INDIVIDUAL DIFFERENCES AND PSYCHOBIOLOGICAL RESPONSES TO MIND-BODY INTERVENTIONS

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Chapter 1

Introduction

1. Introduction

The term mind-body interventions (MBIs) is an umbrella term used to characterise various techniques that focus on the interaction among the brain, mind, body, and behaviour with the intent to use the mind to affect physical functioning and promote health (Elkins & Fisher, 2010). MBIs have been used by religious monastic elites for over two thousands of years, and today they are being practiced by millions of people (Clarke et al., 2015). The scientific interest in meditation and other MBIs such as yoga, Tai Chi or Qigong has grown exponentially in the past 20 years (Figure 1), which enabled the final step of transition of MBIs from religious elites in the East to the top research facilities, book stores, media outlets, retreats or workshops around the world. Today we can even observe the merging of MBIs with technology, which brings these techniques closer to even wider audiences through mobile apps or online videos.

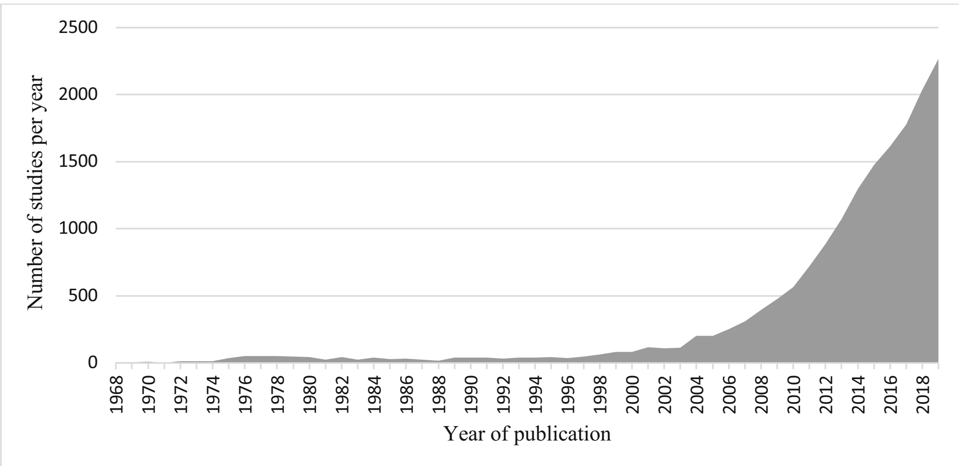

Figure 1. Number of studies related to meditation, mindfulness, yoga, Tai Chi or Qigong published from 1968 to 2019 (data obtained by searching PubMed).

The transition of MBIs from religious to popular culture has been happening for a long time. Eastern MBIs travelled to the West and the rest of the world long before the 20th century due to cultural and merchant trades that introduced meditation in the West already during classical and medieval periods (Ristuccia, 2013), which then spread more widely following European colonial expansion in the 17th century and onwards (King, 2020). However, although the West has been familiar with Asian traditions and MBIs for many centuries, they were generally not viewed positively until the late 20th century (King, 2020). This was because of the Orientalist stereotypes that portrayed the East as superstitious, mystical and irrational, in contrast with the West that was seen as rational and scientific. But in the 20th century, Asian MBIs and traditions have slowly become seen as spiritual instead of mystic (King, 2020). The concept of spirituality paved the way for non-religious and secular engagement with Asian MBIs that gradually became accepted as a normal component of modern life by the end of 20th century.

2. The origins of MBIs

It is estimated that MBIs originated approximately 1000 BCE in the Southeast Asia, but they were not a part of any religion or system of thought until they were adapted by Buddhism, Hinduism and other competing traditions (Bronkhosrt, 1981, Wernicke-Olesen, 2020). However, meditation is not exclusive to Buddhism or Hinduism, and instead it can also be found in mystical traditions of other major religions such as *Kabbalah* (Jewish mysticism), *Hesychasm* (mysticism of Eastern Orthodox Church) or *Sufism* (Muslim mysticism).

The first known description of any MBI is related to yoga and stems from the 3rd century BCE (in *Katha Upanishad,* one of the oldest scriptures about Hinduism):

When the five perceptions are stilled,
together with the mind,
And not even reason bestirs itself;
they call it the highest state.
When senses are firmly reined in,
that is Yoga, so people think.
From distractions a man is then free,
for Yoga is the coming-into-being,
as well as the ceasing-to-be.

(Olivelle, 1998, p. 401)

From this text, it is apparent that the yoga described in this scripture is different from how we describe yoga in the modern day. Yoga is described as method of liberation from constant rebirth by controlling one's senses, but also as a state of consciousness. Therefore, when the term yoga is used in a traditional sense, it is actually closer to what we term meditation today and it does not include physical postures (Wernicke-Olesen, 2020). Although some seated physical postures existed at the time and although they have been closely linked with meditative practices throughout Indian religious history, physical postures were always secondary (Wernicke-Olesen, 2020, Singleton, 2010). For instance, a seminal book from Indian history (*Mahabharata*, written sometime between the 3rd century BCE and the 3rd century CE) contains 884 references to yoga, and only two references to postures (Bryant, 2009). Other important works about yoga written before the 20th century mention physical aspects equally rarely, which indicates that yoga as a set of physical postures is a relatively recent phenomenon (Singleton, 2010). Instead, the central emphasis in yoga throughout history has been on yoga philosophy, where physical postures and meditation are one of its several components. Elaborate descriptions of yoga philosophy can be found in many books from around the first centuries BCE, most notably in *Pātañjalayogaśāstra* where yoga consist of the eightfold path: ethical rules for living (1. *yama* and 2. *nijyama*), physical postures (3. *āsana*), breath-control (4. *prāṇāyāma*), withdrawal of the senses (5. *pratyāhāra*), fixation of the mind on one object (6. *dhāraṇā*), meditation (7. *dhyāna*), and complete union with all consciousness (8. *samādhi*; Maehle, 2011). Similar descriptions can be found in other traditions, such as the Noble Eightfold Path of classical Buddhism, or other paths in Tantric or Ayuverdic traditions (Mallinson and Singleton 2017). In summary, it is generally believed that meditation (*dhyāna*) is practiced by controlling the breath (*prāṇāyāma*), withdrawal of the senses (*pratyāhāra*), and focusing the mind on a single point (*dhāraṇā*) with the goal of reaching the highest state of consciousness (*samādhi*) that may lead to enlightenment, which is the liberation from the cycle of rebirth (termed *mokṣa* in Hinduism or *nirvāna* in Buddhism). More specifically, Buddhist teachings postulate that suffering is caused by our attachment to transient things. Meditation and yoga, along with specific views of the world and prescriptions for living, are used as core methods to achieve detachment and alleviate suffering. It is believed that through practicing these techniques, a person can achieve complete enlightenment that leads to freedom from suffering and liberation from repeated rebirth (Gethin, 1998, Rao 2010). Unlike Buddhism, which does not include a belief in god, Hinduism uses meditation and yoga to achieve unity with the creator and all created beings. It is believed that by doing so and by following other rules for living, a person can reach a complete enlightenment that is the ultimate goal of life and stops repeated rebirth (Flood & Flood, 1996). Although there are many schools of Buddhism and Hinduism, most share these common principles. Therefore, in Eastern religions, meditation and yoga are often used for transformation of the self, rather than stand-alone techniques. However, because in the West mind and body are seen as distinct entities, Buddhist meditation came to be seen as a mental exercise with the goal of maintaining mental health, while Hindu yoga came to be seen as physical exercise that focuses upon posture, fitness and physical health. In reality, this division is misleading because some Buddhist practices are bodily oriented, and what we know as yoga today has many different influences besides Hinduism (Singleton & Byrne, 2008). In fact, yoga only became popular in the West in the 1920s and 1930s when it merged with Indian gymnastics and fitness traditions (Singleton, 2010). While yoga gained its popularity by merging with fitness and emphasising physicality, meditation made it with the help of science. Even the first Zen Buddhism master who taught in the United States presented Buddhist teachings and meditation practices as philosophical and scientific (Payne, 2012). From that point onward, Buddhist meditation was gradually re-contextualised as a secular form of mental training, today known worldwide as mindfulness (King, 2020). Today, there is a vast array of types of meditation, yoga and other MBIs available to the public regardless of their religious background. In the following section, major subtypes of MBIs will be explained: meditation, yoga, Tai Chi and Qigong.

3. What is meditation?

Mindfulness, Transcendental Meditation, Zen meditation or loving-kindness are just some of the many types of meditation can be found in the scientific literature, which raises questions about what meditation is and whether meditation studies are comparable. There have been attempts to categorise different types of meditation into two general categories: focused attention and open monitoring (Lutz, Slagter, Dunne & Davidson, 2008). Focused attention meditation is based on focusing attention on one object, which is commonly a mantra or one’s own breathing (Lutz, Slagter, Dunne & Davidson, 2008). The aim of focused attention meditation is to practice disengagement from thoughts, emotions, and bodily sensations, while trying to maintain attention on the repetition of mantra or on inhales and exhales. The most well-known form of focused attention meditation is Transcendental Meditation.

Transcendental Meditation (TM) was the first type of Eastern meditation that gained popularity outside of Asia when an influential teacher from India, Maharishi Mahesh Yogi, started touring the world in the 1960s and soon thereafter gained a large following. TM has its roots in Hinduism and it is practiced by repeating a mantra in Sanskrit. The central principle is that all living beings are connected through a collective consciousness and that enlightenment can be achieved by practicing this technique (Roth, 1994). A TM course is typically delivered in a standardised format as a seven-step course, which includes introductory and preparatory lectures, a personal interview, and four days of instruction that include an individual instruction meeting and three group meetings (Roth, 1994). The peak of popularity of this type of meditation was in the mid-1970s when more than 1000 people were signing up for TM courses every day (Oman, 2020). The popularity of TM plummeted in the late 1970s when the Siddhi programme that claimed that this type of meditation lead to the ability to levitate failed to provide evidence for this claim.

Open monitoring meditation, on the other hand, is based on observing current thoughts, emotions, or bodily sensations, without getting carried away by thoughts about the past or future. The aim is to maintain awareness of the present moment as it is, without judging it as bad or good. Focused attention is typically a precursor to open monitoring to reduce distractions, and open monitoring gradually becomes the central practice (Lutz, Slagter, Dunne & Davidson, 2008). Mindfulness is the most common type of meditation that has open monitoring as a central technique. While traditional Buddhists believe that right mindfulness is one of the crucial steps towards enlightenment, a form of mindfulness-only meditation was developed in Burma as a branch of Theravada Buddhism and gained popularity in the West since the 1950s (Braun, 2013). This inspired the application of mindfulness in clinical settings in the West from the 1970s when Jon Kabat-Zinn developed a secular format of mindfulness meditation that has Buddhist roots; Mindfulness-Based Stress Reduction (MBSR). MBSR was developed with aim of helping patients with chronic pain, but it was later applied to different clinical and non-clinical populations (Grossman, Niemann, Schmidt & Walach, 2004). MBSR is the most widespread mind-body course that is delivered today and it consists of weekly two-hour group sessions over eight weeks, and one day-long session where all mindfulness techniques are extensively practiced (Kabat-Zinn, 1990). The techniques taught typically include mindfulness of breath, walking meditation (practice of awareness of sensations of walking and external environment), body scan (a meditation based on noticing physical sensations in the body and using visualisation to cultivate greater awareness of the body), and yoga (a slow-paced type of yoga with an emphasis on breathing techniques). The typical approach in mindfulness interventions such as MBSR is to first use focused attention on the breath, which serves as an anchor to help remain in the present. Eventually, the central practice becomes monitoring of whatever occurs in the present experience, without focusing on any specific object (Kabat-Zinn, 1994).

