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# Regulation of perceptual learning by mindfulness meditation : experiential and neurophysiological evidence

Enrico Fucci

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# REGULATION OF PERCEPTUAL LEARNING BY MINDFULNESS MEDITATION

experiential and neurophysiological evidence

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# Abstract

Due to its widespread implementation in clinical settings, the neuroscientific study of mindfulness meditation has seen a rapid growth in the last two decades. Despite the evidence of changes in brain activity and structures, the neurocognitive mechanisms underlying meditation practices are largely unknown. In this work, we investigated the hypothesis that mindfulness meditation entails a cognitive stance towards experience which impacts the formation of mental habits. With this aim, we studied the relationship between the phenomenology of different styles of mindfulness meditation, in expert and novice practitioners, and neurophysiological markers of perceptual learning (i.e. auditory mismatch negativity) and attention in neutral and emotional settings.

We found that, in expert practitioners, a nondual style of mindfulness meditation increases sensory monitoring and reduces perceptual learning compared to a focused attention practice (Study 1). Additionally, we demonstrated that auditory perceptual learning is not affected by unpredictable threat, except for individuals with high dispositional anxiety; an effect that might be downregulated by mindfulness meditation independently of the level of expertise (Studies 2 and 3). Finally, we identified components of the auditory evoked response as putative neural correlates of monitoring processes during mindfulness practices and we highlighted a direct link between changes in subjective experience and emotion regulation in expert practitioners (Studies 1 and 3).

Some of the findings presented here were not reproduced by following studies or were in contrast with the previous literature. As such, they await replication in the healthy and clinical population. Moreover, evidence from this work point to the need of differentiating the effects of mindfulness-related processes during meditation states from general effects of expertise. To this end, future studies should implement more refined methods to track changes in subjective experience and explore uncommon frameworks, such as single-case paradigms and long-term meditation retreats.

Overall, the present work expands and fosters the dialogue between cognitive neuroscience and phenomenological models of meditation. It uses meditation as a tool to question existing theories on neural and bodily processes and provides evidence of the possible neurocognitive mechanisms underlying meditation practices and expertise.

**Keywords:** meditation, mindfulness, EEG, MMN, perceptual learning, anxiety, auditory, attention



# Résumé

De part sa mise en pratique considérable dans des conditions cliniques, l'étude scientifique de la méditation de pleine conscience a vu un développement rapide ces deux dernières décennies. Malgré des preuves de modifications de l'activité et de la structure du cerveau, les mécanismes neuronaux et cognitifs sous-tendant les pratiques méditatives sont encore peu connus. Dans le présent travail nous avons testé l'hypothèse que la méditation de pleine conscience implique un changement dans la cognition de l'expérience vécue, impactant de ce fait la formation des habitudes mentales. Pour cela nous avons étudié la relation entre la phénoménologie de différents styles de méditation, chez des pratiquants experts et novices, et des marqueurs neurophysiologiques de l'apprentissage perceptuel (i.e. négativité de discordance auditive) et de l'attention dans des conditions neutres et émotionnelles.

Nous avons trouvé, chez des pratiquants expérimentés, qu'un style de méditation non-dual augmente la vigilance sensorielle et réduit l'apprentissage perceptuel comparé à une pratique d'attention focalisée (Étude 1). Par ailleurs, nous avons démontré que l'apprentissage perceptuel auditif n'est pas influencé par une menace non prédictible, à part pour des sujets naturellement plus anxieux ; un effet qui pourrait être diminué par la méditation de pleine conscience, quelque soit le niveau d'expertise (Études 2 et 3). Nous avons aussi identifié des composants de la réponse évoquée auditive comme potentiels corrélats neuraux des processus de vigilance à l'œuvre lors des états de pleine conscience. Enfin, nous avons mis en évidence, chez des pratiquants experts, un lien direct entre la régulation émotionnelle et des changements de l'expérience subjective (Études 1 et 3).

Certaines découvertes présentées dans ce manuscrit contrastent avec la littérature passée ou n'ont pas été reproduites par des expériences postérieures et méritent donc réplique au sein de populations saines et cliniques. De plus, certains résultats soulèvent la nécessité de différencier les effets de la méditation de pleine conscience durant l'état méditatif, de ceux plus généraux liés à l'expertise. Pour répondre à cela, les études futures devront implémenter des méthodes plus raffinées pour évaluer des changements dans l'expérience subjective des pratiquants, mais aussi explorer des cadres encore mal connus comme les paradigmes en cas unique ou les longues retraites contemplatives.

Au final, le travail actuel étend et enrichit le dialogue entre les neurosciences cognitives et les modèles phénoménologiques de la méditation. Il utilise la méditation comme un outil pour questionner les théories existantes sur des processus neuraux et physiologiques et apporte des preuves sur les possibles mécanismes neurocognitifs sous-tendant les pratiques méditatives et leur expertise.

**Mots clés :** méditation, pleine conscience, EEG, MMN ou négativité de discordance, anxiété, audition, attention.



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# Table of contents

<i>Abstract</i> .....	4
<i>Résumé</i> .....	6
<i>Acknowledgements</i> .....	8
<i>Contributions of the author</i> .....	13
<i>List of abbreviations</i> .....	14
<b>Chapter 1: Aims and outline</b> .....	<b>16</b>
<b>Chapter 2: Introduction</b> .....	<b>20</b>
2.1 General rationale: meditation as a tool.....	20
2.2 Definitions and context.....	21
2.3 Cognitive processes of mindfulness practices.....	24
2.4 Styles of mindfulness meditation.....	27
2.5 Processes of mindfulness-based practices: neuroscientific evidence.....	30
2.6 Predictive brain: definitions and context.....	33
2.7 Mismatch negativity: a neural correlate of perceptual learning.....	35
2.8 Attention and emotions in perceptual learning.....	37
<b>Chapter 3: Hypotheses</b> .....	<b>42</b>
3.1 General hypotheses.....	42
3.2 Hypotheses for Study 1.....	43
3.3 Hypotheses for Study 2.....	45
3.3 Hypotheses for Study 3.....	45
<b>Chapter 4: General methods</b> .....	<b>48</b>
4.1 Expert practitioners.....	49
4.2 Protocol study: meditation and experiential training.....	50
4.3 Electrodermal activity.....	82
<b>Chapter 5: Perceptual learning in neutral settings</b> .....	<b>89</b>
5.1 Study 1: The impact of open presence and focused attention meditation on perceptual learning and auditory processing in expert and novice practitioners....	89
<b>Chapter 6: Perceptual learning in emotional settings</b> .....	<b>99</b>
6.1 Study 2: Perceptual learning and auditory processing under threat of unpredictable electric shock.....	99



6.2 Study 3: Perceptual learning and emotion regulation in expert and novice practitioners during threat of electric shock.....	115
<b>Chapter 7: General discussion.....</b>	<b>143</b>
7.1 General summary.....	143
7.2 Perceptual learning in neutral and emotional settings: evidence from meditation.....	145
7.3 Subjective dimensions: monitoring and emotion regulation .....	149
7.3 State and trait effects.....	152
<i>Chapter 8: Conclusion.....</i>	<i>155</i>
<i>References.....</i>	<i>157</i>
<i>Annex I: ERC Method Manual.....</i>	<i>178</i>
<i>Annex II: Supplementary information .....</i>	<i>197</i>
II.1 Protocol Study: supplementary information.....	197
II.2 Study 1: supplementary information.....	203
II.3 Study 2: supplementary information.....	210
II.4 Study 3: supplementary information.....	211



# Contributions of the author

**Chapter 4: 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.

**Chapter 5: Study 1.** The task was designed by Drs. Richard Davidson, Matthieu Ricard and Antoine Lutz. Data were collected by Andy Francis and Dr. Antoine Lutz. I contributed to hypotheses formulation and interpretation of the results. I analysed the data and wrote the report with Dr. Antoine Lutz, with inputs from Drs. Oussama Abdoun and Anne Caclin.

**Chapter 6: Study 2 and 3.** I designed the experimental paradigm and formulated the initial hypotheses in collaboration with Dr. Antoine Lutz. I collected and analysed the data, with inputs from Drs. Romain Bouet, Oussama Abdoun and Antoine Lutz. I wrote the reports for both studies.

**Annex 1: 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.

# List of abbreviations

AC = alternate current

ANS = autonomic nervous system

DC = direct current

DFN = default mode network

DDS = Drex Defusion Scale

EDA = electrodermal activity

EEG = electroencephalography

EOG = electrooculogram

ERP = event related potential

FA = focused attention

fMRI = functional magnetic resonance imaging

ICA = independent components analysis

HSD = Tukey honestly significant difference test

MAIA = Multidimensional Assessment of Interoceptive Awareness

MEG = magnetoencephalography

MMN = mismatch negativity

PE = prediction error signal

PTSD = post-traumatic stress disorder

OM = open monitoring

OP = open presence

RE = reading condition

RPE = reward prediction error signal

SCL = skin conductance level

SN = saliency network

STAI = State Trait Anxiety Inventory

VD = silent movie condition



## Chapter 1

# Aims and outline

The present work aims to expand and foster the dialogue between cognitive neuroscience and Buddhist philosophy and practices. It uses meditation as a tool to question existing theories on the neural and bodily processes underlying perception and emotion regulation. In turn, it aims to understand the mechanisms of meditation practices through the study of their neurobiological underpinnings.

The neuroscientific research on mindfulness meditation is still in its infancy, despite considerable developments over the last two decades. Previous studies have been affected by several limitations, such as limited access to subjective accounts of meditation experience in experimental settings, lack of rigorously selected groups of expert and novice practitioners and development of theories that could explain brain functions in a way that favour the confrontation with Buddhist accounts of mental processes. In this work we aimed to address these issues by mapping specific phenomenological profiles related to different practices and levels of expertise into biomarkers of perceptual learning and attention in neutral and emotional settings.

We investigated how the brain processes the auditory environment in a neutral setting and during stress. We formulated hypothesis on how different meditation states and levels of expertise would impact neural markers of perceptual learning and why this framework could be useful in understanding the mechanisms of action of mindfulness practices. Finally, we related third-person data to measures and theories of phenomenological dimensions characterising meditation practices to understand the mechanisms underlying the modulation of neural and bodily markers.

**Chapter 2** is a general introduction to the field of research on mindfulness meditation. It describes theoretical accounts of the cognitive functions cultivated by mindfulness practices and a brief review of neuroscientific studies on this topic. It also introduces the notion of perceptual learning and related biomarkers studied in this work. Finally, it reviews the existing evidence on the modulation of perceptual learning processes by attention, emotions and meditation.

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

**Chapter 4** describes the general methodology used in the present work, with special emphasis on those methods that are new or scarcely implemented in the field of meditation research. Most importantly, this chapter includes the description, and related experimental results, of a training protocol which aimed to introduce control subjects to meditation practices and specific phenomenological dimensions that were investigated in experimental settings (Study 3). This information is provided in a **Protocol Study**, which stems from the collaborative effort of our entire research team in the context of a broader research project.

**Chapter 5** presents findings on the effect of different mindfulness practices on the neural correlates of auditory perceptual learning and attentional monitoring processes in expert and novice meditation practitioners in neutral settings (**Study 1**)

**Chapter 6** explores the impact of unpredictable threat on the neural correlates of auditory perceptual learning and sensory processing in novice practitioners during a control condition (**Study 2**). It also investigates the effect of mindfulness practices and expertise in this emotional setting (**Study 3**), providing evidence of a relationship between the specific attentional and motivation stance cultivated in mindfulness meditation and emotion regulation mechanisms.

In **Chapter 7**, I discuss the findings from studies 1, 2 and 3, draw general conclusions and propose future research directions.





# THEORETICAL FRAMEWORK

## Chapter 2

# Introduction

## 2.1 General rationale: meditation as a tool

When I tell someone about my research topic, I am often asked the question: “so, does meditation work?”. Normally, my answer is: “I cannot say, you should try it yourself!”. It feels surprising and slightly dangerous to be entitled, as a researcher, the faculty of certifying pros and cons of meditation. It is a phenomenon that stems from an intricate mixture of scientific positivism, media sensationalism and a blind faith in “science said”. It derives also from the constant need of self-improvement and healing that seems to prevail in western societies. Certainly, the main aim of Buddhism is to “relieve suffering” in human beings, but I am not sure if that applies to the after-work headache caused by sitting in front of a screen for several hours.

The aim of this slightly provoking paragraph is to affirm that I am not seeking to prove whether meditation works by the means of cognitive neuroscience, but rather trying to elucidate questions in my field through the confrontation with theories and phenotypes that were not previously considered. In my opinion, the study of contemplative practices serves as a tool to falsify existing theories in cognitive science, neurosciences and experimental psychology (and other fields of study that fall outside of my competence). To this aim, the choice of focusing on Buddhist philosophy and practices was made not only because Buddhist scholars were investigating the mechanisms of the mind long before western psychology, but also for the validity of meditation practices as an empirical method of subjective enquiry. Surely, the dialogue between different theories and methods in contemplative science is not unilateral. The investigation of neural mechanisms involved in meditation can also help scholars and practitioners in understanding phenomena that are mostly experienced subjectively, as well as provide a different perspective on existing models.

The study of meditation can help clarifying the functional meaning of brain and bodily processes and developing models of the mechanisms underlying cognition, emotions and sensory processing, to list a few. This can be achieved by operationalising and investigating Buddhist theories in our scientific framework, by the observation of training-induced changes and, most importantly, by informing third-person data with accounts of subjective experience from practitioners. Through the neuroscientific study of meditation we can, for instance: identify the neurophysiological correlates of concentration and mind-wandering (e.g. Braboszcz and Delorme, 2011; Brewer et al., 2011), understand the encoding of values in the brain and how it is influenced by

cognitive inputs (Kirk et al., 2014) and discuss the plausibility of comprehensive theories on brain dynamics, in relation to theoretical accounts coming from different methodological and cultural backgrounds (Pagnoni and Guareschi, 2017). In the present work, meditation was used as a tool to investigate the modulation of perceptual learning processes by attention and emotions, as well as the functional significance of specific neurophysiological responses. On the other hand, through this work we made a small step towards the understanding of the neurophysiological mechanisms of meditation practices; an understanding that is necessary for the implementation of secularised practices in clinical contexts.

## 2.2 Definitions and context

Historically, the term meditation has been used to refer to a wide range of practices that belonged mostly, but not only, to spiritual traditions. From ritual dances of African tribes, to specific Tibetan tantric practices, “meditation” encompassed activities and experiences that were thought to be essentials of any religion (Proudfoot, 1985). Lutz et al. (2007) have previously pointed out that such broad meaning could and did bias the scientific investigation of contemplative practices and they were within the first researchers in the field of cognitive neuroscience to propose a structured conceptual framework for such investigation. They defined meditation as “a family of complex emotional and attentional regulatory strategies developed for various ends, including the cultivation of well-being and emotional balance”

In the context of cognitive neuroscience and experimental and clinical psychology, the type of meditation studied today belongs mostly to Buddhist practices or their secular derivations. This is due to historical and epistemological reasons. Forms of Buddhist meditation have been introduced in western clinical, secular settings in the late 20<sup>th</sup> century (Kabat-Zinn, 1982) and have received increasing scientific interest ever since. Meanwhile, neuroscientists, psychiatrists and psychologists were starting a fruitful and challenging dialogue with Buddhist scholars on topics of high relevance in both western and eastern philosophy, which resulted in the creation of the Mind and Life institute in 1987. As mentioned in the previous section, the focus on Buddhist practices has been motivated by an easiness of confrontation, in epistemological terms, with western science. Buddhist traditions have developed consistent and detailed theories, alongside a comprehensive description of the methodological aspects of the actual practice, in a manner that facilitates their implementation in neuroscientific studies.

### 2.2.1. Mindfulness and its operationalisation

In the specific framework constituted by the interaction between scientific research and contemplative practices, meditation has been operationalised as a constellation of practices that share common aims and features such as 1) the production of a specific phenomenological state, 2) the relationship between state and trait development (such as changes in attention, emotional responses, perception) and 3) a progression in the practice from novice to expert (Lutz et al., 2007). Different practices can share or tap into different cognitive and emotional processes and are developed for various ends, including the cultivation of well-being and emotional balance.

Not all Buddhist techniques have been object of scientific study as much as the so-called “mindfulness practices”. Research on mindfulness meditation has seen a dramatical increase in the last two decades (Van Dam et al., 2017). This is probably since mindfulness meditation includes a variety of practices that have been derived from Buddhist traditions but are applied in secular and clinical contexts. Mindfulness-based practices are described to share the aim of cultivating moment-to-moment awareness, by paying attention in a specific way, in the present moment, as nonreactively, nonjudgmentally, and openheartedly as possible (Kabat-Zinn, 2011). It is not the aim of this work to discuss differences between secular and Buddhist definitions of mindfulness (see Dunne, 2011 for a detailed account), nor to address the critiques on the spreading of mindfulness as a social phenomenon (Van Dam et al., 2017). Nonetheless, similarly to the term “meditation”, defining mindfulness as a single and broad process that encompasses different practices can be detrimental for its operationalisation in the context of scientific research (see chapter 4.2 - *Protocol Study* - for a detailed account of this issue).

To facilitate the scientific study of the neurophysiological mechanisms underlying mindfulness practices in expert and novice practitioners, a recent model has been proposed (Lutz et al., 2015). It is strongly based on the phenomenology of mindfulness practices and conceptualises it 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”. This account deconstructs mindfulness into specific processes that can be modulated by different states (not only associated to the practice of meditation) and levels of expertise. It also allows other families of meditative practices (Dahl et al., 2015) to be incorporated into a model of phenomenological categories. In the present work, we tried to map some of these phenomenological dimensions into neurophysiological processes in expert and novice practitioners during different meditation states. In section 2.3 I provide an operational definition of the dimensions that are most relevant for the present work.

### 2.2.3. Limitations and challenges in the neuroscientific study of meditation

The neuroscientific study of mindfulness meditation has developed together with the implementation of mindfulness-based interventions for the treatment of different psychological and psychiatric conditions. Programs such as mindfulness-based stress reduction (MBSR, Kabat-Zinn et al., 1992) and mindfulness-based cognitive therapy (MBCT, Segal et al., 2002) have been proven to be effective in the treatment of symptoms of several mood disorders (especially anxiety and depression), as well as chronic pain conditions (see Goldberg et al., 2018; Khoury et al., 2013; Veehof et al., 2016 for recent meta-analytic reviews).

The understanding of the neurocognitive processes underlying mindfulness-based practices has increased in the recent years. Neuroimaging studies on different practices and groups of practitioners have described the impact of meditation on neuroanatomical and neurophysiological markers of attention and emotion regulation (see Chambers et al., 2009; Lutz et al., 2008; Tang et al., 2015 for extensive reviews). Nonetheless, this young field of research is characterised by several open questions, challenges and limitations. I provide here a list of the most relevant issues, some of which have been discussed in a recent report (Van Dam et al., 2017):

- Lack of consensus on the neural networks and biomarkers implicated in different practices and at different levels of expertise.
- Limited understanding of the mechanisms underlying the observed changes in brain activity and anatomical structures.
- Lack of uniformed groups of expert practitioners, selected on the basis of rigorous and universal criteria.
- Lack of control groups, in cross-sectional studies, that are introduced to the practices through in-depth training programs.
- Lack of a precise characterisation of subjective accounts of meditation experience and their correlation with neurophysiological and neuroanatomical measures.
- Limited understanding of the neural correlates of highly advanced practices in expert meditators.

In the present work, we implemented theoretical and methodological approaches to address these limitation and challenges.

## 2.3 Cognitive processes of mindfulness practices

In the following section, I provide operational definitions of some of the proposed cognitive processes cultivated in mindfulness practices that are relevant for the present work. Other models of mindfulness meditation (e.g. Hölzel et al., 2011; Shapiro et al., 2006) have theorized mechanisms that partially overlap with those proposed in Lutz et al., (2015). However, the latter model presents two advantages: 1) the operationalisation of different processes is based on phenomenological accounts and 2) it allows the mapping of different states and levels of expertise into different configurations of the relations between such processes.

Altogether, these features permit the formulation of hypotheses on the modulation of different neural processes dimensional configurations (e.g. high level in one or two, but not other dimensions). Moreover, these hypotheses can be tested through the correlation between third-person data and measures of subjective experience during a specific task or practice. I chose to present here just few dimensions of the model (meta-awareness, dereification and clarity) to focus the reader's attention on those processes that we tried to operationalise in terms of brain and bodily physiology in the present work. Surely, the operationalisation, empirical testing and eventual re-formulation of additional processes is the general aim of a broader research agenda (Van Dam et al., 2017).

### 2.3.1 Meta-awareness

Meta-awareness has been defined as the cognitive function of being aware of the processes of consciousness (Smallwood et al., 2007). This definition comes from studies on "mind-wandering" and stimulus-independent thoughts (SIT), which highlight the role of meta-awareness in realising when one's mind has wandered (Schooler et al., 2011). Persistence and recursiveness of mind-wandering, especially when focused on past and future events, has been associated to unhappiness (Killingsworth and Gilbert, 2010) and characterise psychopathological conditions of anxiety and depression (Ottaviani et al., 2013). Previous research has shown the validity of mindfulness-based practices as techniques to reduce the disruptive effects of mind-wandering (Jha et al., 2010; Mrazek et al., 2013). However, in the context of meditation, meta-awareness does not act solely on introspection (Lutz et al., 2015), but also on other processes of consciousness, including perception of external stimuli (Dahl et al., 2015). In meditation practices, meta-awareness is the capacity of developing monitoring processes in relation to a specific task set. This monitoring faculty, or "background awareness", underlies noticing when attention has shifted from a specific object, but also the assessment of the quality of attention in practices that do not have any specific object of focus (e.g. Dunne, 2011). The heightened monitoring of stimuli and processes while maintaining a specific task-set is supposed to produce a

shift in the experience of those processes and stimuli. Specifically, meta-awareness is in contrast with the concept of cognitive fusion, a term used to indicate when one is experientially “fused” with the content of experience (Hayes, 2004). This mode of experience has been proposed to play a crucial role in anxiety and depression (Hoge et al., 2015; Lo et al., 2014) and a downregulation of psychological processes related to experiential fusion was found in depressive patients undergoing mindfulness-based therapy (Bieling et al., 2012). To summarise, meta-awareness, in the form of monitoring the ongoing experience in relation to a specific task-set, is a key process cultivated in mindfulness practices and entails a shift in experience akin to cognitive defusion.

### 2.3.2 Dereification

When using the term dereification, we refer to “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). When thinking of a future stressful event such as a public speech, one can perceive the thoughts linked to this event as being an accurate representation of what will happen, to the point that a physiological response could arise. Similarly, the image of an attractive food can induce a salivary response (Papies et al., 2012). A higher degree of dereification would be represented by processes of perspective taking and creative thinking (Colzato et al., 2012), while at the highest degree “thoughts lose their representational integrity and are experienced simply as mental events” (Lutz et al., 2015).

The process of dereification is thought to play a role in every style of mindfulness practice. It has also been termed as “phenomenological reduction” (Varela, 1996) or simply “mindful attention” (Papies et al., 2012). As for meta-awareness, dereification entails a shift in the way a phenomenological event is experienced. This change in experience is akin to what has been described as “decentring” (Williams, 2010). In fact, in the scientific literature, the processes of cognitive defusion and decentring are not entirely distinguished from one another (Fresco et al., 2007). Similarly, Buddhist accounts do not clearly differentiate meta-awareness from dereification, as meta-awareness is sometimes understood to cause dereification (Lutz et al., 2015). This makes sense in the context of meditation practice: when one realizes that her/his attention has been captured by an event (whether a thought, an external stimulus, a physical sensation), the meta-awareness of this shift can be accompanied by the insight on the mental nature of such event. The capacity to decentre from negative thoughts in relation to an emotionally challenging situation has been associated to positive outcomes in the treatment of several psychopathological conditions, such as depression and chronic pain (Fresco et al., 2007; McCracken et al., 2013). To summarise, dereification of perceptual, physical and mental phenomena is a key process in mindfulness meditation. It is often related to the specific attentional stance cultivated during the practice and, together with meta-awareness plays a crucial role in cognitive defusion and decentering.



### 2.3.3 Clarity

Clarity refers to the degree of vividness with which an experience occurs, whether it is a perceptual stimulus or an internal event (e.g. an affective state) (Lutz et al., 2015). Increased clarity characterises several styles of mindfulness meditation, especially in expert practitioners, and interacts with meta-awareness resulting in heightened and more vivid perception of non-object features of the experience, such as affective tones (Lutz et al., 2015). Keeping balance between meta-awareness and clarity is especially important for novice practitioners. In fact, a high degree of clarity can destabilize the mind of a beginner, and specific techniques were developed to modulate clarity (Namgyal, 2001). Interestingly, phenomenal ‘clarity’ (a translation from the Pali word ‘Vipassana’) is also thought to arise, in the expert practitioner, together with insights about the delusional nature of phenomena (Schoenberg and Barendregt, 2016). This links perceptual clarity to the process of dereification. Very few studies have investigated this phenomenological dimension in the context of scientific research. However, the correlation between subjective reports on the degree of clarity during a specific practice and the neural activity in response to emotional stimuli have yielded interesting results before (Lutz et al., 2013).

As mentioned above, the dimensions presented in this section are not an exhaustive representation of the processes involved in mindfulness meditation, but a smaller list that constitutes the framework of the present work. Additional categories have been termed “object orientation”, “stability” and “effort” (Lutz et al., 2015). Moreover, other models have introduced different processes, such as the temporal dynamics of attention (see Van Dam et al., 2017 for a detailed list). Finally, these processes are cultivated, during and outside of the practice, with specific physical and motivational stances, such as equanimity and acceptance (e.g. Desbordes et al., 2014). In the present work, some of these dimensions have been considered implicitly, as they are mostly modulated by meditation expertise (e.g. stability and effort) but have not been operationalised in terms of putative neural mechanisms.

From this short presentation, one could infer that meta-awareness, dereification and clarity are highly related processes. However, distinguishing between these dimensions is crucial for their operationalisation in the context of scientific studies. In fact, different states and levels of expertise can differ on the level of one single dimension or in the relation between them. Additionally, this finer categorisation allows to describe aspects of different and more advanced practices that are not taken into consideration by canonical models of mindfulness. In the next section, I will present the three practices that have been considered in the present work and try to enrich their description with an account of their impact on the processes described above.



## 2.4 Styles of mindfulness meditation

Mindfulness-based practices have been categorized into two main styles, termed “focused attention” (FA) and “open monitoring” (OM), by theoretical and empirical research based on traditional Buddhist texts and their transposition into the cognitive and neuroscientific framework (Lutz et al., 2008, 2007). These broad categories differ, in terms of task-set, mainly in the way attention is anchored on a chosen object (in FA) or let rest in the moment-to-moment awareness without any specific focus (in OM). The practice of FA is often a preparatory step for OM, although that is not true in every tradition (Lutz et al., 2007). The practice of OM, in turn, is necessarily a precursor of more advanced practices that fall into the definition of non-dual mindfulness (Dunne, 2011). For instance, in the present work we studied and extensively discussed the state of Open Presence (OP) as a paradigmatic case of non-dual meditation. The phenomenological states produced by the practices of FA and OM have been already mapped, as examples, into the dimensions presented in the previous section (meta-awareness, dereification, clarity) (Lutz et al., 2015). However, the authors advised that this mapping is a theoretical proposition and should be confirmed in each study by empirical investigation of third-person data and accounts of practitioners’ subjective experience. The state of Open Presence, on the other hand, have been described by a previous model (Lutz et al., 2007) and is characterised not only by a different profile in terms of the processes that have been already described, but also by differences in the quality of subjective experience.

### 2.4.1 Focused attention

In FA practices, the practitioner narrows and maintains her/his attention on a chosen, single object. The main task-set consists in sustaining the attention on the object and becoming aware of when the mind has wandered, in order to bring attention back to the object. FA is one of the most common practices to be taught to novice practitioners. The instruction can vary slightly in different traditions, and so do the degree of narrowing of attention (Dahl et al., 2015). What distinguishes the practice of FA from a state of attentional absorption, such as watching an enthralling movie or being absorbed into an important conversation, is the presence of meta-awareness. Novice practitioners must develop enough meta-awareness to notice when they lost the attentional focus, as well as a degree of dereification to disengage from distractors and refocus on the object. The state of FA in expert practitioners is characterised by a higher degree of meta-awareness, which entails the capacity of monitoring perturbations of attention before they become distractions while maintaining the focus on the object. Dereification is also supposed to increase with training, permitting a rapid and effortless disengagement from distractors. Overall, the experience is supposed to be characterised by higher clarity in expert, compared to novice practitioners (Lutz et al., 2015).

## 2.4.2 Open monitoring

OM practices can vary in their form and instructions but share a common key feature: the cultivation of meta-awareness without focusing on any specific object. The attentional scope is expanded to incorporate perceptions, affective states, thoughts and, in advanced practitioners, awareness itself. Several accounts of this practice (e.g. Dahl et al., 2015; Lutz et al., 2008; Namgyal, 2001) highlight its dependency on FA to attain a stable monitoring without “grasping”. In fact, a practitioner would firstly develop meta-awareness in relation to the task-set of focusing on a specific object, and then gradually release the attention from the object and rely solely on the monitoring process. In this sense, in the state of OM there is no distinction between foreground and background and different phenomenal features such as emotional tones or the quality of attention remain in the same “space” of awareness. These practices aim to develop a “reflexive awareness of the usually implicit features of one’s mental life” (Lutz et al., 2008), which would impact cognitive and emotional habits resulting in increased sensitivity to environmental and interoceptive stimuli, but decreased emotional reactivity. In terms of phenomenological dimensions, the state of OM would be characterised by increased meta-awareness, compared to FA, in both expert and novice practitioners (Lutz et al., 2015). However, Buddhist accounts do not distinguish between background awareness in relation to a specific task set and reflexive awareness, in the form of monitoring cultivated in OM (Dunne, 2015). This could indicate that, in expert practitioners, the same level of monitoring is reached during FA and OM, although the sense of aperture would be broader in OM. Finally, dereification would be higher compared to FA in both expert and novice meditators and experts would experience higher clarity compared to novices.

## 2.4.3 Open presence

OP can be described as a state that emphasizes the processes cultivated during OM to a stage where a practitioner “is aware of the Clarity or Awareness that makes all cognitions possible” (Lutz et al., 2007). The monitoring aspect of OM is transformed here into abiding in the implicit reflexivity of experience that is normally obscured by the subject-object duality in cognition. In the state of OP, the intentional structure involving the duality of object and subject is attenuated, and so are representational models of the self and the world. In this sense, practices that cultivate OP have been termed “non-dual” (e.g. Dahl et al., 2015). Nonetheless, recent theoretical works have highlighted a parallelism between OP practices and styles of mindfulness meditation that are taught in secular contexts (Dunne, 2011, 2015). The lack of explicit monitoring in OP meditation is the pivotal but finely grained difference from OM practice, and this distinction concerns the Buddhist notion of “reflexive awareness,” as discussed by Buddhist scholars (Coseru, 2015; Dunne, 2015). In OP practice, an awareness of whatever emerges in experience continues without the effortful vigilance that characterizes OM styles of practice. It is thought that only advanced practitioners can

attain this state, and even they may not be able to sustain it for more than a short period of time (Lutz et al., 2007). OP has not been mapped into the dimensions of the model proposed by Lutz et al., (2015), but previous literature suggests that this state should be characterised by a very high degree of clarity and meta-awareness (although, as mentioned, the phenomenal experience related to this process might be different compared to FA and OM). Dereification would also be higher than FA and OM. Additionally, we proposed in the present work that the suspension of subject-object duality could influence the perception of mental phenomena in terms of the how they related to one another and how the brain predicts this relationship.

I presented here the styles of mindfulness meditation that were investigated in the present work, as well as their theoretical operationalisation in terms of cognitive functions, derived from their specific phenomenology. To better understand the mechanisms involved in these styles of practice and operationalise their related cognitive functions in terms of neural and bodily processes, we contrasted periods of practice with specific control states. In both Study 1 (chapter 5) and Study 3 (chapter 7) control conditions were constituted by states that would absorb attention into a specific object, such as reading a newspaper or watching a movie. These states were used as active control conditions that could be operationalised in terms of differences in the phenomenological dimensions described in the previous section. More specifically, these conditions would entail a low degree of meta-awareness and dereification. Expert practitioners were explicitly instructed to undergo these conditions without “meditating” (e.g. watching a movie while in a state of monitoring).

Finally, the distinction between OM and OP is mainly useful in the context of a comparison between expert and novice practitioners. In fact, the expert practitioners involved in the present work were consistently trained in practices 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*), to which OP belongs. Therefore, expert meditators were instructed to practice OP, while novices practiced OM. This difference is inevitable and relates to the degree of expertise in this style of mindfulness practice. If asked, novices could not practice OP and experts could probably not practice OM. Nonetheless, as I mentioned, sustaining the state of OP is highly difficult also for expert practitioners. As we did not implement measures that could explicitly tell if an expert was in such state the whole time of recordings, we hypothesise that some experts oscillated between OP and an advanced form of OM.

## 2.5 Processes of mindfulness-based practices: neuroscientific evidence

The neuroscientific study of mindfulness-based practices is still in an early stage. An increasing number of studies have described the impact of meditation on the neural correlates of attention and emotion regulation, as well as documenting changes in brain structures and bodily physiology as a result of meditation training (see e.g. Cahn and Polich, 2006; Chambers et al., 2009; Tang et al., 2015 for extensive reviews). However, because of the limitations that have affected this field (see chapter 2.2.3), some studies report conflicting results on some topics. Moreover, very few studies have investigated the impact of more advanced states, such as OP, on brain activity (e.g. Josipovic, 2014). In this section, I review some studies that are relevant for the present work and highlight putative markers of the cognitive functions involved in mindfulness practices, especially meta-awareness and dereification. It is important to notice that most of these studies were not based on an operationalisation of the constructs described in the previous sections and did not implement first-person measures of subjective experience, except for rare cases.

### 2.5.1 Meta-awareness

Although not every study explicitly operationalised this construct, meta-awareness has been investigated in protocols measuring monitoring of mind-wandering, present-centeredness, interoceptive awareness and the perturbation of attention by distracting stimuli.

Increased meta-awareness during mindfulness practices entails the capacity of detecting distractions and changes in the perceptual environment and in relation to a specific task set. In line with this hypothesis, Braboszcz and Delorme (2011) found that auditory deviance detection was enhanced during a breath-counting task (a form of FA) compared to mind-wandering. Specifically, they asked participants to report episodes of mind-wandering in relation to the task and used electroencephalography (EEG) to record brain responses to frequent and infrequent auditory stimuli. They found an increase in the mismatch negativity (MMN), a neuroelectric marker of deviance detection in the auditory environment, during breath-counting, compared to mind-wandering episodes. This evidence is supported by studies that used functional magnetic resonance (fMRI) and reported decreased activity in brain regions of the default mode network (DMN, Gusnard and Raichle, 2001) and increased activity in regions of the saliency network (SN, Seeley et al., 2007) during FA and OM meditation (Allen et al., 2012; Brewer et al., 2011). In brief, regions of the DMN have been associated to self-referential thoughts and mental activities such as projecting oneself in the future. The SN, on the other hand, would be involved in the processing of salient internal and external events in a bottom-up fashion, such as interoceptive signals related to affective states. Increased activity of regions related to the SN, such as the

anterior insular cortex, in meditation has been associated with a shift to a self-detached processing of interoceptive and external stimuli (Tang et al., 2015). For instance, Farb et al., (2007) found increased activity in the insular cortex and decreased connectivity with regions of the DMN in subjects who underwent a mindfulness-based intervention when asked to practice focusing on the present moment.

Nonetheless, the hypothesis of increased interoceptive awareness as a result of mindfulness practice is still under debate. Some studies reported no difference in standard measures of interoception (i.e. heartbeat detection) (Daubenmier et al., 2013; Khalsa et al., 2008; Melloni et al., 2013) between expert and novice meditators. On the other hand, other research have found that meditators showed more interoceptive accuracy when measuring respiration (Daubenmier et al., 2013) and tactile sensitivity (Fox et al., 2012).

Increased meta-awareness has also been linked to reduced elaborative processing of distractors and target stimuli. For instance, Slagter et al. (2007) found a reduction in the allocation of mental resources to the first of two target stimuli presented in a stream of distractors in a attentional blink task after an intensive three-months practice of OM. More specifically, they observed a decreased amplitude of the P3b component, a neuroelectric potential associated to attention allocation and stimulus processing, in response to the first target stimulus in meditators after the retreat and compared to a control group. This reduction in the brain response was also associated to higher detection rate of the second target. In a similar study, Cahn and Polich (2009) observed a reduction of the P3a in response to distractors during Vipassana meditation (a practice that can be ascribed to the OM style) in expert practitioners, compared to a control state. The strength of this reduction correlated with the reported number of hours of practice and, interestingly, was not present in those subjects that reported high drowsiness during the task.

### 2.5.2 Dereification

Processes akin to dereification have been investigated in studies that highlight the impact of this dimension on thoughts and perceptions associated to psychological and physical distress. For instance, a short training in mindfulness practices has been associated with reduced craving and activation of related regions in smokers (Westbrook et al., 2013) or to reduced approach bias towards images of attractive food (Baquedano et al., 2017; Papies et al., 2012). The faculty of decentring from self-related ruminative thinking is thought to represent a key element for the efficacy of mindfulness based interventions in preventing depression relapse (see Dimidjian and Segal, 2015 for a review of clinical studies). Finally, the majority of studies on the impact of mindfulness-based intervention on pain processing found decreased pain intensity ratings after meditation training (Reiner et al., 2013).

Despite these intriguing findings, little is known about the neurocognitive mechanisms involved in dereification. Most of the evidence on this topic come from studies that

focused on the activity of brain areas serving emotional processing in response to painful or emotional stimuli, or their anticipation. Short training in mindfulness-based practices has been shown to reduce the activity of the right amygdala in response to emotional pictures (Desbordes et al., 2012). Similarly, studies involving long-term practitioners and focusing on the processing of painful stimuli reported lower activity in the amygdala and higher activity in sensory regions, as well as lower pain unpleasantness compared to controls (Brown and Jones, 2010; Lutz et al., 2013). Interestingly, Lutz et al. (2013) reported decreased activity in the anterior insular cortex in the period preceding a painful stimulus. The authors related these findings to the idea that the cultivation of present-centred, non-judgemental awareness would downregulate anticipatory anxiety. (Lutz et al., 2015).

The findings presented here are not an exhaustive representation of the neuroscientific research on mindfulness but are useful in the context of the present work. The mapping of cognitive processes involved in mindfulness meditation into specific neurophysiological models is still at its infancy. Even in the studies presented here, especially those focusing on the impact of mindfulness-based training on emotion regulation, the interplay between dereification and meta-awareness is not yet clear (Lutz et al., 2015). Additionally, only one study to this date have described a relation between subjective clarity and the intensity of neural activity (Lutz et al., 2013). Most importantly, very little is known about the actual mechanisms that underlie the observed modulation of neural activity in the healthy population and in clinical contexts. The main aim of the present work was to investigate whether we could map the cognitive processes, and related phenomenological dimensions, involved in mindfulness meditation into a specific theoretical and empirical model of brain activity and its related biomarkers. It represents a first attempt to identify the mechanisms of action of mindfulness-based practices in this specific neural framework. I will present the latter in the next section and argue for its validity in the neuroscientific study of mindfulness.



## 2.6 Predictive brain: definitions and context

The need for cognitive neuroscience and experimental psychology to inform third-person data with first-person accounts of mental phenomena, through the study of contemplative practices, was first highlighted by Francisco Varela in his epistemological standpoint, which has been termed “neurophenomenology” (e.g. Lutz and Thompson, 2003; Varela, 1996). As Pagnoni and Guareschi (2017) recently pointed out, a reason for the limited number of neuroscientific studies on meditation that implemented this crucial approach could be found in the lack of a coherent, general and detailed theory of brain functions that can explain different mental processes. In this sense, the neurocomputational theory of predictive coding under the free-energy principle (Friston, 2010) has gained, in the recent year, increasing attention of the neuroscience community. In brief, this theory postulates that every biological system is structured and functions in a way that tries to resist disorder and to maintain internal coherence (an account similar to the “autopoiesis theory”; Maturana and Varela, 1991). It would do so by minimizing the “surprise” between an embodied model of the world and sensory sensations, by either updating such internal model or acting on the environment. Free-energy represents an informational quantity that is tight to the parameters of the internal model and thus “minimizable” despite the lack of knowledge of all possible states of the environment. Within this framework, the brain operates as a predictive machine (Gregory, 1980) and constantly casts hypotheses on the upcoming sensory input based on internal models of the causes of sensory data. More specifically, the hierarchical structure and rich connectivity of the brain would allow for the creation and storage of internal representations encoding the statistical properties of the environment. These representations would result in expectations about the upcoming sensory data, which are tested against the data itself following Bayesian principles. Ultimately, a prediction error signal (i.e. the difference between the expected and actual sensory signal) would be propagated along the hierarchy to eventually update the internal models and account for the present state of the world, permitting subsequent predictions.

Whereas these principles have been previously postulated in the so-called “Bayesian brain hypothesis” (Knill and Pouget, 2004), Friston and colleagues have drastically expanded this field with several works. For instance, they introduced the notion of precision-weighted prediction error signals, which highlights the role of attention in decreasing the uncertainty of sensory signals and increasing the probability of an internal model to be updated (Feldman and Friston, 2010). They provided neurocomputational models that are coherent with the hierarchical structure and connectivity between neuronal populations (Bastos et al., 2012; Friston, 2010) and could possibly explain the functional role of distinct brain oscillations in the context of top-down and bottom-up signalling (Friston et al., 2015). Finally, they applied the same computational and theoretical principles beyond perception and to the understanding of action (Friston et al., 2011).

## 2.6.1 Perceptual inference and learning

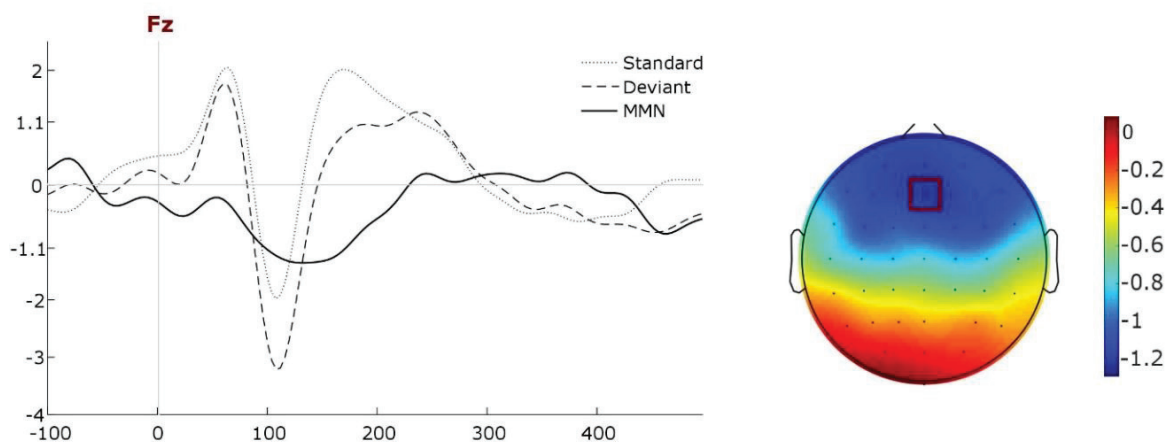
As mentioned above, an organism can minimize free-energy by updating internal models or by acting on the environment. The first way is called “perceptual inference” and the second way “active inference”. In a process of active inference, an organism acts on the environment to match its predictions about sensory data, rather than changing its internal models (Friston et al., 2011). Perceptual inference, on the other hand, is the process of predicting sensory stimuli based on the neural representations of the statistical properties of the environment and selecting the best or updating the current internal model based on the sensory evidence (i.e. prediction error signals). Perceptual inference underlies the process of perception itself (Hohwy, 2012), which would consist in the rapid selection of the best internal model to match the sensory signal, given the information provided by a prediction error. Perceptual inference also underlies learning, which entails a change in parameters of an internal model. More generally, the notion of perceptual inference highlights some issues that are crucial for the present work. Most importantly, perception can be dissociated from sensation (Hohwy, 2012): it relies on internal models, hence on the interaction between a subject and a perceptual object. The *act* of perceiving depends on one’s previous knowledge about the world, which can be inherited or shaped by the experience. It is an act of learning, but the learning itself is based on how much one relies on previous knowledge and on the variety of phenomena that one can experience.

