistic aspirations. Pain becomes an opportunity to integrate deep contemplative insights with the recognition that suffering is part of the shared human experience and with the aspiration to relieve others from suffering. Pain is thus altered accepting, rather than reflexively acting on, thoughts and emotions.

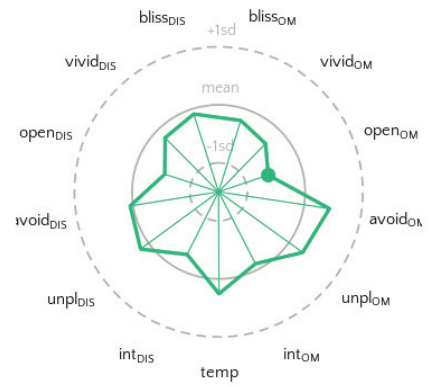
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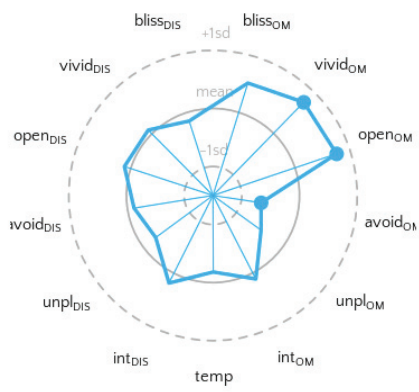
distancing



attunement



deconstruct.



wisdom