Categorising all types of meditation into focused attention or open monitoring helps to increase comparability among studies, but some authors consider that a third category should be added — loving-kindness meditation (Lippelt, Commel & Colzato, 2014) — while others argue that it is a combination of focused attention and open monitoring (Vago & Silversweig, 2012). Loving-kindness meditation stems from a Buddhist tradition and is based on cultivating compassion towards oneself and others (Ricard, 2003). It is practiced by repeating phrases (e.g. ‘May you/I be well, may you/I be safe, may you/I be free from suffering’) that are either aimed to oneself, a good friend, a neutral person, or a difficult person, and eventually this compassion practice is to be extended to all living beings (Ricard, 2003). Therefore, unlike other common meditation types that have a focus on the breath or the mantra, the focus of loving-kindness are specific intentions of good will. The aim of loving-kindness meditation is to shift a self-centred attitude towards a benevolent attitude and to realise connectedness between the self and others (Gethin, 1998). Until additional evidence is presented for more than two categories, the results from studies investigating focused attention methods should not be generalised to open monitoring and vice versa.

There are also distinct patterns in brain activity associated with focused attention and open monitoring (Fox et al., 2016), which supports the idea that they are categorically different practices that may have different outcomes. However, it is important to keep in mind that even MBSR, which is standardised, might have different effects if delivered through a weekly class (as is the usual approach), or if is self-taught through a handbook or a mobile app, though there currently are no studies that compare these different media of learning MBIS. In the same manner, certified meditation teachers will often adapt standardised meditation programmes based on their personal preferences or on the characteristics of people that they are teaching, be it intentionally or unintentionally. One further problem is that it often is difficult to attribute a meditation type to one of these categories because elements of both techniques are commonly used together in meditation programmes such as MBSR. MBSR is multifaceted: it consists of several types of meditation as well as including elements of gentle yoga postures that are referred to as mindful or meditative movement. Therefore, the line between meditation and yoga can be blurred as they often go hand-in-hand. In the following section, I will describe yoga and other movement-based MBIs.

4. Yoga and other MBIs

Modern yoga, which has physical postures as its central component, emerged in Mysore, India, in the 1930s and its founder was Tirumalai Krishnamacharya (Singleton, 2010).

Krishnamacharya was highly educated in traditional yoga (*Pātañjalayogaśāstra*, see page 3), but he wanted to make yoga more appealing to the masses so he brought influences from bodybuilding and gymnastics, and developed a rigorous series of physical postures that werestripped of yoga philosophy (Singleton, 2010; Goldberg, 2016). Krishnamacharya's influence on modern yoga continues to this day through his students and their legacies. Most notably, Krishnamacharya's student Pattabhi Jois founded Ashtanga Vinyasa yoga, which is based on a series of physical postures that are performed in a set order and synchronised with the breath (Singleton, 2010). This vigorous type of yoga has come to prominence in the West since the late 1970s and it is still one of the most popular types of yoga in the world today, just as its different spin-off forms (such as Power Yoga) that have existed since the 1990s. Another well-known student of Krishnamacharya was his brother-in-law B.K.S. Iyengar who founded Iyengar yoga. Unlike Ashtanga, Iyengar yoga uses an approach that emphasises correct alignment above everything else and it is less vigorous (Iyengar, 2007). The majority of types of yoga available today are at least partially based on Krishnamacharya's legacy.

Apart from meditation and yoga, Tai Chi and Qigong are MBIs that have been well-researched and gained popularity in the West. They both originate from traditional Chinese medicine and are based on coordinating movements, breath, and mental focus (Jahnke, 2002). The main difference is that Tai Chi is a form of martial art that consists of a series of precise movements that flow from one to the next and can be used as self-defence, while Qigong is a much simpler and less physically demanding practice accessibly to anyone that is primarily focused on promoting health (Jahnke, 2002). As is the case with yoga or meditation, there are many subtypes of Tai Chi and Qigong that have their own unique characteristics, as well as many shared similarities. As we have seen so far, there are many types of MBIs; some are movement-based, while others are practiced in stillness. I will now review the evidence about their benefits.

5. Benefits of MBIs

The empirical study of MBIs began in late 1950s with studies that aimed to identify physiological outcomes of meditation, such as blood pressure or brain activity in expert meditators (e.g., Bagchi & Wegner, 1957). Parallel with the growing popularity of TM in the West, more studies of meditation started appearing in the 1960s and 1970s (Oman, 2020). Although the popularity of TM decreased after the late 1970s due to false promises of developing levitation abilities, by the 1990s there already had been, published hundreds of studies of transcendental meditation were published that included a wide range of outcomes related to mental and physical health. However, scientific studies of transcendental meditation were mainly conducted by researchers at Maharishi University of Management in Iowa, USA, which was founded by Maharishi Mahesh Yogi and later on received a lot of criticism related to bias and study quality. These studies of TM paved the way for a new wave of studies of other forms of meditation, namely mindfulness. Although mindfulness had been studied empirically from the 1970s (e.g., Deatherage, 1975), an explosion of research and popular interest occurred later in the mid-1990s, and since then there has been a consistent stream of publications on mindfulness (Oman, 2020). At about the same time, studies about modern yoga (i.e., yoga primarily based on physical postures) started appearing (e.g., Raju et al., 1997).

In general, the literature suggests that MBIs are beneficial for various aspects of mental and physical health, but the scientific rigor of many of these studies is questionable. For conclusions about the overall effectiveness of MBIs it is better to examine meta-analyses as they provide average effect sizes and often control for study quality. Meta-analyses have generally found medium effect sizes for MBIs. For instance, a meta-analysis of 20 good quality MBSR studies that tested the effects on physical and mental well-being found a similar medium effect size for controlled and non-controlled studies, and in clinical and non-clinical populations (Grossman, Niemann, Schmidt & Walach, 2004). On the other hand, a meta-analysis that included 22 studies of different mindfulness-based interventions (including MBSR) and did not assess quality of the studies found significantly larger effects sizes (large effect sizes for anxiety and for depression across different clinical and non-clinical populations (Baer, 2003). Finally, another meta-analysis of eight MBSR randomised controlled trials looked specifically at populations with chronic medical illnesses and reported effect sizes for specific mental health symptomatology (Bohlmeijer, Prenger, Tall & Cuijpers, 2010), not just general well-being. Small effect sizes were found for depression and psychological distress, respectively, and a medium effect size was found for anxiety symptoms. However, when low quality studies were excluded, the effects size for anxiety became small. Even though the effect sizes are between small and medium, they are comparable to that of other recognised psychological treatments such as psychotherapy (Cuijpers, van Straten, Bohlmeijer, Hollon & Andersson, 2010). So, these findings support the application of mindfulness interventions as cost-effective programmes that can lead to positive effects on various health conditions.

Similar conclusions were reached in meta-analyses of yoga, which has received less scientific attention than meditation. For example, a meta-analysis of yoga in patients with depressive symptoms found a medium effect size for depression, but the majority of included studies had medium to high risk of bias (Cramer, Lauche, Langhorst & Dobos, 2013). Yoga is similarly beneficial for patients with cancer; a meta-analysis found large effects sizes for distress, anxiety, and depression. Furthermore, the same study found that yoga has medium effects size on fatigue, emotional function, quality of life, and on social function, and a small effect size on well-being (Buffart et al., 2012). When it comes to yoga in older adults, a meta-analysis found a medium to high effect size for depression and for quality of life (Patel, Newstead & Ferrer, 2012). Besides yoga, Tai Chi and Qigong are other movement-based MBIs that have been well researched. Tai Chi has medium effect size on well-being, depression and anxiety and for mood in clinical and non-clinical populations (Wang et al., 2010). Similarly, a meta-analysis of Qigong in healthy adults found a high effect size on anxiety and on perceived stress (Wang et al., 2014).

In conclusion, meta-analyses of MBIs prove their effectiveness across various populations. The observed variability of effect sizes from small to large in some meta-analyses can be due to variations in delivered MBIs, targeted samples or methodology. Nevertheless, the results consistently support that MBIs can be valuable interventions for improving mental and physical health outcomes.

6. Gaps in the literature

Based on the meta-analyses described above, it is clear that studies have repeatedly shown that MBIs work as much as other recognised behavioural interventions, but there are many gaps in the research that need to be addressed. First, it is not clear how MBIs work; what happens in the mind and the body that leads to the benefits people so often report? Second, it is not known for whom do certain MBIs work best and for whom they are contraindicated. Third, studies of MBIs in some clinical samples are underrepresented, and it is unknown if similar effects of MBIs can be found across psychiatric disorders.

The first question can be answered by exploring potential mechanisms of observed positive effects of MBIs. Mechanisms provide precise and intelligible explanations that let us fully understand the observed effects and infer causality. Without identifying mechanisms that connect MBIs with the benefits that people often report after consistent practice, we cannot understand how MBIs work or what components of MBIs are more important. This is a complex problem because MBIs are often multifaceted. For instance, the most researched meditation intervention is MBSR (Kabat-Zinn & Chapman-Waldrop, 1988), which consists of various techniques such as mindful walking, mindful eating, open monitoring, breath awareness, and yoga. An explicit theory of how meditation interventions give rise to observed benefits and what facets of meditation interventions contribute the most would contribute theoretically to academics and it would enable clinicians to optimally tailor their approach to teaching meditation. So far, the attempts to understand the mechanisms underpinning the effects of MBIs have been made in different disciplines. Psychologists have focused on psychological processes that are strengthened with regular practice of mind-body techniques (Shapiro, Carlson, Astin & Freedman, 2006) and have defined which aspects of mindfulness interventions are the most important (Lindsay et al., 2018). Neuroscientists have proposed that structural and morphological changes in the brain which are observed in regular practitioners are the mechanisms by which MBIs work (Lazar et al., 2005; Hölzel et al., 2011a; Vestergaard-Poulsen et al., 2009; Fox et al., 2014). Molecular biologists have focused primarily on proteins and gene expression changes (Bower & Irwin, 2016). In recent year efforts have been made to understand how these processes interact, which requires collaboration across disciplines and formations of interdisciplinary research environments. Starting with a seminal paper in 2015 that proposed neuroanatomical correlates of specific psychological processes that bring about the observed benefits of mindfulness (Tang et al., 2015), more and more researchers are applying measures from multiple levels and investigating complex interactions between mechanisms of different types of MBIs.