The theory of predictive coding, especially in the form of perceptual inference and learning, represents a promising framework for investigating the neurocognitive mechanisms of meditation practices and their associated phenomenological dimensions. In fact, Pagnoni and Guareschi (2017) have discussed parallelisms between this view and Buddhist theories on perception, subjectivity and time-perception, as well as the way meditation practice could act on these mechanisms. Moreover, predictive coding is a theory that is broad enough to encompass different mental phenomena. This comprehensive theory has been used to generate models on the mechanisms underlying conscious perception, attention and agency (Apps and Tsakiris, 2014; Hohwy, 2012; Rudrauf et al., 2017; Synofzik et al., 2013), affective states and interoception (Barrett and Simmons, 2015; Gebauer et al., 2015; Gentsch and Synofzik, 2014; Seth, 2013; Seth and Critchley, 2013), social interactions and theory of mind (Moutoussis et al., 2014; Ondobaka et al., 2017) and psychiatric conditions such as autism, depression and psychosis (Adams et al., 2013; Stephan et al., 2016; Van de Cruys et al., 2014). In the present work, we investigated whether some of the cognitive processes and changes in the quality of experience in meditation could modulate biomarkers of perceptual learning processes. In the next section, I present the most important of these markers, as well as evidence of the modulation of perceptual learning by cognitive processes and emotional contexts.



## 2.7 Mismatch negativity: a neural correlate of perceptual learning

The mismatch negativity (MMN) is a stimulus-evoked electrophysiological response that has received a broad interest of the scientific community in several fields, since its first description by Näätänen and colleagues thirty years ago (Näätänen et al., 1978). It is elicited by a sudden change in a stream of repeating sensory stimuli and it is considered to reflect the fact that the brain has detected such change. Whereas evidence of mismatch detection has been reported in all sensory modalities (e.g. Krauel et al., 1999; Näätänen, 2009; Winkler and Czigler, 2012), most of the research on this neuroelectric response has been conducted using auditory stimuli, and so did we in the present work. Auditory MMN can be observed in paradigms consisting in sequences of repeating auditory stimuli perturbed by infrequent stimuli that can differ in terms of frequency, intensity, duration (to cite a few). This type of paradigm is termed “oddball task” and can be characterized by different configurations of stimuli and timing between them (e.g. Näätänen et al., 2004). In general, the MMN is obtained by subtracting the average response to the last “standard” stimulus before the “deviant” to the one of the “deviant” stimuli. It is a negative component of the obtained waveform, which peaks between 100 and 200 ms after stimulus onset (Sams et al., 1985) and is distributed over frontocentral scalp areas, with prominence in frontal regions (figure 1).



**Figure 1. MMN resulting from the subtraction between the response to standard and deviant stimuli. (left)** An example of event-related responses to standard and deviant auditory stimuli and the resulting difference waveform at the electrode Fz. **(right)** Related scalp topography in the 90-180ms time-window.

### 2.7.1 MMN and predictive coding

The “predictive coding” account of MMN asserts that the repeated presentation of a standard stimulus involves changes in both extrinsic (between-areas) and intrinsic (within areas) connections that underlie the update of an internal model through perceptual learning. Predictions generated by models that are updated over time would become more efficient in suppressing the prediction error signal (PE) between predictions and bottom-up information conveyed by sensory data. This would lead to a reduction in evoked responses to standard stimuli over time. An MMN would emerge when a new, unlearned stimulus is presented, which would cause a higher PE (Garrido et al., 2009b). This view has been proposed as a comprehensive account of the mechanisms underlying the MMN and allows for the coexistence of previously contrasting hypotheses. Specifically, it conciliates evidence supporting the so-called *model adjustment hypothesis*, that considers the MMN to represent the modification of a perceptual model which predicts the next sensory input based on the memory trace of the previous one (e.g. Sussman and Winkler, 2001), and the *adaptation hypothesis*, that postulates the presence of different neuronal populations responding to the different stimuli, resulting in different degrees of neural habituation and thus a difference in response amplitude (Jääskeläinen et al., 2004). The predictive coding account of the MMN has been supported by different neuroanatomical and neurocomputational models that described the role of bottom-up and top-down neural connections in conveying predictions and PEs within a hierarchical structure that encompasses the auditory cortex as well as prefrontal brain regions (Garrido et al., 2008; Wacongne et al., 2012). The MMN can thus be considered as a biomarker of perceptual learning processes. As such, the study of its modulation by the cognitive processes developed in meditative practices can lead to a better understanding of the neural mechanisms underlying mindfulness meditation, as well as providing insights over mechanisms of perceptual learning.

### 2.7.2 Other components of the auditory evoked response

The auditory MMN is one of several components of the auditory evoked response. When averaging several neuroelectric responses to the same type of auditory stimuli, we observe many deflections in the electroencephalography (EEG). These are components of the event-related potential (ERP) and are historically identified as different peaks in the signal after the onset of a given stimulus. Different components have been classified, based on their approximative peak latency, into early, middle and late-latency responses (Picton, 2010; Picton et al., 1974).

For their contextualization in the present work, I will briefly introduce those components that are part of the late-latency responses (LLR). LLR comprise the P50 component (also P1 or Pb), a positive deflection peaking around 50ms and the N1 (or N100, figure 1), a negative deflection at 100ms circa. Both components reflect sensory processing and have been related to sensory gating mechanisms (Boutros et al., 2011).

The P2 (or P200) component has its positive peak at around 200ms (figure 1). This component has been poorly studied and historically thought to be part of the N1-P2 complex in response to auditory stimuli (Tremblay et al., 2014). Nonetheless, there are evidence indicating that N1 and P2 originate from different sources within the auditory cortex and likely serve different functions (Ross and Tremblay, 2009). It has been proposed that P2 reflects mechanism of stimulus attendance and classification, mostly related to excluding a stimulus from further processing or recognizing it as a target (see Crowley and Colrain, 2004 for a review). Finally, LLR comprise the P3a, which peaks around 300ms and reflects change detection in active tasks requiring attending to target stimuli (Escera et al., 2000).

After 300ms, several studies have reported negative deflections that have been termed with different names (e.g. Bendixen et al., 2007; Naatanen, 1982; Recasens et al., 2015) . The functional significance of these components is probably related to attentional monitoring and stimulus attendance, but it is also influenced by the specific paradigm in which they are observed.

## **2.8 Attention and emotions in perceptual learning**

In this section, I review some of the recent studies investigating the modulation of perceptual learning processes by attention and emotions. This literature will be useful for elucidating the impact of cognitive processes developed in mindfulness practices on perceptual learning. In fact, dimensions such as meta-awareness and dereification have already been shown to impact attentional and emotion regulation processes (see section 2.4.1 and 2.4.2). The studies presented here were mostly based on the investigation of the auditory MMN, as a marker of perceptual learning. Nonetheless, additional research on different markers (mainly mismatch-like processes) is included. One relevant message to retain from this brief introduction is that the MMN (and related phenomena) is an automatic response. MMN has been observed during sleep (e.g. Atienza and Cantero, 2001), anesthesia (Chennu and Bekinschtein, 2012), minimally conscious patients (Boly et al., 2011) and patients in coma (Morlet and Fischer, 2014). Therefore, any modulation of the MMN and perceptual learning processes by cognitive or emotional factors will not likely result in its absence.

## 2.8.1 Attention and perceptual learning

A long-lasting debate has been focusing on whether the auditory MMN can be modulated by the amount of attentional resources allocated to the incoming auditory stimulation. Early studies suggested that the MMN amplitude was higher when participants were asked to attend, compared to ignore the auditory stimuli in an oddball task. For instance, Woldorff et al. (1991) showed that the MMN in response to intensity deviants was higher for attended, compared to unattended stimuli in a dichotic listening task. However, other studies pointed out that the true amplitude of the MMN could not be assessed in *attend* conditions (e.g. when subjects were asked to count auditory deviants) because the MMN overlapped with the N2b component, a negative deflection in response to infrequent targets (e.g. Muller-Gass et al., 2005; Shalgi and Deouell, 2007). Additionally, in few studies where the N2b component was dissociated from the MMN, no difference was found in the amplitude of the latter in *attend*, compared to *ignore* conditions (Sussman et al., 2004).

Findings supporting an independent role of attentional engagement in modulating the amplitude of the MMN came from later studies. Haroush et al. (2009) found that increasing the visual load in an “attentional blink” task decreased the MMN amplitude in a concurrent auditory oddball sequence. The same decrease in amplitude was found following attentional shifts (i.e. errors in detecting the first visual target in a sequence). The authors discussed the results in the context of background attentional monitoring, which would decrease in response to increased cognitive demands in a task.

The impact of task-set in modulating perceptual learning processes has been highlighted by studies that used complex auditory sequences and experimental conditions. Sussman et al. (2002) designed an oddball task characterized by patterned sound sequences with regular and rare deviant stimuli (e.g. AAAB ATAB AAAB) and asked the participants to either ignore the sounds, indicate when a rare deviant was present (but they were not instructed on the sequence patterns) or detect changes in the sequence patterns. They found that the MMN was not elicited for regular deviants if the goal of the task was to detect deviant sequences. They interpreted these findings highlighting the role of task goal in determining what constitute a deviation and thus a related mismatch. In accordance to previous studies, the MMN amplitude for the *ignore* condition was lower than when the auditory stream was attended.

In contradiction to these findings, Chennu et al. (2013) showed how expectation and attention interacted to modulate perceptual learning. In their research, subjects were asked to report changes in single tones or global sequences in a complex oddball task (e.g. AAAB AAAB AAAA). In this case, the MMN in response to local deviations was higher when subjects were asked to attend the global patterns, compared to when they were asked to attend each single tone. This finding was in line with previous evidence, coming from studies using magnetoencephalography (MEG), of the attenuation of early auditory responses to expected, compared to unexpected stimuli (Todorovic et al., 2011; Todorovic and Lange, 2012). Additionally, the MMN was reduced when subjects

were ignoring the auditory stream compared to both the *attend patterns* and *attend tones* conditions.

Within the predictive coding framework, the higher the match between a prediction on the upcoming sensory data and the actual sensory information, the lower the prediction error signal that is generated (i.e. lower MMN amplitude in the case of auditory oddball). On the other hand, attention is considered to increase the precision of the sensory prediction error signals (i.e. a reduction in the uncertainty or “noise” surrounding the incoming sensory data). This process is thought to be mediated by specific molecular mechanisms. In a within-subject crossover placebo-controlled double-blind design, Moran et al. (2013) found increased MMN and decreased attenuation of the response to repeating standard stimuli after the administration of galantamine, an enhancer of cholinergic neuromodulation. This result is in line with the hypotheses on the role of acetylcholine in boosting bottom-up attentional processes (Bentley et al., 2004). However, the way attention interacts with expectations and task-set in modulating perceptual learning is still unclear, with studies pointing to both antagonist (e.g. Chennu et al., 2013) and synergic interactions (e.g. Hsu et al., 2014; Kok et al., 2012).

To summarize, auditory perceptual learning seems to be modulated by the amount of attentional resources allocated to the source of sensory data. This modulation would result in increased amplitude and weight of prediction error signals (i.e. the MMN). However, specific task-sets and expectations on the statistical properties of the auditory environment can interact with the attentional modulation in a way that is still unclear and possibly task-specific.

## 2.8.2 Emotions and perceptual learning

In everyday life, perception and learning cannot be dissociated from social and emotional factors. Studies on this topic can be divided into research on the effect of emotional stimuli or on stimulus processing in emotional contexts. In the second research field, an emotional context can be created by the task-related stimuli, or by mood induction within a paradigm with neutral stimuli.

A contribution in the investigation of the modulation of perceptual learning processes by emotional stimuli comes from research on the MMN in various sensory domains. Previous studies have found increased MMN responses to emotional, compared to neutral deviants (Chang et al., 2010; Fan and Cheng, 2014; Vogel et al., 2015). For instance, in Vogel et al. (2015) participants underwent a visual oddball task where two pictures of neutral faces constituted a standard stimulus, while the second face of the pair changed in deviant stimuli. They found that the visual MMN was higher when the deviant face was expressing fear, compared to a neutral expression. They suggested that the increased saliency of the emotional stimuli could increase the amplitude of prediction error signals, as the information conveyed is more different, compared to the original prediction, than the one conveyed by a neutral stimulus. Supporting this



view, some studies have found that the effect of emotional deviants expressing sadness is decreased or absent in depressed patients (e.g. Chang et al., 2010; Pang et al., 2014). In this case, one could presume that sad deviants are somehow less “surprising” for people affected by this mood disorder. Finally, other studies did not observe any modulation of the MMN amplitude by emotional, compared to neutral deviants (e.g. Susac et al., 2004).

Evidence that different emotional contexts impact the dynamics of perceptual learning processes come from studies that investigated repetition suppression of negative and positive stimuli. The term *repetition suppression* refers to the decrease in the amplitude of neural responses to repetitions of the same stimulus over time. Within the predictive coding framework, this process is considered to reflect the “minimising of prediction error through adaptive changes in predictions about the content and precision of sensory inputs” (Auksztulewicz and Friston, 2016). Ishai et al. (2004) used fMRI to investigate how this phenomenon is modulated by emotional contexts. They found that the repetition of fearful, compared to neutral faces, resulted in higher responses to the first repetition and greater decrease of activity over time in the visual cortex. They suggest that this result is due to the sharpening of representations of fearful stimuli in the visual cortex and that this effect could be mediated by a feedback from the amygdala. Differently, another study observed reduced repetition suppression for happy faces in the same brain regions (Suzuki et al., 2011), pointing to a possible differential effect of emotional valence in perceptual learning.

Other evidence on the modulation of perceptual learning by emotional contexts come from studies that focused on associations between cues and outcomes. For instance, in Watanabe et al. (2013) participants learned associations between cues and monetary rewards in trials where the cue was preceded by a neutral or a fearful face. They showed that cue-outcome associations were learnt faster for those stimuli that were preceded by a fearful, compared to neutral faces. Moreover, the authors suggest that this change in learning rate could be caused by the higher reward prediction error signals (RPE; the activity in response to violated outcome predictions) observed in the ventral striatum and amygdala in trials starting with fearful faces. In accordance to these findings, Robinson et al. (2013) found increased RPEs in the ventral striatum when subjects underwent a stress induction procedure (i.e. threat of electric shock). However, this modulation was present only for aversive unpredicted outcomes (i.e. seeing an angry face when one was expecting a happy one). Thus, different emotions could play different roles also in the context of learning cues-outcome association. For instance, Bertels et al. (2013) found that the probabilities of cue-outcome association were not learned faster when participants underwent a sadness induction procedure (i.e. listening to sad stories before the task) compared to a neutral condition.

Finally, there is a consistent body of literature concerning the impact of stress on the auditory MMN. Cornwell et al., (2017) has recently proposed a neurocomputational model of anxious hypervigilance, which would impede perceptual learning by increasing the synaptic gain of prediction error signals while down-regulating descending prediction pathways. This model builds upon previous evidence on the increase of the magnetic counterpart of the MMN (MMNm) during periods of electric

shock threat (Cornwell et al., 2007). Moreover, increased MMN amplitude has been observed in individuals affected by PTSD (Ge et al., 2011) and has been found to correlate with dispositional anxiety (Hansenne et al., 2003). Despite this evidence, contradicting results come from other research that elicited anxious states and used EEG: in these cases, a difference in the amplitude of the MMN was either not found (Ermutlu et al., 2005), observed only in response to a specific type of stimulus deviancy (Simoens et al., 2007) or found to correlate with state anxiety only in an emotionally negative context (Schirmer and Escoffier, 2010). The possible reasons underlying these contradicting studies are extensively discussed in Study 3 (chapter 5).

To summarize, perceptual learning processes are not independent of emotions. Highly affective stimuli can modulate the amplitude of prediction error signals while emotional contexts can modulate repetition suppression and learning processes. It is unclear whether different types of emotions impact perceptual learning in different ways. However, it seems that negative and highly arousing emotions such as stress and fear could constitute an optimal framework for investigating these effects.

### 2.8.3 Meditation and perceptual learning

Up to date, no studies formally investigated the impact of meditation training and states on perceptual inference and learning processes. However, few studies reported an effect of meditation on the amplitude of the auditory MMN in neutral emotional contexts. Increased MMN was observed during FA meditation (Srinivasan and Baijal 2007) and as a trait effect in expert practitioners (Biedermann et al., 2016). Nonetheless, these studies presented several limitations such as the lack of a control condition and the assessment of the MMN amplitude at unconventional scalp areas. Additionally, Braboszcz and Delorme (2011) found a reduction of the MMN amplitude during mind-wandering, compared to an experimental condition akin to FA (i.e. breath-counting task). Finally, other studies have found a reduced startle effect in response to auditory probes (Levenson et al., 2012) and reduced habituation of startle responses (Antonova et al., 2015) in expert practitioners during the practice of OP. Overall, these findings indicate that biomarkers of perceptual inference and learning represent an interesting tool for the understanding of the neural mechanisms of mindfulness meditation. Nonetheless, none of the above-mentioned studies were empirical investigations of the neurocognitive processes of mindfulness practices, operationalised in terms of perceptual inference and learning. In the present work, we addressed this issue formulating specific hypotheses on the differential effects of mindfulness states and expertise on the auditory MMN in neutral and emotional contexts. These general hypotheses are presented in the next chapter.

## Chapter 3

# Hypotheses

### 3.1 General hypotheses

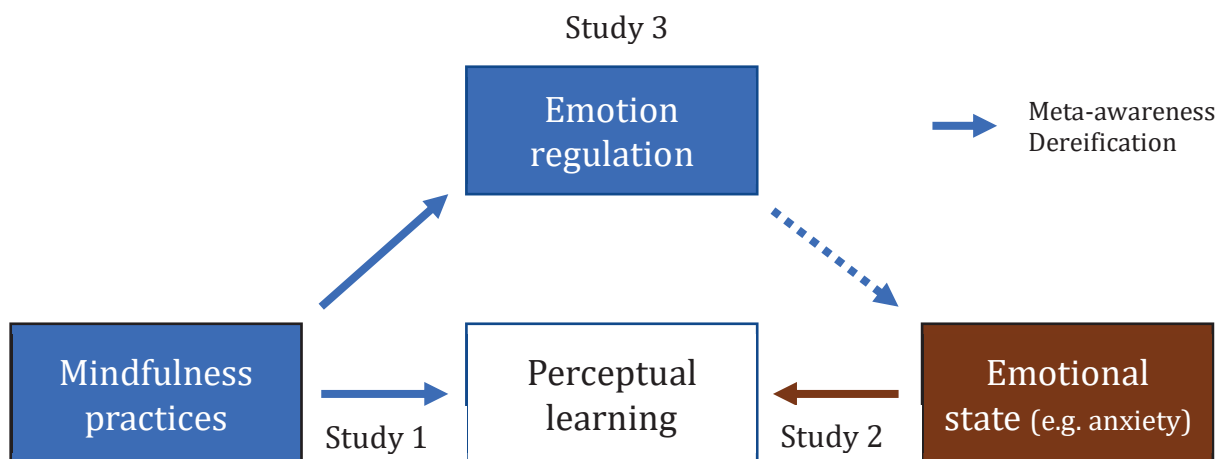
The main hypothesis motivating this project was that the cognitive processes cultivated in mindfulness practices (i.e. meta-awareness and dereification) could modulate biomarkers of perceptual learning and downregulate the impact of emotions on these markers (see figure 1). These effects would be in line with the specific phenomenology of different practices and levels of expertise. More precisely, we considered the EEG mismatch negativity to be a common neural framework for studying attentional and perceptual profiles in neutral and emotional settings. Additionally, we predicted that other components of the auditory evoked responses would be modulated by different meditation states and expertise, especially those underlying attentional control and monitoring<sup>1</sup>. Finally, we expected that the modulation of neural processes could be predicted by moment-to-moment fluctuations in the degree and quality of specific dimensions of subjective experience. We tested this hypothesis by correlating first and third-person measures in different meditation states and groups of expert and novice practitioners.

A secondary hypothesis was that a thoughtful and rigorous selection of expert meditation practitioners, the implementation of a well-defined variety of practices and a detailed training of a control group of participants would 1) reduce the degree of variability caused by the heterogeneity of meditation styles and ways to practice in different traditions and 2) provide a common linguistic framework for the study of specific dimensions of subjective experience. This hypothesis constituted a main feature of the larger research project from which this work is derived. As such, it is presented and discussed in detail in the Protocol Study (see chapter 4.2), which stems from this long-term collaborative work.

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<sup>1</sup> Analyses on the amplitude of different ERP components (e.g. auditory N1, P2, Late Frontal Negativity) have been a rich source of understanding in Study 1 and 3. However, they came from a posteriori hypothesis and are therefore not presented in this chapter.

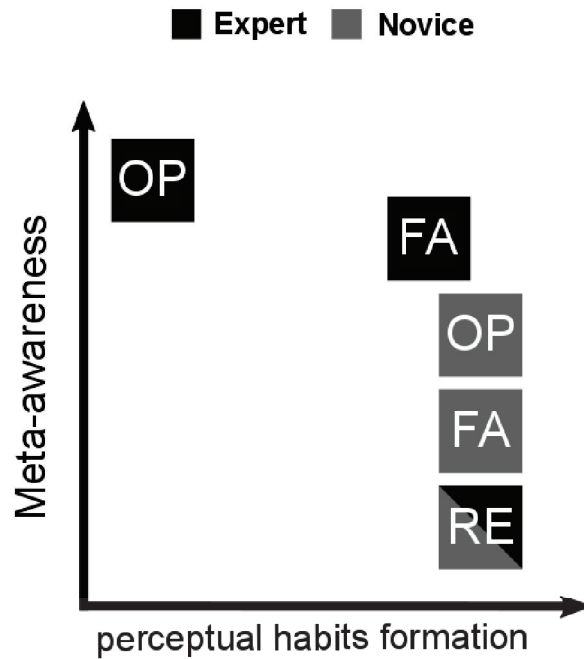




**Figure 1. Schematic illustration of the main hypothesis explored in the present work.** This schema represents the hypothesis that mindfulness practices impact perceptual learning through meta-awareness and dereification of sensory stimuli. Additionally, these same processes modulate emotional responses, downregulating the effect of emotional states on perceptual learning.

## 3.2 Hypotheses for Study 1

In Study 1, we investigated the impact of two styles of mindfulness meditation, Open Presence (OP) and Focused Attention (FA), in expert and novice practitioners on the neural correlates of perceptual learning and attention monitoring processes. We hypothesized that OP practice, in expert meditators, would downregulate the formation of perceptual habits while increasing the monitoring of the sensory environment. Differently, we expected the state of FA to increase monitoring of task-unrelated events and enhance the brain responses to deviations of the auditory environment. These predictions were based on previous theoretical accounts of the two meditation styles (Lutz et al., 2015, 2007). In brief, both meditation states are thought to be characterized by higher meta-awareness, compared to a control condition, which would increase the saliency of prediction error signals in response to deviations in unpredictable sequences of auditory stimuli. However, during the state of OP, the suspension of the representational models of the self and objects in the world would result in a high degree of dereification of the auditory stimuli and a consequent downregulation of prediction error signals in response to deviations (figure 2).



**Figure 2.** *Schematic illustration of degree of meta-awareness and strength of perceptual learning processes in expert and novice meditators during FA, OP and reading (RE).* Here we try to characterize two styles of mindfulness practice in experts and novices in terms of strength of monitoring processes (y-axis) and strength of response to deviations in the auditory environment (x-axis).

In terms of neurophysiological processes, we expected to observe a decrease in MMN amplitude in experts, compared to novice practitioners, during the practice of OP and compared to FA and a control state. On the other hand, the MMN amplitude would increase in experts, compared to novices, during FA and compared to a control state. For further details on the theoretical background of this specific hypothesis, as well as on the exploration of the interplay between the MMN amplitude and components of the auditory evoked response that putatively reflect attention monitoring processes, I invite the reader to refer to Chapter 4 of the present work, where Study 1 is presented.

### 3.3 Hypotheses for Study 2

In Study 2 we tried to replicate previous findings on the modulation of perceptual learning processes by anticipatory anxiety in the context of unpredictable threat (Cornwell et al., 2017, 2007). For this aim, we analysed a subset of data from the paradigm presented in Study 3. The data was from novice practitioners during a control condition (see Chapter 5 for more details). The main hypotheses for this study were the following:

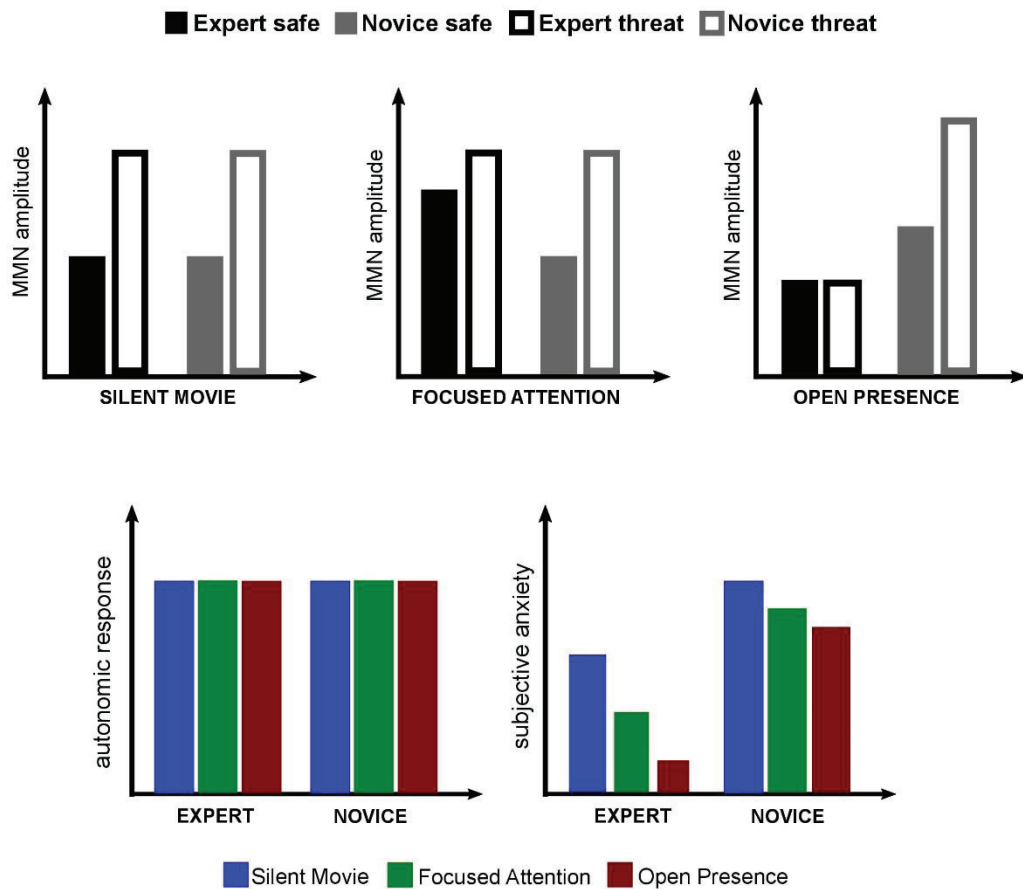
- Skin conductance responses to auditory cues introducing periods of threat would be higher than those in response to cues introducing safe periods (where no shock is delivered).
- The amplitude of skin conductance responses would correlate with the subjective experience of anticipatory anxiety, as measured by self-reports.
- Early brain responses to auditory stimuli would be higher during periods of threat compared to safe periods. This modulation would be an index of increased sensory processing caused by anxious hypervigilance.
- MMN amplitude would increase during periods of threat, compared to safe periods. This modulation would be an index of a biased perceptual learning during anxious states, as suggested by previous neurocomputational models (Cornwell et al., 2017).
- MMN amplitude would correlate with measures of state and trait anxiety, as measured by self-reports and questionnaire, respectively.

### 3.3 Hypotheses for Study 3

In study 3, we investigated the modulation of auditory perceptual learning processes by two styles of mindfulness practice (FA, OP) and a control condition (silent movie, VD) in expert and novice practitioners in the context of unpredictable threat. In this paradigm, we used threat of unpredictable electric shocks to induce a state of anticipatory anxiety and recorded EEG and electrodermal activity during a passive auditory oddball task. We also collected self-reports on several dimensions of subjective experience during the different experimental conditions. Additionally, we explored a relation between questionnaires on cognitive defusion, interoceptive awareness and trait anxiety and brain and bodily physiology.

Our main hypothesis was that the specific cognitive processes instantiated by OP and FA in expert practitioners could impact the effect of anticipatory anxiety on biomarkers of perceptual learning (i.e. the MMN). More specifically, we expected a dissociation between physiological, adaptive responses to threat and the intensity of the experience of anticipatory anxiety in experts, especially during OP. We expected this dissociation to be related to, on one hand, an overall sensitisation of brain responses to auditory stimuli and autonomic responses during threat periods, but decreased intensity of the associated affective state, as a function of the degree of meta-awareness and dereification. Specific hypotheses on the modulation of the MMN amplitude and autonomic and affective responses to threat were the following (see figure 3 for a schematic illustration):

- Skin conductance responses to auditory cues introducing periods of threat would be higher than those in response to cues introducing safe periods in both groups of participants and indiscriminately for meditation states and a control condition.
- Expert meditators would report less anticipatory anxiety during meditation, especially during OP. This modulation would be predicted by measures of dereification and meta-awareness.
- MMN amplitude would increase during periods of threat, compared to safe periods in the VD condition, but not during FA and OP in expert meditators. This effect would be especially strong during OP.
- Early brain responses to auditory stimuli would be higher during periods of threat, compared to safe periods in both groups of participants and indiscriminately for meditation states and a control condition.



**Figure 3. Schematic illustration of some of the main hypotheses for Study 3.** The three graphs at the top describe the expected modulation of MMN amplitude by different states in the two groups during safe and threat periods. The two graphs at the bottom illustrate the expected effect of threat electrodermal activity (left) and subjective experience of anxiety (right).

## Chapter 4

# General methods

The experimental data presented in the present work are divided into three different studies. Whereas Study 1 stands alone in terms of subjects, materials and design, Study 2 and Study 3 were part of a single experimental paradigm. More specifically, in Study 2 we analysed data from novice practitioners during a control state, to investigate the effect of a mood induction procedure in control participants who were not engaging in meditation practices. Additionally, Study 2 and 3 were part of a broader project that investigated the effects of mindfulness meditation on cognitive and emotional processes in expert and novice practitioners throughout several experimental sessions and paradigms.

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 profiles of expert meditation practitioners in Study 1 and 3, 2) the meditation and phenomenological training program attended by novice practitioners who participated in Study 2 and 3 and 3) the use of electrodermal activity as a marker of stress. In all studies, electroencephalography (EEG) was used to investigate brain activity in the form of event-related potentials (ERPs) and spontaneous oscillatory activity (Study 1). A general description of these electrophysiological methods is not provided here, since this topic has been treated in other and more detailed works (Buzsaki, 2006; Luck, 2014; Niedermeyer and Silva, 2005). Specific information regarding the methods of data pre-processing and analysis are provided in the methodological sections of each study presented here. I opted to describe in this chapter only those methodological approaches that are novel or scarcely implemented in the field of neuroscientific research on meditation practices.

Relevant information on the methods implemented in the studies presented in this work are outlined in figure 1. Detailed information on the inclusion procedures, experimental paradigms and main outcome measures of the broader project, to which Study 2 and 3 belong, are provided in Annex 1 of this manuscript (“ERC project manual”; available online at [osf.io/dbwch](https://osf.io/dbwch))

	Study 1	Study 2	Study 3
Subjects	n = 15 novices ; 16 experts	n = <b>36 novices</b>	n = <b>36 novices</b> ; 30 experts
Paradigm	auditory oddball	auditory oddball under threat	auditory oddball under threat
Conditions	FA, OP, Reading	<b>Video</b>	FA, OP, <b>Video</b>
Measures	ERPs, oscillations	ERPs, EDA, self-reports, questionnaires	

**Figure 1. Overview of the studies included in the present work.** Information on subjects, paradigm, experimental conditions and main measures implemented in each study. Information highlighted in red indicate subjects and conditions shared by different studies.

## 4.1 Expert practitioners

The expert meditation practitioners included in Study 1 and Study 3 were selected in a way that tries to address a common issue in the neuroscientific research on meditation, namely the lack of uniformed groups of expert practitioners.

In Study 1, long-term practitioners were selected based on a criterion of at least 10000 hours of formal meditation practice in the Nyingma and Kagyu traditions of Tibetan Buddhism, which have very similar styles of practice (sample mean: 28990 hours, SD: 13885). The length of their training was estimated based on their daily practice and the time they spent in meditative retreats.

The expert practitioners included in Study 3 were selected based on similar criteria: at least 10000 hours of practice (sample mean: 38466 hours, SD: 19439), having followed at least one 3-year meditation retreat and a daily practice of a minimum of 45 minutes over the year prior to the experiment. Most importantly, participants belonged to the same Tibetan traditions as for Study 1. Finally, before being selected they underwent an interview with a member of our team, who is equally experienced, regarding the quality of their everyday practice and motivation (see Annex 1 for additional details regarding selection process and inclusion criteria).

## **4.2 Protocol study: meditation and experiential training**



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

in review at *Consciousness and Cognition*

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## **Abstract**

Empirical descriptions of the phenomenology of meditation states rely on practitioners' ability to provide accurate information on their lived experience. We present a two-day meditation training protocol that was designed to equip meditation-naive participants with a theoretical background and experiential knowledge that would enable them to share their experience with the experimenters. 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) were correlated with behavioral measures (variability of response time). Each of these three effects was better predicted by features of participants' daily practice than by desirable responding. Our results provide evidence that meditation-naive participants can be trained to reliably report their experience along phenomenological dimensions.

## 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 et al. 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 2008). 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 is a European Research project (ERC Consolidator #617739-BRAINandMINDFULNESS) that attempts to practically apply this theoretical framework (for the study manual, see Abdoun et al. 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 (Varela 1996; Lutz & Thompson 2003).

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 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 and colleagues (2006)), (b) a soteriological or spiritual path conceived in therapeutic and health-promotion terms (e.g. in the Mindfulness-Based-Stress-Reduction program), 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"; see Kabat-Zinn 1994). 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 and colleagues' (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 et al. 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]) makes 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).

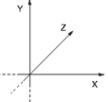
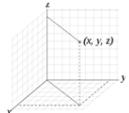
Instead we favor reconceiving mindfulness through a family resemblance approach whereby it can be conceptualized as “a variety of cognitive processes embedded in a complex postural, aspirational, and motivational context that contribute to states that resemble one another along well-defined phenomenological dimensions” (Lutz et al. 2015). This approach draws on previous efforts to conceptualize mindfulness (Chambers et al. 2009; Hölzel et al. 2011; Lutz et al. 2008) and the phenomenology of mindfulness practice. It is compatible with multiple explanatory and analytical frameworks from different subdisciplines, 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 the 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 different meditation instructions and training, congruent with the hypothetical plots previously published?

### COMMON GENERAL FEATURES:

Physical posture, nonaversive affect, axiological framework, task-set maintenance or retention

PRIMARY ORTHOGONAL DIMENSIONS	SECONDARY DIMENSIONS
 <p><b>Object orientation</b> sense that a mental state is oriented toward some objects or class of objects (e.g. perceptions, emotions)</p> <hr/> <p><b>Dereification</b> degree to which thoughts, feelings, and perceptions are interpreted as mental processes rather than as accurate depictions of reality</p> <hr/> <p><b>Meta-awareness</b> extent to which the experience is under monitoring</p>	 <p><b>Aperture</b> broadness of the scope of attention</p> <hr/> <p><b>Clarity</b> degree of vividness with which an experience occurs</p> <hr/> <p><b>Stability</b> degree to which experience presents itself as enduring over time</p> <hr/> <p><b>Effort</b> impression that one's present mental state is easy or difficult to maintain</p>

**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, nonaversive 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 nonaversive affect dimension during a nociceptive paradigm, and we interviewed after this paradigm the participants about the relationship between pain and their worldview.

## 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 (Hurlbert and Heavey 2001).

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 et al. 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 and Thompson 2013). First-person methods refer to methods that allow an investigator to bring a participant close to their subjective experience<sup>2</sup> (Petitmengin 2006), as well as to practices that subjects themselves can use to increase their sensitivity to their own experiences (Varela and Shear 1999; Depraz et al. 2003; Bitbol and Petitmengin 2013; Petitmengin et al. 2013).

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 and Papies 2017 for a study on affiliation motives and goals, and Koole et al. 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 (Khalsa et al. 2008; Melloni et al. 2013; Bornemann and Singer 2017). The inconclusiveness of these studies may be due to a lack of methodological validity (Zamariola et al. 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). 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 her wish to present

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<sup>2</sup> Such techniques were sometimes dubbed 'second person' methods, because they rely on the critical interventions of an interviewer.

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 and Cook 1972). To eliminate this confound, some researchers advocate the use of scales developed to capture individuals' inclination to self-enhancement (Crown & 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 2016). 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 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 and 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<sup>3</sup>. 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 minutes a day for an extended duration (6 to 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 novice 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.

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<sup>3</sup> 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.

The expert group was comprised of 30 healthy long-term practitioners with more than 10,000 hours of formal meditation in their life and trained in the Kagyu and Nyingma schools of the Tibetan Buddhism.

Among these participants, 25 trained novice practitioners and 25 expert practitioners participated to the MEG experiment described below. The novice and expert groups were matched in gender (16 and 15 males, respectively), age ( $53.9 \pm 7.1$  and  $51.6 \pm 8.0$  years, respectively; independent two-sample  $t=.84$ ) and education ( $3.88 \pm 2.15$  and  $3.20 \pm 2.16$  years of higher education, respectively; independent two-sample  $t=.46$ ).

## ***2.2 Meditation training protocol***

### **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 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.

### **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'*.

### **Day 2**

At the beginning of the day, 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.

DAY 1	DAY 2
<b>8.30-11 am</b> Screening	<b>9.30-10.30 am</b> Meditative Awareness ( <i>environment</i> )
<b>11-12 am</b> Effort ( <i>sound</i> ) Absorption & Meditative Awareness ( <i>intro</i> )	<b>break</b>
<b>12-13 am</b> Absorption & Meditative Awareness ( <i>breath</i> )	<b>10.45 am</b> Group Discussion ( <i>difficulties</i> ) Empathy & Compassion ( <i>intro</i> )
<b>break</b>	<b>break</b>
<b>14.30-15.30 pm</b> Absorption & Meditative awareness ( <i>breath</i> )	<b>14-15.45 pm</b> Focused Attention & Open Monitoring ( <i>pain</i> ) Empathy & Compassion ( <i>images</i> )
<b>break</b>	<b>break</b>
<b>16.30-17.30 pm</b> Focused Attention & Open Monitoring Object Orientation & Aperture Background & Foreground	<b>16-17 pm</b> Closing Meditation ( <i>intention to practice</i> ) Research Project Presentation Explanation Homework

**Table 2.** Program of the training weekend.

### ***2.3 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.

## **2.4 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 to 30 minutes 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-minute-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).

### **2.4.1 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*)<sup>4</sup>. Figure 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.

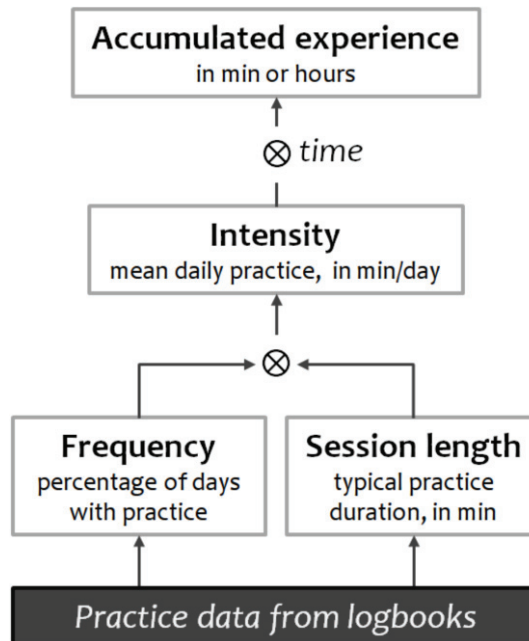
In addition, we calculated an index of balance between focus and open styles of practice, the Focus/Open Balance Index (hereafter referred to as FOB) for each participant. FOB is defined as the absolute difference between OM practice and FA practice, normalized by the sum of the two<sup>5</sup>:

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<sup>4</sup> Capitals are used to distinguish these terms from their common definitions.

<sup>5</sup> 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.

$$1 - \frac{|practice(FA) - practice(OM)|}{practice(FA + OM)}$$



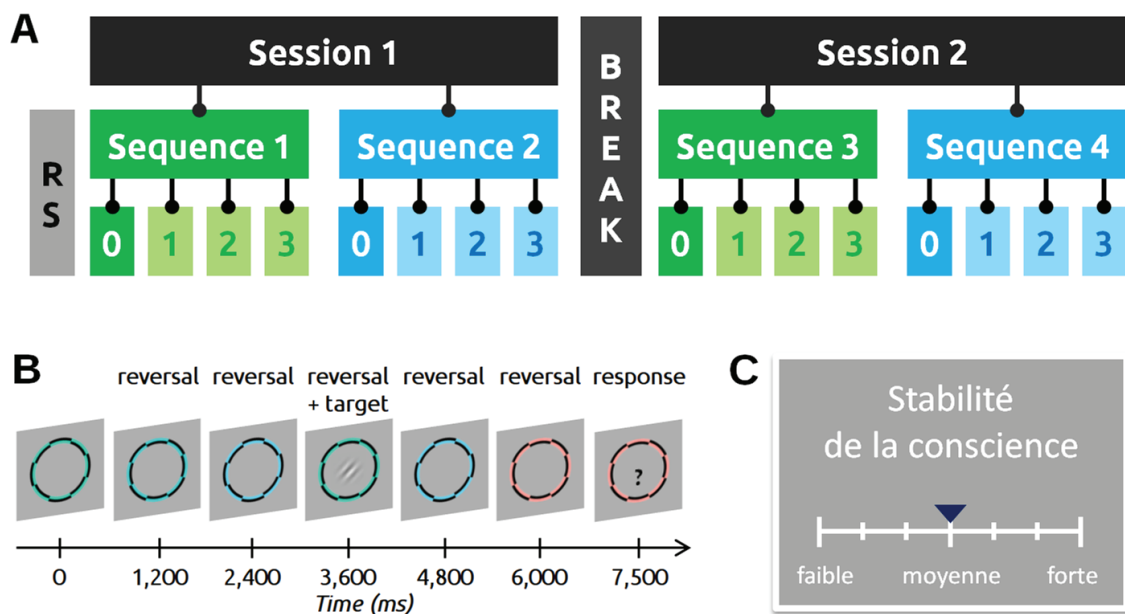
**Fig. 1** Four interrelated metrics were used to assess commitment to home practice.

## 2.5 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, followed by a 7 minutes baseline period. Then, participants practiced FA and OM twice each, in sequences of approximately 24 minutes (figure 3a). Each sequence opened with a 7 minutes-long block of meditation only, during which participants were presented with a 1.5°-wide white dot in the middle of a black screen (figure 3b). 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 (see detailed instructions in Supplementary). This first block was followed by three blocks lasting approximately

5.5 minutes 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 (figure 3c). After each block, participants were invited to rate their experience over 6 different dimensions, using a 7-point Likert-type item (figure 3d): *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<sup>6</sup>. Rating scales were thus introduced: “Compared to your usual experience, how would you rate the last block in terms of Stability/Clarity/Aperture?”



**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 in 2 sessions, with a 5 to 20-minute break in between. Each session was divided in 2 sequences: one of FA and one of OM, 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-minute block of “meditation only” (block 0) followed by three ~6-minute-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 in 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 to 7 reversals. In 36 of the 41 trials, a gabor patch set at threshold contrast was flashed for 50ms. 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.

<sup>6</sup> Just like for practice metrics, capitals are used for phenomenological dimensions to distinguish the terms from their common definitions.

## 2.6 Statistical analyses

**Factorial models.** 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 regressions.** 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 as 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 modelling 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 and 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 and 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 and Tsai 1989). Secondly, we selected models that were within two information criteria (IC) units of the best fitting model (Burnham and 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 and de Mazancourt 2010), comprised between 0 and 1.



## 3. Results

### 3.1 Structure of home practice

The duration of participation ranged from 41 to 163 days ( $99.4 \pm 31.4$  days) after the training weekend. Average daily practice (= Intensity) ranged from 1.3 to 30.5 minutes ( $15.9 \pm 7.3$  minutes; supplementary fig. 1a, top left), suggesting that many participants fell short of the recommended amount of practice (20 to 30 minutes 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 minutes ( $21.2 \pm 5.5$  minutes; 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 ( $F(2,80) = 16.95$ ,  $p < .0001$ ,  $\eta^2 = .30$ ). Post hoc paired t-tests revealed that all comparisons of pairs of practices were significant (supplementary fig. 1c).

Intensity of practice decreased linearly over weeks (supplementary fig. 2a;  $R^2_{adj} = .87$ ,  $p < .001$ ,  $\beta = -.44$ , 95% CI  $[-.53, -.35]$ ). A large portion of this drop (80.9%) is imputable to a sharp decline of Frequency of practice over weeks (supplementary fig. 2b;  $R^2_{adj} = .92$ ,  $p < .001$ ,  $\beta = -.14$ , 95% CI  $[-.16, -.12]$ ). The remaining 19.1% is due to a slight shortening of practice sessions (supplementary fig. 2c;  $R^2_{adj} = .22$ ,  $\beta = -.10$ , 95% CI  $[-.18, -.01]$ ).

Taken together, these results show that participants managed to follow the recommendation of 20-to-30-minute-long practice sessions throughout the study but failed to practice on a daily basis and were increasingly inclined to skip days.

### 3.2 Efficacy of phenomenological training

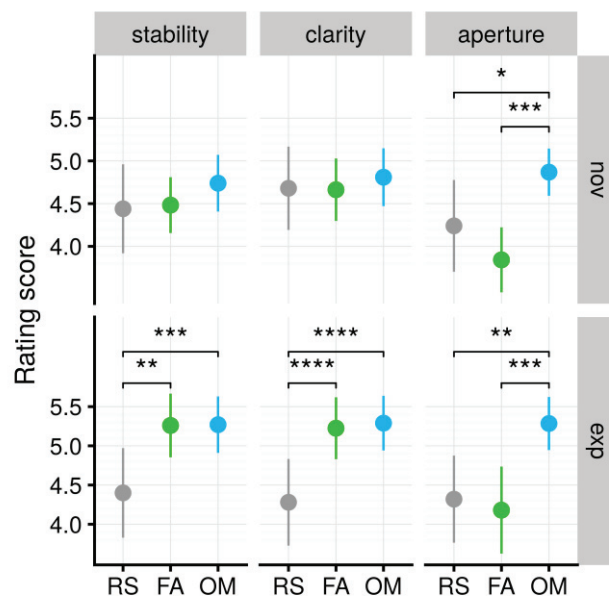
We tested three predictions that, if verified, could provide evidence that the phenomenological training was successful. We examined whether the responses of the novices to the rating scales in the MEG experiment i) were sensitive to the meditation state, in a way consistent with the known phenomenology 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.

### 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.

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 ( $F(2,96) = 19.54, p < 0.001$ ). 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 state by group interaction was found ( $F(2,96) = 5.19, p = .007$  and  $F(2,96) = 10.22, p < .001$ , 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 either Stability nor Clarity, across the 3 conditions, in the novice group (all  $p > .24$ ). To summaries, participants' ratings corroborated the hypothesized phenomenological pattern in the expert group for all three secondary dimensions tested, but only for Aperture in novices.



**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.



### ***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. To test this prediction, 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 *Methods, Variable selection*).

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 (.31). The FOB-by-Experience interaction had a higher evidence across model space than the FOB-by-Intensity interaction (.55 and .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 hours of practice, the FOB index positively predicts ( $p < .05$ ) the self-reported difference in Aperture between FA and OM during the MEG experiment.

### ***3.2.2 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 figure 3). We used a linear mixed model to account for the nested nature of the MEG experiment structure (blocks within sequences within sessions). The model included all possible interactions in fixed effects, as well as random subjects intercepts and by-subject random slopes across blocks, sequences and sessions. We found an effect of block on Stability ratings only

for the first sequence of each session (i.e. sequences 3 and 4; cf. fig. 2). The same model on Clarity ratings produces the same result. Post-hoc pairwise t-tests revealed a significant difference between blocks 1 and 3 in sequences 3 and 4, but no pairwise differences in other sequences.

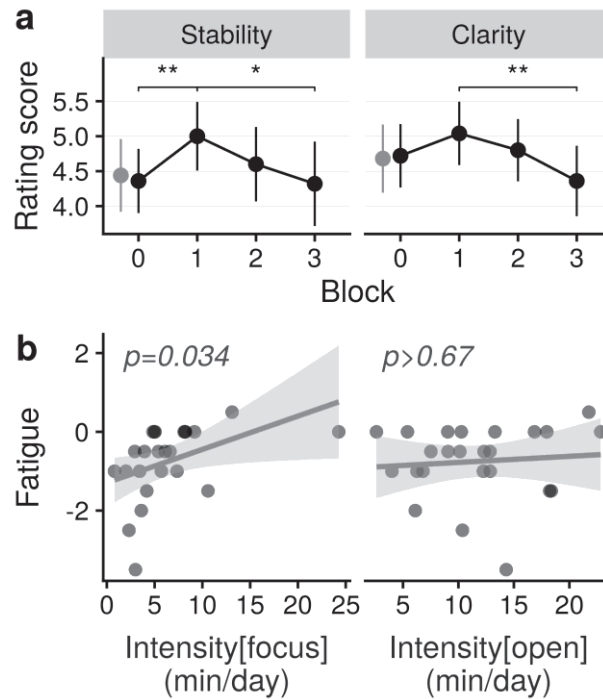
### **Predictors of the fatigue effect**

The decrease of self-reported Stability and Clarity in novices after four blocks (~ 24 minutes) of meditation may reflect fatigue. This is not surprising considering that most novices were not used to meditate for more than approximately 20 minutes 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<sup>7</sup>, 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 (.74 and .66, respectively) closely followed by BIDR (.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 FOBI by the two subcomponents of Intensity, Intensity<sub>focus</sub> and Intensity<sub>open</sub>, corresponding to the two styles of practice. For the sake of parsimony, we also removed Experience, which was already found of low importance. The only selected model from this variable space had a single regressor, Intensity<sub>FA</sub> ( $p=.034$ ,  $\beta=.085$ , 95% CI [.007, .162]; supplementary table 3).

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<sup>7</sup> The same analysis based on data combining 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 during the second block ( $\Delta=.64$ , 95% CI [.03, 1.25],  $p=.036$ ), followed by fatigue in subsequent blocks (Stability:  $\Delta=-.68$ , 95% CI [-1.29, -.07],  $p=.023$ ; Clarity:  $\Delta=-.68$ , 95% CI [-1.20, -.16],  $p=.005$ ). **(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: \*:  $p<.05$ ; \*\*:  $p<.01$

### 3.2.3 Correlation with behavioral measures

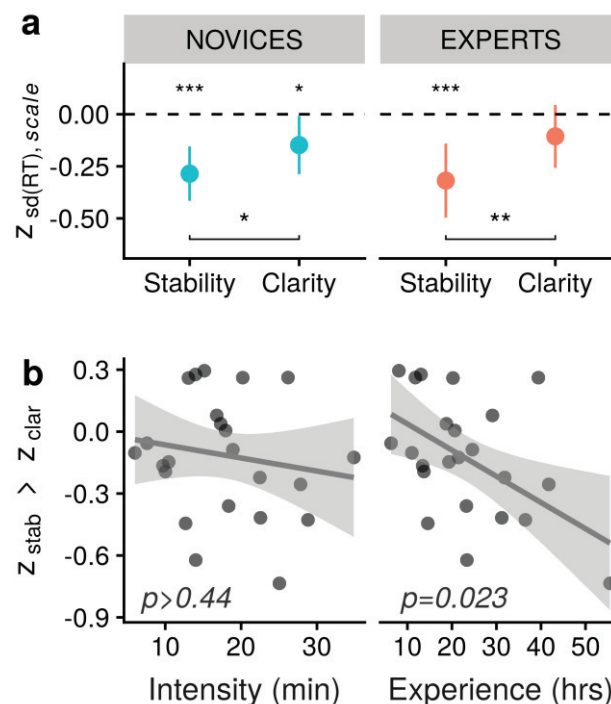
Previous studies have reported intra-individual variability of performance (most notably response times) as a good predictor of whether the participant is on-task at a given moment or not (Batian and Sackur 2013; Seli et al. 2013). Based on this literature, we predicted that self-reported Stability, 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 state and group (see fig. 4).

One sample Wilcoxon signed rank tests show that the RT variability correlated negatively with Stability ( $z=-.26$ , 95% CI [-.40, -.12],  $p<.0003$ ) as expected, but also with Clarity ( $z=-.14$ , 95% CI [-.28, -.003],  $p=.046$ ) (fig. 6a, left). However, a two-sample paired test between  $z_{\text{stability}}$  and  $z_{\text{clarity}}$  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:  $z=.77$ , 95%CI [.62, .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. 6a, 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  $p > 0.1$ ).

### 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 ( $p = .034$ ,  $\beta = -0.011$ , 95% CI [-0.021, -0.002]; fig. 6b). Across all models, Experience had by far the highest evidence weight (.84).



**Fig. 6** Self-reports from novices appear to be functionally relevant. **(a, left)** The variability of response times, for example, correlates negatively with self-reported stability. It also correlates negatively with clarity, but significantly less so, indicating that these two dimensions are properly differentiated by novice participants. **(b)** Functional differentiation of stability and clarity was higher in those 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: \*:  $p < .05$ ; \*\*:  $p < .01$ ; \*\*\*:  $p < .001$

## 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 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, we found that for participants who practiced the most (more than 24 hours in total), their response on the Aperture scale was driven by their practice structure: the better they balanced focus and open styles of meditation, the larger the divergence in Aperture they reported. This finding suggests that equal familiarity with different states is important for their optimal dissociation, at least at a beginner level.

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.



			Predictors' evidence across model space		
DV	Interpretation	Level of DC	BIDR	Practice	
$apr_{OM} - apr_{FA}$	Discrimination of states	strong	.31	.55	FOB x Experience
$\frac{stb_3 - stb_1}{2} + \frac{clr - clr_1}{2}$	Fatigue	moderate	.40	.74	Intensity <sub>focus</sub>
$Z_{RTV, stb} - Z_{RTV, clr}$	Discrimination of phenomenological dimensions	none	.23	.84	Experience

**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; FOB: focus/open practice balance index; Stb: Stability; Clr: Clarity; Apr: Aperture; RTV: response time variability.

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. 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 trained 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 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 et al. 2016). 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 to 40 hours were necessary for novices to reach a level of phenomenal specificity comparable to the one of experts; a minimum of 20 minutes 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 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.

## **5. Conclusion**

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 (Paulhus et al. 2003; Kwan et al. 2004).

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, we remain aware that our approach is tailored to the specific context of our study, and to a particular phenomenological model of meditation among others (Bodhi 2011; Lindahl et al. 2017; Van Dam et al. 2017). 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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## 4.3 Electrodermal activity

### 4.3.1 General definition

The skin is the largest organ of the human body and its principal interface with the environment. It subserves processes spanning from thermoregulation and vitamin production to sensorimotor exploration and emotional communication (Critchley, 2002). In general, we refer to electrodermal activity (EDA) to describe changes in the electrical properties of the skin that result from the activity of the sympathetic branch of the autonomic nervous system (ANS). EDA is considered a sensitive biomarker of psychophysiological processes, reflecting sympathetic arousal in the context of cognitive and emotional states. The most widely used methods for measuring changes in EDA apply either direct current (DC) or alternating current (AC) to the skin, known as *exosomatic* recording. When the voltage is kept constant in DC methods, we refer to the changes in EDA as skin conductance (SC) [Boucsein, 2012, Chapter 1]. Spontaneous fluctuations in SC that occur through time represent the tonic component of a typical recording and are defined as skin conductance level (SCL). An individual's SCL can slowly vary over time depending on specific psychological states, hydration, skin dryness and autonomic regulation. On the other hand, skin conductance responses (SCRs) define changes in EDA in response to discrete environmental stimuli<sup>8</sup>. These phasic changes are identified as abrupt increases in SC occurring few seconds after stimulus onset. The common measure unit for both SCL and SCRs is the micro-siemens ( $\mu\text{S}$ ).

### 4.3.2 Historical background

The first recordings of what was previously termed galvanic skin response date to the last two decades of the 19<sup>th</sup> century. Whereas a detailed account of the historical development of EDA recording can be found elsewhere (Neumann and Blanton, 1970), it is worth considering some specific issues that have been object of debate in the last century to help understanding the rationale and methodological choices of implementing this measure in our research.

A first source of debate had been the general methodology of EDA recording. Working in the same laboratory as the famous neurology Jean Charcot, Féré (1888) discovered that the skin conductance increases in response to external stimuli when applying a small electrical current across two electrodes placed on the skin surface. However, few years later, Tarchanoff (1890) reported that the same changes in EDA could be

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<sup>8</sup> Non-specific skin conductance responses (NS-SCRs) have also been described in the literature. They occur in the absence of clearly identifiable eliciting stimuli and are supposed to represent changes in tonic EDA.



recorded without applying any electrical current. This gave rise to the distinction between *exosomatic* and *endosomatic* methods. In the present days, *exosomatic* recordings are the method of choice among researchers and the one we used in our research.

An important issue that has been discussed in decades of research in physiology regards the mechanisms underlying the observed changes in EDA. Initially, contrasting theories posited that changes in EDA were associated to changes in blood flow (*vascular theory*) or to the activity of sweat glands (*secretory theory*) [Neumann and Blanton, 1970]. Subsequent research has proven the latter to be the most plausible theory of the peripheral mechanisms underlying EDA (see Fowles, 1986 for a review). Notably, this theory proposed the involvement of the sympathetic branch of the ANS, which innervates palmar and plantar sweat glands, in the EDA. Moreover, an evolutionary perspective on the SCRs in different emotional and cognitive contexts comes from the idea that “the function of the secretory activity of the palms is primarily to provide a pliable adhesive surface facilitating tactual acuity and grip on objects” (Darrow, 1937).

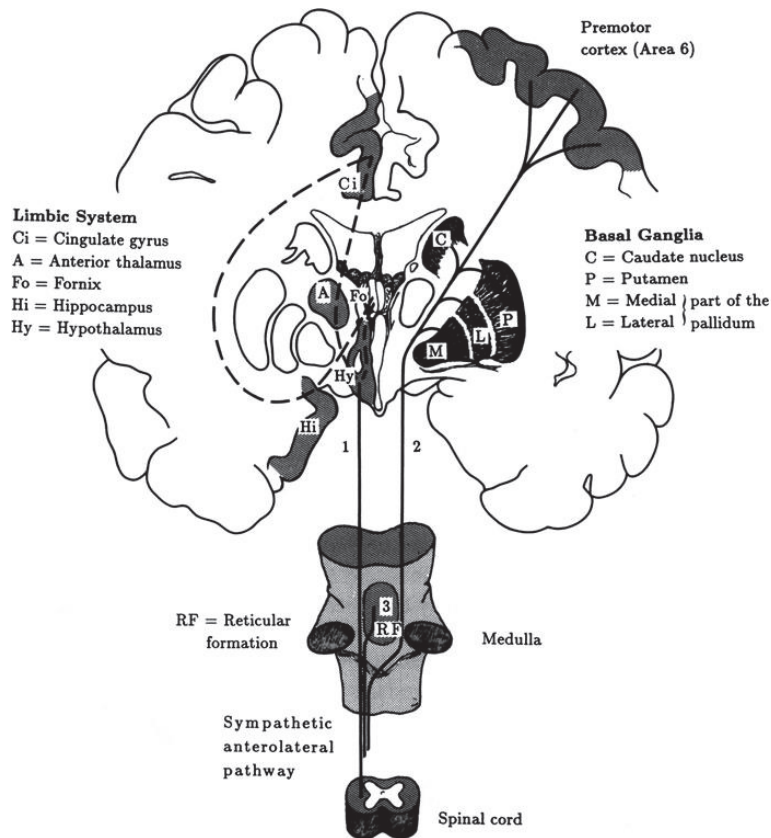
Finally, studies in the last century has helped in elucidating aspects of a research topic that is still of central importance in psychophysiology: the functional significance of the EDA. While early research started to highlight the impact of emotional stimuli on SCRs (Neumann and Blanton, 1970), later studies have described the modulation of SCRs by cognitive factors such as attention and stimulus novelty (R.S. Woodworth and Schlosberg, 1954). The extensive research done on this topic thorough the decades is essential for developing paradigms that consider different aspects of psychophysiology and their differential impact on EDA.

### 4.3.3 Anatomical and physiological basis

There is a broad consensus on the involvement of eccrine sweat glands in the peripheral mechanisms underlying SCRs, and EDA in general. While the primary function of most of these glands is thermoregulation, those located in the palmar and plantar surfaces are thought to be related to grasping behaviour rather than sweating for evaporative cooling (Dawson et al., 2007). It is also known that eccrine glands receive mostly cholinergic afferences from the sympathetic branch of the ANS (Critchley, 2002). This relates EDA to *autonomic arousal*, which is associated with increased heart rate, blood pressure, sweating and diversion of blood from gut toward limb musculature. The aforementioned sympathetic activity is linked to stereotyped fight-flight responses and it is not surprising that increases in EDA accompany movements and motor preparation (Critchley, 2002).

Whereas a variety of EDA phenomena can be explained, at the peripheral level, by the activity of sweat glands (Edelberg, 1993), the contribution of brain sources to the modulation of EDA is far more complex and still under debate. In fact, the production of SCRs could be modulated by three relatively independent pathways (Figure 2). A first pathway is constituted by the descending excitatory projections of neurons

located in the premotor cortex (Brodmann area 6), as well as excitatory and inhibitory efferences from the frontal cortex. A second level of control is delivered by the hypothalamus and limbic system, with excitatory influences from the amygdala and inhibitory activity form the hippocampus. A third level is constituted by the reticular formation, in the brainstem (for detailed reviews see (Boucsein, 2012; Dawson et al., 2007)).



**Figure 2. Regions of the central nervous system that underlie the control of electrodermal activity.** Originally published in Boucsein et al. (2012)

#### 4.3.4 Emotional modulation and habituation

As previously mentioned, the debate on the psychological processes reflected by measures of EDA has characterized a large part of its history. This debate was ascribed to a more general discussion on whether the activity of the ANS reflected general arousal or could be related to specific emotional states. A legitimation of the use of EDA in paradigms investigating emotional states came from the neurophysiologically-oriented emotion theory of Papez (Papez, 1937), which included the activity of the

ANS as part of the neural circuit underlying the formation and control of emotions. The prominent role of EDA in emotions has been subsequently confirmed by neurophysiological models of anxiety (Gray and McNaughton, 1982) and by several studies correlating subjective measures of emotional reactions to changes in EDA. A comprehensive description of the empirical evidence supporting the impact of different emotions on the EDA is out of the scope of this section (for an extensive account see Boucsein, 2012, Chapter 3). However, I provide a brief characterisation of the impact of anxiety on the EDA, as it is useful to understand its implementation in the present project.

Another characteristic of the EDA, which is relevant for the studies we conducted, is its sensitivity to habituation. As for the impact of anxiety, I provide here a brief description of this effect.

#### *4.3.4.1 EDA and laboratory-induced anxiety*

Most of the studies investigating the effect of anxiety on the EDA in experimental settings rely on a common definition of stressor as “subjective and/or objective challenges exceeding a critical level with respect to intensity and/or duration” (Boucsein, 2012, Chapter 3). Such stimuli would induce a state of general arousal and negative, but unspecific, emotion. A reaction that attempts to re-establish the homeostasis at both physiological and psychological levels.

Early studies observed increases in SCL when participants watched stressful scenes in movies (Lazarus, 1966). However, later research reported that the increase of EDA during the anticipation of a stressor is greater than that directly following the presentation of the stimulus. This effect was observed in studies that introduced the threat of electric shock as a stressor (e.g. Folkins, 1970) and it is of great relevance in paradigms that investigate anticipatory anxiety. Increase EDA was observed also during periods that anticipated public speaking, which has been shown to represent an even more powerful stressor than the threat of electric shock (Erdmann et al., 1984). Interestingly, EDA is also influenced by the degree of control that one exerts over the stressor, or by one’s perception of such control. For instance, Geer et al. (1970) showed that SCRs to electric shocks habituated faster in those participants who were told that answering to questions faster during the experiment could reduce the time of the shock.

EDA is nowadays used as a biomarker of stress in response to different kinds of stress-inducing stimuli and it is considered a valuable tool in this field of research (Boucsein, 2012, Chapter 3).

#### *4.3.4.2 Influence of habituation*

The quantification and interpretation of habituation processes in the EDA depends on the definition of this phenomenon in a specific research framework. Habituation can be simply defined as a “decrease in response intensity with repeated stimulation” (Harris, 1943; Humphrey, 1930). Nonetheless, a decrease in amplitude of SCRs has also been investigated as a basic form of learning (i.e. “learning not to respond”, Boucsein, 2012). In the context of the present project, we considered SCRs habituation

phenomena derived from the repetition of the same auditory cues within and between experimental blocks and sessions. We therefore adopted the former definition and general definition of habituation to control for and investigate repetition effects in our paradigm. EDA is one of the most used measures of habituation in human studies and a decrease in amplitude of SCRs from the first to the successive presentations of the same or similar stimuli can be determined by simple visual inspection.

#### 4.3.5 EDA measures in the present project

Measures of skin conductance have been implemented in Study 2 and Study 3 of the present project. The theoretical rationale underlying this implementation is 1) to provide a reliable biomarker of anticipatory anxiety and do not rely solely on self-reports and 2) to explore eventual dissociations between physiological activity and subjective experience in expert practitioners and during meditation states.

The recoding of EDA has required to choose a specific methodological approach, in terms or type of measures (SCRs or SCL) and equipment. Additionally, the common experimental paradigm for Study 2 and Study 3 has been adjusted, in terms of structure and stimuli, to allow for a solid measurement of skin conductance. Specifically, we took advantage of a pre-existing task structure (see Cornwell et al., 2007) that was suitable for recording changes in skin conductance. The repetition of several ~30 seconds safe and threat periods within each block constituted an ideal time-window for the study of EDA, which is a relatively slow-changing measure. Within this framework, we opted to record SCRs to auditory cues introducing safe and threat periods. This allowed us to record clean SCRs, which happen within 1 to 5 seconds after stimulus onset (Society for Psychophysiological Research Ad Hoc Committee on Electrodermal Measures, 2012). We chose to focus on phasic activity to maximise the signal to noise ratio (four measures per block for safe and threat periods) while avoiding confounds caused by other processes that could affect tonic activity (e.g. general level of stress, fatigue, physiological states, general relaxation during meditation). Additionally, we recorder SCRs in response to electric shock stimuli, which were spaced enough from one another to be able to isolate the electrodermal response. For further details on the specific data processing and statistical analyses of SCRs, see the Methods section of Study 2 and Study 3.

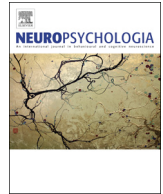


# EXPERIMENTAL RESULTS

## Chapter 5

# Perceptual learning in neutral settings

### **5.1 Study 1: The impact of open presence and focused attention meditation on perceptual learning and auditory processing in expert and novice practitioners**



## Differential effects of non-dual and focused attention meditations on the formation of automatic perceptual habits in expert practitioners

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### ABSTRACT

Non-dual meditation aims to undo maladaptive cognitive and affective patterns by recognizing their constructed and transient nature. We previously found high-amplitude spontaneous gamma (25–40 Hz) oscillatory activity during such practice. Nonetheless, it is unclear how this meditation state differs from other practices, in terms of perceptual information processing. Here, we hypothesized that non-dual meditation can downregulate the automatic formation of perceptual habits. To investigate this hypothesis, we recorded EEG from expert Buddhist meditation practitioners and matched novices to measure two components of the auditory evoked response: the Mismatch Negativity (MMN) and the Late Frontal Negativity (LFN), a potential observed at a latency sensitive to attentional engagement to the auditory environment, during the practices of Open Presence (OP) and Focused Attention (FA), as well as during a control state, in the context of a passive oddball paradigm. We found an increase in gamma oscillatory power during both meditation states in expert practitioners and an interaction between states and groups in the amplitude of the MMN. A further investigation identified the specific interplay between the MMN and the LFN as a possible marker to differentiate the two meditation states as a function of expertise. In experts, the MMN increased during FA, compared to OP, while the opposite pattern was observed at the LFN latency. We propose that the state of OP in experts is characterized by increased sensory monitoring and reduced perceptual inferences compared to FA. This study represents a first attempt to describe the impact of non-dual meditation states on the regulation of automatic brain predictive processes.

### 1. Introduction

We recently proposed a novel classification system that categorizes various styles of meditation into attentional, constructive, and deconstructive families based on their primary cognitive mechanisms and their specific impact on self-related processes and different aspects of well-being (Dahl et al., 2015). While attention-based meditation and compassion-based practices (i.e., the constructive family) are increasingly studied as tools for cognitive neurosciences, little is still known about the basic neurophysiological and cognitive processes underlying the so-called “deconstructive family” (Dahl et al., 2015). Deconstructive style of meditation aims to undo maladaptive cognitive and emotional patterns (e.g. rumination, neuroticism) by exploring the dynamics of perception, emotion, and cognition and generating insights into one's

internal models of the self, others, and the world. This self-inquiry can involve exploring self-related processes with discursive analysis, akin to cognitive-based therapy, or by direct examination of conscious experience through phenomenological methods. This latter approach is especially cultivated in so called non-dual forms of meditation, and familiarity with the contemplative methods involved requires intensive training. Contemplative traditions allege that non-dual meditation practices are important for alleviating suffering, and such practices also play a role in many contemporary mindfulness-based interventions (Dunne, 2011). Apart from very few studies (e.g. (Josipovic, 2014)), the clinical benefits of this approach and its behavioral and neurophysiological mechanisms are still largely unknown.

To explore this topic, we studied the meditative state of “Open Presence” (OP) in Tibetan Buddhist traditions as a paradigmatic case of

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non-dual meditation. Styles of meditation that cultivate OP are described as inducing a phenomenal experience where the intentional structure involving the duality of object and subject is attenuated. In this sense, such styles of contemplative practice are “non-dual” (Lutz et al., 2007). One important phenomenological element of the state of OP is a spontaneously occurring suspension of the representational models of the self and objects in the world. At the same time, OP styles of meditation are said to instantiate a state of relaxed lucidity, where perceptual phenomena are experienced with more saliency and clarity, without acting upon them or avoiding them. In such a way, perceptual phenomena in OP spontaneously appear and vanish in the field of awareness like “patterns drawn on water” (Dowman, 1994).

Based on these phenomenological descriptions, we hypothesized that OP practice downregulates the formation of perceptual habits while increasing the monitoring of the sensory environment, modulating brain predictive processes in relation to a specific profile of spontaneous brain activity. As the stability of OP is considered to require extensive training, we expected this effect to be present in expert practitioners only. To test this hypothesis, we used electroencephalography (EEG) to study a well-characterized component of the auditory-evoked potential, the Mismatch Negativity (MMN) (Näätänen et al., 2004), which measures implicit perceptual learning processes. The MMN reflects the violations of predictions that the brain casts over the regularity of the auditory environment, following the presentation of a “deviant” stimulus after several “standard” tones (Garrido et al., 2009). We expected to observe a decrease in MMN amplitude in experts, compared to novice practitioners, during the practice of OP and compared to a control state where attention is diverted from the auditory stream. To characterize the specificity of OP meditation, we compared this state to a control state of concentrative meditation, or Focused Attention (FA) (Lutz et al., 2008). FA meditation requires the practitioner to monitor ongoing distractors while maintaining attention on the chosen object. During FA, we expected the increased monitoring of task-unrelated events to enhance the brain responses to deviations of the auditory environment, as measured by increased MMN amplitude. Furthermore, we looked at later latencies (after 200 ms) of the auditory-evoked response to characterize differences between states and groups in terms of monitoring and saliency of the sensory environment (e.g. Escera and Corral, 2007; Chennu et al., 2013). As stated above, we expected both meditation states to result in increased monitoring of the incoming stimuli, but having a different impact on brain predictive processes. Previous studies have investigated biomarkers of different meditative practices, focusing especially on brain oscillatory activity (e.g. Cahn and Polich, 2006 for a review). In the present study, we aimed at confirming previous findings in this domain, as well as investigating a putative functional relationship between specific oscillatory profiles and the hypothesized modulation of predictive processes in non-dual practices. More specifically, we predicted increased power of oscillatory activity in the alpha (8–12 Hz) frequency range during meditation, as a correlate of general relaxation and in line with previous studies (Cahn and Polich, 2006). In addition, we also predicted that higher activity in faster oscillatory rhythms (i.e. 25–40 Hz) at frontal scalp regions would underlie the state of high meta-awareness and perceptual saliency in OP, a profile previously identified during a similar form of non-dual practice (Lutz et al., 2004).

## 2. Materials and methods

### 2.1. Ethics statement

All study and task details were approved by the UW-Madison Health Sciences Internal Review Board. Participants provided written informed consent for all study procedures.

### 2.2. Subjects

Sixteen long-term meditation practitioners ( $43.4 \pm 9.4$  years old, 12 males and 4 females) and fifteen age-matched controls ( $42.4 \pm 11.4$  years old, 13 males and 2 females) participated in the study. Long-term meditation practitioners were selected based on a criterion of at least 10,000 h of formal meditation practice in the Nyingma and Kagyu traditions of Tibetan Buddhism, which have very similar styles of practice (mean: 28,990 h, SD: 13.88). The length of their training was estimated based on their daily practice and the time they spent in meditative retreats. Ten hours of sitting meditation were counted per day of retreat. Based on this criterion, these practitioners are referred to as “experts” here for brevity. Control participants were recruited from the local community and had no previous experience with any type of meditation, but expressed interest in learning meditation. Subjects in the control group were familiarized with the meditation instruction for one week before the experiment and were guided by verbal instructions during the practice.

### 2.3. Meditation practices and training

Open Presence (OP) styles of practice are found in both the Mahāmudrā or Chagchen (Tibetan, *phyag chen*) and the Dzogchen (Tibetan, *Rdzogs chen*) traditions of Tibetan Buddhism (Van Schaik, 2004). In this regard, these contemplative traditions overlap so significantly that Tsele Natsog Rangdrol, an influential Tibetan author from the 17th century, combines the Tibetan terms for these two traditions into a single moniker, “Chag-zog” (2). The main focus for Chag-zog styles of practice is to recognize the “nature of the mind” (Tibetan, *sems nyid* or *sems kyi rang bzhün*) or one’s fundamental “awareness” (Tibetan, *rig pa*) and then to sustain that recognition. In this study, the term “rigpa chok zhag” (Tibetan, *rig pa cog bzhag*)—literally, “placing the mind directly in fundamental awareness”—was the term used for OP practice, but various other terms for OP practice are also widely known and are essentially synonymous (Lutz et al., 2007; Rangdrol, 2011). Referring to the Tibetan Chag-zog traditions as “systems of definitive meaning,” Rangdrol describes the key features of OP practice in this way:

“Let go into your natural state, with no need to cling or fixate on even the impetus or the attitude, “I meditate!” Without disturbing yourself with any ambition, such as hoping for a good meditation or fearing it won’t succeed, to let be in unfabricated naturalness free from concepts is the meditation state of all the systems of definitive meaning” (Rangdrol, 2011).

Based on its traditional presentation (Namgyal, 2001; Third Dzogchen Rinpoche, 2008; DBaṅ-phyug-rdo-rje, 2009; Rangdrol, 2011) and scholarly analysis (Lutz et al., 2007; Dunne, 2011, 2015), OP practice is viewed here as an advanced form of Open Monitoring (OM) practice (Lutz et al., 2008), in which practitioners might be found at various levels of achievement. OP meditation consists theoretically of a state where the qualities of effortless openness and acceptance are vividly experienced with minimal control-oriented elaborative processes. The lack of explicit monitoring in OP meditation is the pivotal but finely grained difference from OM practice, and this distinction concerns the Buddhist notion of “reflexive awareness,” as discussed by Buddhist scholars (Coseru, 2012; Dunne, 2015). Briefly, in OP practice, an awareness of whatever emerges in experience continues without the effortful vigilance that characterizes OM styles of practice. For reasons of simplicity, we will continue to use the term “monitoring” in this scientific context to describe this aspect of OP, with the understanding that this term takes a slightly different meaning in OP and OM. In addition to the OP meditation of “placing the mind directly in awareness,” practitioners also engaged in a Focused Attention (FA) style of practice known as “one-pointed concentration” (Tibetan, *rse gcig ting nge’dzin*; see Namgyal, 2001). As with any FA style of practice, in one-pointed

concentration one maintains selective attention on a chosen object, and in this case sustained attention was directed at a fixation cross. This FA style of practice is considered here as second meditation condition to determine the specificity of effects observed in the OP practice. Control participants were given instructions written by a scholar who is familiar with the practices (see [Supplementary material 1](#)), and then told to practice at home 30 min a day for 7 days prior to the experiment.

#### 2.4. Auditory paradigm

Subjects underwent a passive auditory oddball task ([Näätänen et al., 2004](#)), consisting of the variable repetition of a standard tone (1000 Hz; 60 ms duration; 10 ms rise and fall; 80 dB SPL) followed by the presentation of a frequency deviant tone (1200 Hz; 60 ms duration; 10 ms rise and fall; 80 dB SPL). Each block of the task contained 80% standard tones ( $n = 200$ ) and 20% deviant tones ( $n = 50$ ) with a variable inter-stimulus interval of 800–1200 ms (block duration: 4m15s on average). Each subject underwent three blocks per condition and three different conditions: Open Presence (OP), Focused Attention (FA), and Reading (RE) as a control condition. The two meditative practices, OP and FA, are described above. During the control condition (RE), subjects were instructed to read a newspaper and ignore the auditory stimulation. The order of blocks was randomised and each subject underwent the same order, as follows: RE1 - OP1 - FA1, FA2 - OP2 - RE2, OP3 - FA3 - RE3.

#### 2.5. EEG recording

EEG data were recorded at standard extended 10–20 positions with a 128-channel Geodesic Sensor Net (Electrical Geodesics, Eugene, OR), sampled at 500 Hz, and referenced to the vertex (Cz). Data were filtered, using an analogue band-pass filter, between 0.1 and 200 Hz. A digital notch filter was applied to the data at 60 Hz to remove any artefacts caused by alternating current line noise. Bad channels were replaced by using spherical spline interpolation ([Perrin et al., 1989](#)).

#### 2.6. Data pre-processing

Data were first converted into EEGLAB software format ([Delorme and Makeig, 2004](#)), which was used for the first pre-processing steps. Data were filtered between 0.5 and 100 Hz and manually cleared of large movement-related artefacts. Independent Component Analysis (ICA) was applied to the raw data of each participant (on those channels that were not interpolated) using the Runica algorithm ([Makeig et al., 2002](#)) to identify and remove artefacts caused by blink, saccades, and cardiac (EKG) and muscular activity. We further investigated ICA profiles to determine whether some specific components that are prevalently found in expert meditation practitioners, which are characterized by a sustained peak of gamma activity distributed in several locations over the scalp, had to be rejected as caused by muscular activity or rather had to be kept in the EEG analysis as genuine contributions to the brain signal (see [Supplementary material 2.1](#) for a detailed description of these profiles and the methods used to test their contribution to the ERP). After ICA correction, data were re-referenced offline to the average of both mastoids, a non-causal band-pass 1–60 Hz digital filter was applied, and two-second epochs centred on stimulus presentation ( $-1$  to  $1$  s) were generated. For each subject and for each state we generated a “deviant” condition, comprised only of epochs centred on deviant tones, and a “standard” condition, comprised only of epochs centred on standard tones that were presented just before a deviant tone. After manually rejecting artefacts, the number of trials did not differ significantly between states, conditions, and groups. Although there was a trending difference between states ( $F(2, 58) = 3.38$ ;  $p = 0.054$  Huynh-Feldt corrected), we did not take it into account in further data analysis, since the largest difference between states (FA – RE) in the number of trials was only 3% (see [Supplementary material 2.2](#) for descriptive statistics). The epoched data were baseline-corrected

by subtracting the mean value of the signal during the 100 ms before stimulus presentation.

#### 2.7. Event-related potentials

We converted data from EEGLAB into SPM8 (Wellcome Department of Imaging Neuroscience, London, UK) software format, which was used for the following steps of event-related potentials (ERPs) analysis. After conversion into SPM8, we generated ERPs for each subject, state, block, and stimulus type using the robust averaging method implemented in SPM8. We used this procedure as a complementary artefact-correction for any artefacts that were not removed by previous artefact-rejection methods. Since robust averaging can re-introduce high frequencies into the signal, we filtered data again at 1–20 Hz and reapplied baseline-correction. We then performed two streams of analysis to investigate differences between groups and states that appeared in the MMN and later latencies, respectively. Statistical analyses were performed using R software (version 3.4.2) ([R core team, 2017](#)).

To identify the MMN, we computed difference waveforms from the grand average for each group and state, subtracting responses to standard stimuli from those to deviants. We used an a priori region of interest (ROI) for the assessment of this component, basing our ROI on previous literature (e.g. ([Duncan et al., 2009](#); [Näätänen et al., 2011](#))), resulting in a frontal ROI comprised of twelve electrodes, including Fz (see [Fig. S1](#)). Our selection of this ROI was confirmed by observation of the topography of the standard and deviant waveforms and difference waveforms (MMN) across all subjects and states, as well as those for each state and group taken separately.

We computed the mean amplitudes of MMN for each participant and state over a time-window of 90–180 ms after stimulus onset. This time-window was in line with previous literature (e.g. ([Opitz et al., 2002](#))) and confirmed through the observation of the time-course of the MMN waveforms in the main region of interest. We then fitted a linear mixed-effects model using the R package lme4 ([Bates et al., 2014](#)). The model comprised the average MMN amplitude as dependent variable, the interaction between STATE (FA, OP, RE) and GROUP (Experts, Novices) as fixed effect, and subjects as random effect. The model was tested using an ANOVA analysis of variance (Type II Wald chi-square test). Paired  $t$ -tests, corrected for multiple comparisons using Tukey honestly significant difference test (HSD), were used as post-hoc tests comparing least-squared means.

As a second line of analysis that would focus on differences between groups and states in late latencies (after 200 ms), we looked for a time window for which the signal in response to standard tones, within the a priori ROI used for the MMN, was significantly different between the meditation (both FA and OP) and control (RE) conditions, across groups. We corrected for multiple comparison using a non-parametric, permutation-based, cluster-level statistical test ([Maris and Oostenveld, 2007](#)) in MNE v0.14 (cluster-defining threshold = 0.01; cluster-level threshold = 0.05; 10,000 permutations). A temporal cluster was found between 280 and 400 ms post-stimulus. We used this time-window for subsequent analyses of the late negative ERP component, henceforth referred to as Late Frontal Negativity (LFN). We fitted a linear mixed-effects model comprising the average LFN amplitude (combining standard and deviant stimuli) as dependent variable, the interaction between STATE and GROUP as fixed effect, and subjects as random effect. The model was tested using an ANOVA analysis of variance (Type II). Paired  $t$ -tests, corrected for multiple comparisons using Tukey HSD, were used as post-hoc tests comparing least-squared means.

Finally, we explored in a post-hoc analysis the interplay between early (MMN) and late (LFN) components of the auditory evoked potential as a mean of investigating differences between states and groups in terms of monitoring and perceptual inference. Data from each participant and state for the two ERP components was mean-centred by subtracting to each observation the average of the corresponding component across states and groups. Data were then entered in a two-

way repeated measures ANOVA (rmANOVA), with STATE (three levels: FA, OP, RE) and COMPONENT (two levels: MMN and LFN) as within-subject factors and GROUP (two levels: EXPERT, NOVICE) as a between-subject factor.

## 2.8. Spectral analysis

For spectral analysis, we used epoched data before conversion to SPM8 (filtered between 1 and 60 Hz), combining epochs derived from all stimuli (all standard and deviant tones). We computed the power spectral distribution for each electrode and for each 2-s epoch using Welch's method (Welch, 1967), which averages power values across sliding windows (window width = 500 ms, overlap = 50%). We averaged the results from all epochs to obtain the mean power spectral density (PSD) for each experimental condition. We created two sets of data by averaging and log-transforming PSD over two frequency bands: alpha (8–12 Hz) and gamma (25–40 Hz).

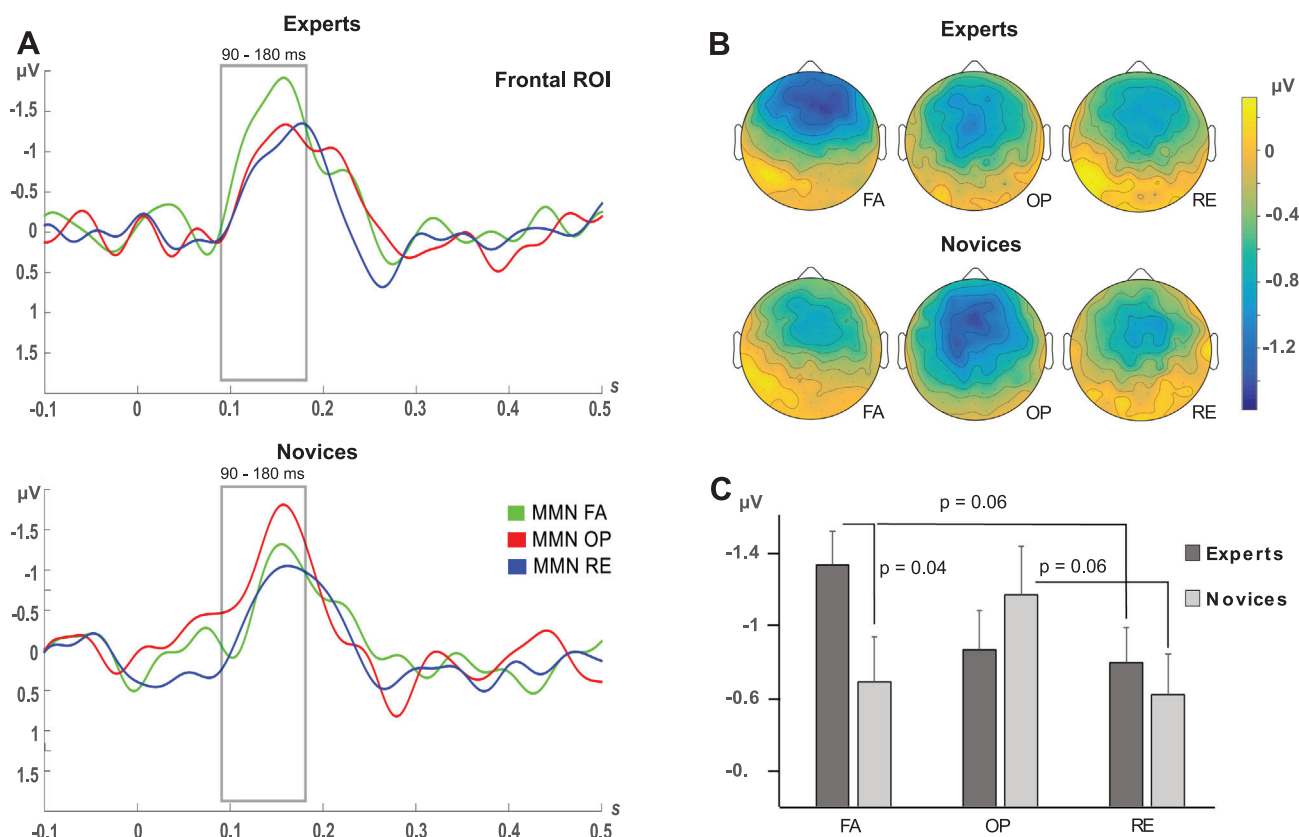
The aim of the spectral analysis was to investigate in two different brain rhythms the presence of: 1) main effects of meditation states across both groups, 2) differences between OP and FA meditation, and 3) whether these differences were specific to expert practitioners. For this purpose, we first entered log-transformed data in a comprehensive general linear model with STATE (FA, OP, RE), FREQUENCY (alpha, gamma), and ROI (frontal, occipital [see Fig. S2]) as within-subjects and GROUP (Experts, Novices) as between-subjects factors. The model was tested using repeated-measures analysis of variance (rANOVA). If interactions were present, different linear mixed-effects models were fitted for each frequency and ROI. Paired and independent-samples *t*-tests, corrected for multiple comparisons using Tukey HSD, were used as post-hoc tests comparing least-squared means.

In some cases, and for illustrative purposes, we performed whole-scalp statistical inferences to identify electrodes that showed significant effects for contrasts of interest. We used a cluster-based approach to control for multiple comparisons, and a permutation scheme to relax the assumptions usually required by parametric methods. More specifically, we used the threshold-free cluster enhancement strategy developed by Smith and Nichols (2009), which offers better localization than other cluster-based methods by performing inference at the electrode level.