However, even if we develop a precise understanding of the interactions among processes, there will always be substantial inter-individual variation in in how people respond to MBIs. Recently, scholars have started to point out that mindfulness or other types of meditation are not a panacea for all types of ailments; not everyone experiences positive effects (Van Dam et al., 2018). Null, negative effects or other unexpected effects of meditation are underreported because researchers normally do not measure them directly (Goyal et al, 2014). Meditation studies typically only report average effects, which means that individual variation in how participants are affected by meditation is masked and considered as noise. Still, dozens of case studies and observational studies reported adverse meditation effects that warranted medical attention, such as psychosis, mania or depersonalisation (Van Dam et al., 2018). A recent study of over a thousand of regular meditators found that 25.6% of participants experienced unpleasant meditation-related experiences (Schlosser et al., 2019). A qualitative study of 60 meditators from various Buddhist traditions described the whole spectrum of variability in experiences during meditation practice that range from very positive to very negative, and mapped them across seven domains: cognitive, perceptual, affective, somatic, conative, sense of self, and social (Lindahl et al., 2017). Based on these interviews, four domains of factors that may influence the outcomes of meditation emerged: participant-related factors, practice-related factors, relationship and health behaviours (Lindahl et al., 2017). Therefore, participant characteristics are likely to influence the variability in the responses to meditation, but surprisingly there is no extensive study on this topic.

Finally, as Figure 1 demonstrates, there are thousands of studies on MBIs that cover various non-clinical and clinical populations. However, there is only a handful of studies that are related to personality disorders, which are highly prevalent (65%) in vulnerable individuals, such as those found in incarcerated populations (Fazel & Danesh, 2002). The scarcity of these studies is most likely due to challenges of reaching and recruiting participants from these populations. More specifically, people with personality disorders are rarely in treatment, they can be non-cooperative and have high drop-out rates (McRae, 2013). Previous studies found positive effects of mindfulness interventions on the mental health of patients with borderline personality disorders, but there are no studies on other personality disorders or studies on MBIs other than mindfulness (Feliu-Soler et al., 2014; Soler et al., 2012; Sng & Janca, 2016). A more considerable amount of evidence is available related to the effects of MBIs on prison populations, and a general finding is that mindfulness and yoga have positive effects on mental health of prisoners (Samuelson, Carmody, KabatZinn, & Bratt, 2007; Sumter, MonkTurner, & Turner, 2009; Bowen et al 2006; Perelman et al, 2012; Suarez et al, 2014; Bilderbeck et al., 2013; Kerekes, Fielding & Apelqvist, 2017), but only a minority of studies have included a control group. Therefore, prisoners, and especially those with personality disorders, are under-researched populations in the context of MBIs. Clinical units for prisoners with personality disorders can be found across the UK and provide a unique opportunity to simultaneously tackle both. These clinical units provide prisoners with psychotherapy and pharmacotherapy, along with workshops that aim to improve their quality of life and keep them in treatment as serving a prison sentence can worsen symptoms of personality disorders (He et al, 2001; Birmingham, 2018; Armour, 2012), and commonly comorbid psychiatric disorders (Hayward & Moran, 2008). MBIs have the potential to aid in keeping prisoners with personality disorders in treatment and in creating a sense of community because they are practiced in a group setting. Any intervention that can maintain the patients in treatment is of great importance because treatment can decrease morbidity and mortality associated with personality disorders (Mullen, 1999). As there are still conflicting results about what treatment works best for patients with personality disorders (Bateman, Gunderson & Mulder, 2015), it is crucial to build an evidence base of all interventions with regard to this neglected population.

In summary, the mechanisms of MBIs, the effects of MBIs on prisoners with personality disorders, and participant characteristics that influence the response to meditation, are three major gaps in meditation research which will be the focus of this thesis.

7. Aims and Objectives

The specific aims of this thesis were to:

a) To systematically review all published studies of MBIs that used gene expression as an outcome measure and to see if there is a common gene expression pattern across different MBIs

It has long been thought that genes are static and that they control our behaviour, but findings over the past three decades have disputed this view. Not only that our genes can control our behaviour, but it also happens vice versa; behaviour can control the activity of our genes (Cole, 2009). Genes represent the potential for behaviour that can be manifested only if the gene is active (i.e., expressed), otherwise it has no effect on health or behaviour (Cole, 2009). Therefore, gene expression can be used to explain how genes and environments interact to shape who we are, how we behave and our health. In the context of MBIs, it remains unknown which MBIs elicit changes in gene expression of which particular genes. Chapter 2 is related to this aim; it is a systematic review of 18 studies that measured gene expression related to MBIs and it included various types of research designs and populations.

b) To conduct a preliminary randomised controlled trial of mindfulness and yoga with prisoners who have personality disorders with a focus on neural, genomic, psychological and cognitive effects

Traditionally, MBIs have been examined using methods from psychology, namely by measuring outcomes with questionnaires. This approach that is based on a single discipline is pragmatic, but it may obscure the full spectrum of the effects that MBIs can have on our phenotype. An interdisciplinary approach that combines methods from several disciplines has the potential to explain how the self-reported benefits emerge and to understand the relationship between the body and the mind. The goal of an interdisciplinary research is to provide a comprehensive picture of biological, neural, behavioural and self-report components and mechanisms of MBIs. The information gained using this framework may help inform the application of MBIs in patients with personality disorders. Chapter 3 is related to this aim and it describes the rationale, methods and results of the randomised controlled trial of mindfulness and yoga in a clinical unit for prisoners with personality disorder.

c) To synthesise findings from studies on individual differences in response to different types of meditation in order to get insight into variables that could be used to predict the response to meditation

The central emphasis in MBI research has been placed on testing its average effectiveness, which has led to the perception that MBIs are a panacea that works for everyone. However, two people that enrol in the same MBI may have completely polar experiences, but it is difficult to pinpoint what specific aspects of the person contributed to variability in responses. In order to create specific clinical guidelines for the use of meditation, a better understanding of the aspects of an individual that lead to individual differences in outcomes of meditation is warranted. The challenge is to how to integrate findings from previous studies, how to generate hypotheses, and which variables to examine first. This is addressed in chapters 4 and 5, though the scope is limited only to meditation interventions. Chapter 4 is a narrative review related to previous studies that examined the influence of at least one baseline participant characteristic on the response to meditation. The findings are summarised in four sections: individual differences due to psychological variables, individual differences due to biological variables, individual differences due to illness severity, and individual differences due to demographic variables. Chapter 5 is a comprehensive meta-analysis of all studies that examined the relationship between participant characteristics and it quantifies the importance of each category of participant characteristics.

The thesis ends with chapter 6 that draws together all results from the previous chapters and discusses how these contribute to the current literature, assess limitations of the studies and presents recommendations for future research.

CHAPTER 2

THE MOLECULAR SIGNATURE OF MIND-BODY INTERVENTIONS

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Abstract

There is considerable evidence for the effectiveness of mind-body interventions (MBIs) in improving mental and physical health, but the molecular mechanisms of these benefits remain poorly understood. One hypothesis is that MBIs reverse expression of genes involved in inflammatory reactions that are induced by stress. This systematic review was conducted to examine changes in gene expression that occur after MBIs and to explore how these molecular changes are related to health. We searched PubMed throughout September 2016 to look for studies that have used gene expression analysis in MBIs (i.e., mindfulness, yoga, Tai Chi, Qigong, relaxation response, and breath regulation). Due to the limited quantity of studies, we included both clinical and non-clinical samples with any type of research design. Eighteen relevant studies were retrieved and analysed. Overall, the studies indicate that these practices are associated with a downregulation of nuclear factor kappa B pathway; this is the opposite of the effects of chronic stress on gene expression and suggests that MBI practices may lead to a reduced risk of inflammation-related diseases. However, it is unclear how the effects of MBIs compare to other healthy interventions such as exercise or nutrition due to the small number of available studies. More research is required to be able to understand the effects of MBIs at the molecular level.

1. Introduction

In the past two decades, mind-body interventions (MBIs) have been gaining empirical support and recognition by mental health professionals. While some MBIs, such as yoga, Tai Chi and Qigong, have a strong physical component, others like meditation and mindfulness, breath regulation techniques, and the relaxation response are mainly sedentary. Despite the variability in these techniques, they all seem to produce various psychological benefits on healthy and clinical populations, such as the reduction of perceived stress (e.g., Chiesa & Serretti, 2009), the alleviation of depression (e.g., Piet & Hougaard, 2011), decreases in anxiety (e.g., Strauss, Cavangh, Oliver, & Pettman, 2011), or to help in coping with a chronic medical disease (e.g., Bohlmeijer, Prenger, Taal, & Cuijpers, 2010). However, it is less clear what are the mechanisms underpinning the self-reported benefits of MBIs. Neuroimaging studies suggest that MBIs increase grey matter in the brain regions related to emotion regulation, learning, memory, self-referential processes and perspective taking (Lazar et al., 2005; Hölzel et al., 2011b; Vestergaard-Poulsen et al., 2009). However, a recent meta-analysis on structural and morphological brain changes associated with one type of MBI (meditation) casts some doubt on the generalisation of such results, as different techniques and length of practice are associated with different neural patterns (Fox et al., 2014).

The search for potential mechanisms of MBIs should not stop at the neural level. The development of gene expression analysis techniques in recent year makes this one important tool for psychologists to gain a deeper understanding of biological mechanisms that underpin, or interact with, psychological variables. Over the past decade studies that implement gene expression analysis in MBIs research have begun to appear. In addition to being an objective measure of evaluating and comparing the effectiveness of MBIs, the analysis of gene expression changes has considerably theoretical value, as it reveals the underlying mechanisms of the psychological and physical effects of MBIs.

In this systematic review, we will explore (1) if MBIs can affect physical health by causing observable molecular changes in the form of differential gene expression and (2) what are the molecular changes underpinning psychological benefits in MBIs. By implementing a biological approach to the study of MBIs, there is an opportunity to fill a crucial gap concerning the underlying mechanisms that give rise to their reported beneficial effects. We have included a range of MBIs in our analysis, such as mindfulness and other forms of meditation, yoga, relaxation response, Tai Chi, and Qigong, all interventions for which there is evidence suggesting similar beneficial effects on mental and physical health (Bower & Irwin, 2016).

Below we start by outlining the principles of gene expression, its detection and analyses, and how they have been applied to MBIs; then we move into a systematic review of the evidence for their effects on gene expression, and what changes in gene expression underpin the psychological benefits of MBIs. Finally, we will discuss the implications of the reviewed studies, their limitations, and offer guidance for future studies.

1.1. The principles of gene expression

Each cell contains the same set of genes that we inherited from our parents, but the activity of genes varies both within the same cell types, depending on cell cycle and chemical signals from other cells, as across cell types. A gene is expressed or active when it produces protein, otherwise it does not have an effect on the observable characteristics of the organism (i.e., the phenotype). This means that simply possessing the genes we have inherited does not necessarily determine our biological and behavioural characteristics. Some genes are very responsive and change activity rapidly while others remain dormant for the entire life cycle of the cell.

The first stage of protein production is called *transcription*, and it is regulated by molecules called *transcription factors* that bind to gene promoters. Promoters are DNA sequences that lie at the beginning of a gene and increase or decrease the rate of its transcription (i.e., upregulate or downregulate a gene, respectively). Transcription refers to the copying of a part of DNA (i.e., a gene) into a single stranded chain of nucleic acids, also known as RNA. Parts of RNA that do not code for amino acids are spliced out of the RNA and what remains is a messenger RNA (mRNA) that then travels to ribosomes. Ribosomes are cell particles that create chains of amino acids (i.e., proteins) according to the specifications provided by the mRNA, which is the final stage of protein production called *translation*.

1.2. Methods of gene expression detection

Gene expression detection is based on measuring levels of mRNA and converting mRNA back to DNA to identify which genes it corresponds to. The first step in gene expression analysis is obtaining samples from participants and then isolating the cell types to be studied. Gene expression analysis is most commonly done on peripheral blood mononuclear cells (PBMCs) that consist of lymphocytes (70-90%) and monocytes (10-30%), which are types of white blood cells (i.e., leukocytes, Figure 1). Density gradient centrifugation is a procedure that separates blood cells based on their density. Cells that are denser than 1,077 g/ml, which are red blood cells and other types of white blood cells (basophils, neutrophils, eosinophils), remain at the bottom of the tube, allowing PMBCs to be easily collected from the top. Individual differences in the prevalence of leukocyte subtypes within PBMC can be controlled for by separately analysing monocytes and all leukocyte subtypes – this is called Transcript Origin Analysis (TOA).

The central limitation of measuring gene expression via mRNA is that it is based on the assumption that if a gene is transcribed, then it will get translated into protein. It is true that mRNA levels and proteins production are highly correlated, but there are several other mechanisms of protein regulation. For example, non-coding parts of RNA such as micro RNA (miRNA) can induce post-transcriptional changes in gene expression (Iorio et al., 2005). Current technology does not allow us to measure all proteins directly – we can only detect about 0.2% in total of one million proteins (Mirza & Olivier, 2008). However, thousands of mRNAs can be measured at once or even the activity of the entire genome.

Technologies that are currently used to detect gene expression include quantitative real-time polymerase chain reaction (qPCR), DNA microarrays and gene expression analysis with RNA sequencing (RNA-Seq). Each of these technologies comes with pros and cons. For instance, qPCR cannot detect the expression of the whole genome simultaneously, thus it is used when there is an *a priori* defined set of genes of interest. On the other hand, DNA microarrays provide data on the expression of almost the entire genome, but compromise sensitivity and accuracy of the detected gene expression changes. RNA-Seq is a next-generation sequencing technique that overcomes problems of standard microarrays and detects even more genes (Wang et al., 2014), but it is more expensive and the data analysis is more complex. In the context of research on MBIs, DNA microarrays are the most commonly used to identify the genes and often followed with qPCR to validate the genes that have changed the most.

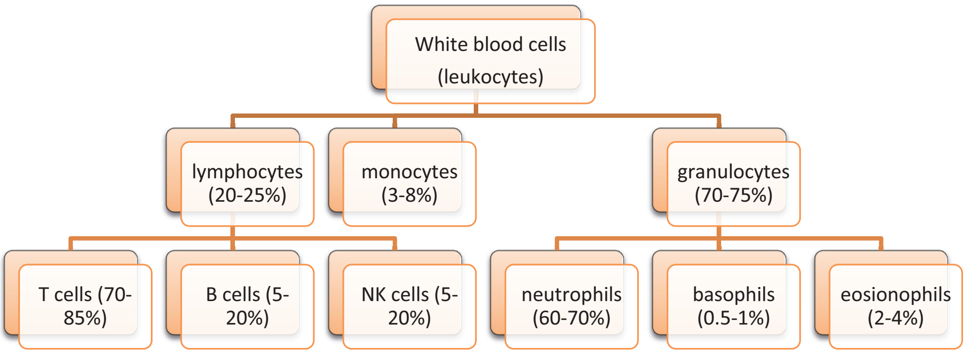

Figure 1. *Types of white blood cells*

1.3. Bioinformatics analysis in MBIs

Gene expression detection techniques produce an enormous amount of quantitative data – a long list of genes. But because genes are most often team players – they work together as a network to produce an observable trait or a measurable biological function – a long list of genes is hard to contextualise and interpret. To make matters more complicated, some genes regulate the activity of other genes. One way to deal with this is to start with statistical analysis, followed by bioinformatics analyses; this is used to identify which of the genes are in the same pathway (i.e., network) and, therefore, have the same function.

The most common bioinformatics analysis in MBIs research is the Transcription Element Listening System (TELiS). This analysis will assess which transcription factor is regulating gene expression amid a set of genes. It does so by scanning the promoters for transcription factor binding motifs that are overrepresented, in relation to their usual prevalence across the genome (Cole et al., 2005). In the context of research on MBIs, the most researched transcription factors are those that have been associated with stress and inflammation. The key transcription factor is the nuclear factor kappa B (NF-kB), which is produced when stress activates the sympathetic nervous system (Bierhaus et al., 2003). NF-kB translates stress into inflammation by changing the expression of genes which code for inflammatory cytokines (Liang, Zhou, & Shen, 2004). Lower activity of NF-kB suggests reduced inflammation.

1.4. Understanding Stress and Conserved Transcriptional Response to Adversity

Stress can be regarded as a bodily response to events that are perceived as a threat or a challenge. This response may precipitate a health risk when stress is severe or it occurs over a long period of time without adequate coping mechanisms. It has been found that exposure to severe stressors can have a profound influence on the body and can lead to detrimental changes in its biology, such as reduced grey matter in several brain regions (Gianaros et al., 2007). The effects of stress go beyond the brain and can be found in our genes in a form of a Conserved Transcriptional Response to Adversity (CTRA; Cole, 2014). CTRA is a common molecular pattern that has been found in people exposed to different types of adversities, such bereavement (O'Connor et al., 2014), cancer diagnosis (Cohen et al., 2012), trauma (O'Donovan et al., 2011), and low socioeconomic status (Miller et al., 2009). The primary characteristic of CTRA is the upregulation of proinflammatory genes leading to major inflammation at the cellular level (Slavich & Irwin, 2014). While acute inflammation is a short-lived adaptive response of our body, which increases the activity of the immune system to fight injury or infections, chronic inflammation is maladaptive because it persists when there is no actual threat to the body. Chronic inflammation is associated with increased risk for some types of cancer, neurodegenerative diseases, asthma, arthritis, cardiovascular diseases and psychiatric disorders (e.g., depression and posttraumatic stress disorder; Mantovani, Allavena, Sica, &

Balkwill, 2008; Slavich, 2015). The secondary characteristic of CTRA is the downregulation of antiviral and antibody-related genes, which is associated with susceptibility to viral infections, such as herpes simplex viruses (Jenkins & Baurn, 1995), HIV-1 (Cole et al., 1996), Epstein-Barr virus (Yang et al., 2010), cytomegalovirus (Prosch et al., 2000) and the Kaposi's sarcoma (Chang et al., 2005). Given this, the CTRA is considered to be a molecular signature of chronic stress.

To understand the impact of environmental factors on the body's immune system through CTRA, we first need to unpack the underlying molecular mechanisms. Consider the path linking a stressful event to an observable psychobiological change, such as the onset of depression. Slavich & Irwin (2014) suggest that the environmental stressor, which might be a physical or social threat, will first activate brain regions associated with pain; then, it will project into lower regions that modulate inflammation via the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). In the first stage of modulation, the SNS initiates the production of the neuromodulators epinephrine and norephinephrine. These will, in turn, promote inflammation by activating the production of molecules called transcription factors. These transcription factors then bind to and activate pro-inflammatory genes that translate them into proteins, called cytokines. These cytokine proteins will travel back to the brain and initiate symptoms of depression (e.g., low mood, fatigue, anhedonia).

Cytokines are a broad category of small proteins that can be regarded as markers of inflammation in the context of stress responses (Irwin & Cole, 2011). Cytokine secreted from one cell can act on other cells and influence their function, which is how they regulate the immune and neural system. According to their function, they can be divided in pro-inflammatory and anti-inflammatory cytokines, which means they either inhibit or initiate inflammation (see Figure 2). Interestingly, one type of cytokine called IL-6 has a dual role in inflammation, depending on the cell type where it is secreted from – it is anti-inflammatory when secreted from muscle cells and pro-inflammatory when secreted from white blood cells (Pal, Febbraio & Whitham, 2014).

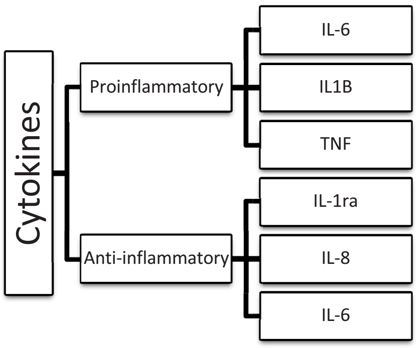

Figure 2. Pro-inflammatory and anti-inflammatory cytokines relevant for mind-body interventions

In the second stage of modulation, the HPA initiates the production of metabolic agents (glucocorticoids) and the neurotransmitter acetylcholine that, in normal conditions, suppress inflammation. In the case of long-term stress, the body adapts to their continuous secretion and becomes less sensitive to their anti-inflammatory effects. These processes lead to CTRA and, if this condition is maintained for years, there is a high risk of inflammation related diseases, infection, accelerated biological aging, and early mortality. It is likely that CTRA played an important role in our hunter-gatherer prehistory, as it linked fight-or-flight response with pro-inflammatory gene expression that provided protection when there was a higher risk of bacterial infections from wounds (Slavich & Irwin, 2014). This immune response might have been adaptive back then, but, in today's modern societies where stress is primarily the result of psychological threats, this response is maladaptive as it promotes inflammation-related diseases, both psychiatric and medical (Cole, 2013).

2. Methods

2.1. Criteria for considering studies for this review

We will now review studies on Mind Body Interventions (mindfulness, yoga, relaxation response, Tai Chi, Qigong) that include gene expression analysis as an outcome measure, in order to assess the evidence for their effects on gene expression, and what changes in gene expression underpin the psychological benefits of MBIs. Studies were identified by searching PubMed through September 2016 using the following combination of keywords: *(meditation OR mindfulness OR relaxation response OR yoga OR tai chi OR Qigong) and (gene expression OR microarray OR transcriptome)*. A total of 716 articles were returned and their titles and abstracts were screened (see Figure 3). We excluded studies that did not meet the following eligibility criteria:

1. The population studied should only contain adults.
2. Both clinical and non-clinical samples were allowed (for example, students, cancer patients and caregivers) and studies with all sample sizes were included.
3. Studies with experienced practitioners or non-experienced practitioners were allowed, making both cross-sectional and longitudinal studies eligible.
4. Gene expression changes had to be one of the outcome variables (any number of analysed genes, cell type and any gene expression technology were eligible).
5. The independent variables had to be any type of MBI.
6. Articles should be written in English.
7. Only research papers were included. Review papers, meta-analyses, commentaries, and conference proceedings were excluded.

The screening narrowed the search results to 18 articles (Figure 3). The references of included articles were searched to identify other relevant articles, but no additional studies were found. Therefore, a total of 18 studies with 846 participants were included in this review (Table 1). Three studies had cross-sectional designs: they compared experienced practitioners to non-practitioners. Eight studies were longitudinal: they monitored changes over time that happened as one learns an MBI. Two studies measured immediate effects of a meditation session in experts, and the three remaining studies have elements of both cross-sectional and longitudinal designs. In the next section, we will describe the rationale for each of the included studies, along with the procedures employed and their results. We divided the studies across three sections, based on the research design, and taking into account their chronological order to highlight how complexity increases as gene expression technologies advance.