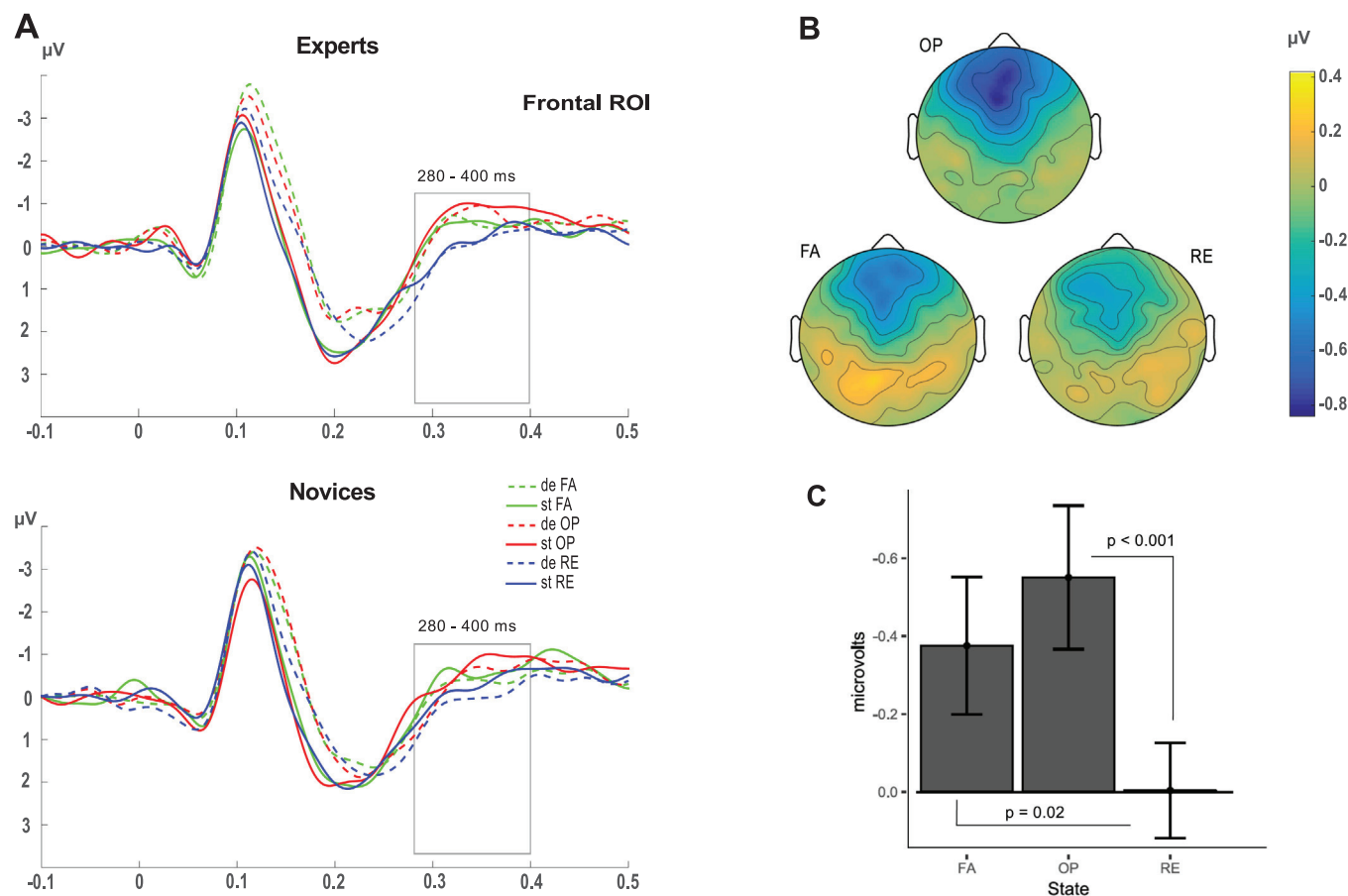
## 3. Results

### 3.1. Auditory event-related potentials

Fig. 1 B shows the topographies at the scalp level for the mean amplitude of the MMN (90–180 ms) for experts and novices, and for each experimental condition. To test our hypothesis of a down-regulation of the MMN during OP in expert meditators only, we tested a linear mixed-effects model at the frontal ROI (Fig. S1). In line with our prediction, we found a significant STATE by GROUP interaction ( $\chi^2(2) = 7.81$ ;  $p = 0.02$ ), showing how different meditative states modulate the amplitude of the MMN differently for expert and novice practitioners (Fig. 1A). More specifically, in the expert group, the MMN amplitude marginally increased during FA, compared to RE (*t*-ratio (58) =  $-2.3$ ;  $p = 0.06$ ) while no difference was found between OP and RE (*t*-ratio (58) =  $-0.3$ ;  $p = 0.94$ ). Contrary to our hypothesis, the increase in FA, compared to OP, was present only as statistical trend (*t*-ratio (58) =  $-1.9$ ;  $p = 0.12$ ) (Fig. 1C). In novice practitioners, the MMN amplitude was marginally higher during OP, compared to RE (*t*-ratio (58) =  $2.2$ ;  $p = 0.06$ ), while no difference was observed between



**Fig. 1. Meditation states modulate mismatch negativity (MMN) differently between expert and novice meditators.** (A) Subtraction (deviant minus standard, i.e. MMN) waveforms at frontal ROI (see Fig. S1) for FA, OP and RE conditions (FA: focused attention meditation, OP: open presence meditation, RE: reading a newspaper) in experts (top) and novices (bottom). (B) Average voltage scalp maps of MMN between 90 and 180 ms after stimulus onset for experts (top) and novices (bottom) during FA, RE and OP. (C) Mean values of MMN from (B) at frontal ROI. Error bars represent standard errors of the mean. P-values indicate significant and marginally significant differences within groups, between experimental conditions, as a result of paired *t*-tests (Tukey HSD corrected).



**Fig. 2.** Open Presence meditation modulates late auditory evoked-potential (Late Frontal Negativity, LFN) in expert and novice practitioners (A) Event-related responses to standard (solid lines) and deviant (dashed lines) tones at frontal ROI (see Fig. S1) during FA, OP and RE in experts (top) and novices (bottom). (B) Average voltage scalp maps, combining standard and deviants and the two groups, between 330 and 500 ms after stimulus onset. (C) Mean values of LFN from (B) at frontal ROI. Error bars represent the standard errors of the mean. P-values indicate significant differences between experimental conditions, as a result of paired *t*-tests (Tukey HSD corrected).

FA and RE ( $t$ -ratio (58) =  $-0.2$ ;  $p = 0.95$ ) and an increase in OP, compared to FA, was observed only as statistical trend ( $t$ -ratio (58) =  $-1.9$ ;  $p = 0.12$ ) (Fig. 1C). We also explored differences in MMN amplitude between groups for each state separately. We found a significantly higher MMN amplitude in experts, compared to novice practitioners in the FA condition ( $t$ -ratio (62.4) =  $-2$ ;  $p = 0.04$ ). Contrary to our hypothesis, no group difference was found in OP ( $t$ -ratio (62.4) =  $-0.5$ ;  $p = 0.5$ ). In line with our prediction that reading was a non-specific control state, there was no group difference RE conditions ( $t$ -ratio (62.4) =  $-0.9$ ;  $p = 0.35$ ).

Additional statistical analysis, performed separately on standard and deviant stimuli, did not yield informative results regarding the specific contribution of each stimulus type to the observed differences in the MMN amplitude (see Supplementary material 2.3 for details).

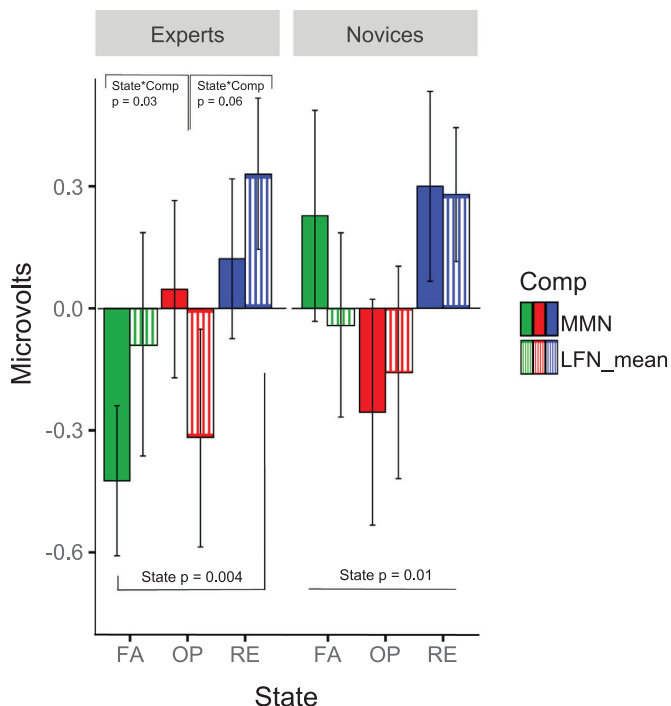
We assessed differences in stimulus attendance and attentional monitoring, between states and groups, that could have contributed to the modulation of the auditory-evoked potential in the earlier latency (MMN), by looking at later latencies of the evoked response (see Methods section).

Fig. 2B shows topographies at the scalp level for the mean values of the Late Frontal Negativity (LFN), combining responses to both standard and deviant stimuli, in the selected time window (280–400 ms) for experts and novices and for each experimental condition. The ANOVA performed at the frontal ROI (Fig. S1) yielded a significant effect of STATE ( $\chi^2(2) = 16.7$ ;  $p < 0.001$ ; Fig. 2A). We further investigated differences between each state (Fig. 2C). A significant increase in the amplitude of the LFN was found in OP and FA compared to RE ( $t$ -ratio

(58) =  $-3.9$ ;  $p < 0.001$  and  $t$ -ratio (58) =  $-2.711$ ;  $p = 0.02$  respectively), while no difference was found between FA and OP ( $t$ -ratio (58) =  $-1.7$ ;  $p = 0.18$ ).

To determine whether the interplay between attentional monitoring and perceptual habits formation would represent a more sensitive marker to differentiate the two practices in expert meditation practitioners, we included data from the MMN and the LFN in an integrated model. We performed an exploratory analysis on the interaction between MMN and LFN in expert and novice practitioners and between experimental conditions (Fig. 3). A statistically significant interaction between STATE, COMPONENT and GROUP resulted from the repeated-measures ANOVA ( $F(2, 58) = 3.42$ ;  $p = 0.03$ ). Given this interaction, we investigated the two groups separately. A marginally significant interaction between STATE and COMPONENT was present in experts ( $F(2, 30) = 3.07$ ;  $p = 0.06$ ), while a main effect of STATE was present in the novice group ( $F(2, 28) = 5.28$ ;  $p = 0.01$ ). We further tested interactions between pairs of states and the two components in the expert group to investigate the sensitivity of this combined measure to differentiate each pair of states. An interaction between STATE and COMPONENT was present when comparing FA and OP ( $F(1, 15) = 5.6$ ;  $p = 0.03$ ), showing how the LFN amplitude increased during OP while the MMN amplitude increased during FA. An interaction between STATE and COMPONENT was also present when comparing OP and RE ( $F(1, 15) = 3.8$ ;  $p = 0.06$ ), showing an increase in the LFN but not in the MMN amplitude during OP compared to RE. Finally, a main effect of STATE was present when focusing on FA and RE ( $F(1, 15) = 11.08$ ;  $p = 0.004$ ) showing how the amplitude of both components increased





**Fig. 3.** Different interplay between LFN and MMN amplitudes between experimental conditions as a function of meditation expertise. Mean difference in microvolts, relative to the average across groups and conditions, of MMN (full colour) and LFN (lines pattern) in FA (green), OP (red) and RE (blue). P-values indicate significant main effects and interactions resulting from repeated-measures ANOVAs. A significant three-way interaction was found between states, components and groups ( $F(2, 58) = 3.42; p = 0.03$ ). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

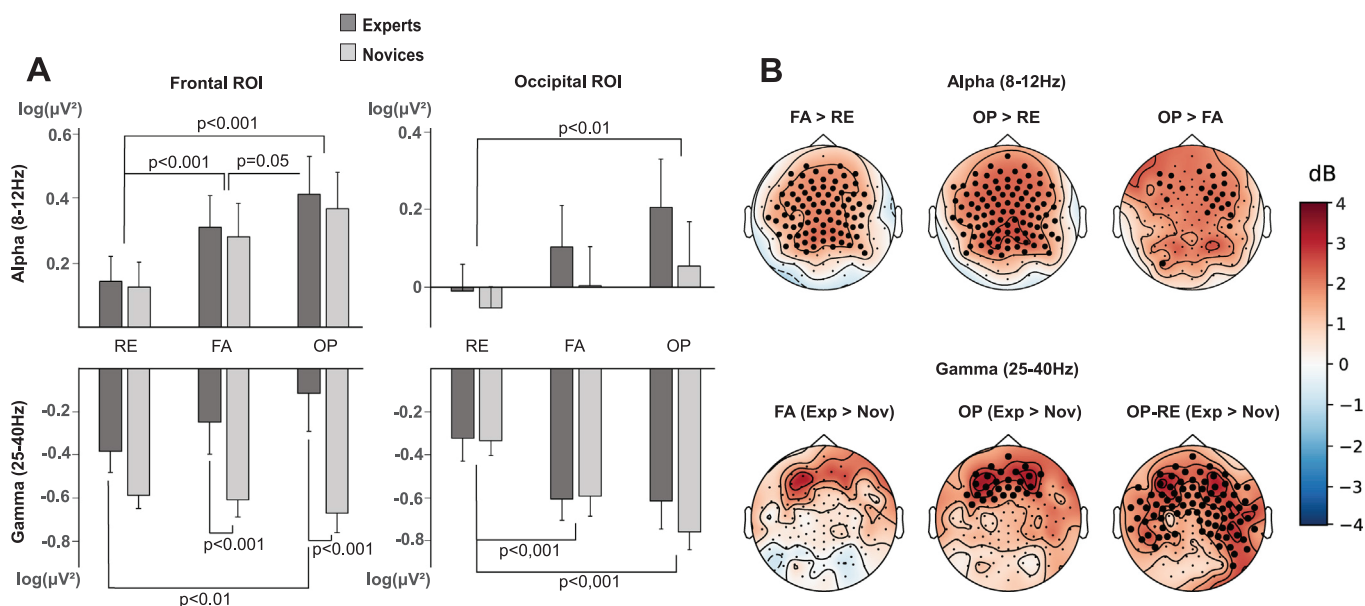
during FA compared to RE. Altogether this composite analysis revealed a double dissociation in experts between OP and FA and RE, respectively.

### 3.2. Spontaneous Alpha (8–12 Hz) and gamma (25–40 Hz) EEG oscillatory activity

Fig. 4A shows mean log-values of alpha and gamma power, in two different ROIs, for expert and novice practitioners; Fig. 4B shows the topographical distribution of these oscillatory activities. A statistically significant interaction between STATE, FREQUENCY, ROI and GROUP resulted from the main model tested ( $F(1.7, 49.9) = 3.87; p = 0.03$ ; Huynh-Feldt corrected). Given the significant interaction, we investigated the two frequency bands and ROIs separately.

A significant effect of STATE on average alpha power was present in both the frontal and occipital ROIs ( $\chi^2(2) = 43.1; p < 0.001$  and  $\chi^2(2) = 9.8; p = 0.007$ , respectively). This analysis showed how alpha power increases in both groups during meditation and how, between the two practices, OP meditation is characterized by the most powerful alpha oscillatory activity in the frontal ROI (OP vs RE:  $t$ -ratio (58) = 6.4,  $p < 0.001$ ; FA vs OP:  $t$ -ratio (58) = -2.4,  $p = 0.05$ ; FA vs RE:  $t$ -ratio (58) = 4,  $p < 0.001$ ). The main effect of state observed at the occipital ROI was mostly caused by the increased alpha power during OP compared to RE (OP vs RE:  $t$ -ratio (58) = 3.1,  $p = 0.008$ ; FA vs RE:  $t$ -ratio (58) = 1.6,  $p = 0.24$ ; FA vs OP:  $t$ -ratio (58) = -1.4,  $p = 0.31$ ).

As for the differences in gamma power, we found a significant STATE by GROUP interaction at the frontal ROI ( $\chi^2(2) = 7.87; p = 0.02$ ), showing how gamma oscillatory power increased during OP, compared to RE, in experts only ( $t$ -ratio (58) = 3;  $p = 0.008$ ) while no difference was found between FA and RE, and OP and FA ( $t$ -ratio (58) = 1.5;  $p = 0.27$  and  $t$ -ratio (58) = -1.5;  $p = 0.28$ , respectively). No difference between states was found in the novices. Between-group  $t$ -tests highlighted a significant increase in gamma oscillatory power in experts, compared to novices, during OP and FA ( $t$ -ratio (42.8) = 3.3;  $p = 0.002$  and  $t$ -ratio (42.8) = 2.1;  $p = 0.03$ , respectively), but not RE ( $t$ -ratio (42.8) = 1.2;  $p = 0.23$ ). At the occipital ROI, a significant main effect of state was present ( $\chi^2(2) = 45.3; p < 0.001$ ), showing how gamma power increased during RE compared to OP and FA ( $t$ -ratio (58) = -6.4;  $p < 0.001$  and  $t$ -ratio (58) = -4.8;  $p < 0.001$ , respectively). We did not find a relationship between spontaneous gamma activity and hours of meditation practice in expert practitioners. This hypothesis was tested at the frontal ROI used in the present study, as



**Fig. 4.** Meditation states differently modulate spontaneous oscillatory activity between expert and novice meditators. (A) Mean log-transformed values of spectral power in alpha (8–12 Hz) and gamma (25–40 Hz) frequency bands at the frontal ROI and occipital ROI for experts and novice practitioners. Error bars represent standard errors of the mean. P-values indicate significant differences between groups and between experimental conditions within groups, as a result of paired  $t$ -tests (Tukey HSD corrected). (B) Corresponding whole-scalp topographies for a few selected contrasts. Large dots indicate electrodes for which the contrast is statistically significant ( $p < 0.01$ , corrected for multiple comparisons: see Section 2).

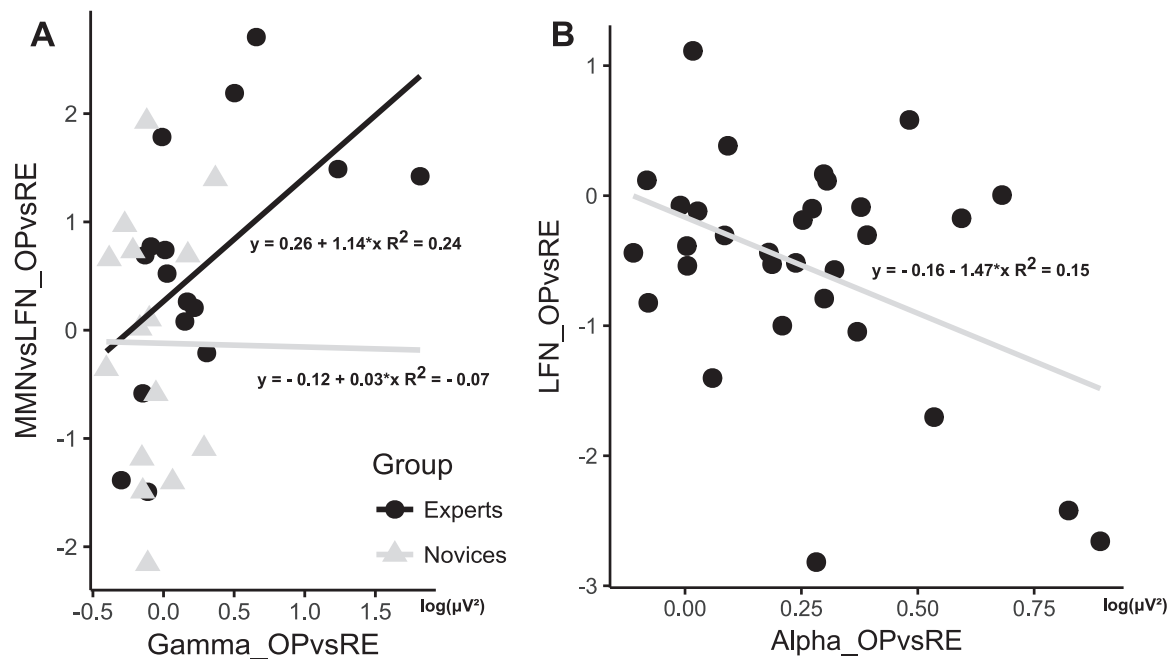


Fig. 5. Spontaneous oscillatory activity in the gamma and alpha range correlates with changes in the auditory evoked potential between OP and RE conditions. (A) Scatter plot for single-subject mean values of difference in gamma (25–40 Hz) power between OP and RE (x-axis) and difference between MMN and LFN between OP and RE (y-axis) for novice (grey) and expert (black) practitioners. Regression lines and relative equations, as well as R-squared values, show the direction of the correlation for each group. (B) Scatter plot for differences in alpha (8–12 Hz) power between OP and RE (x-axis) and difference in LFN amplitude between OP and RE (y-axis) across both groups. Regression line and relative equation, as well as R-squared value, show the direction of the correlation across subjects.

well as at the ROI used in a previous study, when a relationship was found (Lutz et al., 2004).

### 3.3. Correlation between spontaneous oscillatory activity and auditory evoked responses

Following the results obtained after the analysis of ERP components and oscillatory power, we aimed to further characterize the relation between state measures and brain responses to auditory stimuli (Fig. 5). Firstly, we explored the relationship between the difference between MMN and LFN amplitude and the frontal gamma activity, as both measures exhibited a group by state interaction, particularly between OP and RE, as both states differed for experts only on these two measures. We found a significant correlation between these two measures in experts, but not novices ( $\rho_{X,Y} = 0.54$ ;  $p = 0.03$  and  $\rho_{X,Y} = -0.006$ ;  $p = 0.98$  respectively) and this correlation was marginally different between the two groups ( $z$ -score = 1.5;  $p = 0.06$  following (Cohen et al., 2014)). Secondly, the common profile of the state effect found in both LFN amplitude and frontal alpha activity suggested a possible relationship between them, particularly in the contrast between OP and RE (see Figs. 4 and 2). We found a negative correlation between the increase in alpha power and the increase in LFN amplitude during OP, compared to RE condition; this effect was present across both groups ( $\rho_{X,Y} = -0.42$ ;  $p = 0.01$ ).

## 4. Discussion

In the present study, we showed how an Open Presence style of nondual meditation can be differentiated from a style of concentrative meditation, named Focused Attention, in terms of the interplay between saliency and monitoring of the sensory environment and perceptual learning processes as measured by a composite measure of EEG ERPs. The observed patterns are in line with the specific phenomenology of the two different states. Moreover, both meditation states are characterized by increased power of brain rhythms in the gamma frequency range in experts compared to novices, and by increased power

in alpha frequency range for both groups. We also found some relationship between meditation-induced changes in ERPs and meditation-induced changes in brain oscillatory rhythms in both gamma and alpha frequency bands.

Theoretical accounts of the MMN suggest that it is a neural correlate of prediction error signals (Garrido et al., 2009; Lecaigard et al., 2015). Elaborating on this notion, recent studies have highlighted the role of attention in increasing the precision of such prediction errors, resulting in an increase of the MMN amplitude (e.g. (Chennu et al., 2013; Aukstulewicz and Friston 2015)). These studies are in line with theoretical and experimental work on the role of attention in modulating prediction error signals in different sensory domains (e.g. (Feldman and Friston, 2010; Kok et al., 2012)). In the present study, we found that two meditation practices and a control state differently modulate the MMN amplitude in groups of expert and novice practitioners. During the state of Focused Attention, the MMN amplitude increases in experts compared to a control, Reading condition and compared to novices. Contrary to our hypothesis, the MMN in OP was not statistically different from FA, even if there was a trend toward this effect. The increase in FA compared to RE could be related to the specific task-set of focusing on and selecting a perceptual object, which increases the saliency of task-unrelated stimuli and entails higher meta-awareness of the sensory environment (Lutz et al., 2015). Previous studies have reported an increase of the MMN during concentrative meditation (Srinivasan and Bajjal, 2007) and in expert practitioners (Biedermann et al., 2016). Nonetheless, these studies presented several limitations such as the lack of a control condition and the assessment of the MMN amplitude at unconventional scalp areas. In line with our findings, a previous study showed how the MMN increased during a concentrative state (breath-counting task), compared to mind-wandering (Braboszcz and Delorme, 2011). In the novice group, the MMN amplitude increases during the practice of OP compared to RE, while a difference between OP and FA was observed only as a statistical trend. Higher MMN during OP meditation in novices could also reflect higher attentional resources being allocated to the auditory stream of the oddball paradigm, compared to Reading, in line with the recent

literature on attention modulation of prediction error signals. This view is corroborated by the effect of meditation states on the late negative component of the auditory evoked response, here referred to as Late Frontal Negativity, which is highly similar, in terms of location and latency, to previously observed components that have been linked to stimulus attendance and attention orienting (e.g. (Karayanidis and Michie, 1996; Bendixen et al., 2007)). The fact that there was no increase in MMN in FA versus RE in novices could reflect a less stable capacity to maintain attentional focus compared to experts.

Based on the results obtained from separate tests performed on the two components of the auditory evoked potential, we sought to characterise the interplay between attentional monitoring of the sensory environment (indexed by the LFN amplitude) and the modulation of predictive processes (reflected in the MMN amplitude). This exploratory analysis was driven by the interest in highlighting specific profiles of perceptual information processing in line with our operational hypotheses regarding the two different meditation states in expert practitioners. In this group, indeed, the practices of OP and FA have a different impact on the two ERP components, when compared between them and to the RE condition. More specifically, the state of OP increases the LFN amplitude, compared to RE, but not the MMN, whereas during FA both components show a higher amplitude compared to RE. Finally, compared to FA, the state of OP shows higher LFN amplitude but lower MMN. As stated earlier, we hypothesized that the distinct phenomenology of OP in expert practitioners would correlate with a reduction of the interpretation of sensory information across time by perceptual habits. The modulation of the strength of prior predictions on the auditory environment could be, in this case, a suitable mechanism underlying this hypothesized process. This modulation would be orthogonal to the increased saliency of perceptual stimuli. By contrast in novices, the dissociation between these two processes was not found, as reflected by a state effect but not by a state by component interaction: increasing perceptual saliency during OP condition (i.e. high LFN) was associated to increase in MMN, whereas decreasing perceptual saliency during RE condition (i.e. lower LFN), was associated to decrease in MMN (Fig. 3). In line with the phenomenological description, the specific pattern of auditory response in MMN combined with LFN observed in expert practitioners represents a key finding of the present study. Such modulation of predictive processes could also explain results from a previous studies that found a reduction of the auditory startle response in one expert meditator during OP (Levenson et al., 2012) and a reduction of habituation to startle stimuli in expert practitioners (Antonova et al., 2015).

Expert meditators also show increased gamma oscillatory power over the frontal scalp region during both meditative states compared to the control condition and to novices. These results are in line with a previous study characterizing an increase in gamma power in experts during a non-dual form of compassion meditation (Lutz et al., 2004) and in contrast with a recent study that did not find an interaction between states and group, but rather a trait effect in gamma power (Braboszcz et al., 2017). Yet, in this last study, novice practitioners did not engage in the same practice as the experts, and the inclusion criteria for experts, as well as the type of practices, were different from the present study.

Fast frequency oscillatory activity (> 25 Hz) is considered to play a prominent role in a variety of mental processes, such as attention, feature integration and conscious perception (e.g. Lachaux et al., 2012; Fries, 2015). It has been previously hypothesized that, in the context of nondual meditation states, modulation of endogenous gamma activity could reflect changes in the quality of awareness, especially regarding the chronometry of stimulus processing (Lutz et al., 2004). We explored a possible relation between the difference in gamma power between OP and RE in experts and the difference between the same states in modulating the interplay between MMN and LFN amplitude (Fig. 5). The relationship we observed in expert practitioners between these two measures points towards a putative link between spontaneous profiles

of oscillatory brain activity during meditation and the modulation of information processing. Nonetheless, as no difference was found between OP and FA in the power of frontal gamma, this analysis remains exploratory. Further studies should clarify whether a direct relationship exists between spontaneous gamma and auditory predictive processes in meditation.

Finally, an increase in alpha oscillatory power was found across both groups during meditation, compared to the RE condition, and especially during OP. Since early studies, increased alpha power during meditation has been consistently reported (see (Cahn and Polich, 2006) for a recent review) and linked to a general increase in relaxation as a state effect of numerous practices. Nonetheless, more recent theories describe the prominent role of alpha oscillatory activity in inhibiting task-unrelated stimuli when attention is sustained (Clayton et al., 2015; Fries, 2015), as well as when it is redirected to a specific task-set (Jensen et al., 2002), hence its involvement in working memory. In a recent study, alpha power increased during the transition from mind-wandering to breath-focus (Braboszcz and Delorme, 2011). Here we found a correlation between the increase in alpha power and the increase in LFN amplitude during OP compared to RE, across both groups. This finding highlights a putative link between alpha oscillatory activity in meditation and attentional processes (e.g. reorienting attention from auditory stimuli to the main task-set of the practice).

This study presents some limitations: first of all, while a complete cessation of the MMN response would not be plausible (MMN has been consistently observed during sleep and even in minimally-conscious patients (Atienza and Cantero, 2001; Boly et al., 2011)), one might expect OP meditation in experts to have a deeper impact on predictive processes and to actually reduce the MMN amplitude, compared to a control condition. The reason why we did not observe such modulation could be due to the relatively small sample size and, most importantly, to the various degrees at which the state of OP could be achieved and maintained between experts and, within the same session, by the same subject. This heterogeneity is also a possible reason why we did not find a significant difference between FA and OP in MMN and frontal gamma power in expert practitioners. When the state of OP is not fully realised, some degree of concentration might be required, hence sharing brain processes with the state of FA. On the other hand, once the “nature of the mind” is realised, it will be always present to some extent, therefore reducing the gap between OP and FA in terms of spontaneous brain activity. Future studies should address differences in the subjective experience of expert practitioners during advanced nondual states, relating quantitative data to online self-reports and qualitative accounts of single-subject profiles. Finally, future research should explore the mechanisms underlying the modulation of the MMN by OP meditation implementing trial-by-trial analysis of the auditory responses, based on strong computational hypotheses and modelling (e.g. (Lieder et al., 2013)).

Overall, the present study provides evidence of the brain processes underlying a non-dual meditation practice and describes the impact of meditation on predictive processes. This will foster the understanding of the brain mechanisms involved in the formation of perceptual habits and shed light on the mechanisms of meditation practices in clinical settings.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neuropsychologia.2018.07.025](https://doi.org/10.1016/j.neuropsychologia.2018.07.025).

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## Chapter 6

# Perceptual learning in emotional settings

### **6.1 Study 2: Perceptual learning and auditory processing under threat of unpredictable electric shock**

# Auditory perceptual learning is not affected by anticipatory anxiety in the healthy population except for highly anxious individuals: EEG evidence

In review at *Clinical Neurophysiology*

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## Abstract

**Objective:** A recent neurocomputational model proposed that anxious hypervigilance impedes perceptual learning, a view supported by the frequently observed modulation of the mismatch negativity (MMN), a biomarker of perceptual learning processes, in PTSD patients. However, other studies found that anxious states sensitize brain responses to stimuli, with no impact on learning. The present research aimed at elucidating the impact of anticipatory anxiety on the neural correlates of early stimulus processing in the healthy population. **Methods:** We used electroencephalography (EEG) to investigate the impact of threat of unpredictable electric shocks on the amplitude of the MMN and other components of the auditory evoked response in healthy participants during a passive auditory oddball task. **Results:** We found no increase in the MMN amplitude during periods of threat, except for those participants that reported a high degree of anticipatory anxiety or scored high in dispositional anxiety. On the other hand, we found a general sensitization of early components of the auditory evoked response and changes in subjective and autonomic measures of stress during threat. **Conclusion:** Based on these results, we propose that anxiety, as dimensional construct, sensitizes early brain responses to unspecific environmental stimuli but affects perceptual learning processes unrelated to the threat only when an individual is located at the higher end of the spectrum of anxiety. **Significance:** This view might distinguish between an adaptive role of anxiety on processing efficiency and the detrimental impact on perceptual learning observed in psychiatric conditions.

Keywords: MMN, N1, EEG, threat, anxiety, perceptual learning

## 1. Introduction

The adaptive interplay between perception and emotional states is fundamental for optimal goal-oriented behaviour in complex and volatile environments. Essential to this process is the capacity to screen out irrelevant sensory information detect stimuli that are relevant or can constitute a threat. Anxiety serves this purpose via affective, cognitive and physiological changes that create a state of hypervigilance in response to unpredictable threats in novel and uncertain settings (Grupe and Nitschke, 2013). Evolutionary, anxiety increases the odds of survival in threatening situations (Kalin and Shelton, 1989), but it can become maladaptive if sustained over time and associated to otherwise innocuous stimuli. This is the case in psychopathological conditions such as PTSD and anxiety disorders (Cisler and Koster, 2010; Newport and Nemeroff, 2000). A putative disruptive effect of anxiety on cognitive functions, and related performance impairments, is also described in the healthy population by nowadays widespread and influential theories (Eysenck et al., 2007; Eysenck and Derakshan, 2011). In the framework of cognitive neurosciences, anxiety-induced hypervigilance is considered to impact sensory-perceptual processing through the sensitisation of neural responses to environmental stimuli (see Jafari et al., 2017; Robinson et al., 2011 for recent reviews).

A recent study has proposed a neurocomputational model of anxious hypervigilance. The latter would impede perceptual learning by increasing the synaptic gain of prediction error signals while down-regulating descending prediction pathways. This mechanism is suggested to tap into early stimulus processing and could underlie the detrimental effects of anxiety on higher-order cognitive processes (Cornwell et al., 2017). This model is ascribed to the predictive coding framework (Friston, 2009) and considers the mismatch negativity (MMN, e.g. Näätänen et al., 2004), a neuro-electric response to violations of statistical regularities in the sensory environment, as a marker of implicit perceptual learning processes in the form of precision-weighted prediction error signal (Garrido et al., 2009b). Several studies support the idea of an impact of anxiety on perceptual learning: increased MMN amplitude has been observed in individuals affected by PTSD (e.g. Ge et al., 2011) and correlates with dispositional anxiety (Hansenne et al., 2003). Moreover, a study using magnetoencephalography (MEG), has reported increased responses to stimulus deviance under threat of electric shock (Cornwell et al., 2007).

Despite this evidence, contradicting results come from other research that elicit anxious states and use electroencephalography (EEG): in these cases, a difference in the amplitude of the MMN was either not found (Ermutlu et al., 2005), observed only in response to a specific type of stimulus deviancy (Simoens et al., 2007) or found to correlate with state anxiety only in an emotionally negative context (Schirmer and Escoffier, 2010). Additionally, several studies reported higher brain responses to environmental stimuli at early and middle latencies of the sensory event-related potential (ERP) during anxious states in the auditory and visual domains, independently of the stimulus type (e.g. Ermutlu et al., 2005; Qi et al., 2018; Scaife et

al., 2006; Shackman et al., 2011). However, these studies did not use threat of electric shock to induce anticipatory anxiety as in Cornwell et al. (2017) or their focus did not encompass both general sensory processes and perceptual learning markers (i.e. the MMN).

In the present study, we tried to shed light on the ambiguous findings concerning the effect of anticipatory anxiety on perceptual learning and early stimulus processing. Specifically, we used EEG to measure the amplitude of the MMN under threat of electric shock during a passive oddball task (as Cornwell et al., 2017, 2007), as well as the amplitude of early components of the auditory-evoked response. In addition to subjective self-reports, which are commonly used in the above-mentioned studies, we measured changes in the electrodermal activity in response to periods of threat to provide a marker of the autonomic response to the anxiety-induction procedure (Folkens, 1970; Nomikos et al., 1968). Finally, we investigated whether an anxious state had a different impact on perceptual learning and early sensory processing than the one of anxiety measured as a trait. We hypothesized that the observed modulation of perceptual learning in psychiatric conditions could be due to the dimensional aspect of anxiety and be present in those healthy individuals that are located on a higher position in the spectrum (Endler and Kocovski, 2001).

## **2. Materials and Methods**

### **2.1 Subjects**

Thirty-six healthy individuals ( $52 \pm 7.6$  years old, 17 females) participated in the study. Subjects were recruited from the local community to participate as controls in a broader project that investigated the effects of mindfulness meditation on cognitive and emotional processes. For a detailed description of the recruitment procedure, as well as inclusion and exclusion criteria, readers can refer to the project manual (Abdoun et al., 2018; available online at [osf.io/dbwch](https://osf.io/dbwch)). Regarding the present study, relevant exclusion criteria were the following: use of psychoactive medication, history of neurological or psychiatric conditions, history of chronic pain or other conditions involving sensitisation to pain, personal or family history of epilepsy, severe hearing loss. All participants were affiliated to social security, provided written informed consent before the start of the study and were paid for their participation. Ethical approval was obtained from the appropriate regional ethics committee on Human Research (CPP Sud-Est IV, 2015-A01472-47). Each subject completed the trait subscale of the State Trait Anxiety Inventory (STAI, [Spielberg, 1970]) before participating in the experiment.

## ***2.2 Task design and stimuli***

Subjects underwent a passive auditory oddball task (e.g. Näätänen et al., 2004), consisting of the variable repetition of a standard tone (880Hz; 80ms duration ; 10ms rise and fall) followed by the presentation of a frequency deviant (988Hz; 20% of all auditory stimuli) presented binaurally (fix Inter-stimulus interval [I.S.I] = 500ms). The overall paradigm consisted of six blocks over two experimental sessions with three different experimental conditions: two different meditation practices and one control condition (one block per condition in each session). In the present report, we analysed data from the control condition only. The sequence of blocks was randomised within a session and the block order has been considered in the statistical analysis. During a block, subjects were asked to watch a silent documentary and ignore the auditory stimuli. As in Cornwell et al. (2007), short oddball sequences were embedded in alternating 30s periods (8 periods per block) in which participants were informed of the possibility of receiving an electric shock (threat periods,  $n = 4$ ) or that no shocks would have been delivered (safe periods,  $n = 4$ ). The information was conveyed by auditory cues at the beginning of each period, before the oddball sequence. The same amount of standard and deviant stimuli was delivered during safe and threat periods ( $n = 56$  deviants and  $n = 224$  standards when combining four periods). After each block, participants were asked to answer, on a 7-point Likert-item, how much anxiety they felt during threat and safe periods, as well as how much they were distracted during the block and how much they were listening to the auditory stimuli (see Supplementary Information 1 for the specific questions asked).

## ***2.3 Electric-shock stimuli and intensity work-up procedure***

In line with the procedure described in Schmitz and Grillon (2012), electrodes from a direct current stimulator were placed on the participant's lower wrist. Participants were asked to rate delivered electric stimuli on a scale from 1 to 5 (1 = barely felt, 5 = very uncomfortable). Stimuli were presented at intensities starting from 2mA and up to 16mA (duration = 100ms), until the participant rated the stimulus 4 out of 5 on the scale. If the subject's threshold reached 16mA, stimuli were delivered at this maximal intensity. In our sample, the mean shock intensity was 8.29mA (SD = 4.41). Five shocks were delivered randomly throughout the two blocks. No more than two shocks were delivered during the same threat period. Subjects were told that the number of delivered shocks could vary randomly and that the experimenter had no control over their frequency.

## ***2.4 EEG recordings and pre-processing***

EEG was recorded at 512 Hz using the ActiveTwo system (BioSemi, Amsterdam, Netherlands), consisting of 64 active electrodes that were placed in an EEG cap according to the standard 10/20 system. The horizontal and vertical EOG was measured by placing electrodes on the outer canthi and above and below the subject's left eye.

Pre-processing was done using EEGLAB (Delorme and Makeig, 2004) and in-house Matlab scripts (version R2015a). The EEG signal was downsampled to 250Hz and re-referenced offline using the electrodes placed at the level of the mastoids (average activity of the two channels). Data were visually inspected to identify bad channels, which were marked for successive interpolation. Independent Component Analysis (ICA) was applied, separately for the two sessions, to the continuous data using the Runica algorithm (Makeig et al., 2002). Recordings that underwent ICA were manually cleared of big artefacts, filtered between 1 and 20Hz and did not comprise channels that would have been subsequently interpolated. Resulting ICA matrices were then transferred to the original raw data and ICA components were visually inspected to remove blinks and saccades. Data were high-pass filtered at 2Hz to avoid contamination of slow frequencies and drifts in the signal caused by sweating during the stress periods. Previously marked bad channels were interpolated and 50Hz noise was removed using the CleanLine algorithm. Epochs were created between -200 and 500ms after stimulus onset for standard and deviant stimuli and baseline-corrected (-100ms baseline). The epoched data were visually inspected with the help of a  $\pm 70$ mV amplitude threshold and epochs including artefacts were removed. All outer ring channels were rejected due to consistent high-frequency noise, leading to 41 channels remaining (see Figure S1 for a visual layout). For each subject, epoched data from one session was removed if the number of deviants, after rejection, was lower than thirty-five for the safe or threat condition. All data from two subjects, and the second session from one subject, were excluded from further analysis because of not enough epochs after pre-processing. Finally, a low-pass filter of 20Hz was applied to the epoched data for the analysis of the evoked responses.

## ***2.6 Event-related potentials***

Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). For the analysis of event-related potentials (ERPs), only standard stimuli that directly preceded a deviant were considered. The average number of standards was 52.25 and 51.42 for safe and threat conditions (SD = 6.06 and 5.70 respectively) and the average number of deviants was 52.24 and 51.62 (SD = 6.03 and 5.43).

To identify the MMN, we computed difference waveforms from the grand average across all subjects, separately for each of the two experimental sessions. We used an a priori region of interest (ROI) that included the channel Fz and four surrounding channels (see Figure S1 for a visual layout), consistent with previous literature (e.g. Duncan et al., 2009; Näätänen et al., 2011). The MMN amplitude was calculated based on a 20ms time-window centred around the most negative peak of the difference waveform for each condition (safe and threat) and session between 90 and 200ms after stimulus onset. Amplitude values for each subject were extracted within this identified time-window.

Additionally, we performed analysis on the amplitude of classical auditory ERP components, such as the N1 and P2 (Picton et al., 1974), on the frontal ROI. Single-subject amplitudes for each condition (safe and threat), session and stimulus (standard



and deviant) were extracted from a 20ms time-window centred around the most negative peak between 90 and 200ms for the N1, and around the most positive peak between 160 and 300ms for the P2.

For each of the three components of interest (MMN, N1, P2) we tested the effect of condition (threat and safe periods) and stimulus type (for N1 and P2) using linear mixed-effects models (R package lme4, [Bates et al., 2014]) that allow for unbalanced designs (e.g. missing data from one session for a subject) and the inclusion of random effects such as, in the present case, session and block order information for each observation. Mixed-effects models were evaluated using an ANOVA analysis of variance (Type II Wald chi-square test). Paired t-tests, corrected for multiple comparisons using Tukey honestly significant difference test (HSD), were used as post-hoc tests comparing least-squared means. We report, in the results section, estimates of effect size in the form of pseudo- $R^2$  as proposed by Nakagawa and Schielzeth (2013). Notice that the calculation of effect sizes in linear mixed models is not unambiguous and should be handled with consideration.

Finally, we performed an additional analysis looking for time-electrode pairs where the MMN amplitude differed significantly between safe and threat periods. We corrected for multiple comparison using a non-parametric, permutation-based, cluster-level statistical test as implemented in the Matlab toolbox Fieldtrip (Oostenveld et al., 2011) (cluster-defining threshold = 0.001; cluster-level threshold = 0.05; 10,000 permutations).

## **2.7 Skin conductance data acquisition and analysis**

For the recording of electrodermal activity, two passive electrodes were placed on the participant's non-dominant hand, on the volar surface of the distal phalange of the 2nd and 3rd fingers. Data were recorded using the 16Hz coupler provided with the ActiveTwo system (BioSemi, Amsterdam, Netherlands) with a sampling rate of 250Hz. Data were down-sampled at 25Hz and analysed with the Matlab software Ledalab V 3.4.9 ([www.ledalab.de](http://www.ledalab.de)) applying Continuous Decomposition Analysis (Benedek and Kaernbach, 2010), separating the tonic electrodermal activity throughout a block from the phasic activity. Our measure of interest was the event-related phasic activity after the onset of auditory cues preceding safe and threat periods. Data were visually inspected and sessions where very weak or no phasic response was present were excluded from further analysis. Following this inspection, three subjects and six single sessions were excluded due to lack of data (equipment failure) or the lack of phasic responses. Subsequently, skin conductance responses (SCRs) were calculated for each subject and session over a 1 to 5 seconds window after stimulus onset (threat or safe cue) with a minimum threshold of 0.1 microSiemens ( $\mu$ S). A log-transformation was applied to raw SCRs to normalize values between and within subjects.

Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). We used linear mixed models to test the effect of condition (safe and threat) and session on the log-transformed SCRs. The information about block order and auditory cue order within a block were entered in the model as random effects. Mixed-effects

models were evaluated using an ANOVA analysis of variance (Type II Wald chi-square test). Paired t-tests, corrected for multiple comparisons using Tukey honestly significant difference test (HSD), were used as post-hoc tests comparing least-squared means.

## **2.8 Self-reports and regression analysis**

Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). The analysis of condition (safe and threat) and session effects on self-reported anxiety was performed using linear mixed models and treating Likert items as interval data. As in previously described models, the information on block order was entered as a random effect.

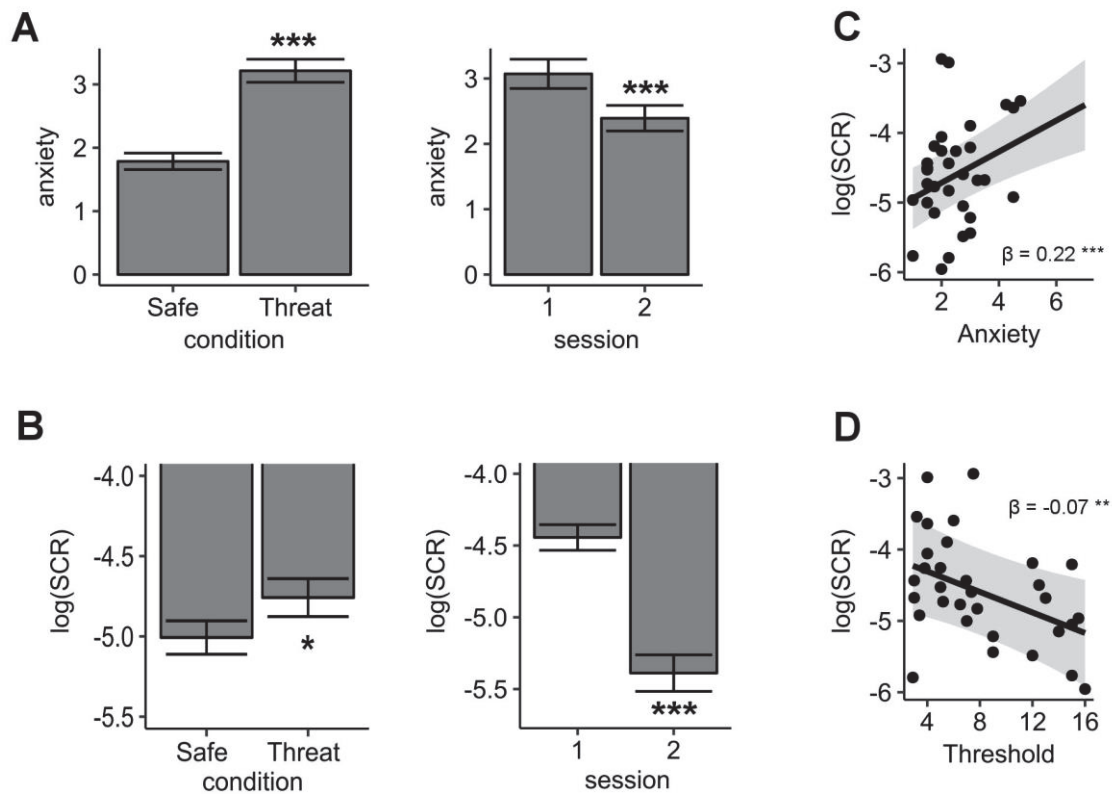
Finally, we investigated the relationships between answers to self-report questions and third-person variables (e.g. ERP components amplitude and SCRs), as well as between trait (STAI questionnaire scores) and state measures. To minimize the number of statistical tests and allow for unbalanced designs (e.g. SCR or EEG data missing for some subjects), we used linear mixed models entering independent variables and factors as fixed effects, as well as session and block order information as random effects for all the fitted models. Eventual interactions between an independent variable and levels of a factor were explored post-hoc comparing the regression slopes between each factor level using the function “lrends” (R package “lsmeans”, Lenth, 2016). In the context of interactions, we tested whether a specific slope for one factor level was different from zero using the function “sim\_slopes” (R package “jtools”, Long, 2018).

## **3. Results**

### ***3.1 Manipulation of anxiety***

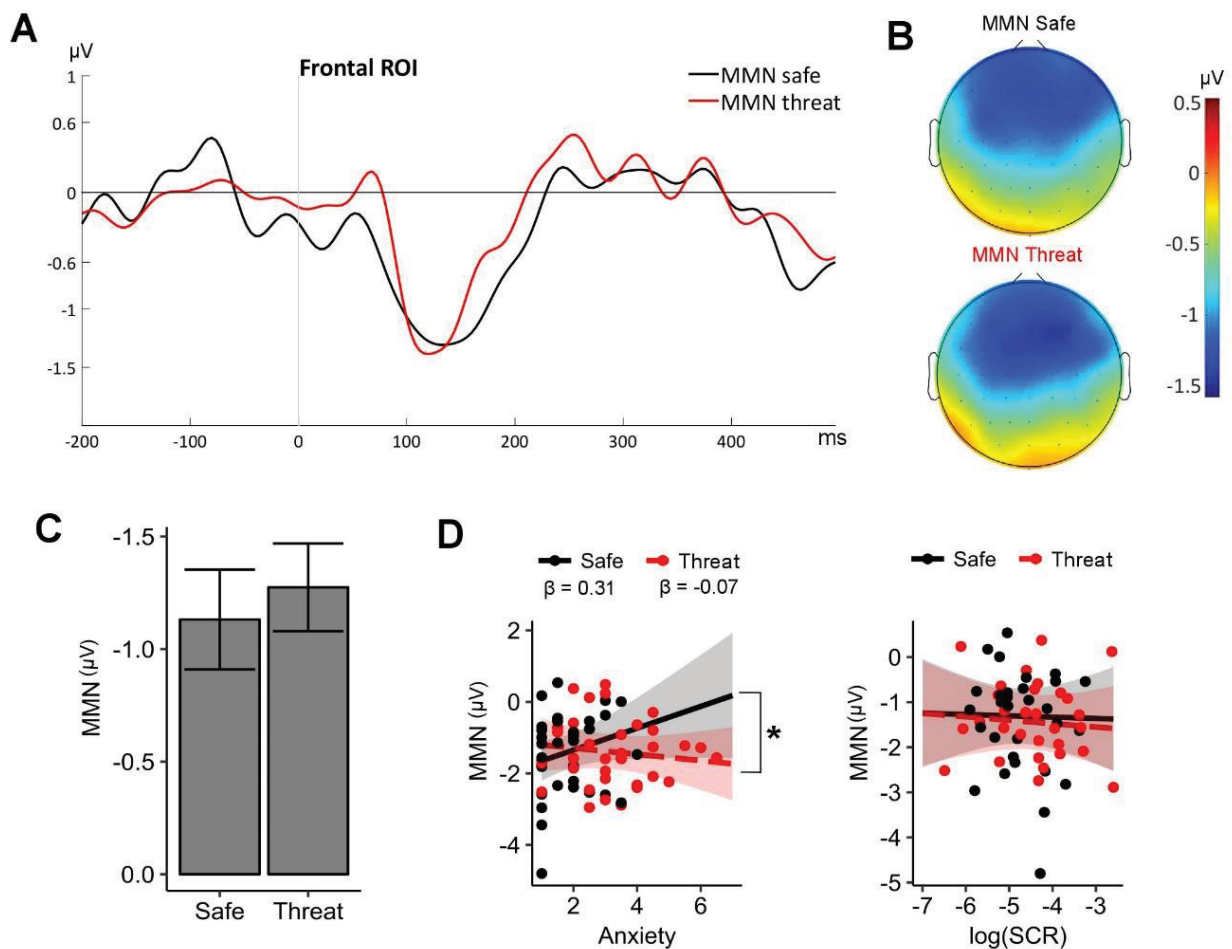
Participants underwent two experimental sessions (2 to 3 hours apart) where they were exposed to two conditions during the EEG recordings. A THREAT condition, when the participant was informed of the possibility of receiving an electric shock, and a SAFE condition, when no shock was delivered, were alternated during the block. Self-reported anxiety was significantly higher during THREAT, compared to SAFE condition ( $\chi^2(1) = 72.54$ ;  $p < 0.001$ ) and was generally lower in the second session ( $\chi^2(1) = 11.54$ ;  $p < 0.001$ ) [Figure 1.A; Pseudo- $R^2 = 0.56$ , Pseudo- $R^2$  (fixed effects) = 0.26]. No interaction was present between condition and session. For some sessions (16 out of 72) participants reported no difference in anxiety between conditions. We decided to keep these observations in further analyses because in several sessions (8 out of 16) self-reported anxiety was higher than 1. Nonetheless, additional analyses on the MMN amplitude were performed excluding these observations (see results section 3.2).





**Figure 1. Threat of electric shock increases anticipatory anxiety as measured by self-reports and skin conductance responses.** (A) Mean values of self-reported anxiety during threat and safe periods (left) and during session 1 and 2 (right). (B) Mean amplitude of log-transformed skin conductance responses (SCRs) after threat and safe cues (left) and on average during session 1 and 2 (right). For (A) and (B), error bars represent standard errors of the mean. (C) Scatter plot for single-subject mean values of self-reported anxiety and SCRs amplitude. The regression line and coefficient  $\beta$  are derived from a linear mixed model including SCRs and condition (safe, threat) as fixed effects and session, block order and subjects as random effects. (D) Scatter plot for single-subject subjective pain threshold and mean SCRs amplitude. The regression line and coefficient  $\beta$  are derived from a linear mixed model including threshold and condition (safe, threat) as fixed effects and session, block order and subjects as random effects. For (C) and (D) the grey area around the regression line indicates 95% confidence intervals. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$  as a result of paired t-tests (Tukey HSD corrected).

Skin conductance responses (SCRs) were significantly higher during THREAT, compared to SAFE condition ( $\chi^2(1) = 5.3$ ;  $p = 0.02$ ) and were lower in the second session ( $\chi^2(1) = 35.45$ ;  $p < 0.001$ ) [Figure 1.B; Pseudo- $R^2 = 0.45$ , Pseudo- $R^2$  (fixed effects) = 0.06]. No interaction was present between condition and session. Higher self-reported anxiety significantly predicted higher SCRs ( $\chi^2(1) = 15.23$ ;  $p < 0.001$ ;  $\beta = 0.22$  [95% c.i. = 0.11, 0.34]) [Figure 1.C; Pseudo- $R^2 = 0.45$ , Pseudo- $R^2$  (fixed effects) = 0.11]. Lower subjective discomfort thresholds to the electric shocks predicted higher SCRs ( $\chi^2(1) = 6.64$ ;  $p = 0.009$ ;  $\beta = -0.07$  [95% c.i. = -0.13, -0.02]) [Figure 1.C; Pseudo- $R^2 = 0.47$ , Pseudo- $R^2$  (fixed effects) = 0.08]. For the last two regression models, condition and session were entered as random effects.



**Figure 2. Threat of electric shock does not modulate neural correlates of perceptual learning, except at high degrees of anxiety.** (A) Subtraction (deviant minus standard, i.e. MMN) waveforms at frontal ROI (see fig. S1) for safe and threat conditions. (B) Average voltage scalp maps of MMN in safe and threat conditions at 30ms around peak latencies (safe = 130-150ms; threat = 110-130ms). (C) Mean values of MMN from (B) at frontal ROI. Error bars represent standard errors of the mean. (D) Scatter plot for single-subject mean values of self-reported anxiety and MMN amplitude (left) and mean SCRs and MMN amplitude (right) in safe and threat conditions. Regression lines and coefficients  $\beta$  for both plots were derived from linear mixed models that included self-reported anxiety (left) or SCRs (right) and condition as fixed effects and session, subject and block order as random effects. The grey and red areas around the regression lines indicate 95% confidence intervals for safe and threat conditions, respectively. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$  as a result of paired t-tests (Tukey HSD corrected).

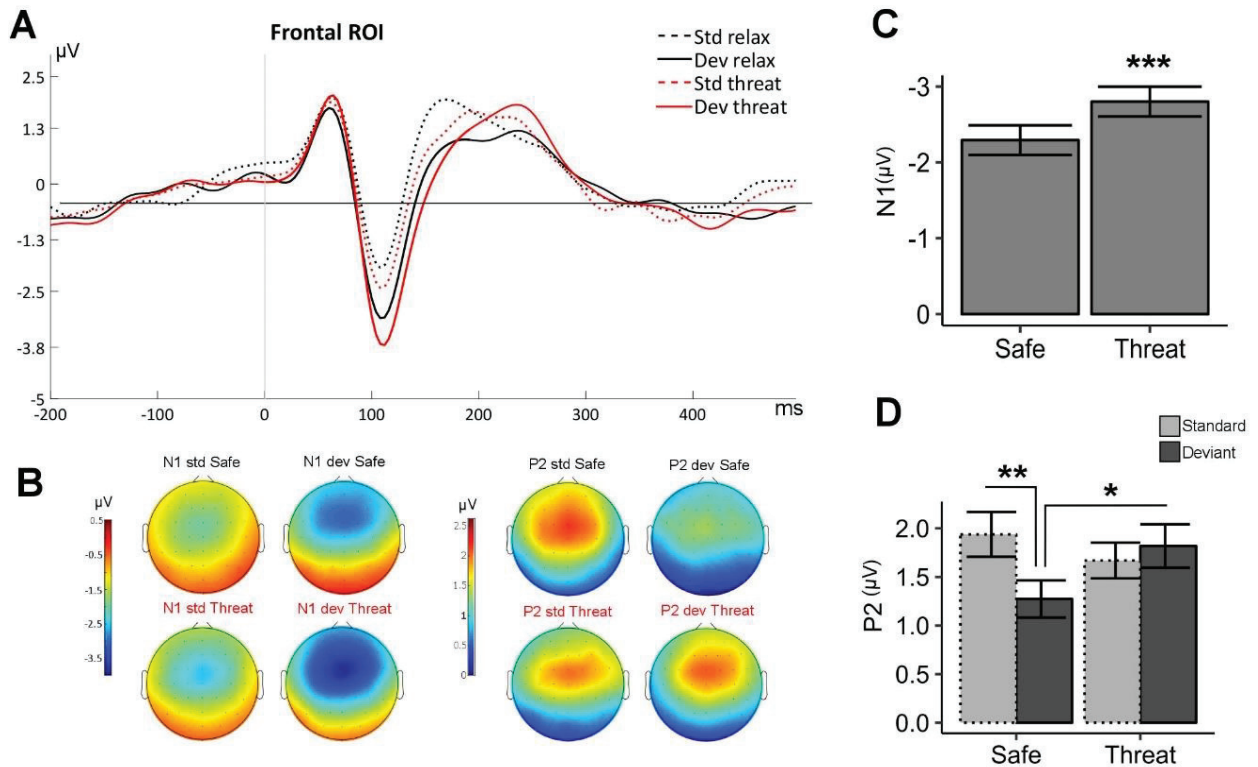
### 3.2 MMN amplitude

Our main question was to investigate whether the MMN amplitude was modulated by the threat of electric shock. As no interaction between condition and session was found on self-reported anxiety or SCRs, we did not test this interaction in the model on the MMN amplitude, but rather included session as a random effect. Figure 2.A and 2.B show the time-course of the mean amplitude of the difference waveforms, across

participants and sessions, and topographies at the MMN time-window for the SAFE and THREAT conditions. There was no effect of condition on the MMN amplitude when all observations were included ( $\chi^2(1) = 7 \times 10^{-4}$ ;  $p = 0.97$ ) [Figure 2.A; Pseudo- $R^2 = 0.04$ , Pseudo- $R^2$  (fixed effects) = 0], as well as excluding observations with no difference in self-reported anxiety ( $\chi^2(1) = 0.03$ ;  $p = 0.84$ ) [Pseudo- $R^2 = 0.04$ , Pseudo- $R^2$  (fixed effects) = 0]. To rule out a possible bias from focusing on a frontal ROI, as well as to explore a possible effect of condition on the MMN in unconventional scalp locations, we performed an electrode-wise cluster-based analysis in time and space dimensions. We did not find any significant cluster of electrodes that showed a difference between the two experimental conditions at any time point of the difference waveform. Additionally, we explored a possible relation between self-reported anxiety and the MMN amplitude. In this case, we found a significant interaction between anxiety and condition ( $\chi^2(1) = 3.75$ ;  $p = 0.05$ ) showing that higher self-reported anxiety predicted lower MMN amplitude in the SAFE condition and higher MMN amplitude in the THREAT condition [Figure 2.D; Pseudo- $R^2 = 0.06$ , Pseudo- $R^2$  (fixed effects) = 0.03]. Nonetheless, none of the two slope coefficients were significantly higher than zero ( $\beta = 0.31$  [95% c.i. = -0.02, 0.63];  $p = 0.2$  and  $\beta = -0.09$  [95% c.i. = -0.33, 0.15];  $p = 0.51$  for SAFE and THREAT conditions respectively). Finally, we explored a relationship between the SCRs and MMN amplitudes. No main effect or interaction between SCRs and MMN resulted from this regression model (Figure 2.D).

### **3.3 N1 and P2 amplitude**

We investigated the impact of threat of electric shock on components of the auditory evoked response that are related to early sensory processing for standard and deviant stimuli. Again, we included session as a random effect in the tested models. Figure 3.A shows the time-course of the auditory evoked responses across participants and sessions for standard and deviant stimuli during THREAT and SAFE condition. Figure 3.B shows the respective topographies at the N1 and P2 time-windows. The best fitting model at the N1 latency showed how the N1 amplitude increases during THREAT, compared to the SAFE condition ( $\chi^2(1) = 11.16$ ;  $p < 0.001$ ). A main effect of stimulus was present, representing the MMN ( $\chi^2(1) = 67$ ;  $p < 0.001$ ), while there was no interaction between stimulus and condition [Figure 3.C; Pseudo- $R^2 = 0.71$ , Pseudo- $R^2$  (fixed effects) = 0.08]. At the P2 latency, the best fitting model resulted in an interaction between stimulus and condition ( $\chi^2(1) = 6.07$ ;  $p = 0.01$ ) [Figure 3.D; Pseudo- $R^2 = 0.39$ , Pseudo- $R^2$  (fixed effects) = 0.02]. At this latency, the amplitude of the evoked response increases during the THREAT condition only for deviant stimuli (t-ratio (231) = -2.33;  $p = 0.02$  for deviants and t-ratio (231) = 1.15;  $p = 0.25$  for standards) and a difference between standard and deviant stimuli is present during the SAFE condition only (t-ratio (231) = 2.84;  $p = 0.004$  for safe and t-ratio (231) = -0.64;  $p = 0.52$  for threat conditions). Additionally, we tested whether self-reported anxiety and the amplitude of SCRs mediated the effect of condition on the N1 amplitude. In this case, we did not find any relation between self-reported anxiety, or SCRs, and N1 amplitude during threat or safe conditions.



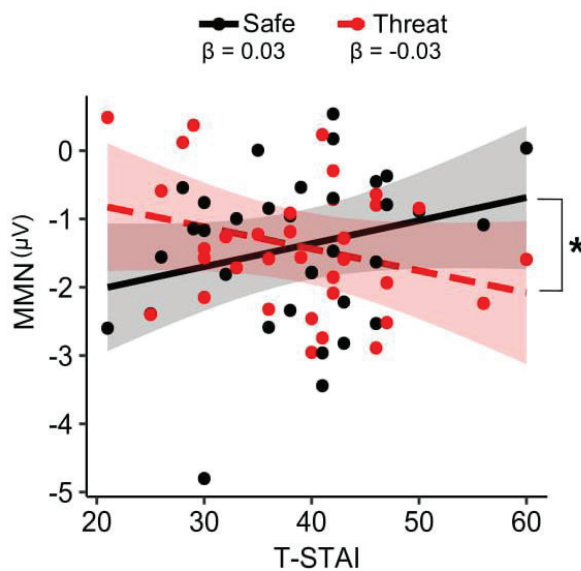
**Figure 3. Threat of electric shock increases the amplitude of neural correlates of early sensory processing.** (A) Event-related responses to standard (solid lines) and deviant (dashed lines) tones at frontal ROI (see fig. S1) during safe and threat conditions. (B) Average voltage scalp maps of standard and deviant stimuli in safe and threat conditions at 30ms around peak latencies for the N1 (30-200ms) and P2 (160-300ms) components of the auditory evoked response. (C) Mean values of N1 amplitude from (B) at frontal ROI for safe and threat conditions, combining standard and deviant stimuli. (D) Mean values of P2 amplitude from (B) at frontal ROI for safe and threat conditions and separately for standard and deviant stimuli. For (C) and (D), error bars represent standard errors of the mean. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$  as a result of paired t-tests (Tukey HSD corrected).

### 3.3 Modulation of MMN and N1 amplitude by trait anxiety and attention

We investigated the relation between trait anxiety, derived from the STAI questionnaire scores, and the amplitude of the MMN and N1 components of the auditory evoked response during SAFE or THREAT conditions. Averaged trait anxiety scores across participants were 39.39 (SD = 9.06). We found a significant interaction between STAI scores and condition in predicting the MMN amplitude ( $\chi^2(1) = 4.54$ ;  $p = 0.03$ ) [Figure 4; Pseudo- $R^2 = 0.07$ , Pseudo- $R^2$  (fixed effects) = 0.03]. As for the interaction between self-reported anxiety and MMN amplitude, a higher score in trait anxiety was related to decreased MMN amplitude in the safe condition and increased amplitude in the threat condition. Nonetheless, when the two slopes coefficients were

tested, none was significantly different than zero ( $\beta = 0.03$  [95% c.i. = -0.01, 0.08];  $p = 0.23$  and  $\beta = -0.03$  [95% c.i. = -0.08, 0.01];  $p = 0.24$  for SAFE and THREAT conditions respectively). As for the self-reported anxiety, no relation was found between STAI scores and N1 amplitude.

Finally, we explored whether a modulation of the MMN and N1 amplitude was related to self-report measures of distraction and attention to sounds. More specifically, participants were asked, at the end of each block, to which degree they have got distracted from the task (i.e. watching a movie) and to which degree they were listening to sounds during the task. No interaction or main effect was present when we tested whether attention to sounds or general distraction during the block predicted higher MMN or N1 amplitude.



**Figure 4. High degrees of trait anxiety modulate the neural correlates of perceptual learning under threat of electric shock.** Scatter plot for single-subject mean values of trait anxiety (T-STAI score) and MMN amplitude in safe and threat conditions. The regression lines and coefficients  $\beta$  are derived from a linear mixed model including T-STAI score and condition (safe, threat) as fixed effects and session, block order and subjects as random effects. The grey and red areas around the regression lines indicate 95% confidence intervals for safe and threat conditions, respectively. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$  as a result of paired t-tests (Tukey HSD corrected).



## 4. Discussion

The main aim of the present study was to clarify the impact of anticipatory anxiety on early sensory processing. We investigated whether an induced anxious state affects brain correlates of perceptual learning (i.e. the MMN amplitude) or results in a general sensitisation of neural early stimulus processing. Contrary to previous EEG studies, we relied on threat of electric shock as a well-established state anxiety manipulation procedure, to provide results that are comparable with recent findings (Cornwell et al., 2017) and account for limitations of other methods (Robinson et al., 2013 for a review). Participants reported higher levels of anxiety during periods of threat, compared to safe periods. Additionally, electrodermal activity was affected by electric shock threat, resulting in higher skin conductance responses (SCRs) to auditory cues introducing threat, compared to safe periods. These results confirm the involvement of the sympathetic branch of the autonomic nervous system in the anticipation of unpredictable noxious stimuli (Epstein and Roupelian, 1970). Moreover, SRCs and self-reports of state anxiety were strongly related in this paradigm, highlighting a high degree of specificity of electrodermal activity compared to other physiological measures. In a previous study, for instance, measures of salivary cortisol, a widely used marker of stress, did not correlate with subjective ratings (Simoens et al., 2007).

Both the average self-reported anxiety and SCRs decreased from the first to the second experimental session. Despite a well-known relation between repetitive exposure to stressors and habituation of electrodermal activity (Epstein, 1971), an alternative explanation for these results could be found in an effect of general fatigue and in the fact that the second session took place within an hour after lunch. However, the general decrease in anxiety between the first and second session did not modulate or disrupt the induction of an anxious state during the threat periods.

Although we can maintain, based on the above-mentioned results, that the experimental paradigm effectively manipulated levels of anticipatory anxiety, we did not find a difference in the amplitude of the MMN between safe and threat periods. This result held true regardless of whether a difference in MMN amplitude was tested in a canonical frontal ROI or using an electrode-wise cluster-based approach. No effect of the experimental manipulation was found when subjects that did not report any difference in anticipatory anxiety between conditions were excluded from the analysis. The findings are in line with previous studies that either did not find differences in MMN amplitude to frequency deviants at the level of scalp EEG (Ermutlu et al., 2005; Simoens et al., 2007) or found that state anxiety modulates differences in MMN in negative, but not neutral contexts (Schirmer and Escoffier, 2010). Our results contradict previous studies that reported increased brain responses to auditory deviants after the induction of an anxious state (Cornwell et al., 2017, 2007; Elling et al., 2011). Elling et al. (2011) used EEG to measure the MMN amplitude during a cold pressure task (CPT); the MMN increased right after the application of the stressor. Beside the ambiguity on the CPT effectiveness in inducing anticipatory anxiety (e.g. Robinson et al., 2013), the statistical analysis implemented in this study is

questionable. The MMN amplitude after the stressor application was compared, using an a priori contrast, to the average amplitude of measures at other nine time-points combined. This approach can increase the probability of false positives since the two conditions tested differ in terms of signal-to-noise ratio. Cornwell et al. (2007) used MEG to locate brain regions of increased response to stimulus deviance under threat of electric shock. Greater activity in several regions was found to correlate with differences in self-reported anticipatory anxiety. Nonetheless, a relatively lax threshold for detecting regions of activity was used (at least two contiguous voxels with the probability of the average  $t$  statistic  $p < 0.05$ , with no correction for multiple comparisons). Cornwell et al. (2017) replicated the previous MEG results, but restricting the analysis on a priori regions of interest that are part of a neuroanatomical model of the MMN (Garrido et al., 2009a). Within specific sources, they found an interaction between treatment (benzodiazepine) and condition (safe and threat) on the magnetic equivalent of the MMN. The authors, however, do not report results on the direction of the interaction and one could presume that the response to deviants was higher in threat, compared to safe periods, in the placebo condition, whereas the opposite was true when subjects underwent a pharmacological treatment.

A possible reason underlying the different results between the present EEG study and previous MEG studies could come from the role of attention in modulating the size of prediction error signals, described in different sensory domains (Feldman and Friston, 2010; Kok et al., 2012b). In the cited research, subjects underwent a passive oddball task, but were not instructed to ignore the auditory stimuli (the information is not present in the reports). In the present study, participants were instructed to watch a silent movie and ignore the auditory stimulation. However, we did not find any significant relation between self-reported attention to the auditory stimuli and the MMN amplitude. As we did not conceive the paradigm to elucidate this question, we can hypothesize that attentional shifts during the oddball session were not that consistent to determine a modulation of the MMN.

A further explanation could be found in the different statistical power and sensitivity between a source-based approach using MEG and the analysis of electric currents at the scalp level with EEG. Previous MEG studies did not report statistical analysis on sensors, hence no comparison with the present findings is possible at the scalp level. In spite of this, previous researches have described a considerable degree of correspondence between sources of MEG activity and electric MMN responses (Huotilainen et al., 1998).

Despite the lack of replication of studies that propose a general effect of anticipatory anxiety on perceptual learning, we hypothesize that this effect could be present for subjects with high degrees of state or trait anxiety. Specifically, we found a different modulatory effect of self-reported, as well as trait anxiety, on the MMN amplitude in the threat and safe conditions. The observed interactions point towards a possible difference in the MMN during threat, compared to safe periods, in subjects that scored high in the trait anxiety measure, as well as in those who reported high levels of state anxiety. This is in line with views of anxiety as a dimensional construct (Endler and Kocovski, 2001) and neurophysiological accounts of disfunctions in executive

networks related to high levels of trait anxiety (Sylvester et al., 2012). The putative impact of anxiety on perceptual learning as a function of the degree of trait and state severity can also explain the relative consistency found in studies that investigated the modulation of MMN amplitude by anxiety-related psychopathologies and dispositional anxiety (e.g. Bangel et al., 2017; Chen et al., 2016; Ge et al., 2011; Hansenne et al., 2003). The present findings raised a methodological consideration: when explored separately, no relationship was found between state or trait anxiety and the amplitude of the MMN in either safe or threat conditions. This result suggests that the MMN could be used as a marker of trait-anxiety only when one is contrasting the modulatory effect of trait-anxiety in a neutral compared to an anxiogenic state.

An interesting hypothesis is that state anxiety is generally linked to alerting and hyper vigilance and doesn't necessarily impact more complex processes such as perceptual learning, unless high levels of state or trait anxiety are reached (Pacheco-Unguetti et al., 2010). In the present study, we found an impact of the experimental manipulation on the amplitude of early neural responses to auditory stimuli. Similarly to previous studies (Ermutlu et al., 2005; Scaife et al., 2006b; White et al., 2005) we found an increased auditory N1 during threat, compared to safe periods. These results are also in line with research that reports an impact of mild stress on the sensitisation of early sensory processing in other domains (Qi et al., 2018; Shackman et al., 2011a). In the auditory domain, the increase in N1 amplitude has been related to an increase in noradrenergic activity, affecting the ability to filter out irrelevant sensory information (Ermutlu et al., 2005). Here we found that the modulation of neural correlates of early sensory processing by anticipatory anxiety is present for all stimuli at the N1 latency but is limited to auditory deviants at the P2 latency. A possible explanation is that, at later stages of sensory processing, only stimuli that are characterised by a higher degree of saliency are affected by the experimental manipulation. Nonetheless, this hypothesis remains exploratory.

Finally, contrary to the MMN, the modulation of the N1 amplitude by the experimental conditions was not mediated by self-reported or trait anxiety. In this sense, we can affirm that the sensitisation of early sensory processing by a state of hypervigilance is a robust phenomenon, which impacts brain responses even at a mild degree of anxiety.

To summarise, in the present study we sought to elucidate the influence of anticipatory anxiety on early sensory processing. We found that, contrary to recent findings, state anxiety does not modulate a common neural marker of perceptual learning, but rather sensitises early brain responses to auditory stimuli. Perceptual learning processes seem to be affected only at high levels of state and trait anxiety. Such a scenario is plausible if we consider anxiety as a dimensional construct. At mild levels of anxiety, brain responses to otherwise irrelevant stimuli are increased, an adaptive feedback to unpredictable threats in uncertain environments. However, when a state of anxiety is highly intense, or sustained across time, it affects the way the brain makes sense of the environment and learns about its features. Ultimately, such view distinguishes between an adaptive role of anxiety on processing efficiency and the detrimental impact on perceptual learning observed in psychiatric conditions.



## **6.2 Study 3: Perceptual learning and emotion regulation in expert and novice practitioners during threat of electric shock**

# Emotion regulation and perceptual learning under threat: EEG evidence from expert meditation practitioners

*In preparation*

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## **Abstract**

The impact of mindfulness meditation on emotional responses and emotion regulation has been widely explored. Nonetheless, little is known about the neurocognitive mechanisms underlying mindfulness practices in emotional contexts and their relation to a practitioner's subjective experience. In this work, we investigated the effect of anticipatory anxiety on auditory perceptual learning and early stimulus processing during different meditative states in expert and novice meditators. We used electroencephalography to study the mismatch negativity (MMN), a neural marker of perceptual learning processes. Previous studies suggested that the MMN can be modulated by anxiety. We hypothesized that this modulation would not be present in experts during meditation states and that this effect would be related to specific phenomenological configurations. We found that the MMN amplitude increased during periods of unpredictable threat only in individuals with high dispositional anxiety during a control state, but not during meditation. Additionally, expert meditators showed a dissociation between physiological responses to threat and subjective measures of anxiety. This dissociation was predicted by the experts' specific subjective experience, characterised by higher phenomenal clarity and meta-awareness, compared to novices. These two dimensions also predicted higher amplitude of a later component of the auditory evoked response during meditation, associated to attentional monitoring processes, compared to a control state. Overall, the present work provides empirical evidence of the mechanisms underlying emotion regulation in expert meditation practitioners.

Keywords: MMN, perceptual learning, anxiety, mindfulness, emotion regulation, subjective experience

## 1. Introduction

In everyday life, cognitive functions are intertwined with emotional and motivational states (Lazarus, 1982; Pessoa, 2008). This interaction applies also to perceptual learning, the process of casting predictions on the state of the sensory environment and comparing them with the incoming sensory evidence, in the form of prediction error signals (Friston, 2003). Within this framework, recent studies have shown that reward prediction errors (i.e. the difference between expected and observed outcomes) are modulated by emotional contexts (Robinson et al., 2013a; Watanabe et al., 2013). Emotions can also impact the perception of stimuli that are unrelated to the causes of the emotional state itself and are otherwise neutral. It is the case of anxiety, which instantiates a state of hypervigilance in response to unpredictable threats in novel and uncertain settings (Grupe and Nitschke, 2013). It is known that anticipatory anxiety impacts sensory-perceptual processing through the sensitisation of neural responses to environmental stimuli (see Jafari et al., 2017; Robinson et al., 2013b for recent reviews). Whereas anxiety maintains an evolutionary meaning in increasing the odds of survival in threatening situations (Kalin and Shelton, 1989), such state can become maladaptive if sustained over time and associated to otherwise innocuous stimuli. In fact, according to a recent neuroanatomical model, anticipatory anxiety can impede perceptual learning processes (Cornwell et al., 2017); a view supported by the research on anxiety-related psychopathologies, such as PTSD, and dispositional anxiety (e.g. Cisler and Koster, 2010; Newport and Nemeroff, 2000).

The effect of mindfulness meditation on emotional responses and emotion regulation has been widely investigated (see Hölzel et al., 2011; Keng et al., 2011; Tang et al., 2015 for recent reviews). Several studies have shown that meditation training downregulates the activity of brain regions underlying affective responses to emotional stimuli (e.g. Desbordes et al., 2012; Kral et al., 2018; Taren et al., 2015) and anticipatory processes of nociceptive triggers (Lutz et al., 2013). Interestingly, reduced affective responses to nociceptive stimuli after meditation training is not caused by decreased sensitivity. In fact, activity in brain regions related to stimulus saliency increases in response to nociceptive triggers in expert practitioners (Lutz et al., 2013). This evidence points towards a role of meditation training in dissociating the encoding of emotional stimuli from its related affective experience. The mechanisms underlying the regulation of emotional responses by meditation are still unclear and they possibly rely on top-down or bottom-up processes, depending on the amount of practice and expertise (Chiesa et al., 2013). Theoretical accounts suggest that the cultivation of *meta-awareness*, the cognitive function of being aware of the processes of consciousness, could play a crucial role in reducing the degree of experiential fusion with one's emotional experience, promoting cognitive control and non-judgmental acceptance (Dahl et al., 2015).

No previous studies have explored the effect of mindfulness meditation on anticipatory anxiety of unpredictable threat stimuli and little is known about the interplay between the specific attentional and motivational stance cultivated during meditation and the

neurocognitive processes affected by emotional states. Recent findings suggest that neural perceptual learning processes can be regulated by different mindfulness practices, as a function of meditation expertise, in a neutral environment (Fucci et al., 2018). It is unknown, however, whether meditation has an impact on perceptual learning in emotional contexts.

In this research, we investigate the effect of anticipatory anxiety on perceptual learning and early stimulus processing and its modulation by different meditative states in expert and novice practitioners. Specifically, we used EEG to measure the amplitude of the mismatch negativity (MMN), which reflects implicit perceptual learning processes (Garrido et al., 2009b), and the amplitude of early components of the auditory-evoked response under threat of electric shock during a passive auditory oddball task (as in Cornwell et al., 2017, 2007). We expected an overall sensitisation of brain responses to auditory stimuli during threat periods in both groups of participants and indiscriminately for meditation states and a control condition. Differently, we hypothesised that the MMN amplitude would have been affected by threat during a control condition but not during meditation, as results of the regulation of threat by the meditation practice, especially in experts compared to novice practitioners. In experts, we expected to observe a dissociation between physiological responses to threat and the intensity of the experience of anticipatory anxiety. This dissociation would downregulate the impact of threat on learning processes and would be related to the specific attentional and motivational stance cultivated during mindfulness practices. Finally, we hypothesized that this downregulation would be stronger during a state of nondual mindfulness (Open presence, OP; Lutz et al., 2007), compared to a state of concentrative meditation (Focused attention, FA; Lutz et al., 2008) due to the higher degree of meta-awareness and dereification of subjective experience that characterises the former practice.

We implemented a neurophenomenological approach, integrating self-reports of different dimensions of subjective experience during meditation with measures of bodily physiology (i.e. electrodermal activity) and components of the auditory evoked response. More precisely, we collected reports on the degree of meta-awareness and clarity during FA and OP meditation [open monitoring (OM) for novices; see Methods section 2.2] and a control condition. Clarity refers to the degree of vividness with which an experience occurs and it is linked to meta-awareness and expertise in different styles of mindfulness (Lutz et al., 2015). Additionally, we explored the relationship between self-reports and trait measures of interoceptive awareness and cognitive defusion (Forman et al., 2012; Mehling et al., 2012).

## 2. Materials and Methods

### 2.1 Subjects

Thirty expert meditation practitioners (52±7.8 years old, 13 females) and thirty-six control healthy individuals (52±7.6 years old, 17 females) participated in the study. Meditation naive participants were recruited locally through flyers and posters in public places, on mailing lists, Facebook and notifications to research participant databases. Expert practitioners were recruited from multiple meditation centres, predominantly in France but also internationally, with the help of a long-term practitioner with extensive contacts within the Nyingma and Kagyü meditation community. The present study was part of a larger research project that included several experimental sessions. A detailed description of the general inclusion and exclusion criteria for expert and novice practitioners, as well as the inclusion process is provided in a separate document (Abdoun et al., 2018; accessible online at [osf.io/dbwch](https://osf.io/dbwch)). All participants were affiliated to social security, provided written informed consent before the start of the study and were paid for their participation. Ethical approval was obtained from the appropriate regional ethics committee on Human Research (CPP Sud-Est IV, 2015-A01472-47). 36 novices and 23 experts completed the trait scale of the State Trait Anxiety Inventory (STAI, [Spielberg, 1970]) before participating in the experiment. Additionally, 24 novices and 23 experts completed the Drexel Defusion Scale (DDS, Forman et al., 2012) and the Multidimensional Assessment of Interoceptive Awareness (MAIA, Mehling et al., 2012).

### 2.2. Meditation practices and training

The distinction between focused attention (FA) and open monitoring (OM) styles of meditation has been extensively discussed in previous theoretical work (Lutz et al., 2008). In the present study, during the FA condition, participants were asked to concentrate on a fixation cross as the object of meditation. The choice of this specific object was done to allow an unbiased comparison with the control condition, when subjects watched a silent documentary on the same screen. A fixation cross was present on the screen in the OM practice as well and subjects were asked to keep their eyes opened. Practicing meditation with eyes opened is a common feature of the Nyingma and Kagyü schools, which all expert practitioners who participated in this research belonged to. It is also suggested in the training program proposed to the control subjects, which derives from the same Buddhist traditions. In the present study, keeping the eyes opened helped avoiding the contamination of the EEG signal by alpha oscillatory activity.

It is important to notice that novice and expert practitioners differ in their style of practicing objectless meditation. Specifically, the present group of expert meditators was intensively trained in practices related to the “realization of the nature of mind” (Tib. *rig pa*). In their case, practicing meditation without object is related to maintaining a state previously referred to as open presence (e.g. Lutz et al., 2007).

Within this state, an awareness of whatever emerges in experience continues without the effortful vigilance that characterizes OM styles of practice (see the notion of “reflexive awareness” in previous works; e.g. Coseru, 2015; Dunne, 2015). However, as we mentioned in previous research (Fucci et al., 2018), the state of OP is characterised by a high degree of variability between subjects and within a specific session. In the present study, experts were engaged with such practice for few minutes within each experimental session and there was no way to tell whether the participant’s subjective experience was more akin to OM or OP.

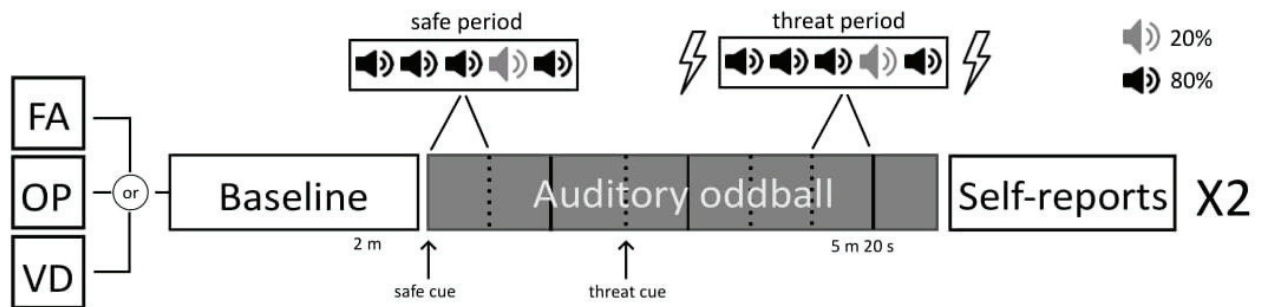
Novice practitioners were introduced to the practice of meditation during a weekend-long training program. During the program, they not only familiarised with the specific practices, but were introduced to the terminology used to describe dimensions of the subjective experience in the context of research in contemplative science. This was done to create a common linguist framework between the researchers and the participants and to allow for an accurate description of the participant’s subjective experience. In a separate report (see *Protocol Study*), we provide a comprehensive account of this methodological approach, as well as empirical data supporting the assumption that novice practitioners were indeed familiar with specific phenomenological categories that are related to meditation practice.

Novices were asked to practice at home during the period preceding the experiment (see Abdoun et al 2018 for a detailed account of subjects’ degree of compliance to the home practice).

### ***2.3 Task design and stimuli***

Subjects underwent a passive auditory oddball task (e.g. (Näätänen et al., 2004)), consisting of the variable repetition of a standard tone (880Hz; 80ms duration ; 10ms rise and fall) followed by the presentation of a frequency deviant (988Hz; 20% of all auditory stimuli) presented binaurally (fixed I.S.I = 500ms). The overall paradigm consisted in six blocks over two experimental sessions with three different experimental conditions (figure 1): focused attention meditation (FA), open presence meditation (OP) and a control condition (VD) during which subjects were asked to watch a silent movie and ignore the auditory stimuli. The sequence of blocks was randomised within each session and the block order has been considered in the statistical analysis. Each block started with a 2 minutes period with no auditory stimuli. During this time, subjects were asked to meditate or watch the silent movie, depending on the block. Subsequently, short oddball sequences were embedded in alternating 30s periods (8 periods per block) in which participants were informed of the possibility of receiving an electric shock (threat periods,  $n = 4$ ) or that no shocks would have been delivered (safe periods,  $n = 4$ ) [ as in Cornwell et al., 2007]. The information was conveyed by auditory cues at the beginning of each period, before the oddball sequence. The same amount of standard and deviant stimuli was delivered during safe and threat periods ( $n = 56$  deviants and  $n = 224$  standards when combining four periods). After each block, participants were asked to answer, on a 1 to 7 Likert-item, how much anxiety they felt during threat and safe periods. Additional questions were

asked after each block, to be answered using the same response format. Questions pertained to different dimensions of the participant's subjective experience during the block and were not specific for safe and threat periods (see Supplementary Information 1 for the specific questions and response scales).



**Figure 1. Schematic illustration of the experimental paradigm.** Each experimental block started with a 2 minutes baseline period, followed by auditory oddball sequences embedded in safe and threat periods. Participants underwent three blocks, in a random order, during focused attention (FA) and open presence (OP) meditation and a control condition in which they were instructed to watch a silent movie and ignore auditory stimuli (VD). After each block, they answered questions on a 7-points Likert-like item. The paradigm consisted of two sessions including three blocks each.