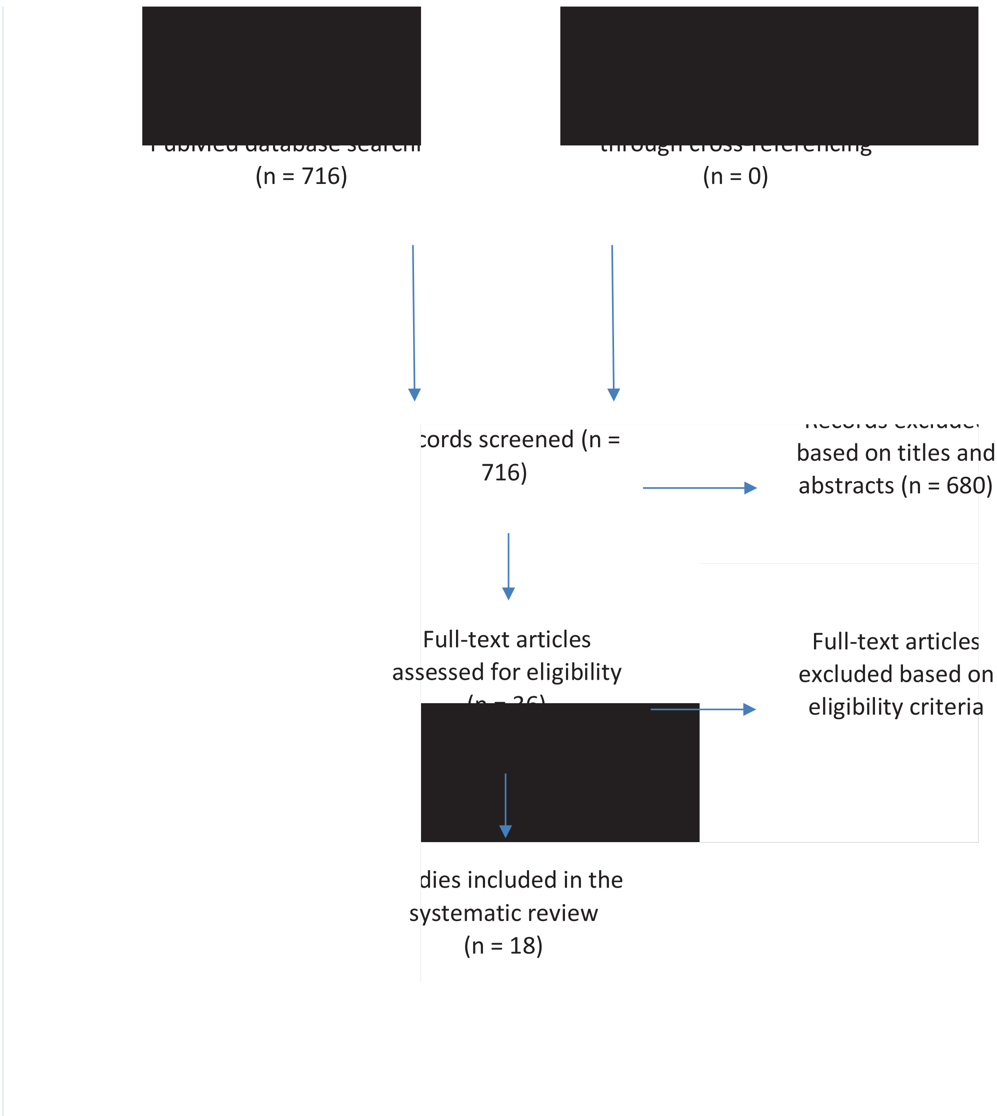

Figure 3. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart: The process of selecting relevant studies

2.2. Summary of studies on MBIs using gene expression analysis

In Table 1, we summarise the biological and psychological outcomes for each study, including which genes were upregulated or downregulated, as well as the type of MBI, control group and gene expression technology used. Below, we briefly describe the rationale and results for each study (please see Table 1 for further details).

a) Cross-sectional studies

Genomic profiling of neutrophil transcripts in Asian Qigong practitioners: A pilot study in gene regulation by mind-body interaction

The very first study of mind-body therapies that included gene expression compared gene profiles of six long-term Falun Gong Qigong practitioners and six healthy controls (Li et al., 2005). Falun Gong is a form of Qigong that requires an intensive daily practice of one to two hours, which includes reading spiritual Qigong books and a light physical activity in the form of meditative movement. Qigong practitioners had been using this technique from one to five years, every day from one to two hours, while controls had been physically inactive for at least 1 year and did not practice any mind-body technique. In this study, gene expression analysis was carried out from neutrophils, which are the most prevalent type of white blood cells and are crucial in fighting infection (see also Figure 1). Using a microarray of 12,000 genes, they found that Qigong practitioners had 132 downregulated and 118 upregulated genes in comparison with controls. Some of the differentially expressed genes have common functions, thus the results suggest that Qigong enhances immunity, downregulates cellular metabolism and delays cell death.

Gene expression profiling in practitioners of Sudarshan Kriya

Sharma and colleagues (2008) explored the effects of Sudarshan Kriya (SK) by comparing 42 long-term practitioners with controls who do not practice any MBI. SK is commonly practiced for one hour per day and it consists of several breathing techniques, some of which are paired with movement. Controls were not only matched for age and sex, but also for socioeconomic status, body mass index, diet, smoking and alcohol consumption. Their hypothesis was that regular SK practice improves stress regulation, which should be reflected in gene expression. To test this, white blood cells were obtained from participants, but only a relatively small number of genes was analysed. The nine genes of interest were related to oxidative stress, DNA damage, cell cycle control, aging and cell death. Although psychological stress was not measured, based on the gene expression results researchers suggested that SK attenuates the effects of stress on cells due to an increase in expression of one gene, although four stress-related genes remained unchanged. Additionally, they concluded that SK enhances the immune system because it upregulates genes that inhibit cell death.

To study the effect of the sequence of seven pranayama by Swami Ramdev on gene expression in leukaemia patients and rapid interpretation of gene expression

Kumar & Balkrishna (2009) conducted a study on the effects of seven breathing patterns developed by a popular Indian yoga teacher, Swami Ramdev. The sample consisted of eight patients with chronic lymphocytic leukaemia, some of whom practiced breathing techniques, while others served as control. The exact number of participants per group is not reported, neither is the practice frequency. Surprisingly, the results showed that 4,428 genes (out of 28,000 analysed) were upregulated up to two-fold in leukaemia patients who practiced breathing techniques. However, the published report lacks further details about used methods and procedures and it was not externally peer reviewed. Of 4,428 differentially expressed genes, only a set of upregulated stress-related genes is reported, along with upregulated pair of genes that delays cell death, which suggests improved immune regulation.

b) Longitudinal designs

Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomised controlled trial

Creswell and colleagues (2012) attempted to reduce loneliness in older adults as this is one of the leading risk factors for morbidity and mortality. Forty healthy older adults (age 55-85) were randomly assigned either to an 8-week a MBSR course or to a wait-list control group. The MBSR course is a standardised program that consists of eight weekly 2-hour meetings and one day-long retreat. Additionally, participants are expected to practice mindfulness every day at home for 30 minutes during the 8-week period. MBSR cannot be delivered effectively in large groups, so they formed three groups, each with a different teacher. The researchers tested if increased inflammation is a mechanism by which loneliness promotes disease in older adults. Inflammation was measured through changes in transcriptome and in protein markers of inflammation (CRP and IL-6). Blood samples were taken at baseline and after completion of MBSR. There also were self-report measures of loneliness and mindfulness. MBSR class attendances and minutes of daily home practice were measured as control variables.

Genome-wide transcriptional profiling was done from peripheral blood mononuclear cells (PMBCs) controlling for sex, age, ethnicity, body mass index (BMI), as well as the contribution of sleep quality and exercise. Effect size cut-off of 25% was used in statistical analysis, which was followed with bioinformatics analysis of differentially expressed genes to see how many of them are targeted with NF-kB transcription factors (TELiS transcription factor search). They were interested in NF-kB because previous studies found that genes targeted with this transcription factor are more expressed in people who are lonely (Cole et al., 2007), which promotes inflammation.

At baseline, older adults who reported more loneliness showed higher expression of proinflammatory genes targeted with NF-kB transcription factor. After MBSR participants reported reduced loneliness and gene analysis showed a reversal of proinflammatory gene expression pattern. Further analysis showed that genes that changed expression originated mostly from monocytes and B lymphocytes. Regarding protein biomarkers of inflammation, there were no significant changes in CRP and IL-6 after MBSR.

Yogic meditation reverses NF-κB and IRF-related transcriptome dynamics in leukocytes of family dementia caregivers in a randomized controlled trial

Black and colleagues (2013) did a study on a sample of people who were caring for a frail or demented family member. Caregivers tend to have worse mental and physical health than matched controls, probably due to stress-induced upregulation of inflammation-related genes and downregulation of innate antiviral genes. Previous studies found that interventions aimed at stress reduction improve immune functioning among caregivers, so Black and colleagues (2013) wanted to explore molecular mechanisms by which inflammation is reduced. Twenty-three caregivers did a 12-minute Kirtan Kriya Meditation (KKM) practice guided by an audio recording every day for 8 weeks. The practice starts with 1 minute of mind and body awareness followed by chanting “birth, life, death, rebirth” in Sanskrit with accompanying hand gestures, and it ends with breathing deeply and visualising light. The effects of KKM were actively controlled; 20 caregivers were listening to relaxing music with eyes closed for 12 minutes, every day for 8 weeks. The levels of depression and mental health were measured with questionnaires before and after the intervention and blood samples were taken to obtain PBMCs for transcriptional profiling. Gender, illness burden and BMI were controlled for.

There was a significantly greater reduction of depressive symptoms and an improvement in mental health in the meditation group. Further, 49 genes were downregulated and 19 upregulated in the KKM group in relation to the relaxation group. These differentially expressed genes were further analysed with TELiS, which confirmed the hypothesis that there is a decrease in proinflammatory gene expression (related to NF-kB) and an increase in antiviral gene expression (IRF-1). This suggests that KKM improved the immune system in terms of inflammation reduction and creating better defence against viruses. Transcript origin analysis found that most of the observed gene expression changes stem from B lymphocytes and plasmacytoid dendritic cells.

Tai Chi, Cellular Inflammation, and Transcriptome Dynamics in Breast Cancer Survivors with Insomnia: A Randomised Controlled Trial

Irwin and colleagues (2014) explored the effects of Tai Chi, a Chinese practice that combines moderate exercise, deep breathing and meditation, on inflammation and sleep in breast cancer survivors in comparison with cognitive behavioural therapy for insomnia (CBT-I). Both breast cancer and sleep deprivation are associated with inflammation, thus this sample had high levels of inflammation at baseline. The study adopted a multi-level approach to measuring effects of Tai Chi on inflammation that included systemic (circulating levels of CRP), cellular (toll-like receptor (TLR)-4-activated production of proinflammatory cytokines IL-6 and TNF) and genome-wide gene expression followed with bioinformatics analyses. Both Tai Chi and CBT groups had 40 participants who attended 2-hour meetings once a week for three months. BMI and physical activity changes during interventions were controlled for, as they usually are associated with inflammation.