#### 2.4 Electric-shock stimuli and intensity work-up procedure

In line with the procedure described in Schmitz and Grillon (2012), electrodes from a direct current stimulator were placed on the participant's lower wrist. Participants were asked to rate, on a scale from 1 to 5 (1=barely felt, 5=very uncomfortable), delivered electric stimuli. Stimuli were presented at intensities starting from 2mA and up to 16mA (duration = 100ms), until the participant rated 4 out of 5 on the scale the currently delivered stimulus. If the subject's threshold reached 16mA, stimuli were delivered at this maximal intensity. In our sample, the mean shock intensity was 8.29mA (SD = 4.41) and 8.41mA (SD = 5.1) for the novices and experts group, respectively. A total of five shocks were delivered randomly throughout the two blocks of each experimental condition (FA, OM, VD). No more than two shocks were delivered during the same threat period. Subjects were told that the number of delivered shocks could vary randomly and that the experimenter had no control over their frequency.



## **2.5 EEG recordings and pre-processing**

EEG was recorded at 512 Hz using the ActiveTwo system (BioSemi, Amsterdam, Netherlands), consisting of 64 active electrodes that were placed in an EEG cap according to the standard 10/20 system, with CMS-DRL serving as the reference-ground. The horizontal and vertical EOG was measured by placing electrodes on the outer canthi and above and below the subject's left eye.

Pre-processing was done using EEGLAB (Delorme and Makeig, 2004) and personal Matlab scripts (version R2015a). The EEG signal was downsampled to 250Hz and re-referenced offline using the electrodes placed at the level of the mastoids (average activity of the two channels). Data were visually inspected to identify bad channels, which were marked for successive interpolation. Independent Component Analysis (ICA) was applied, separately for the two sessions, to the continuous data using the Runica algorithm (Makeig et al., 2002). Recordings that underwent ICA were manually cleared of big artefacts, filtered between 1 and 20Hz (using *eegfiltnew* function, which applies a Hamming windowed sinc FIR filter. High-pass and low-pass filters were applied separately. High-pass 1Hz order = 1650; low-pass 20Hz order = 166) and did not comprise channels that would have been subsequently interpolated. ICA was applied only on recordings from the control video condition. This choice was made to be able to clearly identify saccades and blinks across all experimental conditions while allowing for faster calculations. Resulting ICA matrices were then transferred to the original raw data of each experimental condition within a session. Subsequently, ICA components were visually inspected to remove blinks and saccades. Data were high-pass filtered at 2Hz (filter order = 414) to avoid contamination of slow frequencies and drifts in the signal caused by sweating during the stress periods. Previously marked bad channels were interpolated and 50Hz noise was removed using the *Cleanline* algorithm. Epochs were created between -200 and 500ms after stimulus onset for standard and deviant stimuli, and baseline-corrected (-100ms baseline). The epoched data were inspected and bad epochs were removed. All outer ring channels were rejected due to consistent noise, leading to 41 channels remaining (see figure S1 for a visual layout). For each subject, epoched data from one block was removed if the number of deviants, after rejection, was lower than thirty-five for the safe or threat condition. Following this procedure, one expert practitioner was excluded from further analysis. Additional data from specific experimental conditions and blocks were excluded (see Supplementary Information 2.2 for a summary table). Finally, a low-pass filter of 20Hz was applied to the epoched data for the analysis of the evoked responses.

## **2.7 Event-related potentials**

Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). For the analysis of event-related potentials (ERPs), only standard stimuli that directly preceded a deviant were considered (see Supplementary Information for a summary of the mean number of epochs in each session separately for group, state, condition and stimulus type).



To identify the MMN, we computed the difference waveforms from the grand average between all subjects, separately for each group, state (FA, OM, VD), condition (safe, threat) and session. We used an a priori region of interest (ROI) that included the channel Fz and four surrounding channels (figure S1). The ROI was consistent with previous literature (e.g. Duncan et al., 2009; Näätänen et al., 2011). Nonetheless, we performed additional exploratory analysis on the MMN amplitude at the channel Cz, to investigate a possible effect of threat periods on unconventional MMN sites. The MMN amplitude was calculated based on a 20ms time-window centred around the most negative peak of the difference waveform for each condition (safe and threat), session, state and group between 90 and 200ms after stimulus onset. Amplitude values for each subject were extracted within this identified time-window.

Additionally, we performed analysis on the amplitude of classical auditory ERP components, such as the N1 and P2 (Picton et al., 1974) on the frontal ROI. Single-subject amplitudes for each condition (safe and threat), session, state, group and stimulus type were extracted from a 20ms time-window centred around the most negative peak between 90 and 200ms for the N1, and as the average amplitude between 180 and 280ms for the P2.

For each of three components of interest (MMN, N1, P2) we tested the effect of condition, group, state, and stimulus type (for N1 and P2) using linear mixed-effects models (R package lme4, [Bates et al., 2014]) which allow for unbalanced designs (e.g. missing data from one block for a subject) and the inclusion of random effects such as, in the present case, session and block order information. Mixed-effects models were evaluated using an ANOVA analysis of variance (Type II Wald chi-square test). Paired t-tests, corrected for multiple comparisons using Tukey honestly significant difference test (HSD), were used as post-hoc tests comparing least-squared means. We report, in the results section, estimates of effect size in the form of pseudo- $R^2$  as proposed by Nakagawa and Schielzeth (2013). Notice that the calculation of effect sizes in linear mixed models is not unambiguous and should be handled with consideration.

## ***2.8 Skin conductance data acquisition and analysis***

For the recording of electrodermal activity, two passive electrodes were placed on the participant's non-dominant hand, on the volar surface of the distal phalange of the 2nd and 3rd fingers. Data were recorded using the 16Hz coupler provided with the ActiveTwo system (BioSemi, Amsterdam, Netherlands) with a sampling rate of 250Hz. Data were downsampled at 25Hz and analysed with the Matlab software Ledalab V 3.4.9 ([www.ledalab.de](http://www.ledalab.de)) applying Continuous Decomposition Analysis (Benedek and Kaernbach, 2010), separating the phasic from the tonic electrodermal activity in a block. Our two measures of interest were 1) the event-related phasic activity after the onset of auditory cues preceding safe and threat periods and 2) the event-related phasic activity in response to the electric shock stimuli. Data were visually inspected and sessions where very weak or no phasic response was present were excluded from further analysis. Following this inspection, three control subjects and ten single sessions were excluded due to missing data (equipment failure) or lack of phasic

responses. Subsequently, skin conductance responses (SCRs) were calculated for each subject and session over a 1 to 5 seconds window after stimulus onset with a minimum threshold of 0.1 microSiemens ( $\mu\text{S}$ ). As previously mentioned, three types of stimuli were included: cues preceding safe and threat periods, and electric shock stimuli. A log-transformation was applied to raw SCRs to normalize values between and within subjects.

Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]) using linear mixed models. We tested 1) the effect of condition (safe and threat), state, group and session in response to the auditory cues and 2) effect of group, state and session in response to the electric shocks on the log-transformed SCRs. The information about block order and auditory cue order within a block were entered in the model as random effects. Mixed-effects models were evaluated using an ANOVA analysis of variance (Type II Wald chi-square test). Paired t-tests, corrected for multiple comparisons using Tukey honestly significant difference test (HSD), were used as post-hoc tests comparing least-squared means.

### ***2.9 Self-reports and regression analysis***

Analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). The analysis of condition (safe and threat), state, group and session effects on self-reported anxiety was performed using linear mixed models and treating Likert items as interval data. An integrative model including all items was used to investigate group, state and session effects on the different scales of self-report questions (see Supplementary Information 1 for each specific question). As in previously described models, the information on block order was entered as a random effect.

We investigated the relationships between self-reports and third-person variables (e.g. ERP components amplitude and SCRs), as well as between trait (STAI, MAIA and DDS questionnaires scores) and specific state measures. To minimize the number of statistical tests and allow for unbalanced designs (e.g. SCR or EEG data missing for some subjects), we used linear mixed models entering independent variables and factors as fixed effects, as well as session and block order information as random effects for all the fitted models. Eventual interactions between an independent variable and levels of a factor were explored post-hoc comparing the regression slopes between each factor level using the function “*lstrends*” (R package “*lsmeans*”, Lenth, 2016). In the context of interactions, we tested whether a specific slope for one factor level was different from zero using the function “*sim\_slopes*” (R package “*jtools*”, Long, 2018). Finally, when an interaction between two continuous variables was present, we analysed Johnson-Neyman intervals, which provide cut-off values of one continuous variable at which the conditional slope between the other continuous variable and the dependent variable is statistically significant (Johnson and Fay, 1950).

For all the linear regression models, session was entered as a random effect together with info on block order. The relationship between MAIA and DDS was assessed separately by a linear regression model using DDS scores as dependent and MAIA scores as independent variable.

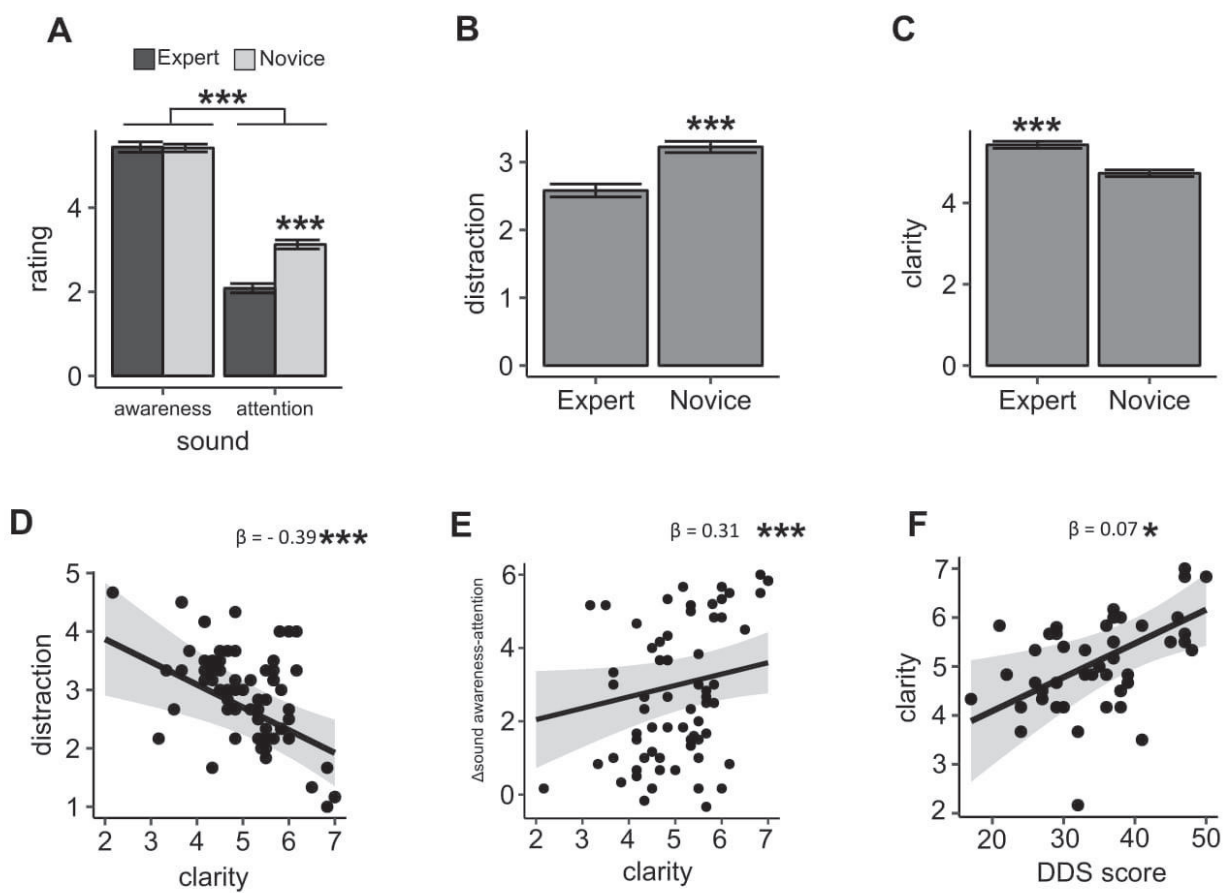
### 3. Results

#### 3.1 Dimensions of subjective experience

At the end of each block, participants were asked to answer questions about aspects of their subjective experience during the paradigm. Questions tapped into the following dimensions: sound awareness and sound attention (i.e. listening to the auditory stimuli), distraction and clarity of mind (see Supplementary information 1 for the specific questions). When pulling together questions from all the scales, we found a group by scale interaction on the overall ratings ( $\chi^2 (3) = 101.3, p < 0.001$ ) which showed how expert and novices differed for some but not all scales. A scale by session interaction was also present ( $\chi^2 (3) = 17.2, p < 0.001$ ) [model Pseudo- $R^2 = 0.52$ , Pseudo- $R^2$  (fixed effects) = 0.47]. Subsequently, we explored group and session effects on each separate dimension (however, we considered sound awareness and sound attention to pertain to the same dimension of “relation to sounds”). We found a group by scale (sound awareness, sound attention) interaction (Figure 2.A;  $\chi^2 (3) = 32.08, p < 0.001$ ) showing that experts and novices were equally aware of sounds during a block (t-ratio (92.09) = 0.07,  $p = 0.93$ ) but experts were listening less to sounds, compared to novices (t-ratio (92.09) = -4.56,  $p < 0.001$ ) [model Pseudo- $R^2 = 0.61$ , Pseudo- $R^2$  (fixed effects) = 0.47]. Expert practitioners reported less distraction (Figure 2.B;  $\chi^2 (1) = 10.75, p = 0.001$ ) and more clarity of mind (Figure 2.C;  $\chi^2 (1) = 9.7, p = 0.002$ ) during a block. For both scales (distraction and clarity) a main effect of session was present (Figure S2;  $\chi^2 (1) = 10.75, p = 0.001$  and  $\chi^2 (1) = 10.75, p = 0.001$  for distraction and clarity respectively) [distraction model: Pseudo- $R^2 = 0.36$ , Pseudo- $R^2$  (fixed effects) = 0.09; clarity model Pseudo- $R^2 = 0.56$ , Pseudo- $R^2$  (fixed effects) = 0.09].

Furthermore, we explored whether the difference in clarity between groups mediated the difference observed in the degree of distraction between groups, as well as the difference between sound awareness and attention. We found that high clarity predicted less distraction in general (Figure 2.D;  $\chi^2 (1) = 56.37, \beta = -0.39$  [95% c.i. = -0.63, -0.15],  $p < 0.001$ ; model Pseudo- $R^2 = 0.42$ , Pseudo- $R^2$  (fixed effects) = 0.21). More clarity during a block also predicted a higher difference between sound awareness and sound attention (Figure 2.E;  $\chi^2 (1) = 15.9, \beta = 0.31$  [95% c.i. = 0.16, 0.46],  $p < 0.001$ ; model Pseudo- $R^2 = 0.69$ , Pseudo- $R^2$  [fixed effects] = 0.09).

Finally, we investigated whether self-reported clarity was related to the degree of cognitive defusion, measured as a trait through the DDS questionnaire. We found that higher DDS scores predicted higher clarity across all states and participants (Figure 2.F;  $\chi^2 (1) = 4.37, \beta = 0.07$  [95% c.i. = 0.02, 0.12],  $p = 0.03$ ; model Pseudo- $R^2 = 0.62$ , Pseudo- $R^2$  (fixed effects) = 0.16). DDS scores were predicted by the degree of interoceptive awareness, as highlighted by a linear regression model including the MAIA scores as independent variable ( $F (3,42) = 16.13, p < 0.001, \beta = 0.29$  [95% c.i. = 0.13, 0.45]).



**Figure 2. Differences in dimensions of subjective experience between expert and novice practitioners and relationship between clarity and other state and trait measures.** (A) Mean values of self-reported sound awareness and attention to sounds in experts and novices. (B-C) Mean values of self-reported distraction and clarity in experts and novices. For A, B and C, error bars represent standard errors of the mean. (D-E) Scatter plots for single-subject mean values of self-reported clarity and distraction and clarity and  $\Delta$ sound (sound awareness – attention). (F) Scatter plot for single-subject DDS scores and mean values of self-reported clarity. In D, E and F, the regression lines and coefficient  $\beta$  are derived from linear mixed models including state and group as fixed effects and session, block order and subjects as random effects. The grey area around the regression line indicates 95% confidence intervals. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ .

### 3.2 Self-reported anxiety and skin conductance responses

A group by condition (safe, threat) interaction was present on self-reported anxiety (Figure 3.A;  $\chi^2(1) = 49.6, p < 0.001$ ). Specifically, expert practitioners reported being less affected by the threat condition, compared to novices (Safe minus Threat: experts estimate =  $-0.58, t\text{-ratio}(714) = -6.16, p < 0.001$ ; novices estimate =  $-1.47, t\text{-ratio}(714) = -17.2, p < 0.001$ ). Additionally, expert practitioners reported less anxiety than novices in both conditions, but especially during threat periods (Experts minus Novices: safe period estimate =  $-0.48, t\text{-ratio}(81) = -2.57, p = 0.01$ ; threat period estimate =  $-1.38, t\text{-ratio}(81) = -7.3, p < 0.001$ ). Differently, skin conductance responses (SCRs) were significantly higher during threat, compared to safe periods, among all groups and

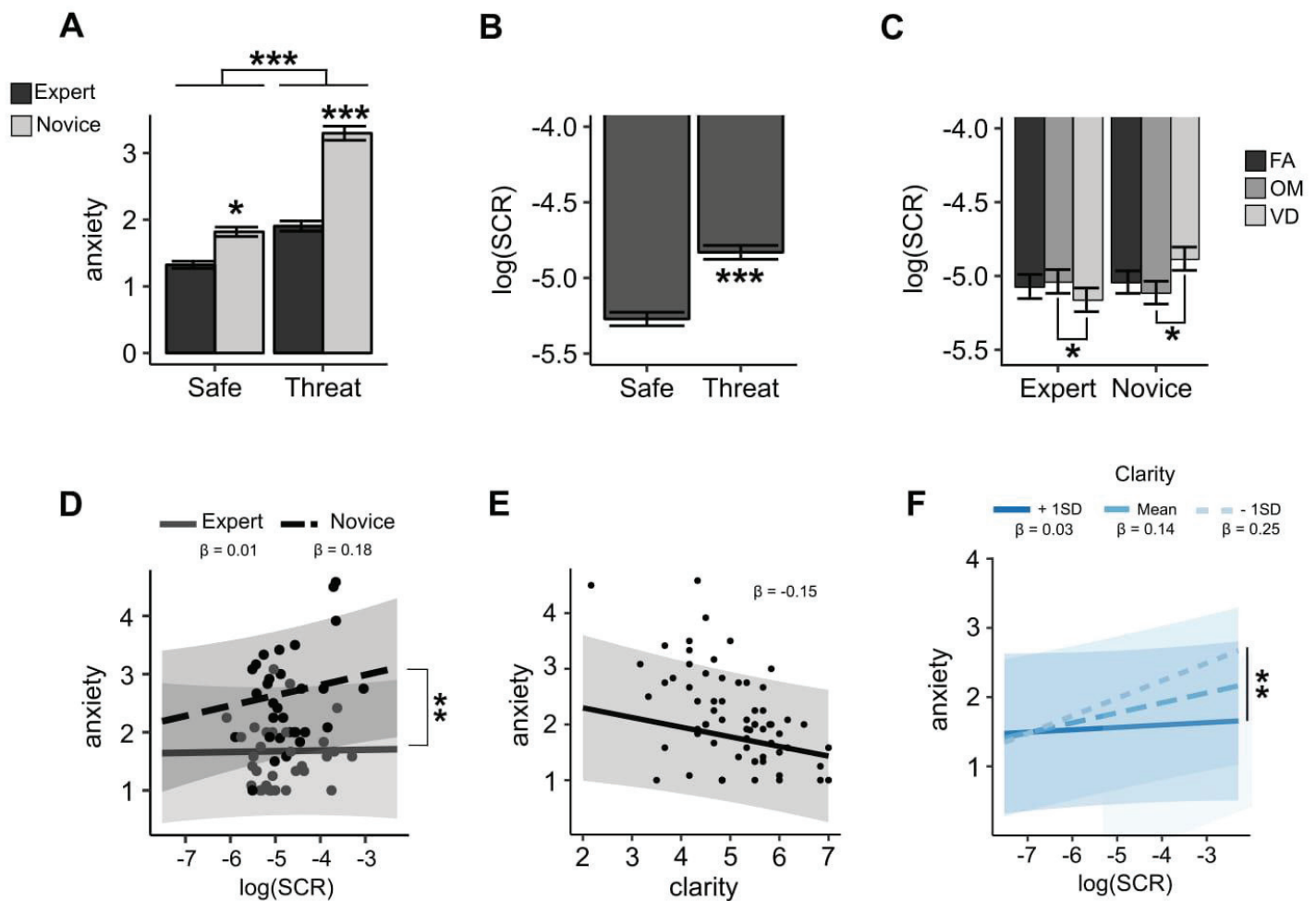
states (Figure 3.B;  $\chi^2(1) = 95.53$ ;  $p < 0.001$ ). Additionally, a state by group interaction was present on the SCRs across conditions (Figure 3.C;  $\chi^2(1) = 13.53$ ;  $p = 0.001$ ). SCRs were higher during OM, compared to VD in experts ( $t\text{-ratio}(2575) = 2.67$ ,  $p = 0.02$ ), while the opposite pattern was observed in novices ( $t\text{-ratio}(2575) = -2.46$ ,  $p = 0.03$ ). A main effect of session was present both on self-reported anxiety and SCRs ( $\chi^2(1) = 29.1$ ,  $p < 0.001$  and  $\chi^2(1) = 303.33$ ,  $p < 0.001$ , respectively. See figure S2) [Self-reported anxiety model: Pseudo- $R^2 = 0.58$ , Pseudo- $R^2$  (fixed effects) = 0.32; Skin conductance responses model Pseudo- $R^2 = 0.53$ , Pseudo- $R^2$  (fixed effects) = 0.08].

We observed an increase in electrodermal activity after threat cues among both groups, but a different impact of threat on subjective anxiety in experts, compared to novices. To further understand this differential interplay, we investigated the relation between these two measures in each group. We found an interaction between SCRs amplitude and group in predicting subjective anxiety ( $\chi^2(1) = 7.49$ ;  $p = 0.006$ ) [Figure 3.D; Pseudo- $R^2 = 0.61$ , Pseudo- $R^2$  (fixed effects) = 0.13]. The interaction pointed towards a direct relation between SCRs and self-reported anxiety in novice, but not expert practitioners. However, none of the two slope coefficients were significantly higher than zero ( $\beta = 0.01$  [95% c.i. = -0.17, 0.19],  $p = 0.91$  and  $\beta = 0.18$  [95% c.i. = -0.01, 0.37],  $p = 0.25$  for experts and novices respectively).

Furthermore, we explored whether differences in self-reported anxiety between groups were mediated by the difference in self-reported clarity, and whether the latter was also a mediating factor for the observed dissociation between SCRs amplitude and self-reported anxiety in expert practitioners. We found that higher clarity predicted less anticipatory anxiety in general (Figure 3.E;  $\chi^2(1) = 13.08$ ,  $\beta = -0.15$  [95% c.i. = -0.22, -0.07],  $p < 0.001$ ; model Pseudo- $R^2 = 0.61$ , Pseudo- $R^2$  [fixed effects] = 0.12). Moreover, a significant interaction between clarity and SCRs was present among both groups ( $\chi^2(1) = 8$ ,  $p = 0.004$ ; model Pseudo- $R^2 = 0.62$ , Pseudo- $R^2$  [fixed effects] = 0.15).

In this case, Johnson-Neyman interval analysis showed that a significant relation ( $p < 0.05$ ) between SCRs amplitude and self-reported anxiety was present only for those observations when reported clarity was less than 5.5 out of 7 (Figure S3). For those observations where subjects scored less than 5.5 in clarity, the slope coefficient diminished as the reported clarity increased. This analysis confirmed that the dissociation between physiological responses and the subjective experience of anticipatory anxiety was mediated by the degree of clarity reported by a participant in a block. For some blocks, participants reported no difference in anxiety between conditions (the participant scored 1 both in safe and threat periods). Specifically, 130 out of 360 blocks for experts and 40 out of 432 blocks for novices. We decided to keep these observations in further analyses because: 1) the decreased subjective anxiety in experts represented an effect of interest, rather than a bias (especially considering the dissociation between SCRs and self-reported anxiety), 2) the effect of threat on the N1 amplitude was present when the subjects reporting no difference in anticipatory anxiety were considered separately (see Results section 3.3). However, we performed an additional analysis on the modulation of the MMN amplitude by electric shock threat, excluding these observations (see Results section 3.3).





**Figure 3. Subjective and physiological measures of anxiety are dissociated in expert meditators and this effect is mediated by self-reported clarity.** (A) Mean values of self-reported anxiety in experts and novices during safe and threat periods. (B) Mean amplitude of skin conductance responses (log-transformed) to auditory cues introducing threat and safe periods, in experts and novices. (C) Mean amplitude, across safe and threat periods, of skin conductance responses (SCR; log-transformed) to auditory cues in experts and novices during FA, OP and VD blocks. For A, B and C, error bars represent standard errors of the mean. (D) Scatter plot for single-subject mean values of self-reported anxiety and mean amplitude of SCRs in novice (black) and expert (grey) practitioners. (E) Scatter plot for single-subject mean values of self-reported anxiety and clarity across both groups. (F) Interaction plot between mean values of self-reported anxiety and SCRs as a function of clarity (+/- 1SD). In D, E and F, the regression lines and coefficient  $\beta$  are derived from linear mixed models including state, group and condition (safe, threat) as fixed effects and

### 3.3 MMN amplitude

Our main question was to investigate whether the MMN amplitude was differently modulated by the threat of electric shock between groups and states. As no interaction between condition and session was found on self-reported anxiety or SCRs, we did not test this interaction in the present model and session was included as a random effect. Figure 4.A shows the time-course of the mean difference waveforms, across participants and sessions, during threat and safe conditions and during FA, OP and VD separately for expert and novice participants. Figure 4.B shows the respective scalp topographies of the mean MMN peak amplitude for the above-mentioned conditions

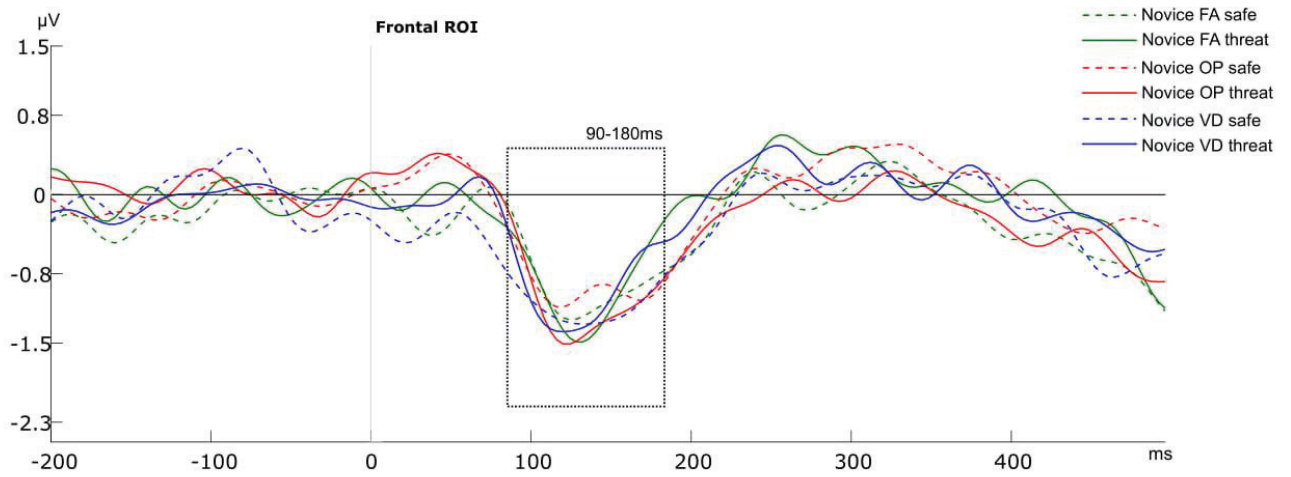
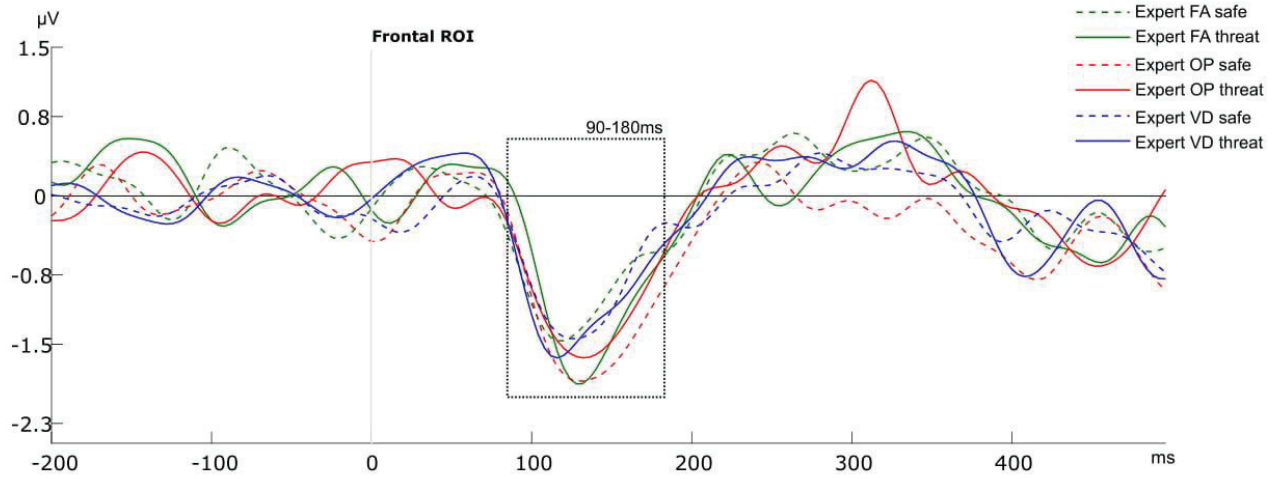
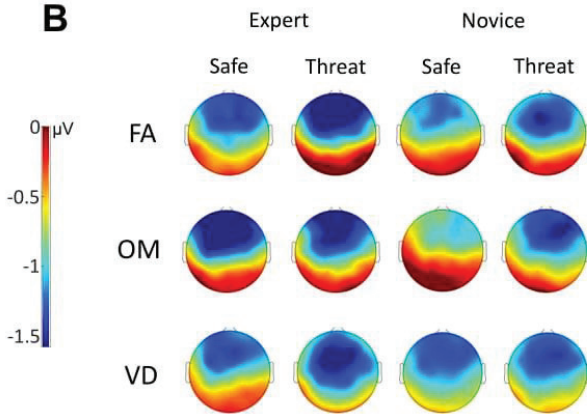
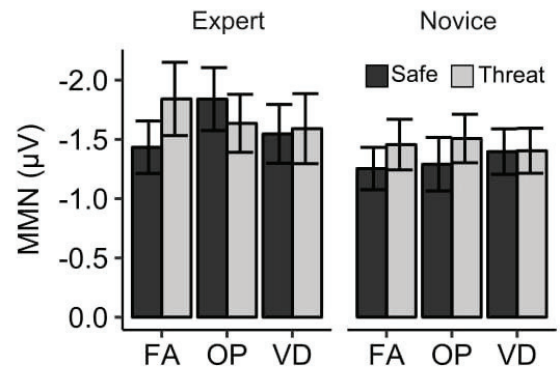
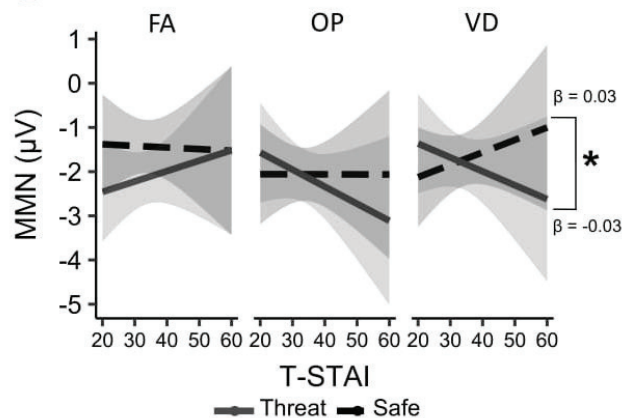
and groups. We did not find a significant interaction between group, state and condition (safe, threat) on the MMN amplitude when all observations were included ( $\chi^2(2) = 0.07$ ;  $p = 0.78$ ) [Figure 4.C; Pseudo- $R^2 = 0.14$ , Pseudo- $R^2$  (fixed effects) = 0.01] and excluding observations with no difference in self-reported anxiety ( $\chi^2(2) = 1.85$ ;  $p = 0.39$ ) [Pseudo- $R^2 = 0.14$ , Pseudo- $R^2$  (fixed effects) = 0.02]. A main effect of condition was not present either. The same model tested at the electrode Cz did not yield any significant interaction or main effect of condition.

Additionally, we explored a possible relation between self-reported anxiety, as well as levels of trait anxiety, and the MMN amplitude during FA, OP and VD in expert and novice practitioners. In the former case, we did not find any significant relation between self-reported anxiety and MMN amplitude. Regarding the relation between trait anxiety and MMN amplitude, we found a significant interaction between T-STAI questionnaire scores, state (FA, OP, VD) and condition (safe, threat) in predicting the MMN amplitude (Figure 4.D;  $\chi^2(2) = 6.67$ ;  $p = 0.03$ ) [Pseudo- $R^2 = 0.17$ , Pseudo- $R^2$  (fixed effects) = 0.04]. Specifically, higher degrees of trait anxiety predicted a difference in the MMN amplitude between safe and threat periods among both groups but only during VD (t-ratio (583.32) = 2.25,  $p = 0.02$  for VD; t-ratio (583.32) = 0.67,  $p = 0.5$  for OP; t-ratio (583.32) = -1.22,  $p = 0.22$  for FA). Nonetheless, none of the two slope coefficients (safe, threat) during VD were significantly higher than zero ( $\beta = 0.03$  [95% c.i. = -0.02, 0.08],  $p = 0.12$  and  $\beta = -0.03$  [95% c.i. = -0.07, 0.01],  $p = 0.18$  for safe and threat conditions respectively).

A secondary aim of this study was to replicate previous findings that indicated a differential modulation of the MMN amplitude between experts and novices and between states. To investigate this hypothesis, we tested a linear mixed model where condition (safe, threat) was entered as random effect. We did not find a significant interaction between groups and states in modulating the MMN amplitude ( $\chi^2(2) = 0.59$ ;  $p = 0.74$ ). For possible interpretations of the lack of interaction between group and states in this specific paradigm, see the Discussion section of this report.

**Figure 4. MMN amplitude is not modulated by threat of shock or meditation states and expertise, except for subjects with high trait anxiety.** (A) Subtraction (deviant minus standard, i.e. MMN) waveforms at frontal ROI (see fig. S1) for safe and threat conditions during FA, OP and VD in experts (top) and novices (bottom). (B) Average voltage scalp maps of MMN in safe and threat periods during FA, OP and VD, in experts and novices, at 30ms around the peak in a fixed latency window (90-180ms). (C) Mean values of MMN from (B) at frontal ROI. Error bars represent standard errors of the mean. (D) Interaction plot between STAI scores and self-reported anxiety in threat (grey lines) and safe (black-dashed lines) periods during FA, OP and VD. The regression lines and coefficients  $\beta$  are derived from the same linear mixed model including state, group and condition (safe, threat) as fixed effects and session, block order and subjects as random effects. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ .

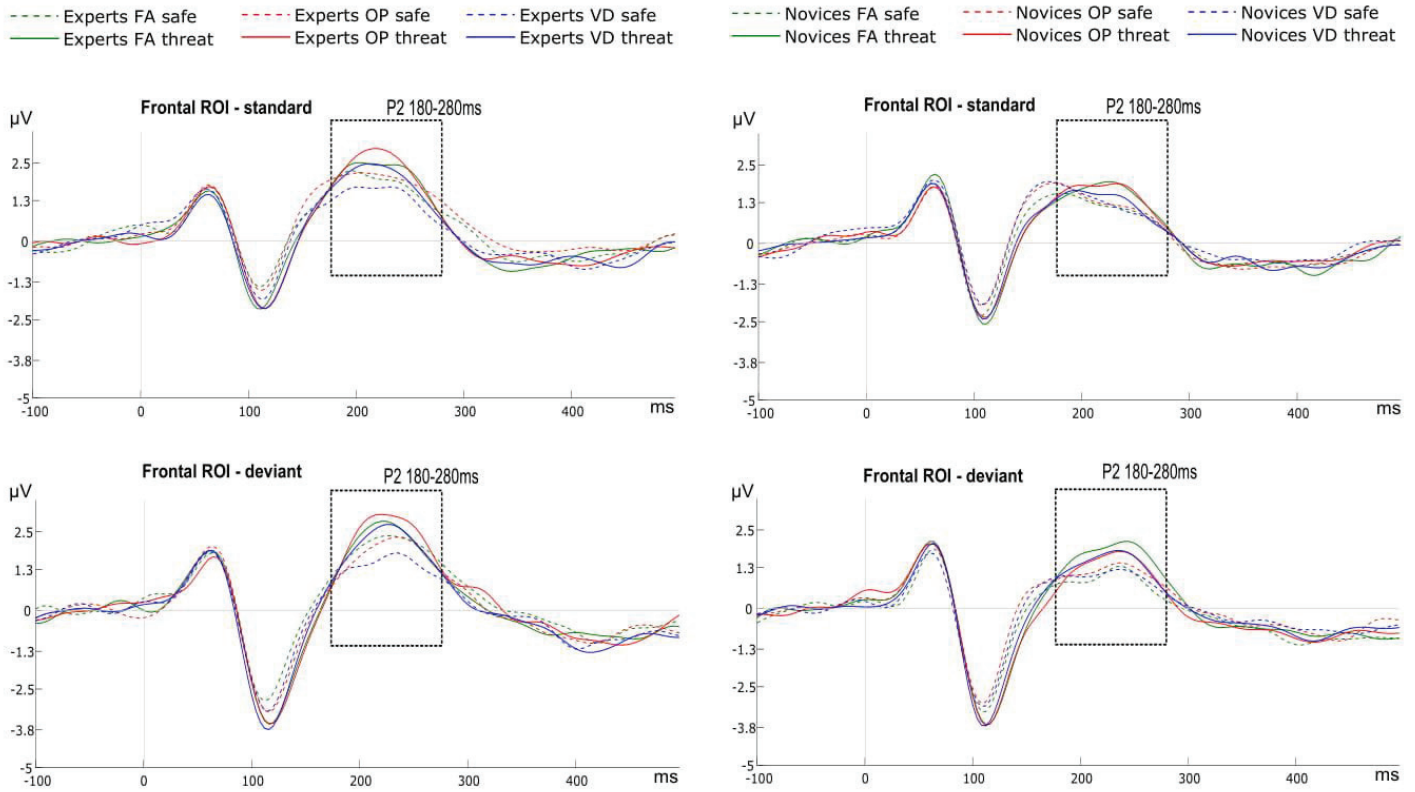
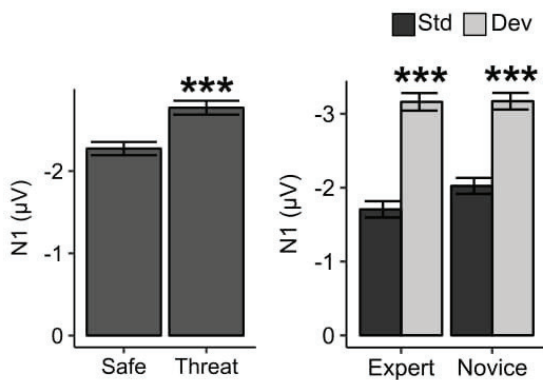
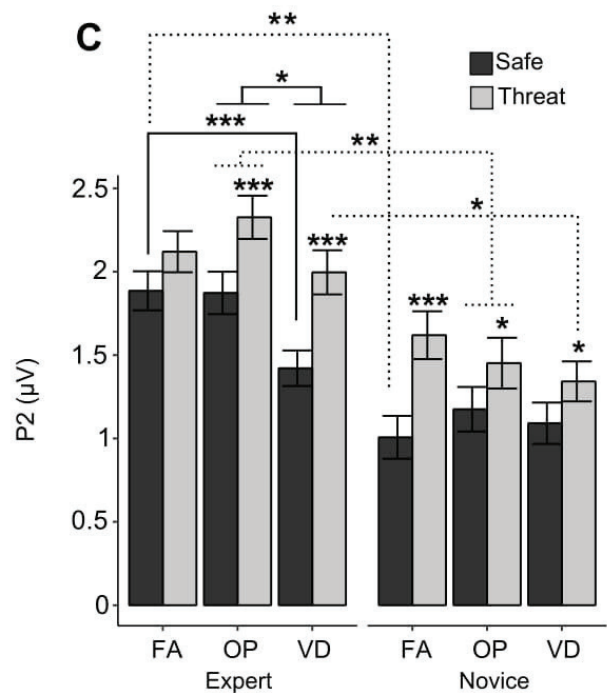


**A****B****C****D**

### 3.4 N1 and P2 amplitude

We investigated the interplay between state, group and threat of electric shock on the N1 and P2 components of the auditory evoked response for standard and deviant stimuli. Again, as no interaction between condition and session was found on self-reported anxiety or SCRs, we included session as a random effect in the tested models. Figure 5.A shows the time-course of the auditory evoked responses across participants and sessions during threat and safe conditions and during FA, OP, and VD, separately for experts and novices and for standard and deviant stimuli. The best fitting model at the N1 latency showed how the N1 amplitude increases during threat, compared to the safe condition across all groups and states (Figure 5.B;  $\chi^2 (1) = 50.83$ ;  $p < 0.001$ ). A group by stimulus interaction was present (Figure 5.B;  $\chi^2 (1) = 4.85$ ;  $p = 0.03$ ), possibly showing a greater difference between standard and deviants for experts, compared to novices (experts estimate = 1.45, t-ratio (1426) = 14.12,  $p < 0.001$ ; novices estimate = 1.14, t-ratio (1426) = 12.09,  $p < 0.001$ ) [N1 model Pseudo- $R^2 = 0.66$ , Pseudo- $R^2$  (fixed effects) = 0.09]. Interestingly, a main effect of condition (safe, threat) on the N1 amplitude was present also for those subjects that reported not difference in anticipatory anxiety between conditions ( $\chi^2 (1) = 16.29$ ;  $p < 0.001$ ).

At the P2 latency, the best fitting model resulted in an interaction between group, state and condition ( $\chi^2 (2) = 7.9$ ;  $p = 0.02$ ) [Figure 5.C; Pseudo- $R^2 = 0.53$ , Pseudo- $R^2$  (fixed effects) = 0.08]. At this latency, the amplitude of the auditory evoked response increased during the threat condition in all states, but especially during FA, for the novices group (FA estimate = -0.61, t-ratio (1417) = -4.89,  $p < 0.001$ ; OP estimate = -0.27, t-ratio (1417) = -2.17,  $p = 0.03$ ; VD estimate = -0.25, t-ratio (1417) = -1.97,  $p = 0.05$ ). In the experts group, P2 amplitude increased during threat in OP and VD, while this increase was only marginally significant in FA (FA estimate = -0.23, t-ratio (1417) = -1.7,  $p = 0.08$ ; OP estimate = -0.45, t-ratio (1417) = -3.29,  $p = 0.001$ ; VD estimate = -0.57, t-ratio (1417) = -4.21,  $p < 0.001$ ). Additionally, P2 amplitude was higher for experts compared to novices in safe periods only during meditation (FA t-ratio (93) = 3.14,  $p = 0.002$ ; OP t-ratio (93) = 2.39,  $p = 0.01$ ; VD t-ratio (93) = 1.17,  $p = 0.24$ ). P2 in threat periods was higher in experts compared to novices during OP and VD, and marginally higher during FA (FA t-ratio (93) = 1.81,  $p = 0.07$ ; OP t-ratio (93) = 3,  $p = 0.003$ ; VD t-ratio (93) = 2.3,  $p = 0.02$ ). Finally, the amplitude of P2 was higher during meditation states, compared to VD, in expert practitioners in safe periods (FA-VD t-ratio (1418) = 3.65,  $p < 0.001$ ; OP-VD t-ratio (1418) = 3.63,  $p < 0.001$ ; FA-OP t-ratio (1417) = 0.01,  $p = 0.99$ ) and during OP, compared to VD, in threat periods (FA-VD t-ratio (1418) = 1.17,  $p = 0.46$ ; OP-VD t-ratio (1418) = 2.75,  $p = 0.01$ ; FA-OP t-ratio (1417) = -1.57,  $p = 0.25$ ). No difference between states was present in the novices group.