While CRP did not change after either of the interventions, IL-6 was marginally reduced and TNF was significantly reduced after Tai Chi, indicating that it can reduce cellular inflammatory responses. Similarly, gene expression analysis found a 9% reduction in expression of 19 proinflammatory genes and a 3.3% increase in expression of 34 genes involved in the production of proteins that regulate anti-viral response and tumour activity in the Tai Chi group relative to CBT-I. In total, 68 genes were downregulated and 19 upregulated after Tai Chi. The downregulated genes are involved in the generation of white blood cells and inflammation. Similar to previous studies, TELiS bioinformatics analysis found a significant reduction of activity of proinflammatory transcription factor NF-kB.

Yoga reduces inflammatory signalling in fatigued breast cancer survivors: A randomised controlled trial

Bower et al. (2014a) explored the effects of three months of Iyengar yoga on inflammatory processes in breast cancer survivors with fatigue. There were 16 people in the yoga group and 15 in the health education control group. Inflammation is associated with cancer and previous studies have found that breast cancer survivors with fatigue have higher levels of inflammation than non-fatigued breast cancer survivors (Bower et al., 2011). The hypothesis was that Iyengar yoga (a form of Hatha yoga with emphasis on precise alignment and breath control in each posture) would reduce inflammation-related gene expression, as well as decrease levels of circulating markers of inflammation.

Instead of measuring cytokines directly, Bower and colleagues chose downstream markers of proinflammatory cytokine activity, which are easier to detect as they are produced in a greater amount. The downstream markers are also considered a more accurate and stable measure of inflammation than the cytokines that produces them. Downstream markers were included: sTNF-RII (a marker of TNF activity), IL-1ra and CRP (markers of IL activity). These markers were measured from blood, while cortisol was measured from saliva (samples collected by participants themselves) immediately after waking, 30 minutes and 8 hours after waking, and before bedtime.

Genome-wide transcriptional profiling identified 282 genes that were upregulated and 153 downregulated genes after three months of yoga. A 15% gene expression change was considered statistically significant, unlike other studies that set 20% as a cut-off point. The majority of downregulated genes were related to type I interferon responses (i.e. cytokines that are released when a virus infects a cell), which has previously been associated with fatigue in cancer patients. Similarly, behavioural measures of fatigue were significantly reduced after months of yoga and remained reduced at a 3-month follow-up.

TELiS showed that yoga reduced the activity of NF-kB, which is suggestive of lower inflammation, as this is a key regulator of proinflammatory gene expression. CREB is another transcription factor whose activity was reduced with yoga, suggesting a downregulation of the sympathetic nervous system. Lastly, TELiS found that yoga increased the activity of anti-inflammatory glucocorticoid receptor activity, which indicates a change in HPA axis in terms of responding better to cortisol and stopping the stress response more quickly. However, such change in the HPA axis should lead to reduced levels of cortisol, which was not verified with the cortisol analysis from saliva. Regarding downstream markers of inflammation, sTNF-RII increased in the control group, but remained at the same level in the yoga group. There were no significant changes for IL-1ra and CRP.

Mindfulness meditation for younger breast cancer survivors: A randomised controlled trial

Bower and colleagues (2014b) conducted another study, this time to assess cost-effectiveness of mindfulness intervention for women who had been diagnosed with early stage breast cancer (from stage 0 to stage 3) before the age of 50 and had finished treatment from 3 months to 10 years ago. Mindful Awareness Practices (MAP) is a program similar to MBSR, but tailored for cancer survivors. It consists of 6 weekly 2-hour group meetings and daily practice increasing from 5 to 20 minutes. Thirty-nine participants were assigned to MAP and 32 were assigned to a wait-list. Unlike previous studies, Bower and colleagues used several psychological measures (stress and depression as primary outcomes; positive affect, intrusive thoughts, fear of recurrence, peace and meaning, and sleep quality as secondary outcomes) and measures of physical symptoms (fatigue, pain and hot flashes). They examined gene expression changes in the whole genome and measured proteins related to increased inflammation (IL-6, CRP) and one protein related to cancer – soluble tumour necrosis factor receptor type 2 (sTNF-RII). Marital status, radiation treatment, smoking and depressive symptoms differed between groups at baseline and were included as covariates in the data analysis. Additional covariates were minutes of meditation practice, time since diagnosis, chemotherapy and endocrine therapy.

MAP significantly reduced stress, fatigue, sleep disturbance, hot flashes and marginally reduced depressive symptoms. Conversely, it significantly increased positive affect and peace and meaning. A set of 19 proinflammatory genes was significantly downregulated with MAP when compared to the control condition. TELiS analysis of significantly changed genes found that transcription factor NF-kB showed a significant decrease while anti-inflammatory glucocorticoid receptor (GR) and interferon-related transcription factors (IRF) increased and CREB remained the same. IL-6 was not significantly changed in general, but those who practiced meditation more frequently had lower levels of IL-6, while other proteins were non-significant even after the adjustment for the practice frequency. Downregulated genes mostly originated from monocytes and dendritic cells, while upregulated genes mostly originated from B lymphocytes.

Effects of lifestyle modification on telomerase gene expression in hypertensive patients: A pilot trial of stress reduction and health education programs in African Americans

Duraimani and colleagues (2015) compared the effectiveness of a program that consisted of transcendental meditation and health education with a program of extensive health education alone in hypertensive adults. Extensive health education used lectures, videos, field trips and social support to motivate participants to lose weight, adopt a healthy diet, exercise, eat less sodium and drink less alcohol. Forty-eight hypertensive adults were randomly assigned to each group and attended weekly sessions for four months. Researchers only assessed the expression of two genes related to telomeres (hTR and hTERT), which are nucleotides at the end of chromosomes that shorten every time a cell divides and are associated with aging. They also measured blood pressure, lifestyle (diet and physical activity), and anger.

Both interventions equally increased the expression of telomerase related genes. Telomeres themselves did not change with either intervention, though this rarely happens over the course of just a few months. Extensive health education proved to be better for hypertensive adults because it lowered diastolic blood pressure more than transcendental meditation and led to healthier lifestyle behaviours.

Cognitive Behavioural Therapy and Tai Chi Reverse Cellular and Genomic Markers of Inflammation in Late Life Insomnia: A Randomised Controlled Trial

Irwin and colleagues (2015) conducted another study on the effects of Tai Chi, but this time on a sample of 120 older adults with insomnia. CBT-I was another experimental condition that was compared to Tai Chi, while a sleep seminar education was the control group. Each group consisted of 2-hour weekly meetings over 4 months. As in the study described above (Irwin et al., 2014), they adopted a multi-level approach to inflammation and measured CRP, TLR-4 activation of TNF and IL-6, and gene expression, while controlling for BMI and physical activity changes during interventions.

Behavioural outcomes regarding sleep were not reported in this paper. Four months after the intervention had finished, CRP was significantly reduced in CBT-I group and remained at the same level after 16 months. In the Tai Chi group, CRP was only marginally reduced after 4 months and it became non-significant afterwards. On the other hand, proinflammatory cytokines were reduced in both groups 2 months after the intervention, but they remained reduced for 16 months in the Tai Chi group alone. Gene expression profiling was carried out on a random subsample of 78 older adults at a 4-month follow-up. Relative to sleep education, CBT-I downregulated 347 genes and upregulated 191 genes, while Tai Chi downregulated 202 genes and upregulated 52 genes. The majority of downregulated genes after CBT-I and Tai Chi are involved in inflammation. On the other hand, the majority of upregulated genes after CBT-I are involved in interferon and antibody responses, while those upregulated after Tai Chi do not have a known common function. TELiS found that both CBT-I and Tai Chi reduced activity of NF-kB relative to sleep education, though the difference was only marginally significant in the Tai Chi group. Both interventions reduced activity of CREB as well, while Tai Chi also reduced activity of activator protein 1 (AP-1, controls cellular differentiation, proliferation and cell death) and marginally increased GR activity. TOA found that the genes that are downregulated by CBT-I and Tai Chi originated mostly from monocytes and dendritic cells.

Genomic and clinical effects associated with a relaxation response mind-body intervention in patients with irritable bowel syndrome and inflammatory bowel disease

Kuo et al. (2015) undertook an uncontrolled trial with a mixed sample of 19 patients with irritable bowel syndrome (IBS) and 29 patients with inflammatory bowel disease (IBD).

Both IBS and IBD are chronic diseases of the digestive system that are exacerbated with stress, though they have different underlying physiology and symptoms. Previous studies found that psychological interventions such as psychotherapy and stress management can reduce symptoms and improve quality of life in IBD (Timmer et al., 2011) and even more so in IBS (Mahvi-Shirazi et al., 2012). In this study, researchers explored if a relaxation response-based mind-body intervention (RR-MBI) could affect quality of life, inflammatory markers and gene expression in IBS and IBD patients. The RR-MBI consisted of nine weekly meetings of 1.5 hours and daily home practice of 15-20 minutes. The meetings included a variety of practical skills that induce the relaxation response (e.g. breath focus, imagery, mindful awareness, yoga) and cognitive skills that help to cope with stress. The theoretical part included lectures about the physiology of stress and digestion, and promotion of health behaviours. Participants completed a set of self-report measures of common symptoms to both IBS and IBD (pain symptoms and catastrophizing, state and trait anxiety) and a set of disease specific self-report measures (quality of life, severity of symptoms). Inflammation was measured as rate of sedimentation of red blood cells (ESR) and levels of C-reactive protein (CRP).

Immediately after RR-MBI and at a short-term follow-up 3 weeks later, both IBS and IBD patients showed greater quality of life and a significant reduction of symptoms of their condition and of anxiety. They reported improved coping with pain, but no change in how pain interferes with their functioning. Regarding biological measures, there was no change in ESR and CRP. In the IBD group, a total of 1059 genes had changed. These were related to improvements in inflammatory response, cell growth, proliferation and oxidative stress-related pathways – kinases, inflammation, cell cycle and proliferation. In the IBD group 119 genes that are related to cell cycle regulation and DNA damage changed expression. Bioinformatics analysis of genes that changed expression (by using Interactive network analysis) found that NF-kB is a key molecule for both IBS and IBD.

Biomarkers of Resilience in Stress Reduction for Caregivers of Alzheimer's Patients

Ho and colleagues (2016) chose a sample of caregivers, a chronically stressed population, to test the effects of MBSR. The intervention was slightly modified by shortening the length of weekly classes from regular 2.5h to 1.5h to meet the demanding daily schedules of caregivers, but the content remained the same. There was no control group in this study and the sample consisted of only 25 participants. Psychological outcomes were measured with a detailed Caregiver Self-Assessment Questionnaire (CSAQ) that consists of items about depression, burden, stress, grief and represents overall psychological distress. After MBSR, caregivers showed improvements on CSAQ that positively correlated with mindfulness score, which means that benefits were more pronounced in those that increased their levels mindfulness.