**A****B****C**

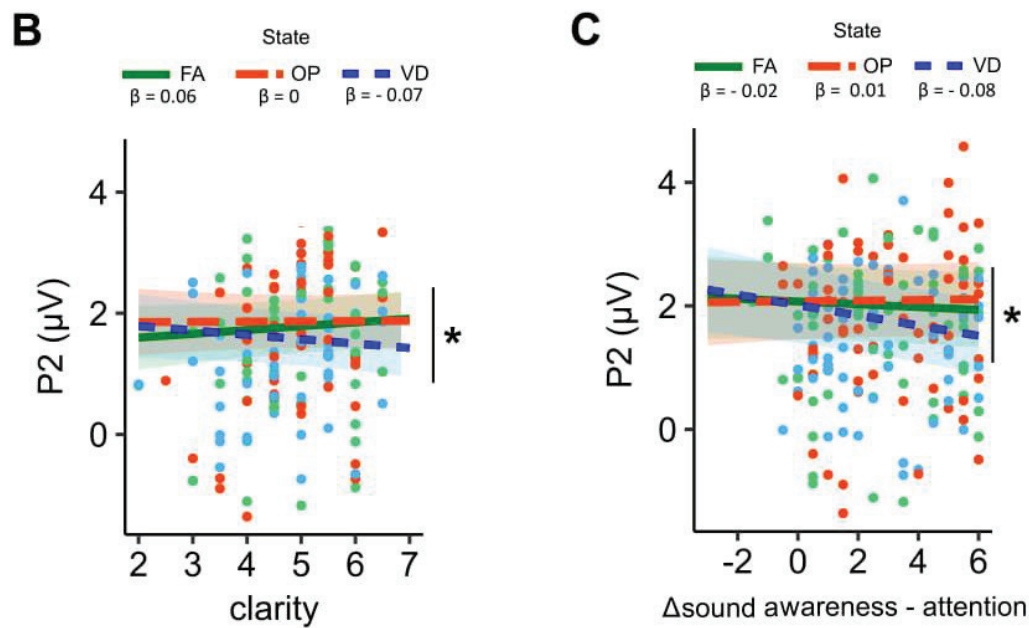
**Figure 5. Electric shock threat increases the amplitude of early brain responses to auditory stimuli. P2 amplitude is modulated by meditation states and expertise.** (A) Event-related responses to standard (top) and deviant (bottom) tones at frontal ROI (see fig. S1) in safe (dashed lines) and threat (solid lines) periods during FA, OP and VD for experts (left) and novices (right). (B) Mean amplitude of responses in a 20ms time-window centred around the most negative peak between 90 and 200ms (N1) during safe and threat periods (left) and for standard and deviant tones in experts and novices (right). (C) Mean amplitude of responses in a fixed time-window (P2; 180-280ms) for safe and threat periods, during FA, OP and VD, in experts and novices. For B and C, error bars represent standard errors of the mean. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ .

### ***3.5 Modulation of the P2 amplitude by meta-awareness and clarity***

As an exploratory analysis, we sought to better understand the functional significance of the P2 component of the auditory evoked response, which was differently modulated by meditation states in expert and novice practitioners. At the same time, we aimed to characterize the phenomenological dimensions, explored through self-reports, in terms of neurophysiological correlates. We investigated how clarity, and the difference between sound awareness and attention ( $\Delta$ sound), modulated the P2 amplitude.

We found a significant interaction between clarity and states in predicting the P2 amplitude (Figure 6.A;  $\chi^2$  (2) = 6.42;  $p$  = 0.04; Pseudo- $R^2$  = 0.53, Pseudo- $R^2$  (fixed effects) = 0.07). The observed interaction showed that higher P2 during meditation was present when more clarity is reached. Post-hoc analyses showed that regression slopes differed between FA and VD, but not OP and VD (FA-VD t-ratio (1431) = 2.53,  $p$  = 0.03; OP-VD t-ratio (1438) = 1.31,  $p$  = 0.38; FA-OP t-ratio (1432) = 1.05,  $p$  = 0.54). Moreover, none of the slope coefficients for FA, OP and VD were higher than 0 (FA  $\beta$  = 0.06 [95% c.i. = -0.03, 0.15],  $p$  = 0.18; OP  $\beta$  = 0 [95% c.i. = -0.10, 0.11],  $p$  = 0.94; VD  $\beta$  = -0.07 [95% c.i. = -0.16, 0.02],  $p$  = 0.13).

A significant interaction between  $\Delta$ sound and different states on the P2 amplitude was also present (Figure 6.B;  $\chi^2$  (2) = 7.88;  $p$  = 0.02; Pseudo- $R^2$  = 0.54, Pseudo- $R^2$  (fixed effects) = 0.06). In the same way as for clarity, the interaction showed that higher P2 amplitude during meditation was predicted by higher  $\Delta$ sound. Post-hoc analyses showed that regression slopes differed between OP and VD in this case, while a difference between FA and VD was observed only as a statistical trend (FA-VD t-ratio (1434) = 1.94,  $p$  = 0.12; OP-VD t-ratio (1432) = 2.75,  $p$  = 0.01; FA-OP t-ratio (1435) = -0.9,  $p$  = 0.63). In this case, when the slope coefficients were tested separately, only the one of VD was significantly different than 0 (FA  $\beta$  = -0.02 [95% c.i. = -0.08, 0.03],  $p$  = 0.47; OP  $\beta$  = 0.01 [95% c.i. = -0.05, 0.06],  $p$  = 0.87; VD  $\beta$  = -0.08 [95% c.i. = -0.14, -0.02],  $p$  = 0.05).



**Figure 6. Higher P2 amplitude during meditation is mediated by clarity and meta-awareness.** (A) Scatter plot for single-subject mean values of self-reported clarity and mean P2 amplitude during FA (green), OP (red) and VD (blue). (B) Scatter plot for single-subject mean values of self-reported  $\Delta$ sound (sound awareness – attention) and mean P2 amplitude during FA (green), OP (red) and VD (blue). In A and B, the regression lines and coefficients  $\beta$  are derived from linear mixed models including state, group and condition (safe, threat) as fixed effects and session, block order, stimulus type (standard, deviant) and subjects as random effects. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ .

## 4. Discussion

In the present study, we investigated the effect of anticipatory anxiety on perceptual learning and early stimulus processing and its modulation by different meditative states and meditation expertise. We also explored the relation between specific dimensions of subjective experience and third-person data, testing the hypothesis that the attentional and motivational stance cultivated during meditation underlies, at least in experts, emotion regulation mechanisms. We found that threat of electric shock did not modulate perceptual learning processes but resulted in a sensitisation of early brain responses to auditory stimuli in both groups of practitioners. However, a dissociation between physiological responses to threat and the experience of anticipatory anxiety was present in expert practitioners. This dissociation was predicted by subjective measures of clarity, which was higher in the experts group and associated to trait measures of cognitive defusion and interoceptive awareness. The amplitude of the P2 increased during threat periods and was higher in expert, compared to novice practitioners. Within this group, the P2 amplitude increased during meditation compared to a control condition. The increased amplitude of this component during meditation was predicted by subjective measures of clarity and meta-awareness.



#### ***4.1 Subjective experience in experts and novices***

The analysis of self-reports outlined different profiles between expert and novice practitioners in terms of phenomenological categories that are thought to be modulated by meditation training. Specifically, expert meditators reported less distraction, less engagement of attention, but same degree of awareness, to auditory stimuli and higher clarity compared to novice practitioners.

Improved attentional stability and conflict monitoring in expert meditators have been reported in previous studies (e.g. Jo et al., 2016) and are within the main cognitive mechanisms proposed to be cultivated and fostered in mindfulness practices (e.g. Hölzel et al., 2011; Lutz et al., 2008). Nonetheless, it is possible that shorter forms of meditation training exert a negligible impact on attention regulation (MacCoon et al., 2014). Here we found that reduced distractibility in expert meditators was present across all states; a trait effect that is supported by previous findings that found increased attentional stability after extensive meditation training (Lutz et al., 2009). Improved attentional stability and reduced mind wandering could impact emotion regulation (Jazaieri et al., 2016; Killingsworth and Gilbert, 2010). However, as we did not test this specific question in the present study and we did not implement any form of active attentional task, we will not discuss this result any further.

Whereas experts and novices were equally aware of sounds during the oddball paradigm, expert practitioners' attention was less captured by auditory stimuli. This dissociation possibly reflects the process of meta-awareness as developed in mindfulness practices. In the context of meditation, meta-awareness is intended as the capacity of becoming aware of transient internal (e.g. thoughts, bodily states) and external (e.g. auditory stimuli) events while retaining a specific task-set (e.g. focusing attention on an object or maintaining awareness of the present-moment) (Lutz et al., 2015). Here, participants underwent a passive auditory oddball task and were instructed to ignore auditory stimuli. Therefore, the increased dissociation between sound awareness and attention in experts can be considered as an index of higher meta-awareness in the expert group. Based on the above-mentioned model (Lutz et al., 2015), we would have expected higher meta-awareness in experts during OP, compared to FA, and during meditation compared to the control condition. It is unclear whether extensive meditation training could lead to changes in the subjective experience of background awareness in relation to any form of task-set, whether it is meditation practice or simply watching a movie. In general, few studies have tried to operationalise this phenomenological category in terms of underlying neural mechanisms (see Discussion section 4.4 for more details on this topic).

Finally, expert practitioners reported higher phenomenal clarity during the paradigm, independently of the experimental condition. Clarity is described as the degree of vividness at which an experience occurs, whether it is a perceptual stimulus or an internal event (e.g. an affective state) (Lutz et al., 2015). It is thought to be intertwined with meta-awareness (Namgyal, 2001), a theoretical account confirmed in the present study by the strong relation that was found between self-reported clarity and the difference between sound awareness and attention (Figure 2.E). Interestingly, phenomenal 'clarity' (a translation from the Pali word 'Vipassana') is also thought to

arise, in the expert practitioner, together with insights over the delusional nature of phenomena (Schoenberg and Barendregt, 2016). Clarity could therefore be associated with the shift in the perception of phenomena as transient mental events rather than accurate representations of reality in mindfulness practices (Chambers et al., 2009b), a process referred to as “dereification” (Lutz et al., 2015) or simply “mindful attention” (Papies et al., 2012). This view is supported here by the observed relation between self-reported clarity and the score in the DDS questionnaire, that represents a trait measure of “cognitive defusion” (i.e. “the ability to achieve psychological distance from internal experiences such as thoughts and feelings” , Forman et al., 2012) (Figure 2.F).

To summarize, when asked about specific dimensions of their subjective experience during the task, expert practitioners reported low distractibility and high degree of phenomenal clarity and meta-awareness across all states, compared to novices. Higher clarity was associated with higher meta-awareness and lower distractibility (Figure 2.D) and was predicted by a trait measure of cognitive defusion. This specific profile of subjective experience is discussed in the following paragraphs in relation to third-person measures of bodily physiology and brain responses to auditory stimuli during threat and safe periods.

#### ***4.2 Self-reported anxiety and skin conductance***

Participants in both groups reported higher levels of anticipatory anxiety during periods of threat, compared to safe periods. However, expert practitioners reported lower anticipatory anxiety, compared to novices, especially during threat periods (figure 3.A). Skin conductance responses (SCRs) were higher for auditory cues announcing the beginning of threat, compared to safe periods. The effect of threat cues on SCRs did not differ between groups or states. Interestingly, the amplitude of SCRs predicted the degree of self-reported anticipatory anxiety in novice but not expert practitioners (figure 3.D). This evidence highlights a dissociation between physiological responses to threat and the subjective experience of anticipatory anxiety in expert meditators and represents a key finding of the present study. There is a consistent body of literature describing the impact of mindfulness meditation on the regulation of emotional responses to nociceptive and emotionally negative stimuli (see Tang et al., 2015 for a recent review). However, very few studies have investigated the impact of meditation training on the anticipation of negative stimuli (Brown and Jones, 2010; Lutz et al., 2013) and, to our knowledge, no previous research has focused on the anxious response to unpredictable threat. Here, the relation between the amplitude of SCRs and self-reported anxiety in the novices group confirms the involvement of the sympathetic branch of the autonomic nervous system in the anticipation of unpredictable noxious stimuli (Epstein and Roupelian, 1970). The dissociation between these two measures, observed in experts, is in line with theoretical accounts which propose that emotion regulation in expert meditators is a bottom-up process mediated by the specific attentional and motivation stance cultivated in the practice (Chiesa et al., 2013; Dahl et al., 2015; Lutz et al., 2015). Extensive meditation training would result in an increased sensitivity to physical and mental events, but a decreased emotional reactivity and lingering to such stimuli. This dissociation would be



meditated by the development of meta-awareness and dereification of thoughts and emotions associated to a specific event. Such perceptual configuration would favour cognitive defusion and de-centering from one's own affective states while maintaining a functional, if not increased, awareness of bodily responses to stimuli that convey an emotional meaning. This view is corroborated here by the fact that the level of clarity mediated the dissociation between the subjective experience of anxiety and SCRs (figure 3.F). Moreover, the degree of clarity was predicted by trait measures of cognitive defusion and interoceptive awareness.

### ***4.3 Modulation of MMN amplitude by anticipatory anxiety and meditation states***

We can maintain, based on the results discussed in the previous section, that the experimental paradigm effectively manipulated levels of anticipatory anxiety in both expert and novice participants. However, we did not find a difference in the amplitude of the MMN between safe and threat periods during meditation states or during a control condition in experts or novices. This result held true regardless of whether a difference in MMN amplitude was tested in a canonical frontal ROI or at a central scalp site (electrode Cz). No effect of the experimental manipulation was found when subjects that did not report any difference in anticipatory anxiety between conditions were excluded from the analysis.

Possible reasons underling the lack of modulation of the MMN amplitude by threat of electric shock are discussed in detail in a separate report (see *Study 2*). In brief, we tried here to replicate previous findings from studies that used electric shock threat as mood induction procedure (Cornwell et al., 2017, 2007) and recorded brain activity with magnetoencephalography (MEG). As we discussed in the separate report, that included only data from novice participants during the control state, a lack of modulation of the MMN amplitude is in line with previous EEG studies. We proposed that MMN amplitude could be affected by threat only in subjects that scored high in state or trait anxiety. Regarding the present study, a possible explanation for the lack of modulation could be because data were averaged across two experimental sessions. Nonetheless, while an effect of session was present on both self-reported anxiety and SCRs (figure S1), it did not interact with the effect of threat, that was present in both sessions.

In the present study, we found that MMN amplitude was higher in threat, compared to safe periods, for those subjects that scored high in dispositional anxiety, as measured by the trait scale of the STAI questionnaire, but only during the VD condition (figure 4.D). This result indicates that both meditation practices could downregulate the effect of threat on perceptual learning processes in individuals with high dispositional anxiety. Increased MMN amplitude has been previously reported in EEG studies that investigated the modulation of the MMN by anxiety-related psychopathologies and dispositional anxiety (e.g. Bangel et al., 2017; Chen et al., 2016; Ge et al., 2011; Hansenne et al., 2003). If replicated, the present findings could be of clinical relevance, showing how meditation can downregulate the effect of high trait anxiety on perceptual learning processes. However, the result reported here should be handled

with consideration. When tested separately none of the two slope coefficients (safe, threat conditions) during VD were significantly higher than zero.

When we tested whether different meditation states and expertise modulated the amplitude of the MMN, regardless of the experimental condition (safe, threat), we did not replicate our previous findings (Fucci et al., 2018). This result was unexpected because previous research has shown an impact of meditation on the MMN amplitude. Especially, several studies reported increased MMN amplitude during FA meditation (Braboszcz and Delorme, 2011; Fucci et al., 2018; Srinivasan and Baijal, 2007) or as a trait effect in experts (Biedermann et al., 2016). There are several reasons that could explain the lack of replication in the present study. Firstly, participants underwent short oddball sequences embedded in safe or threat periods. Previous studies did not investigate the MMN modulation in the context of mood induction. It is possible that the emotional context masked effects that would otherwise be present in a neutral situation. Moreover, short sequences (~30 seconds) might not be long enough to capture subtle shifts in the interplay between predictions and prediction errors observed in longer oddball paradigms. Secondly, this paradigm was characterized by a short and fix inter-stimulus interval (I.S.I. 500ms). This is considered to be a reliable interval to elicit MMN signals (Duncan et al., 2009) and was used here to maximize the number of stimuli and conform to previous studies on MMN modulation by threat (Cornwell et al., 2017, 2007). However, it is possible that longer and variable intervals are required to highlight a modulation of expectations and deviance saliency by different meditation styles.

#### ***4.4 Modulation of N1 and P2 amplitude by anticipatory anxiety and meditation states***

We found an impact of unpredictable threat on the amplitude of early neural responses to auditory stimuli unrelated to the source of threat. This effect was present across states and groups.

Similarly to previous research (Ermutlu et al., 2005; Scaife et al., 2006b; White et al., 2005), we found increased amplitude of the auditory N1 during threat, compared to safe periods (figure 5.B). This result is also in line with research that reports an impact of mild stress on the sensitisation of early sensory processing in other sensory domains (Qi et al., 2018; Shackman et al., 2011a). In the auditory domain, the increase in N1 amplitude has been related to an increase in noradrenergic activity, affecting the ability to filter out irrelevant sensory information (Ermutlu et al., 2005). This effect was not modulated by meditation states and expertise. It represents, in our opinion, a robust mechanism of increased vigilance in response to unpredictable threats and an adaptive response in volatile environments. This view is supported by the fact that this effect was present also in those participants that did not report any degree of anxiety in either safe or threat periods.

In the other latency explored (180-280ms), the amplitude of the auditory P2 increased in periods of threat, compared to safe periods, across all stimuli, participants and states. P2 was higher for experts compared to novices during OP in both safe and threat

periods, but only in safe periods during FA and threat periods during VD. Within expert practitioners, it increased during OP compared to VD, and during FA compared to VD in safe periods only (figure 4.C). To summarize, this component was sensitive to threat, meditation expertise and especially high during OP in expert meditators. The P2 component of the auditory evoked response has been poorly studied and historically thought to be part of the N1-P2 complex in response to auditory stimuli (Tremblay et al., 2014). Nonetheless, there are evidence indicating that N1 and P2 originate from different sources within the auditory cortex and likely serve different functions (Ross and Tremblay, 2009). It has been proposed that P2 reflects mechanism of stimulus attendance and classification, mostly related to excluding a stimulus from further processing or recognizing it as a target (see Crowley and Colrain, 2004 for a review). Indeed, P2 amplitude was found to decrease in response to target stimuli in dicotomic listening tasks (Novak et al., 1992) and increase in response to non-target stimuli in oddball paradigms (García-Larrea et al., 1992). Few studies have investigated the modulation of this component by meditation training. Cahn and Polich (2009) reported lower P2 amplitude in response to distracters during Vypassana meditation. Interestingly, Lutz et al. (2009) found increased P2 amplitude to unattended stimuli in a dicotomic listening task after three months of intensive meditation training.

Based on these premises, we believe that, in the present study, the higher P2 amplitude reflects increased monitoring of auditory stimuli in response to unpredictable threat. Higher P2 in expert meditators is in line with theoretical accounts that hypothesise an increase in meta-awareness and dereification during meditation, and especially during OP, as a function of meditation expertise (Lutz et al., 2015). Thus, P2 amplitude could represent a biomarker of monitoring processes in meditation training. Supporting this hypothesis, we found that the difference in P2 amplitude between meditation and control condition was predicted by the self-reported measures of meta-awareness and clarity.

Overall, the present work provides empirical evidence of the mechanisms underlying emotion regulation in expert meditation practitioners. It describes the relation between the attentional and motivational stance cultivated in mindfulness practices and the modulation of early stimulus processing in unpredictable threatening situations. Most importantly, it shows how the phenomenological dimensions of clarity and meta-awareness are strongly related and predicted by trait measures of cognitive defusion and interoceptive awareness. This phenomenological profile mediates the regulation of emotions and impacts neurophysiological responses to auditory stimuli that are related to attentional monitoring processes.

It is unknown whether mindfulness meditation modulates perceptual learning processes in emotional contexts. A possible mediating effect was observed for individuals with high trait anxiety and future studies could focus on this specific population. Finally, the findings reported here are unclear in terms of state and trait effects on emotion regulation and neurophysiological processes. It is possible that, in

emotional contexts, trait differences prevail over subtle changes in states that could be observed in neutral environments. Future research could try to elucidate this question implementing paradigms that allow for longer periods of neutral and negative valence.



DISCUSSION  
and  
CONCLUSION

# General discussion

## 7.1 General summary

In this work, we aimed to understand the mechanisms of mindfulness meditation in neutral and emotional settings by investigating the effect of different meditation states and levels of expertise on neurophysiological markers of perceptual learning and attention. This objective is ascribed into a broader research on the biomarkers of cognitive functions that are thought to be fostered by mindfulness practices, according to recent theoretical models based on Buddhist phenomenological accounts. We hypothesized that the cognitive processes cultivated in mindfulness practices, and their related phenomenological categories, would differentially modulate the auditory mismatch negativity in neutral contexts, depending on the level of expertise (Study 1). Furthermore, we thought that a previously observed effect of unpredictable threat on the MMN would be downregulated during meditation states in expert practitioners (Study 3). In both studies we also explored neurophysiological responses to auditory stimuli that have been related to attentional processes, with the aim of individuating putative neurophysiological markers of the heightened monitoring of perceptual phenomena that is supposed to characterise mindfulness practices. Finally, we sought to clarify the role of specific cognitive and motivational processes in emotion regulation, by relating self-reports of subjective experience to third-person measures of neural and bodily physiology.

We implemented cross-sectional studies including cohorts of expert meditation practitioners who were rigorously selected based on quantitative and qualitative criteria that addressed current limitations in this field of research. Additionally, an active control group of naïve practitioners was trained to practice different styles of meditation, as well as to recognise and describe changes in several dimensions of their subjective experience during and outside of the practice. These methods were implemented to create a common linguistic and experiential framework between expert and novice practitioners and researchers in the context of neurophenomenological investigations (Study 3).

In Study 1, we found that open presence, a nondual mindfulness practice, could be differentiated from a focused attention style of practice in terms of their impact on perceptual learning processes (i.e. MMN amplitude) in expert and novice practitioners.



This differential effect was better characterised by looking at the interplay between the MMN amplitude and neurophysiological responses related to attentional monitoring and was predicted by differences in brain oscillatory activity. Specifically, we found that, in experts, the MMN increased during FA, compared to OP, while the opposite pattern was observed on the amplitude of an ERP component linked to stimulus attendance (late frontal negativity). However, these findings were not replicated in Study 3. Here, no effect of meditation or expertise was found on the amplitude of the auditory MMN, when controlling for the effect of different emotional contexts (safe and threat periods). On the other hand, we found an increased amplitude of the P2, another ERP component related to stimulus attendance and attention, during meditation states (especially OP) in expert practitioners.

Concerning the impact of emotional context on perceptual learning processes and its modulation by mindfulness practices, the findings contradicted our initial hypotheses. In Study 2, which focused on the group of novice practitioners during a control state, we were not able to reproduce results from previous studies that found increased amplitude of the auditory MMN during threat, compared to safe periods. In Study 3, we did not find any effect of mindfulness practices or expertise on the MMN amplitude in either of the two periods. However, we found that a modulation of the MMN by unpredictable threat was present for subjects with high trait anxiety and that meditation might downregulate this effect.

In Study 3, we found a dissociation between physiological responses to threat periods and the subjective level of anxiety in expert meditation practitioner. This finding is in line with previous reports on the downregulation of affective responses, but increased interoceptive sensitivity, as a result of meditation training. Here, we found that this dissociation was predicted by subjective measures of clarity, which was higher in the experts group and associated to trait measures of cognitive defusion and interoceptive awareness. In general, Study 3 highlighted different profiles between expert and novice practitioners, independently of meditation or control states, in terms of phenomenological dimensions that are thought to be modulated by meditation training and how these dimensions impact emotion regulation and monitoring processes.

In the next sections, I discuss these findings in relation to the existing issues in cognitive neuroscience and research on meditation. Specifically: 1) I consider different explanations for the lack of coherence in the results on the modulation of perceptual learning processes, within the present work and between this work and existing literature; 2) I analyse the relation between some of the cognitive functions, and associated phenomenological dimensions, cultivated in mindfulness practices and their putative neurophysiological markers, in terms of attentional monitoring and emotion regulation; 3) I examine possible reasons underlying differences in state and trait effects observed within the groups of expert and novice meditators, with specific emphasis on the characterisation of the state of open presence. For all these points, I suggest directions for future research.

## 7.2 Perceptual learning in neutral and emotional settings: evidence from meditation

In this project, we considered the auditory MMN, a neurophysiological marker of perceptual learning, to constitute an intriguing framework for investigating the neurocognitive mechanisms of mindfulness practices and their associated phenomenological dimensions. The notion of perceptual learning is embedded in a theory of brain functions which is broad enough to encompass different mental phenomena and permits suitable comparisons with theoretical accounts of the processes developed in mindfulness meditation. Our investigation has led to interesting findings as well as new questions.

### 7.2.1 Perceptual learning in neutral settings and replication issues

In Study 1, we demonstrated that different meditation states impact perceptual learning processes differently in expert and novice practitioners. It was the first study, to our knowledge, to characterise a nondual practice (OP) in terms of its effect on brain predictive processes. We hypothesized that the radical suspension of subject-object duality in OP would downregulate the formation of perceptual habits while increasing the monitoring of the sensory environment. In this sense, exploring the interplay between the LFN, an ERP component related to stimulus attendance and attention monitoring, and the amplitude of the auditory MMN represented the best way to test our hypothesis. In fact, the LFN increased in both OP and FA in experts, reflecting higher attentional monitoring or “background awareness”, as described in recent theoretical models (Lutz et al., 2015). However, these two practices differ significantly in terms of task-set. While in OP the monitoring aspect is unrelated to any object, it is cultivated during FA in relation to a task-set of focusing on and selecting a perceptual object, which increases the saliency of task-unrelated stimuli. As it has been shown by studies on the effect of attention and expectations on the MMN amplitude (chapter 2.8.1), specific task goals play a crucial role in modulating perceptual learning processes. The results of Study 1 enrich this view by showing, for instance, that the MMN amplitude increases during FA although auditory stimuli were not selectively attended, while during OP, in experts, the MMN does not increase compared to a state of absorption even if the auditory stimuli were attended more (this was probably the case for novice practitioners, that showed an increase in the MMN during OP compared to the other states). These findings suggest that studying the impact of mindfulness meditation on perceptual learning processes could lead to 1) a better characterisation of the neural mechanisms underlying different practices, which are widely implemented in clinical interventions, and levels of expertise and 2) foster the understanding of the factors that modulate these processes in neutral settings.

In Study 3, we sought to replicate our previous findings on the modulation of the MMN by different states and levels of expertise. More specifically, we tested the same

hypothesis as in Study 1, performing the same analysis on the MMN amplitude but controlling for the effect of different emotional conditions (this factor was entered as a random effect in a linear mixed model). In this case, we did not find any interaction between meditation states and the level of expertise. This result was unexpected and could be due to several different reasons (some of which are discussed in Study 3):

- 1) Even if a possible effect of emotional contexts was controlled for in the statistical model, the paradigm implemented in Study 3 differed significantly from previous studies that found a modulation of the MMN during FA or as a trait effect in expert practitioners (Biedermann et al., 2016; Braboszcz and Delorme, 2011; Srinivasan and Baijal, 2007). Subtle differences between states, in terms of MMN amplitude, could have been obscured by the increased variability introduced by embedding oddball sequences in safe and threat periods.
- 2) The task differed from previous studies not only in terms of emotional context, but also concerning the structure of the oddball sequences. Specifically, compared to previous studies, we implemented shorter sequences (~30 seconds) and a shorter fixed inter-stimulus interval of 500ms. It is possible that longer and variable intervals, as well as longer sequences, are required to highlight a modulation of perceptual learning by different meditation styles, which might not be a phenomenon that happens as soon as a new sequence is presented.
- 3) Another reason for the lack of replication could be due to the small subjects' sample size in Study 1. It has been recently highlighted that small sample sizes could undermine reproducibility of neuroscientific findings, especially in studies using fMRI (Button et al., 2013). Although no such analysis has been performed on studies using EEG, we cannot exclude that Study 1 was somehow underpowered and at risk of false positives, given the smaller sample ( $n = 31$ ) compared to Study 3 ( $n = 65$  after data pre-processing).

Overall, the lack of replication between the studies of the present work could be due to a concomitance of the factors outlined above. Future studies are needed to address these specific issues and clarify the impact of mindfulness states and expertise on auditory perceptual learning in neutral settings.

### 7.2.2 Perceptual learning under threat and replication issues

In study 2, we sought to replicate previous findings on the impact of anticipatory anxiety on auditory perceptual learning in the healthy population (especially, Cornwell et al., 2017, 2007). To this aim, we analysed a subset of data from Study 3 (i.e. data from novice practitioners during a control state). We can maintain that the experimental paradigm effectively manipulated levels of anticipatory anxiety, as measured by self-reports, skin conductance responses and a sensitisation of early brain responses to auditory stimuli during periods of threat. However, we did not find differences in the MMN amplitude between safe and threat periods. We extensively discussed these

findings in relation to previous EEG and MEG literature on this topic in Study 2 and provided some putative explanations. Here, I provide a summary and additional suggestions on the possible reasons underlying the lack of replication of previous findings:

- 1) It is possible that novice practitioners did not represent a typical sample of healthy subjects in this study. In fact, they were trained and practiced meditation during the period preceding data acquisition (see Protocol Study for further details). Even if practiced for a short period of time, meditation has been shown to downregulate the effect of stress on cognitive functions (Mohan et al., 2011). However, it seems unlikely that the short training only affected the modulation of the MMN amplitude by periods of threat, and none of the other subjective and physiological measures. This view is corroborated by the findings in Study 3, where an effect of meditation training, in experts, was found on subjective measures of anxiety.
- 2) Previous studies have used analysis methods and ways of reporting findings that could have biased a rigorous assessment of this phenomenon. As discussed in Study 2, previous findings reporting differences in the MMN amplitude during threat periods (or after the application of different stressors) presented some limitations. Some of these limitations are related to the implementation of statistical analyses and significance thresholds that could increase the rate of false positives (Cornwell et al., 2007; Elling et al., 2011). Other studies did not report any post-hoc analysis that should have been used to clarify the direction of effects in different conditions (Cornwell et al., 2017).
- 3) More generally, these issues can be discussed in the recent and ongoing debate on the reproducibility of scientific studies in the field of experimental psychology and neurosciences (John et al., 2012; Munafò et al., 2017; Open Science Collaboration, 2015). Besides the biases associated to small sample sizes (as discussed in the previous section 6.2.1) and the use of analysis methods that could lead to false positives, previous literature on this topic could have been affected by the lack of publications reporting negative results (i.e. *positive bias*).

Surely, some of the reasons discussed above (especially point 3) represent a personal speculation in light of unexpected results. Future studies should clarify these issues with accurate replications of the paradigm used in the present project (derived from Cornwell et al., 2017, 2007) using EEG or through meta-analyses of existing studies.

Given the lack of modulation of auditory perceptual learning by unpredictable threat, it is not surprising that, in Study 3, we did not find any difference in the MMN amplitude during safe and threat periods between experts and novices and during meditation compared to a control state. However, we found that the MMN could indeed be modulated by unpredictable threat, but only in those subjects with high trait anxiety, and that meditation could downregulate this effect. These findings are discussed in the next section.

### 7.2.3 Anxiety as a dimensional construct: effect of meditation states

Anxiety is not an on-off response. Previous theoretical models have highlighted how stressful situations can exert different effects, according to the interaction between situational and individual factors (Endler and Kocovski, 2001). Person variables, such as the level of dispositional anxiety, interact with situational variables (e.g. an unpredictable threat) and lead to changes in state anxiety and reactions (e.g. behavioural and biological changes) that depend on the type of interaction. Considering anxiety as a dimensional construct can help conciliating different results on the effect of threat on perceptual learning and general auditory processing, as well as its modulation by meditation.

In study 2 and 3, we found that perceptual learning processes seem to be affected (i.e. higher MMN amplitude during threat periods) only in individuals who scored high in trait anxiety (data from Study 2 showed also a dependency on the level of state anxiety, but this effect was lost when data were combined with those from experts and meditation conditions). At mild levels of anxiety, brain responses to otherwise irrelevant stimuli are increased, an adaptive feedback to unpredictable threats in uncertain environments. However, when specific dispositional factors (i.e. high trait anxiety) interact with a threat situation, it affects the way the brain makes sense of the environment and learns about its features. Such view distinguishes between an adaptive role of anxiety on processing efficiency and the detrimental impact on perceptual learning observed in anxiety disorders (e.g. Bangel et al., 2017; Ge et al., 2011). Interestingly, the increase in MMN amplitude during threat, compared to safe periods, for those subjects that scored high in dispositional anxiety, was observed only during a control condition. This result indicates that both meditation practices could downregulate the effect of threat on perceptual learning processes in individuals with high dispositional anxiety. While this is an interesting finding that could be of clinical relevance, it should be taken with consideration due to some unclear points. When taken separately, none of the two regression slopes (safe and threat periods) in the control condition was significantly different from zero, although a significant difference between the slopes was present. Most importantly, it is unclear why a general state effect was present across both groups of participants, whereas a trait effect was present on the level of self-reported anxiety. Finally, we included only healthy participants and it is unclear whether these findings could be translated into a clinical population.

#### 7.2.4 Future directions

As discussed in the previous sections, investigating the effect of mindfulness meditation on perceptual learning processes, in neutral and emotional settings, has led to a number of open questions and unclear findings. Future studies and analyses will be able to address several issues, clarify different points and improve the validity of results.

Future research should replicate the same paradigm used in Study 1, increasing the sample size. Moreover, different parameters of oddball sequences can be manipulated to identify an optimal setting, in terms of temporal and physical features, that can be sensitive to differences between states and levels of expertise. Additionally, it will be crucial to determine whether a specific meditation state is being instantiated by a practitioner in a given period (e.g. an experimental block). This would limit confounds on the reasons underlying the variability of neurophysiological responses to experimental stimuli. A promising field, in this sense, is the study of neural oscillatory activity in different states and levels of expertise. Specifically, an analysis of spontaneous patterns of oscillations will be performed on the data from Study 3 to assess whether the lack of replication of findings from Study 1 was due to different oscillatory profiles.

Finally, a way to drastically improve the research on this topic in both emotional and neutral contexts is the implementation of computational models that can test mechanistic hypotheses. This methodological approach has received increasing interest in the recent years and has provided relevant insights on the mechanisms underlying the MMN and the modulation of perceptual learning processes by attention, expectations and emotional contexts (e.g. Lieder et al., 2013; Mathys et al., 2014; Watanabe et al., 2013). Most importantly, computational approaches allow the formulation of hypothesis regarding changes learning parameters that can be tested on a trial-by-trial basis.

### **7.3 Subjective dimensions: monitoring and emotion regulation**

The present work is embedded in a broader research agenda that aims to confirm and update theoretical models of mindfulness meditation. This can be achieved through investigating the relationship between dimensions of subjective experience that are thought to be modulated by meditation training and neurophysiological and bodily responses. To this aim, we collected and analysed data unrelated to perceptual learning processes (i.e. the MMN), which constituted our main outcome measure. In Study 1 and



3, we explored additional components of the auditory evoked response, as well as measures of bodily physiology (EDA). In Study 3, we collected data on different dimensions of subjective experience through self-reports and related them to the above-mentioned measures. What emerges is that different phenomenological profiles, related to meditation states and expertise, can be mapped into neural and bodily correlates of attention and emotions. Especially, the present work helped in identifying neural correlates of meta-awareness and monitoring processes and in elucidating the role of meta-awareness, clarity and dereification in emotion regulation.

### 7.3.1 Do late ERP components reflect monitoring processes in meditation?

In both Study 1 and 3, we found that late components of the auditory evoked response were sensitive to meditation states. Specifically, in Study 1 we found higher amplitude of the *late frontal negativity* (LFN) during meditation, compared to a control state and across both expert and novice groups. In Study 3, we found higher amplitude of the P2 component in experts, compared to novices, and during meditation, compared to a control state, within the expert group (this represents a general description; some post-hoc comparisons were significant during threat or safe periods only).

Previous studies have linked components in these latencies to processes of stimulus attendance and monitoring (Bendixen et al., 2007; Crowley and Colrain, 2004; Karayanidis and Michie, 1996) and an effect of meditation training on the P2 amplitude has been reported in practitioners after a three-months retreat (Lutz et al., 2009). In our opinion, the modulation of these components reflects increased meta-awareness of auditory stimuli during mindfulness meditation (Lutz et al., 2015). This view was supported, in Study 1, by the correlation between the difference in alpha oscillatory activity between periods of OP meditation and a control condition (i.e. reading, RE) and the difference in amplitude of the LFN between OP and RE (see Study 1 for a discussion on the role of alpha oscillations in this context). Most importantly, in Study 3 we found a direct link between the subjective experience of meta-awareness and the increased amplitude of the P2 during meditation states. Based on these findings, it is possible that the increased monitoring of stimuli unrelated to a specific task-set during meditation (i.e. meta-awareness) is reflected by increased responses to sensory stimuli in late components of the evoke responses previously associated to stimulus attendance and monitoring.

This view presents some limitation and open questions. First, the effect of meditation was present on different components in Study 1 and 3. Whereas responses in these latencies have been related to similar processes, we cannot converge on a clear biomarker of monitoring processes in meditation. On the other hand, it is possible that the modulation of different components between the two studies was due to differences in the oddball paradigm, especially concerning the inter-trial interval. Additionally, effects on later components in Study 3 could have been masked by the high-pass filter (2hz) implemented. As it has been previously shown, late ERP



components (after 200ms) are sensitive to the choice of high-pass filtering frequency (Acunzo et al., 2012; Tanner et al., 2015). Secondly, it is unclear whether these components are affected differently by different states and levels of expertise. Results on this topic are contradictory and does not necessarily confirm the hypotheses of previous models in terms of differences in meta-awareness between experts and novices and between FA and OM meditations (Lutz et al., 2015). As discrepancies between trait and state effects were present on different measures in the present work, they are discussed separately in section 6.3 of this chapter.

### 7.3.2 Understanding emotion regulation through subjective experience

In Study 3, we found a dissociation between physiological responses (SCRs) to threat and the subjective experience of anticipatory anxiety in expert meditators. It is, to our knowledge, the first evidence of the effect of meditation training on the anticipation of unpredictable nociceptive stimuli. Previous studies have considered the nonevaluative, accepting, moment-to-moment experiential stance cultivated by mindfulness practices as a mediating factor for eliminating the conditions that establish anticipatory anxiety of predicted nociceptive stimuli (Lutz et al., 2013). This is in line with theories that describe emotion regulation by mindfulness practices as a bottom-up process mediated by a specific attentional and motivation stance (e.g. Chambers et al., 2009). However, similarities between mindfulness and different emotion regulation strategies (such as top-down reappraisal mechanisms) have been largely debated (see Chiesa et al., 2013 for a review), mostly in the context of contrasting description of mindfulness as a construct or a state.

Here we showed that operationalizing mindfulness practices as the modulation of specific cognitive functions, based on phenomenological dimensions, can help elucidating the mechanisms of emotion regulation. We found that the dissociation between physiological and subjective state of anticipatory anxiety was mediated by the level of clarity reported by each participant and the end of an experimental block and was significantly higher in expert practitioners. As mentioned in the introduction of the present work (chapter 2.3.3), phenomenal clarity does not only refer to the degree of vividness of perceptual events, but is thought to be related to the process of dereification (Schoenberg and Barendregt, 2016). This view is supported here by the fact that the level of self-reported clarity was predicted by a participant's score in a questionnaire measuring the general degree of cognitive defusion (Forman et al., 2012). Self-reported clarity also predicted subjective measures of meta-awareness, highlighting the relation between the latter and dereification in meditation practices (Lutz et al., 2015). Nonetheless, as we did not implement a self-report measure of dereification during the paradigm, but relied on correlations with trait measures, these associations remain exploratory and future studies are required to address this issue.

This was the second study highlighting an association between phenomenal clarity and measures of emotional responses (Lutz et al., 2013). Overall, we demonstrated that collecting data on different dimensions of a participant's subjective experience can

help understanding the mechanisms underlying emotion regulation in mindfulness meditation. Future studies should try to operationalize these measures in terms of neurophysiological correlates, to investigate biological causes of regulatory processes.

## 7.3 State and trait effects

In the present work, we found that different neurophysiological, subjective and bodily measures were modulated either by 1) meditation states across all groups of participants, 2) by meditation states but only in experts or 3) by the level of expertise across all experimental conditions. For instance, in Study 1, we found a state by group interaction on the MMN amplitude and on the power of gamma oscillatory activity, but a general effect of meditation on the amplitude of the LFN and on the power of oscillations in the alpha frequency band. In Study 3, we found a state by group interaction on the P2 amplitude, but a main effect of expertise on subjective measures and on the relation between SCRs and the degree of subjective anxiety. In Study 1, OP and FA could be differentiated, in experts, by looking at the interplay between LFN and MMN amplitude. In Study 2, the P2 amplitude in experts was not different during OP, compared to FA, but was higher in OP during both safe and threat periods, compared to novices, while the same was not true during FA. Overall, it is unclear which measures are sensitive to meditation states and levels of expertise, and in which context.

Recent models of mindfulness meditation have been constructed following the hypothesis that the phenomenological dimensions, and related cognitive functions, cultivated in the practice are modulated by different states and levels of expertise. For instance, meta-awareness would be higher in experts, compared to novices, and during OM styles of practice, compared to FA (Lutz et al., 2015). According to previous operationalisation attempts, the state of OP in experts should be the one characterised by the highest phenomenal clarity (Lutz et al., 2007). On the other hand, other theories affirm that practicing mindfulness meditation repeatedly across sessions, individuals can develop a greater tendency to exhibit mindful attitudes and behaviours in the everyday life. As such, processes such as increased meta-awareness, dereification and clarity could develop into a trait in expert practitioners as a result of neuroplastic changes in brain activity and structure (e.g. Davidson and Kaszniak, 2015; Kiken et al., 2015). Not many studies have investigated different meditation states and compared them to control conditions, and those that did it reported contrasting results. It is the case, for instance of the state by group interaction on gamma oscillatory power observed in Study 1, that contrasts with a previous study reporting a main effect of expertise on this measures (Braboszcz et al., 2017).

Within the present work, we can discuss some trends and speculate on possible cofounds that limit the sensitivity of a study for state or trait effects:

- 1) Findings from Study 1 and 3 indicate a main effect of meditation states on ERP components related to attentional monitoring (LFN, P2). Nonetheless, in Study 3, a trait effect was present on subjective measures of meta-awareness. It is possible that in complex paradigms, comprising different states and experimental conditions (e.g. safe and threat periods), subjective measures lose some discriminatory power as subjects are prompted to report changes in experience that were not necessarily of high relevance for them.
- 2) From another perspective, it is possible that in emotional settings trait effects prevail over subtle effects of different states. In fact, paradigms eliciting affective states can be more similar to everyday-life scenarios and therefore trigger mechanisms that are embedded outside the meditation practice.
- 3) Although we tried to apply rigorous methods of selection of expert and training of novice practitioners, the quality of experience during meditation can change between subjects and within a single session for the same individual. This is especially true for the state of OP, which is known to be difficult to stabilise, especially when people are asked to meditate for short periods of time.

Overall, accessing differences in subjective experience, and related neurobiological changes, in experts and novices during different states is not an easy challenge. However, developments on this topic are very much needed and necessary for progressing in this field of research.

### 7.3.2 Future directions

The present work highlights several limitations for the study of the neural mechanisms of meditation states at different levels of expertise. Nonetheless, this field is still in its infancy and the studies presented here can generate new methodological questions and causes for improvements.

Future studies should construct paradigms and select participants according to the specific aim and field in which the study is positioned. For instance, if there is an interest in studying emotion regulation mechanisms, selecting a group of participants with a regular and long-term practice and focusing on trait differences might increase a paradigm's sensitivity. On the other hand, if one is interested in the specific neural dynamics of different states, it would be ideal to measure practitioners attending intensive retreats and acquire data during longer sessions. This is especially true for the study of advanced practices such as open presence, which could benefit from single-case studies on practitioners that are known to be able to maintain such state for long periods of time or who are practicing intensively in the context of a traditional retreat.

In general, developing methods for describing and keeping track of changes in subjective experience during a practice or a paradigm is a crucial point that need to be addressed by future studies. To let practitioners, and participants, guide the research with accounts of their experience is fundamental and a key aspect of the

neurophenomenological framework. Additionally, meditation practitioners could and should be involved in the conception, design and piloting of experimental paradigms.

## Chapter 8

# Conclusion

In this work, we addressed several unresolved issues in the field of neuroscientific research of mindfulness meditation. We implemented specific methods of participants selection and data analysis, and we collected and related different types of data in line with the epistemological framework of neurophenomenology.

We studied the impact of different practices and levels of expertise on auditory perceptual learning processes in neutral and emotional settings, as a proxy to understand the neurocognitive mechanisms of mindfulness practices. This investigation has led to intriguing results and many open questions. Specifically, we characterised different mindfulness practices in expert practitioners in terms of the interplay between biomarkers of attentional monitoring and perceptual learning, in line with the specific phenomenology of each state. Nonetheless, these findings await future replication. We demonstrated that auditory perceptual learning is not affected by anticipatory anxiety, except for individuals with high dispositional anxiety. This effect on learning could be downregulated by during mindfulness meditation. Again, future studies are needed to confirm these findings, especially in clinical contexts.

A broader aim of this work was to map phenomenological dimensions underlying cognitive processes cultivated in mindfulness practices into neural and bodily markers of attention and emotions. In this context, we identified late components of the auditory evoked responses as putative neural correlates of heightened monitoring during mindfulness styles of meditation. Moreover, we highlighted a direct link between phenomenal clarity, dereification and emotion regulation in expert meditation practitioners.

Further research is needed to differentiate effects of mindfulness-related processes during meditation states or as general correlates of expertise. In this sense, future studies will have to implement more refined methods to track changes in subjective experience. Finally, future studies could rely on uncommon frameworks, such as single-case paradigms and long-term retreats, to elucidate the general questions raised by the present work.



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*References for Protocol Study and Study 1 can be found at the end of their corresponding sections*

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# ANNEXES

Annex I

# ERC Method Manual



# *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.

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# Table of contents

<b>Foreword</b>	<b>3</b>
<b>Context and goals</b>	<b>4</b>
<b>Participants</b>	<b>5</b>
Recruitment	5
Inclusion and exclusion criteria	7
General	7
Specific to novices	7
Specific to experts	7
Task-specific	8
Meditation training	8
Novices	8
Experts	8
<b>Outcome measures</b>	<b>9</b>
Self-administered questionnaires	9
Behavioral, neurophysiological and phenomenological measures	10
<b>Contributions</b>	<b>13</b>
<b>Acknowledgments</b>	<b>14</b>
<b>Funding</b>	<b>14</b>
<b>References</b>	<b>15</b>
<b>List of publications</b>	<b>17</b>

## 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.

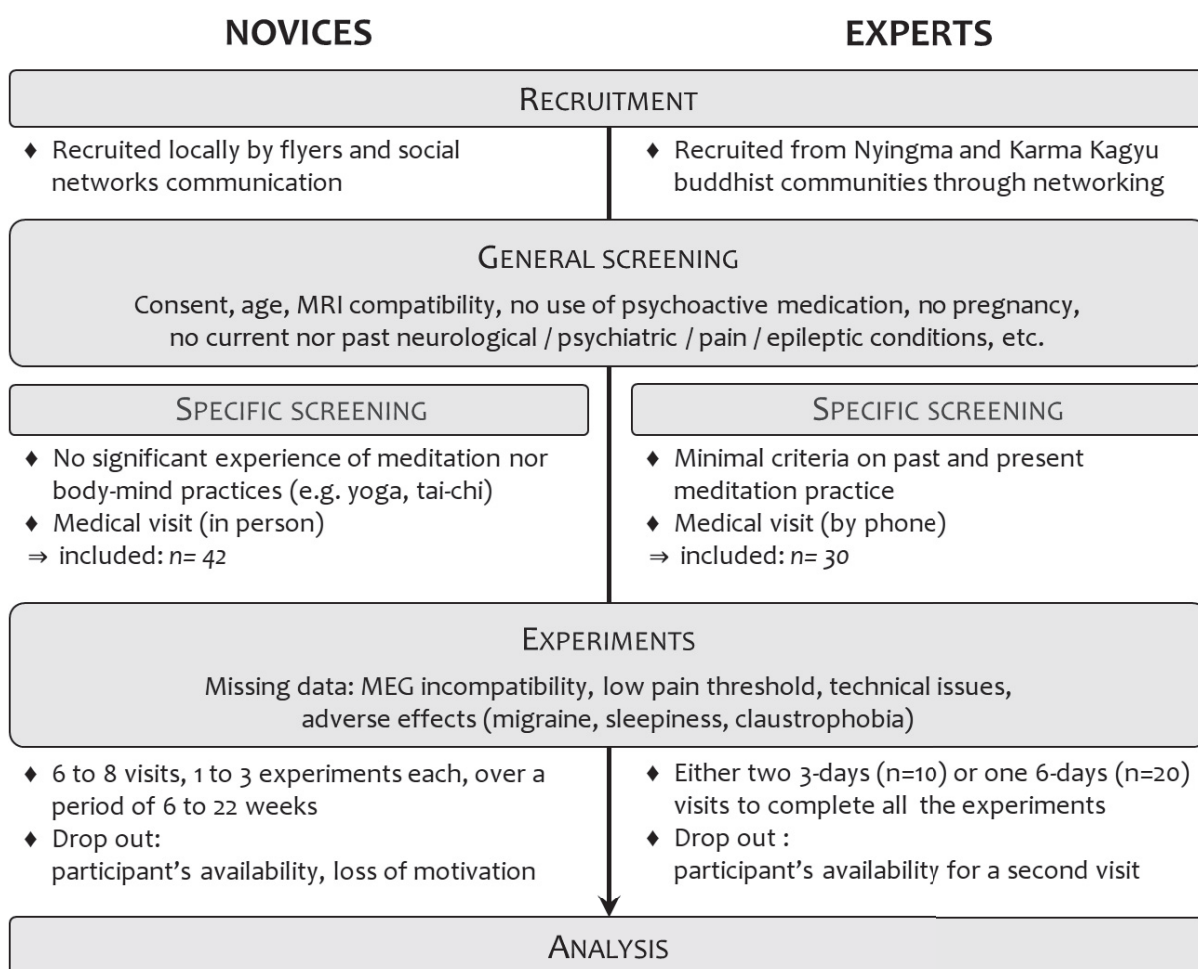
This project tries to address these limitations by proposing a methodological approach that 1) takes into account the variety of meditation practices such as Focused Attention (FA), Open Monitoring (OM) and Compassion, 2) provides a detailed meditation introduction to novice practitioners through experiential 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"> <li>- MEG</li> <li>- ECG, EGG, respiration</li> <li>- behavior</li> <li>- Likert ITEMS</li> <li>- semi-structured interview</li> </ul>	<ul style="list-style-type: none"> <li>- Visual passive oddball</li> <li>- Visual consciousness report</li> </ul>	Stefanics et al. 2014 Park et al. 2014 Richter et al. 2016
SMEG	<ul style="list-style-type: none"> <li>- MEG</li> <li>- ECG, respiration</li> <li>- Likert scales</li> <li>- semi-structured interview</li> </ul>	<ul style="list-style-type: none"> <li>- Resting-state</li> </ul>	

### Experimental session 4

**Modalities:** EEG

**Duration:** one full day

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

### Experimental session 5

**Modalities:** EEG

**Duration:** half a day

CODE	MEASURES	PARADIGM	REFERENCES
CAAT	<ul style="list-style-type: none"> <li>- behavior</li> <li>- ECG, respiration</li> <li>- skin conductance</li> <li>- Likert scales</li> <li>- semi-structured interview</li> </ul>	<ul style="list-style-type: none"> <li>- Approach-avoidance</li> <li>- Emotional videos</li> </ul>	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

<b>Principal investigator</b>	LUTZ	Antoine	<i>PhD</i>
<b>Medical investigators</b>	JUNG SONIÉ	Julien Sandrine	<i>MD, PhD</i> <i>MD</i>
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<b>Novices recruitment</b>	AARTS	Kristien	<i>post-doctoral fellow</i>
<b>Novices training</b>	TRAN	Titi	<i>meditation instructor</i>
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## List of publications

Last update: 10/09/2018

# Supplementary information

## II.1 Protocol Study: supplementary information

### *1. Experiential exercises implemented in the phenomenological training protocol*

#### **Effort**

The dimension of effort was introduced in the context of practicing Focused Attention on the sound of a bell. The teacher asked the participants to experience the difference between concentrating on a specific sound while preventing the mind from wandering and simply recognizing the same sound in the field of awareness (“just listen to the sound”).

#### **Absorption and Meditative Awareness**

The difference between being absorbed in a mental phenomenon and being aware of it and its nature has been described during teachings throughout all the course of the training weekend. In particular, participants have been invited to recognize the switch between absorption and awareness that occurs at the very moment they realize their mind has wandered away during meditation.

#### **Object Orientation and Aperture**

In the context of a guided practice, subjects were asked to focus their attention over a small visual object (a flower, a piece of tissue, etc.). Subjects were first asked to concentrate on a specific detail of the object, then on the entire object and finally on the entire visual field. This exercise was implemented to introduce the concepts of object orientation and aperture with a direct experience of the different degree of attentional focus in a given sensory modality, and the aperture of the field of awareness.

#### **Foreground and Background Awareness**

During the weekend, participants were guided through a meditation practice using physical sensations as support and then shifting the attention over the visual field. Participants could experience that, although their attention shifted and changed the

main object of focus, physical sensations that were previously in the “foreground” could still be experienced in the “background”.

### **Empathy and Compassion**

During the second day of the training weekend, subjects were introduced to the processes of empathy and compassion with the help of an experiential exercise. The aim of this exercise was to help the subject experiencing and understanding the practical meaning of compassion, as intended in the Buddhist framework. The access to this understanding and experiential testing was fostered by the contrasting experience of empathy, based on the process of eidetic reduction and imaginative variation (Husserl 2008).

In practice, two highly emotional pictures, depicting people suffering, were shown to the subjects. The pictures were taken from the Internal Affective Picture System database (IAPS, Lang et al. 1997) and selected based on negative valence and high arousal. Subjects were warned that the pictures were characterised by a strong emotional content. They were first asked to look at the picture without any instruction (for about 3 minutes). Subsequently, they rested their mind for some minutes and shared their experience of looking at the pictures. The teacher acknowledged the subjects’ experiences and introduced the concept of empathy and the practice of compassion.

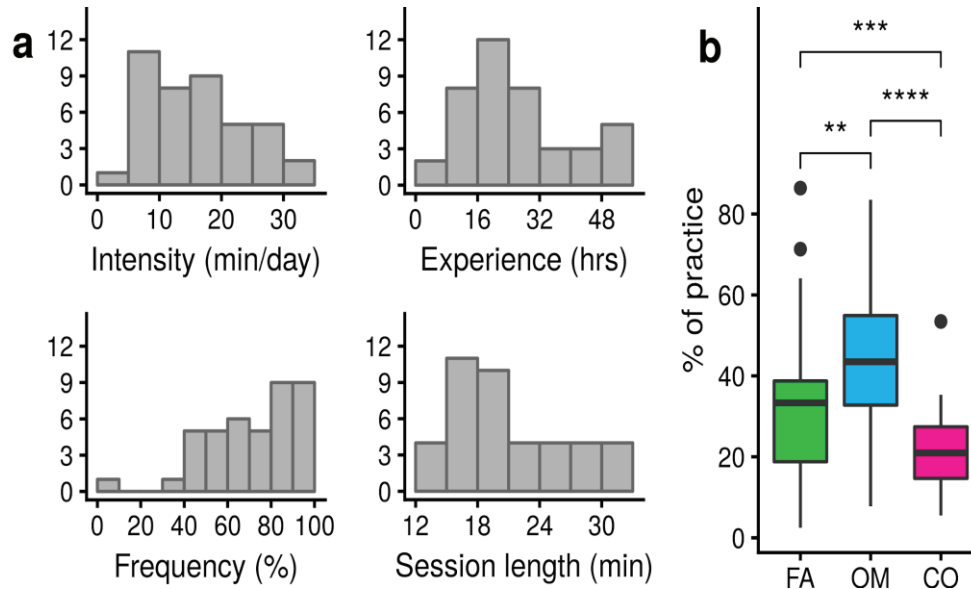
Subjects were asked to look at the pictures again and were guided by the teacher to empathize with the sufferer with sentences such as: “the person suffers, and you suffer with her”. They were also prompted to silently repeat sentences such as: “I feel your sufferance” or “Your sufferance is my sufferance”. Moments of “empathy training” were intermixed with the practice of open awareness. Subjects were then guided through a practice of compassion, using the same pictures as support. This practice followed the classical form of compassion meditation as implemented in the secular program of the Buddhist tradition on which the training was based.

Finally, participants were encouraged to share their thoughts and comment on the difference between the two experiential exercises and the processes of compassion and empathy, as well as their understanding of these processes before and after the exercise.

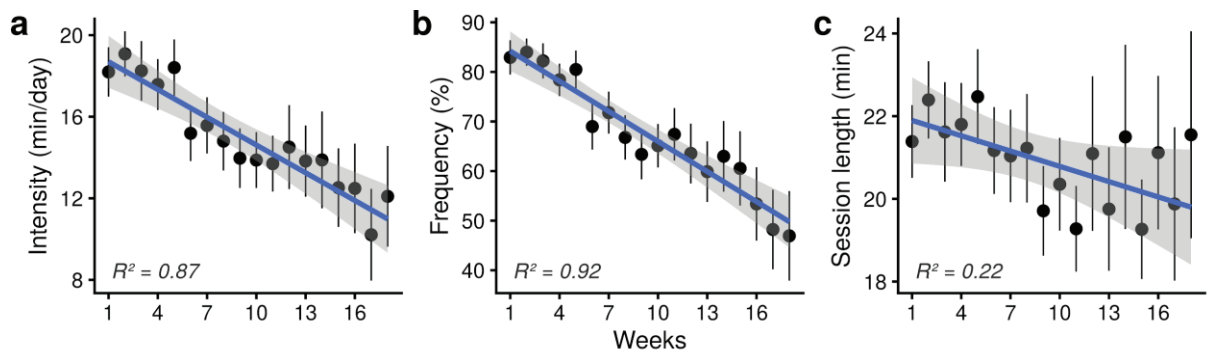
### **Clarity**

The dimension of clarity was introduced and described to the participants at the end of the weekend. They were asked to recall how clear their mind was when undergoing the thermal pain threshold calibration, compared to trying to use drowsiness as a support for meditation. The practice on drowsiness was proposed after lunch on the weekend days. This exercise aimed to help novices familiarizing with different degrees of clarity of their mental experience, which can partly depend, at least at an early stage of the meditation practice, on physiological states.

## 2. Characteristics of novices' practice

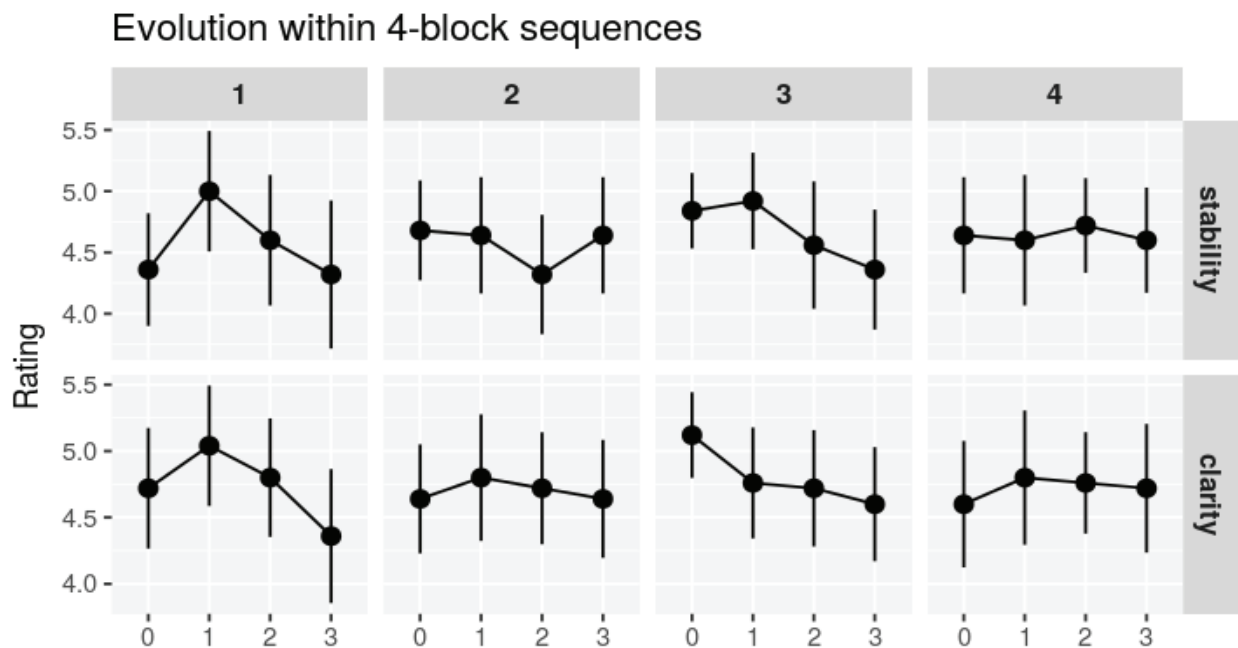


**Supplementary Fig. 1** Distributions of the four metrics over the group of novice participants. Participants were asked, but not required, to meditate daily for 20 to 30 minutes for the whole duration of the study, which ranged from 6 to 23 weeks. **(b)** Participants favored the practice of Open Monitoring (OM) over Focused Attention (FA) and tended to neglect the practice of Compassion (CO). We did not find any effect of type of practice (FA, OM, CO) on Session length (one-way repeated measure ANOVA:  $F(2,80)=1.47$ ,  $p=.23$ ). In order to determine whether individual preferences towards a given practice were present at the outset or emerged over time, we used the percentage of weekly practice time dedicated to the preferred practice as a measure of practice bias. Thus defined, practice bias ranges from 33.3% (no bias: the participant dedicates the same amount of time to each of the three practices) to 100% (full bias: the participant engages in only one practice). Practice bias was found high already in the first week after the training weekend ( $M=59\%$ ,  $SD=16\%$ ), and increased linearly over weeks ( $R^2_{adj}=.27$ ,  $p<.016$ ,  $\beta=.46$ , 95% CI [.10, .81]; data not shown). Significance levels: \*:  $p<.05$ ; \*\*:  $p<.01$ ; \*\*\*:  $p<.001$



**Supplementary Fig. 2** The amount of daily practice decreased steadily over time (a). A closer look reveals that this effect is mostly due to a decline of the Frequency of practice (b) rather than a shortening of Session lengths (c). Errors bars are 95% confidence intervals.

### 3. Temporal dynamics of Stability and Clarity



**Supplementary Fig. 3** The temporal dynamic of Stability and Clarity ratings in novices. Error bars = 95% CI.



#### 4. Model selection for self-reported phenomenological effects

Presented below are the detailed results of each of the model selections performed. The following information is provided for each model: the variables that compose it, the difference between the AICc of the model and the AICc of the best model ( $\Delta\text{IC}$ ), the variance explained by the model ( $R^2_{\text{adj}}$ ), the global level of significance of the model ( $p$ ), and the  $p$ -value of each of the model's terms (main effects and two-way interactions, if any; bold:  $<.05$ ; italics:  $<.1$ ; n.s.:  $>.1$ ). In addition, we provide the *relative evidence weight*, a measure of relative importance of each term across the entire model space (Calcagno and de Mazancourt 2010), comprised between 0 and 1.

model #	$\Delta\text{IC}$	$R^2_{\text{adj}}$	$p$	BIDR	INT	EXP	FOB	FOB:INT	FOB:EXP
A1	0	.38	<b>.010</b>		<b>.007</b>	n.s.	<i>.09</i>		<b>.007</b>
A2	1.13	.25	<b>.048</b>		<b>.04</b>	n.s.	n.s.	<i>.053</i>	
A3	1.44	.27	<b>.025</b>		<i>.07</i>		n.s.	<b>.033</b>	
<b>Relative evidence weight</b>				.31	<b>.85</b>	.66	<b>.86</b>	.35	.55

Supplementary Table 1 Models selected for the state effect on Aperture

model #	$\Delta\text{IC}$	$R^2_{\text{adj}}$	$p$	BIDR	INT	EXP	FOB	BIDR:INT	BIDR:EXP
B1	0	.34	<b>.016</b>	n.s.	n.s.		<b>.007</b>	<b>.017</b>	
B2	0.90	.17	<b>.050</b>		<i>.066</i>		<i>.071</i>		
B3	1.69	.45	<b>.010</b>	n.s.	n.s.	n.s.	<b>.004</b>	<b>.003</b>	<i>.056</i>
B4	1.81	.08	<i>.098</i>		<i>.098</i>				
B5	1.97	.07	n.s.				n.s.		
<b>Relative evidence weight</b>				.60	<b>.66</b>	.34	.74	.36	.10

Supplementary Table 2 Models selected for the fatigue effect

model #	$\Delta$ IC	$R^2_{adj}$	p	BIDR	INT <sub>focus</sub>	INT <sub>open</sub>
C1	0	.15	<b>.034</b>		<b>.034</b>	
<b>Relative evidence weight</b>				.40	.74	.34

**Supplementary Table 3** Models selected for the fatigue effect, after differentiating Intensity<sub>focus</sub> and Intensity<sub>open</sub>.

model #	$\Delta$ IC	$R^2_{adj}$	p	BIDR	INT	EXP	FOB
D1	0	.19	<b>.023</b>			<b>.023</b>	
<b>Relative evidence weight</b>				.23	.30	<b>.84</b>	.21

**Supplementary Table 4** Model selected for phenomenological specificity, defined as the difference between correlations between variability of reaction time on one hand, and Stability and Clarity on the other hand.

	BIDR	Intensity	Experience
Intensity	<b>0.431 *</b> [0.034, 0.711]		
Experience	0.131 [-0.287, 0.508]	<b>0.617 **</b> [0.284, 0.817]	
FOB	0.197 [-0.224, 0.556]	-0.061 [-0.454, 0.351]	-0.058 [-0.451, 0.354]

**Supplementary table 5** Pearson cross-correlations between variables of interest. Values between square brackets are 95% confidence intervals. Values in bold are significant. Significance levels: \*: p<.05; \*\*: p<.01

## **II.2 Study 1: supplementary information**

### **1. Meditation instructions for novices**

#### **Training for Focused Attention:**

This state is better known as the Buddhist practice of “one-pointed concentration”. This is a state in which one tries to focus all one’s attention upon one object, keep it on that object, and bring it back to that object when one finds that one has been distracted (by outer perceptions or inner thoughts). During the training session, the participant should focus his/her attention on a small object (coin, shirt etc.). For this experiment, it is important that the object on which one focuses is visual, rather than focusing on the breath, mantra, or a mental image. Ideally, this “one-pointed concentration” should be clear (vivid) and unwavering (calm and stable), free from all types of distraction, the main types being sinking into dullness and being carried away by mental agitation.

#### **Cultivation of Open Presence:**

Generate a state of total openness, in which the mind is vast like the sky. Maintain a clear awareness and presence open to the surrounding space. The mind is calm and relaxed, not focused on something in particular, yet totally present, clear, vivid and transparent. When thoughts arise, simply let them pass through your mind without leaving any trace in it. When you perceive noises, images, tastes, or other sensations, let them be as they are, without engaging into them or rejecting them. Consider that they can’t affect the serene equanimity of your mind.

## **2.1 Subject-specific ICA profiles: a formal test to investigate their contribution in brain signal.**

Independent component analysis highlighted an intriguing set of components, subject-specific and mainly found in subjects belonging to the Expert group. After inspection of time-course, spectrogram, and topography, we noted a component characterized by a peak of activity in the gamma-range that tends to decline over higher frequencies, is sustained along particularly wide time-windows during the whole session (possibly reflecting the meditation state), and presents a variable scalp-distribution (although mainly concentrated in fronto-central regions) and a rather superficial possible dipole (i.e. see Figure S3). We classified these components as “decline”. From a visual inspection, these components have some common characteristic with components related to muscle activity, such as dipole location and increase in gamma frequencies. Nevertheless, muscle activity does not tend to decline at higher frequencies, is not sustained as much over time, and is more superficial and localized at the edges of the scalp compared to the components we found. Moreover, previous studies have already found an increase in oscillatory gamma activity in the frontal regions for expert meditators (e.g. Lutz et al., 2004), but have treated such findings with caution due to the possible contribution of high frequency muscle activity.

To be able to determine whether the components found in the present study were caused by muscle activity or rather represented a source of genuine brain signal, we implemented a formal and rather conservative method to test for the contribution of each single component in the ERP. Epochs were generated for each subject (see Methods section for the epochs generation method) who had one or more “decline” component, after rejecting all other components (including typical brain signal). Each “decline” component was tested alone. Epoched data were not baseline-corrected and a normal averaging method was applied to generate ERPs. Before averaging, data from three consecutive blocks and for all states were concatenated for the “deviant” stimulus condition, while epoched data for standard stimuli (this time including all presented standard stimuli) were concatenated across blocks, while keeping the different states separated. The ERPs for each subject were subsequently z-transformed to the mean and standard deviation of the baseline signal 300ms before stimulus onset, and the global mean field was calculated across all electrodes at each time point of the ERP. Finally, an arbitrary stimulus-locked time-window was chosen (0-600ms after stimulus onset) and we computed the percentage of time-points in the latter window which were above or below three standard deviations (3 sigma) from the baseline (the 3 sigma threshold was arbitrarily set after inspecting with the same method components clearly reflecting brain signal, as well as others clearly reflecting artefacts). Following a conservative approach, we set a threshold of 15% of time-points trespassing 3 sigma, above which the specific component was kept for ERP and future spectral analyses; it was otherwise rejected.

We found that, even after applying this rather conservative method (components did not necessarily have to contribute to the ERP and stringent thresholds were used), several “decline” components could still be interpreted as reflecting genuine brain signals. This is further supported by the fact that some subjects, showing these special profiles of activity, lacked “normal” components reflecting brain signal (characterized by a peak of activity in the alpha-range, a broad topography, and a deeper source). The results of the above method thus usefully supported the results of spectral analysis, which were free of contamination from muscle activity.

## 2.2 Average number of trials after data pre-processing

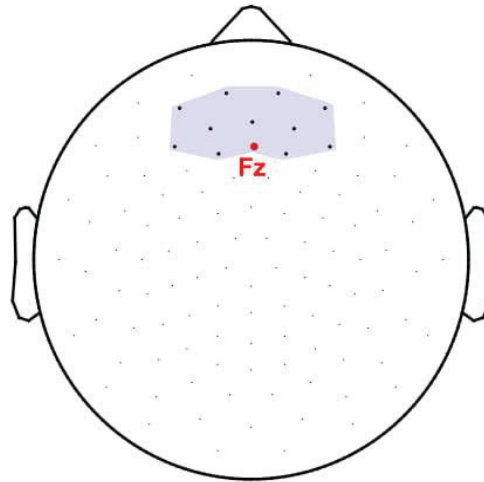
	std_FA	std_OP	std_RE	dev_FA	dev_OP	dev_RE
MEAN EXP	146.6	143.9	141.6	145.7	144.4	141.8
STD EXP	2.1	8.7	9.8	2.8	7.6	9.8
MEAN NOV	145.0	145.7	140.4	144.7	145.9	139.8
STD NOV	3.3	10.9	11.6	4.6	9.9	11.6

Table showing mean number of trials (MEAN) and standard deviation (STD) for each group (EXP = experts; NOV = novices), stimulus type (std = standard; dev = deviant) and state (FA, OP, RE). Notice that only standard tones preceding deviants were included in the analysis.

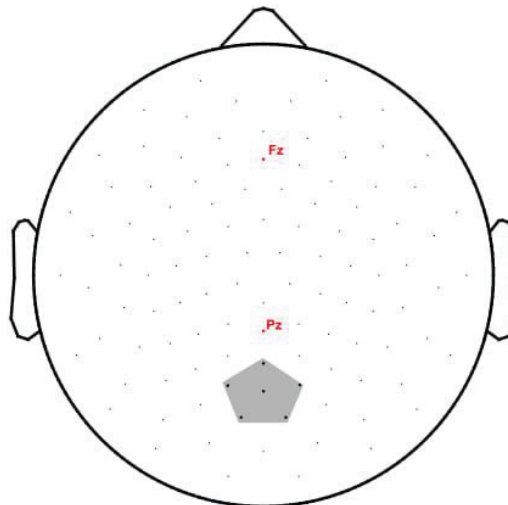
### 2.3 Differences in response to standard and deviant stimuli

To investigate differences in response to standard and deviant stimuli between experimental conditions and groups, we performed additional statistical analysis in the MMN time-window (90 to 180 ms) and frontal ROI. More specifically, we fitted two linear mixed-effects models, comprising the average response amplitude to either deviant or standard stimuli as dependent variable, the interaction between STATE (FA, OP, RE) and GROUP (Experts, Novices) as fixed effect, and subjects as random effect. The model was tested using an ANOVA analysis of variance (Type II Wald chi-square test). Paired t-tests, corrected for multiple comparisons using Tukey honestly significant difference test (HSD), were used as post-hoc tests comparing least-squared means. The analysis of responses to standard stimuli yielded a marginally significant interaction between STATE and GROUP ( $\chi^2(2) = 4.7$ ;  $p = 0.09$ ). Descriptive statistics showed how the average response to standard stimuli during OP was decreased, compared to other states, in novices and increased in expert practitioners (see figure S4). Nonetheless, post-hoc tests did not highlight significant differences between states and groups in response to standard stimuli. The analysis of response to deviant stimuli yielded a statistically significant main effect of STATE ( $\chi^2(2) = 9.6$ ;  $p = 0.007$ ). Post-hoc tests showed how, across both groups, the response to deviants was lower during RE compared to OP and FA (t-ratio (58) = -2.3;  $p = 0.05$  and t-ratio (58) = -2.9;  $p = 0.01$ , respectively).

None of these tested yielded informative results to explain the interaction between states and groups, observed in the analysis of the MMN component. The marginally significant interaction, resulted from the analysis of responses to standard stimuli, might point towards understanding differences in the MMN in terms of different average amplitude of response to this stimulus type between states and groups, especially concerning the OP condition. A trial by trial analysis, with the help of computational modelling, could help elucidate this critical research question.

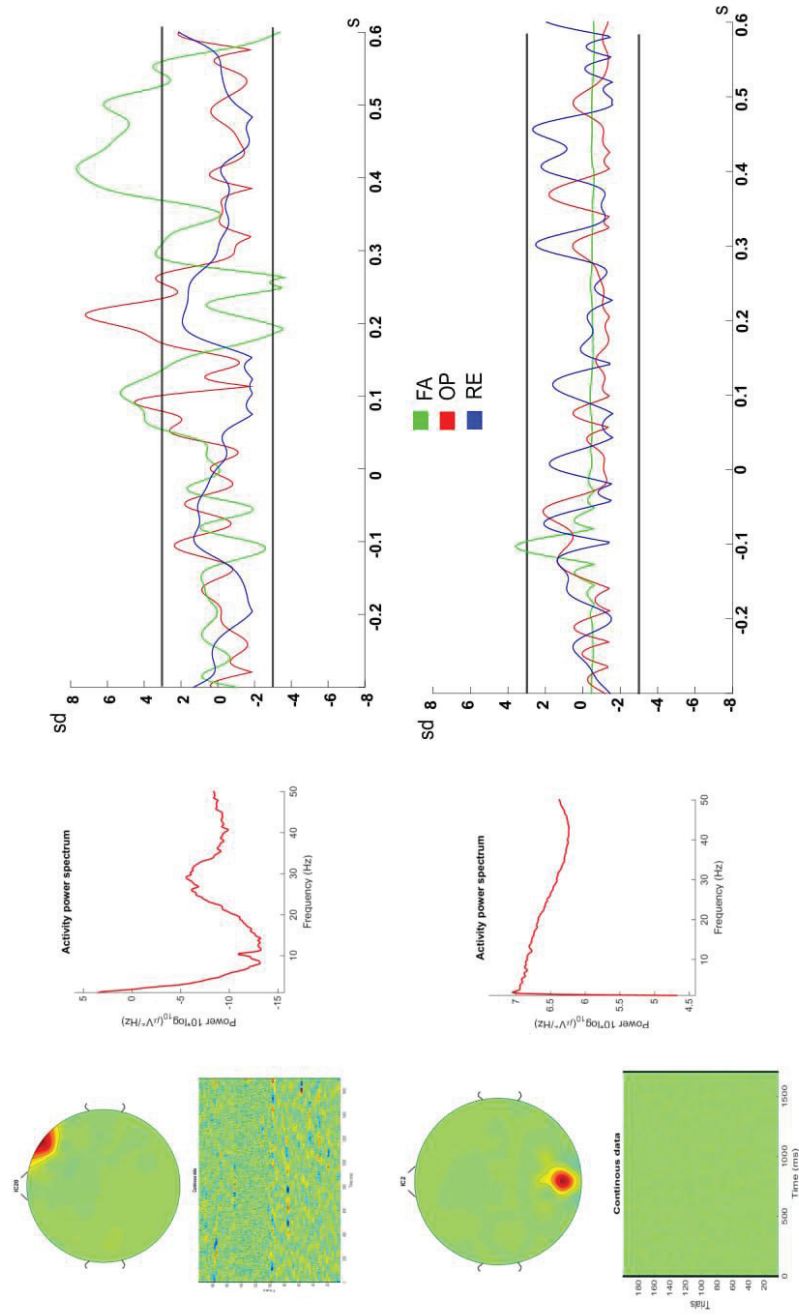


**Fig. S1. Frontal ROI selected for the analysis of event-related potentials.** EGI GSN200 system electrodes layout, plotted on a head template. The frontal ROI is highlighted, comprising eleven frontal electrodes, including Fz (highlighted in red).

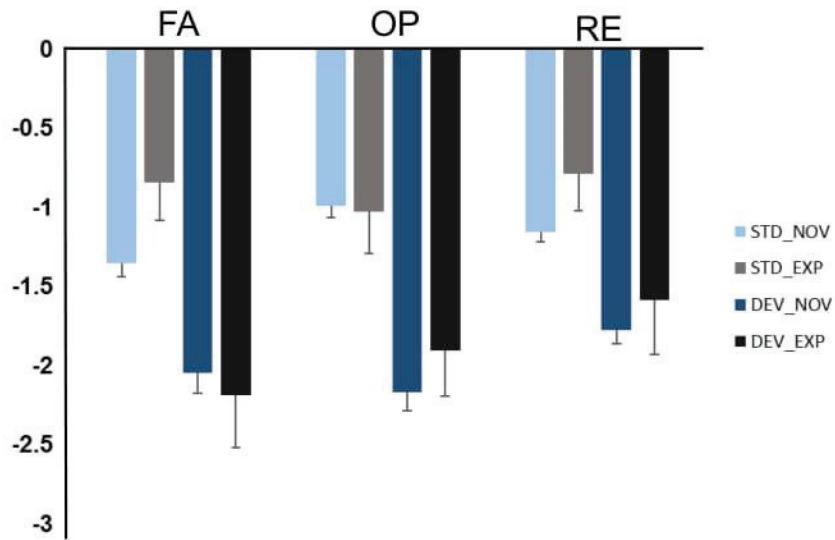


**Fig. S2. Occipital ROI selected for the spectral power in the alpha (8-12Hz) and gamma (25-40Hz) frequency ranges.** EGI 128-channels GSN200 system electrodes layout, plotted on a head template. The ROI is highlighted in grey. For display reasons, electrodes Fz and Pz are also highlighted (in red).





**Figure S3.** Comparison between an ICA component defined as “decline” (top) and one displaying an artefact (bottom). From left to right: topography of the component and time-course, spectral power and graph showing the contribution of the component in the global mean field for each state (FA, OP, RE). Grey lines on the graph represent the 3 sigma threshold for the inclusion criteria.



**Figure S4.** Mean values of responses to standard and deviant auditory stimuli in MMN latency (90-180ms) at frontal ROI for FA, OP and RE conditions. Grey bars represent expert practitioners (standards: light grey; deviants: dark grey) and blue bars represent novice practitioners (standards: light blue; deviants: dark blue).

## II.3 Study 2: supplementary information

### 1. Self-report questions

1) To which degree did you experience anxious feelings in the “threat” condition?

*Labels: 1=“not at all” 5=“moderately” 7=“very much”*

2) To which degree did you experience anxious feelings in the “safe” condition?

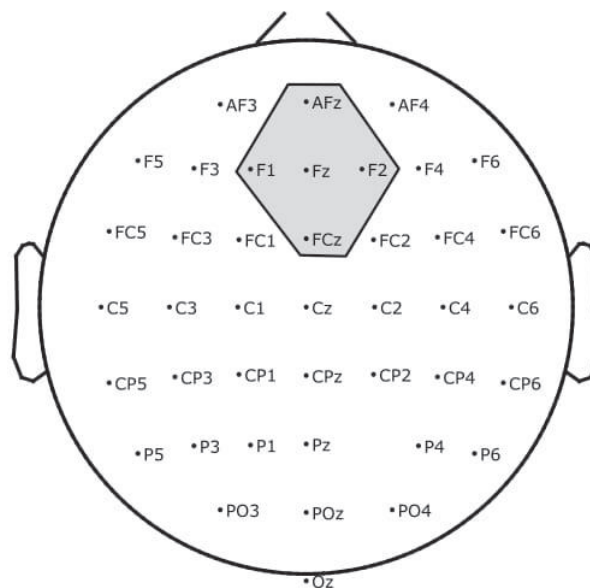
*Labels: 1=“not at all” 5=“moderately” 7=“very much”*

3) To which degree, on average, were you aware of listening to sounds during this block?

*Labels: 1=“never” 5=“sometimes” 9=“always”*

4) To which degree, on average, were you distracted during this block?

*Labels: 1=“never” 5=“sometimes” 9=“always”*



**Figure S1.** Electrodes layout after data pre-processing and frontal ROI (grey area) used in the analysis of MMN amplitude and N1 and P2 components of the auditory evoked response.

## II.4 Study 3: supplementary information

### 1. Self-reports

To which degree did you experience anxious feeling in the “threat” condition?

*Labels: 1 = not at all 5 = moderately 7 = very much*

To which degree did you experience anxious feeling in the “safe” condition?

*Labels: 1 = not at all 5 = moderately 7 = very much*

To which degree, on average, were you aware of sounds during this block?

*Labels: 1 = never 5 = sometimes 9 = always*

To which degree, on average, were you aware of listening to sounds during this block?

*Labels: 1 = never 5 = sometimes 9 = always*

To which degree, on average, were you distracted during this block?

*Labels: 1 = never 5 = sometimes 9 = always*

To which degree, on average, your mind was clear?

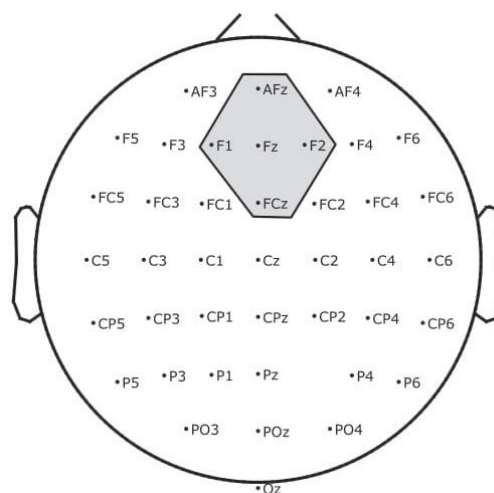
*Labels: 1 = not at all 5 = moderately 9 = very much*

### 2.1. Number of blocks for each experimental condition following data preprocessing

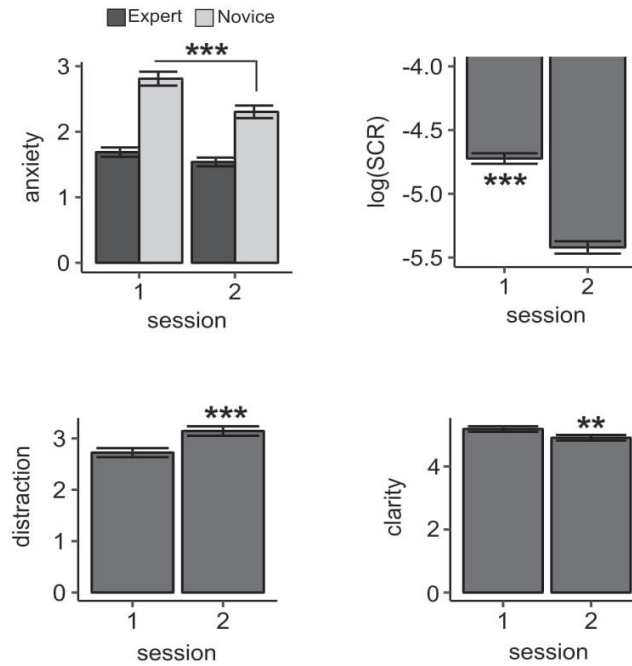
	FA	OP	VD
Expert	57	57	59
Novice	69	68	67

## 2.2 Mean epochs per session for group, state, condition and stimulus type

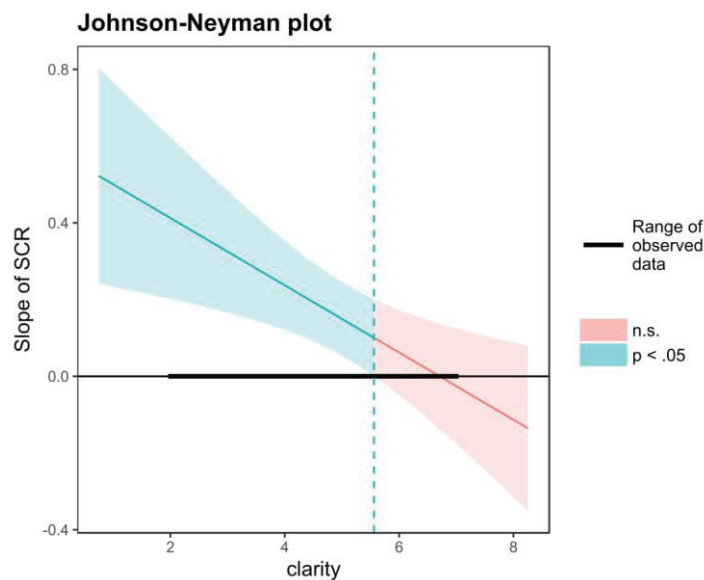
Group	State	Cond	Stim	Mean	SD
Exp	FA	Safe	std	55.0	2.1
Exp	FA	Safe	dev	54.9	2.3
Exp	FA	Threat	std	54.0	2.7
Exp	FA	Threat	dev	54.1	2.8
Exp	OP	Safe	std	54.9	2.1
Exp	OP	Safe	dev	54.8	2.0
Exp	OP	Threat	std	53.8	2.6
Exp	OP	Threat	dev	54.1	2.3
Exp	VD	Safe	std	55.1	1.8
Exp	VD	Safe	dev	55.1	2.1
Exp	VD	Threat	std	54.4	2.3
Exp	VD	Threat	dev	54.4	2.7
Nov	FA	Safe	std	52.4	5.6
Nov	FA	Safe	dev	52.3	5.8
Nov	FA	Threat	std	51.4	5.7
Nov	FA	Threat	dev	51.3	5.7
Nov	OP	Safe	std	51.8	6.1
Nov	OP	Safe	dev	51.9	6.0
Nov	OP	Threat	std	51.7	5.8
Nov	OP	Threat	dev	51.9	5.5
Nov	VD	Safe	std	52.3	6.1
Nov	VD	Safe	dev	52.2	6.0
Nov	VD	Threat	std	51.4	5.7
Nov	VD	Threat	dev	51.6	5.4



**Figure S1.** Electrodes layout after data pre-processing and frontal ROI (grey area) used in the analysis of MMN amplitude and N1 and P2 components of the auditory evoked response.



**Figure S2. Session effect on self-report and skin conductance responses.** Mean values of self-reported distractibility and clarity (bottom), mean amplitude of skin conductance responses (top right) and mean values of self-reported anxiety in experts and novices (top left) for the two sessions of the experimental paradigm. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$



**Figure S3. Clarity mediates the relation between SCRs and subjective anxiety.** Johnson-Neyman plot representing the estimated cut-off value (light-blue dashed line) of clarity (x-axis) at which the regression slope coefficient of SCRs and anxiety (y-axis) is statistically significant (light blue slope) at  $p < 0.05$ .