Based on the variability in the CSAQ score, researchers classified all 25 participants into 3 MBSR responder categories: poor responder, moderate responder and good responder. This categorisation was the basis for the gene expression analysis. Researchers identified 194 differentially expressed genes that can be used to predict to which responder category each caregiver belongs. These genes were related to inflammation, stress response and depression, which suggest that psychological benefits of MBSR might be emerging due to reduction in these variables. Furthermore, researchers identified 91 genes that can be measured at baseline to predict with 94.7% accuracy the likelihood that a caregiver will get psychological benefits from MBSR. These genes were related to immune system functions, such as toll signalling and insulin, which suggests that the likelihood to benefit from MBSR depends on immunological status.

c) **Rapid response**

Genome-wide expression changes in a higher state of consciousness

Ravnik-Glavac and colleagues (2012) explored gene expression changes in two highly experienced practitioners (one with 23 years of experience and the other with 25) who claimed to occasionally move into a higher state of consciousness (a state of 'pure awareness' without thoughts, feelings or perceptions) that can last for several days after a single meditation session. They both practiced similar forms of meditation that stem from Buddhist traditions and aim to extend awareness (Zen, Kriya yoga, Kunadlini yoga, and pranayama). Researchers obtained blood samples while meditators were in their 'normal' state of consciousness, which was used as a control sample. When each of the meditators felt he entered a 'higher' state of consciousness, he was invited to the lab to record Electroencephalography (EEG) while he meditated. For this purpose, one participant practiced Zen and Kundalini meditation and the other meditated on mental quietness and a Buddha visualisation. Blood samples were collected after meditation at the same time of the day (no more than 1.5 hours apart) in order to control for circadian gene expression changes.

EEG showed almost identical patterns in both meditators: increased theta and alpha frequency range. Genes that changed expression for 30% or more after entering into higher consciousness were considered significant. For one participant, 1688 genes changed expression (1559 downregulated and 109 upregulated) and 608 for the other (338 upregulated and 270 downregulated). Although the number of changed genes differed between meditators, they shared 118 genes. The genes that changed in both meditators suggest a downregulation of metabolism and cell cycle processes. Additionally, some of the genes involved in immune system, cell death and the stress response were downregulated. However, the two gene expression profiles were too different and thus difficult compare and make generalisable conclusions.

Rapid gene expression changes in peripheral blood lymphocytes upon practice of a comprehensive yoga program

Qu, Olafsurd, Meza-Zepeda and Saatcioglu (2013) were interested in rapid changes in gene expression that take place immediately after contemplative practice. Intervention consisted of gentle yoga postures, breathing exercises and meditation, which they termed Sudarshan Kriya and related practices (SK&P). They had 10 participants, all of whom were recruited at a yoga retreat and their experience in SK&P ranged from 1.5 months to 5 years. In the first two days, participants practiced SK&P led by experienced teachers for 2 hours. In the remaining two days, they had a walk in nature (to control for the physical aspect of yoga in SK&P) followed by listening to relaxing music (to control for the relaxation aspect of meditation and breathing exercise in SK&P), which lasted 2 hours as well and was at the same time of the day. They were only interested in gene expression and no other measures were taken besides daily blood samples to obtain PBMCs. Gene profiles were compared for each participant before and after each day of practice.

Hierarchical clustering showed that SK&P changed expression of 3-fold more genes than the control program: 111 genes after SK&P (54 upregulated and 57 downregulated), 38 after the walk and relaxing music (15 upregulated and 23 downregulated), and 14 genes were commonly affected by both interventions. Thirty-six per cent of the genes that were changed after walking and relaxing music were also changed after SK&P, which suggests that a yoga program has more benefits in addition to those provided by physical activity and relaxation. Although there were many significant gene expression changes, bioinformatics analysis (by using different methods of gene ontology analysis) did not find a significant pathway (e.g. NF-kB as commonly found in other studies).

d) Mixed designs

Genomic counter-stress changes induced by the relaxation response

The Relaxation response (RR) has been defined as a physiologic state that represents the opposite state of the stress response (Benson, Beary & Carol, 1974). It is characterised by decreased oxygen consumption and carbon dioxide elimination, reduced blood pressure, heart and respiration rate. RR is elicited by focusing on a word, phrase, sound or movement while attempting to disengage from thoughts. Meditation is just one of the many methods to induce the relaxation response, along with yoga, tai chi, Qi Gong, breathing exercises, meditation, progressive muscle relaxation and repetitive prayer. Beneficial clinical effects of the RR have been amply reported (for a review see Astin, Shapiro, Eisenberg, & Forys, 2003), and in this cross-sectional study, researchers explored differences in gene expression that occur with regular practice of this MBI (Dusek et al., 2008). First, they compared long-term practitioners (n=19) with age and gender matched controls and found differences in the expression of 2 209 genes (1,275 upregulated and 934 downregulated). Then the control group (n=20) went through 8-weeks of RR training and the analysis of differences in their gene profiles before and after training identified that 1,561 of genes had changed expression (874 upregulated and 687 downregulated). However, there were significant overlaps of differentially expressed genes among all three groups: only 595 of 2,209 genes that were changed in long-term practitioners were unique to this group. Bioinformatics analyses showed that long-term practitioners presented a downregulation of ubiquitin, proteasome, and stress response, an upregulation of ribosomal protein, and mixed directions of change in apoptosis and immune system. On the other hand, 418 of 1,561 genes were changed with short-term practice only – when naïve participants went through 8 weeks of RR practice, there was a significant enrichment of gene sets related to stress responses and metabolism. This means that short-term and long-term RR practice may lead to distinct gene expression changes.

The results were validated in a separate independent analysis on a new set of samples derived from previous groups (5 controls, 5 short-term practitioners and 6 long-term practitioners). Validation results were similar to the original results from the full sample, which supports the assumption that these changes do not occur randomly.

Relaxation Response Induces Temporal Transcriptome Changes in Energy Metabolism, Insulin Secretion and Inflammatory Pathways

Bhasin and colleagues (2013) explored differences in gene expression changes after one RR session in expert meditators and novices. They assessed both long and short-term effects of the RR. Expert participants had between four and twenty years of experience in RR, while novices did not have any experience and undertook the RR training as a part of the study intervention; this consisted of eight weekly private sessions with an experienced clinician and a 20-minute audio recording with an RR sequence for daily home practice. The RR sequence consisted of diaphragmatic breathing, body scan, mantra repetition, and mindfulness meditation. Both experts and novices listened to the same audio recording in a laboratory session. Prior to the RR training, novices listened to a health education audio of the same length that served as a control intervention. In both cases, blood samples were obtained at three time-points: before, immediately after and 15 minutes after listening to the audio recording. The only outcome measures were gene expression and the amount of fractional exhaled nitric oxide (FeNO), which influences blood pressure. Results showed that more genes were changed in experts than in short-term practitioners or novices, and that the group difference was the most pronounced 15 minutes after the RR. They then proceeded to undertake various analyses, including Molecular Functions Enrichment Analysis and Gene Set Enrichment Analysis (GSEA).

Results showed that experts and short-term practitioners had different gene expression profiles at baseline. Following a RR session, experts showed more consistent and pronounced gene expression changes than short-term practitioners. Both experts and short-term practitioners presented changes that have been linked to energy metabolism, electron transport chain, biological oxidation and insulin secretion – all these pathways are crucial for mitochondrial energy mechanics, oxidative phosphorylation and cell aging. Using systems biology analysis, it was found that the most upregulated critical molecules were ATP synthase and insulin, which promote mitochondrial energy production and utilisation (resilience), and the most downregulated NF-kB pathway genes. Changes were generally more pronounced in experts. Upregulated genes were related to energy metabolism, mitochondrial function, insulin secretion and telomere maintenance. Downregulated genes were related to inflammatory response and stress pathways. Finally, FeNO was increased or showed a trend towards increase during relaxation response in all practitioners regardless of experience.

Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators

Kaliman and colleagues (2014) explored immediate effects of an intensive 8-hour mindfulness meditation retreat in experienced meditators on the expression of three sets of genes with common functions (7 circadian, 10 chromatin modulatory and 6 inflammatory genes), and on stress reactivity in a laboratory induced stressful situation. Experienced meditators were compared to a control group with no meditation experience who had engaged in leisure activities of the same length. Against their hypotheses, they found no differences in the tested genes between expert and naïve groups before the meditation, but after the intervention there was a significant silencing of 2 out of 6 proinflammatory genes (RIPK2, COX2) in experienced meditators only. Additionally, there were significant changes in the global modification of histones (H4ac, H3K4me3) and silencing of several histone deacetylase genes (HDAC 2,3 and 9), all of which regulate the activity of other genes. The extent to which proinflammatory genes were silenced was associated with faster cortisol recovery to social stress. On the other hand, the expression of circadian genes was not affected with intensive mindfulness meditation.

Meditation and vacation effects have an impact on disease-associate molecular phenotypes

Epel and colleagues (2016) were primarily interested in the effects of a 4-day residential retreat on people who did not have experience with meditation, but they wanted to control for what they called ‘the vacation effect’. They considered that when people go on retreats, they are not only meditating but are also away from the demands of their daily lives, which should significantly lower stress levels and change gene expression. They thus used an active control group that resided at the same location for the same amount of time, but without participating in any meditation or relaxing programs offered by the retreat centre. The other group consisted of people who were new to meditation and who attended a 4-day intensive program of mantra meditation (4h/day), yoga (3h/day), lectures and self-reflective exercises. Additionally, to be able to contrast the effects of a 4-day intensive meditation on novice meditators with experienced meditators, a group of regular meditators attended the same retreat. Psychological outcomes were depression, stress, vitality and mindfulness – all of which improved for all groups after the intervention and remained positively changed at a 1-month follow-up. After a 10-month follow-up, novice meditators had less depressive symptoms than the vacation group, which suggests that learning meditation may have psychological benefits that last longer than those of merely going on a holiday.

The central biological outcome of this study was gene expression. There were 390 genes that changed expression in all three groups, most likely due to the relaxation component that was common to all groups. These gene expression changes referred primarily to lower expression of genes related to stress response, wound healing and injury. In addition to these changes common across groups, regular meditators showed lower expression of genes involved in protein synthesis, viral expression and viral infectious cycle, while the novice meditators had no distinctive gene expression changes.

The researchers also assessed other biological outcomes, including telomerase (an enzyme that can stabilise or lengthen telomeres), TNF alpha and amyloid beta (Aβ) metabolism. Greater ratio of proteins Aβ42/ Aβ40 is associated with lower risk of dementia (Koyama et al., 2012) depression (Baskaran, Carvalho, Mansur & McIntyre, 2014) and mortality (Gabelle et al., 2014). The vacation group had significantly more TNF- than regular meditators and marginally more than novice meditators, which suggests an acute inflammatory response, possibly due to sun exposure or exercise. All groups in this study had a higher Aβ42/ Aβ40 ratio after the retreat, most likely due to relaxation. An unexpected finding was that regular meditators had shorter telomeres, which is associated with aging, diabetes, cardiovascular disease and some types of cancer.

Table 1. *Summary of 18 reviewed studies*

Study	Study type	Sample type (experime-ntal group size)	Control group type (size)	MBI	Practice frequency, training time	Gene expression technology (bioinforma-tics analysis)	Cell type	Biological outcomes	Psychological and other outcomes
Li et al., 2005	CS	Experienced practitioners (n=6)	Naïve (n=6)	Qigong	60-120 min/day, 1-5 years	Genome wide: Affymetrix Human Genome U95, (N/A)	Peripheral blood neutrophils	Genes related to: apoptosis -, cell metabolism -, immune regulation +	N/A
Sharma et al., 2008	CS	Experienced practitioners (n=42)	Naïve (n=42)	Sudarshan Kriya (breath regulation)	>60 min/day, at least 1 year	RT-PCR of 9 genes, (N/A)	Peripheral blood lymphocytes	Genes related to: oxidative stress ns, DNA damage ns, cell cycle control ns, aging ns, apoptosis +	N/A
Kumar and Balkrishna, 2009	CS	Leukaemia patients (n=8)	Naïve (n=N/A)	Pranayama (breath regulation)	N/A	Genome wide: Expression Array System of Applied Biosystems, (N/A)	Peripheral blood lymphocytes	Genes related to: immune regulation + Apoptosis +	N/A
Creswell et al., 2012	LG	Normal older adults (n=20)	Waitlist (n=20)	Mindfulness Based Stress Reduction, 8 weeks	30 min/day, 8 weeks	Genome wide: Illumina HT 12 BeadChip (TELiS, NF-kB)	PBMC	Transcription factors: NF-kB-; Proteins: CRP-IL-6 ns	Loneliness -
Black et al., 2013	LG	Dementia caregivers (n=20)	Relaxing music (n=20)	Kirtan Kirya Meditation	12 min/day, 8 weeks	Genome wide: Illumina HT 12 BeadChip (TELiS, NF-kB and IRF)	PBMC	NF-kB -, IRF +; IL-6 ns, IL-8 ns, IL1B ns, TNF ns	Depression - Mental Health +
Irwin et al., 2014	LG	Breast cancer survivors with insomnia (n=40)	Cognitive behavio-ural therapy (n=40)	Tai Chi	2h/week, 12 weeks	Genome wide: Illumina HT 12 BeadChip (TELiS, NF-kB)	PBMC	NF-kB -; CRP ns IL-6 ns TNF -	N/A
Bower et al.,2014 a	LG	Breast cancer survivors with fatigue (n=16)	Health education (n=15)	Iyengar Yoga	90 min/twice a week, 12 weeks	Genome wide: Illumina HT 12 BeadChip (TELiS: NF-kB, GR and CREB)	PBMC	NF-kB -, CREB -, GR +; Cortisol ns, sTNFRII-IL-1RA ns, CRP ns Il-6 ns	N/A
Bower et al., 2014b	LG	Breast cancer survivors (n=39)	Wait-list (n=32)	Mindful Awareness Practice	2h/week, 6 weeks	Genome wide: Illumina HT 12 BeadChip (TELiS: NF-kB, GR,CREB, IRF)	PBMC	NF-kB – GR + IRF +CREB ns; sTNFRII ns CRP ns IL-6 ns	Stress -. Fatigue -, sleep disturbance -, hot flashes -, depression -, positive affect +, peace and meaning +, intrusive

									thought ns, fear of recurrence ns
Duraimani et al., 2015	LG	Hypertensive adults (n=24)	Extensive health education (n=24)	Transcendental meditation	40min/day, 16 weeks	2 genes related to telomeres: RT-PCR	Whole blood	hTR ns, hTERT ns, Telomere length ns	Blood pressure ns, healthy lifestyle ns, anger ns
Irwin et al.,2015	LG	Older adults with insomnia (n=49)	Cognitive behavioural therapy for insomnia (n=49), sleep education (n=25)	Tai Chi	2h/week, 16 weeks	Genome wide: Illumina HT 12 BeadChip (TELiS: NF-kB, CREB, GR, AP, IRF1, IRF2)	PBMC	NF-kB -, CREB -, GR +, AP -, IRF1 ns, IRF2 ns; CRP ns TLR4 -	N/A
Kuo et al., 2015	LG	Irritable bowel syndrome and inflammatory bowel disease (n=48)	None	Relaxation Response-Mind-Body Intervention	20 min/day, 9 weeks	Genome wide: Affymetrix HG U133 Plus(Interactive network analysis: NF-kB)	PBMC	NF-kB -. ESR ns, CRP ns	Quality of life +, Symptoms of IBS/IBD -, Pain catastrophizing -, Pain interference with daily life ns, Anxiety -
Ho et al., 2016	LG	Caregivers (n=25)	None	MBSR	1.5h/week (8 weeks)	Genome-wide: Affymetrix HuGene 1.0 ST arrays(WebGestalt2)	PBMC	Genes related to inflammation -, stress response -, depression -	Psychological stress +, mindfulness +
Ravnik-Glavac et al., 2012	RR	Experienced practitioners (n=2)	None	Buddhist forms of meditation	N/A, more than 23 years of experience	Genome-wide: Affymetrix HG U133 Plus, ArrayStar Human LncRNA Array (Gene Enrichment Analysis)	PBMC	Genes related to metabolism and cell cycle processes -, immune system ns, apoptosis ns, stress response ns; EEG: theta +, alpha+	N/A
Qu, Olasfurd, Meza-Zepeda & Saatcioglu, 2013	RR	Experienced practitioners (n=10)	Within-subject controls (relaxation)	Sudarshan Kriya and yoga	2 days for 2 hours, 1.5 months to 5 years of experie-nce	Genome-wide: Illumina Human WG-6 v3 Bead Chip, 9 genes: qPCR (Gene ontology)	Peripheral blood lymphocytes	All pathways ns	N/A

Dusek et al.,2008	CS + L	Experienced practitioners (n=19)	Naïve (n=20)	Relaxation Response	20 min/day, 8 weeks	Genome-wide: Affymetrix HG U133 Plus(GSEA)	PBMC	CS: ubiquitin -, proteasome -, stress response-, ribosomal protein +. L: stress response -, metabolism -	N/A
Bhasin et al., 2013	CS + L + RR	Experienced practitioners (n=26)	Naïve (n=26)	Relaxation Response	20 min/day, 8 weeks	Genome-wide:HR U133A (GSEA)	PBMC	ATP +, INS +, NF-kb – FeNO +	N/A
Kaliman et al.,2013	CS + RR	Experienced practitioners (n=19)	Naïve (n=21)	Mindfulness meditation	>30 min/day, 3 years	RT PCR of 23 genes	PBMC	CS: ns RR: Inflammatory genes -, circadian genes ns , chromatin genes +, Cortisol -	Stress reactivity -
Epel el al, 2016	CS + L + RR	Experienced practitioners (n=30)	Naïve (n=33)Vacation (n=31)	Meditation and yoga retreat	4h of meditation and 3h of yoga per day, 4 days	Genome-wide: RNA-Seq (Gene ontology)	PBMC	All groups: stress response -, wound healing -, injury – Experienced: protein synthesis -, viral expression -, viral infectious cycle -TNF - Aβ42/ Aβ40 + Telomerase (experienced +, novice ns)	Depression -, Stress -, Vitality -, Mindfulness -
Summary	CS=17% LG=50% RR=11% Mixed =22%	Mean participants per group =23.55 Normal population = 50% Stressed populations = 50% (33% breast cancer + 22% caregivers + 45% other)	No control group = 22% Passive control = 11% Active control = 67% (50% naïve +17 % CBT + 17% HE + 6% other)	Mindfulness = 22% Relaxation response =17% Other MBI = 61% Interventions with a physical component = 44%	46% of MBIs lasted 8-12 weeks; 33% of MBIs had only weekly meetings	44% of studies used TELiS and all found NF-kB downregulation	72% of studies did gene expression analysis from PBMC, 17% from lymphocytes	81% of studies found a reduction Inflammation related genes and/or transcription factors	56% of studies did not measure any psychological outcomes

Note. Study design types used: CS, cross-sectional; L, longitudinal; RR, rapid response. Technologies and analysis used: RT PCR, real-time polymerase chain reaction; RNA-Seq, RNA sequencing; TELiS; Transcription Element Listening System; CBT, cognitive behavioural therapy; GSEA, Gene Set Enrichment Analysis. Cell types: PBMC, peripheral blood mononuclear cells. Transcription factors: GR, glucocorticoid receptor; IRF, interferon regulatory factor; NF-κB, nuclear factor kappa B; CREB, cAMP response element-binding protein; AP, activator protein; INS, insulin. Proteins: CRP, C-reactive protein; IL, interleukin; TNF, tumour necrosis factor; TLR, toll-like receptor. Other biological measures: FeNO, fractional exhaled nitric oxide; ESR, erythrocyte sedimentation rate; Aβ, amyloid beta.

3. Discussion

The 18 examined studies indicate that MBIs reverse skewing of the transcriptome that is related to adversity, which counteracts the effects of stress on the immune system. Although most genes showed small or moderate effect sizes individually, a general pattern emerges: proinflammatory genes and pathways get downregulated (see Table 1 for a summary). Most studies (81%) that measured the activity of inflammation-related genes and/or NF-kB, a key transcription factor that controls the expression of inflammation-related genes, found a significant downregulation. The exceptions were two uncontrolled trials that measured the immediate effects of MBIs in experienced practitioners, which is probably the consequence of the sample sizes of 10 and 2 (Qu, Olafsurd, Meza-Zepeda and Saatcioglu, 2013; Ravnik-Glavac et al., 2012, respectively), the norm being that 15 participants per group are necessary to provide statistical power greater than 80% for the gene expression outcome (Black et al., 2013; Creswell et al., 2012). A further exception was one controlled trial that compared 19 long-term practitioners to 20 short-term practitioners of relaxation response and did not detect changes in inflammatory pathways (Dusek et al., 2008). This could be due to the different methods of gene expression detection and analysis, as all studies that employed genome-wide profiling followed with TELiS bionformatics analysis consistently found a downregulation of NF-kB. Therefore, the results of the reviewed studies tentatively suggest that the various psychological and physiological benefits of MBIs may be mediated through the downregulation of proinflammatory genes and pathways. However, for this research to be able to show with greater confidence that the level of effectiveness of MBIs is predicated on these genetic expression changes, we need to address the severe limitations of the reviewed studies.

A major shortcoming of the literature is the lack of active control groups that carefully mirror the MBIs (e.g., length of time, meaningfulness of the practice). This should be a mandatory procedure in studies of gene expression analysis with behavioural interventions to account for the many non-specific effects of MBIs, such as social support or teacher-student relationship. An active control group was included in 6 out of the 9 randomised controlled studies, but control conditions ranged from relaxation — which produces similar effects to MBIs regarding stress reduction — to education. Black and colleagues (2013) probably achieved the most balanced solution, as both the meditation and the relaxation control group practiced at home with an audio CD of the same length of time and with eyes closed, thus making both conditions very similar. The effects of MBIs depend to a great extent on the amount of regular practice, but most studies did not measure practice frequency, simply assuming high adherence. Only two studies (Bower et al., 2014b; Creswell et al., 2012) controlled for the frequency of practice in their gene expression analysis and found that some biological results became significant, when those individuals that practiced regularly were analysed separately. It is important that future studies measure practice frequency and report dosage dependent effects in addition to overall effects of MBIs on gene expression.

One other problem to consider are the various environmental and lifestyle factors that may change gene expression in similar ways to MBIs. For example, similar differences can be observed when analysing gene expression from peripheral blood mononuclear cells (PMBCs) after exercise. Although at first there is an increase in the expression of proinflammatory genes due to regeneration of muscles after exercise, the long-term effects show a decrease in the expression of proinflammatory genes (Gjevestad, Holven & Ulven, 2015). In fact, 44% of interventions in this systematic review included a physical component, thus making it very difficult, if not impossible, to discern between the effects of MBIs from the effects of exercise. Similarly, food can contribute to inflammation. Diets rich in saturated fats are associated with proinflammatory gene expression profile, which is commonly observed in obese people (van Dijk et al., 2009). On the other hand, consuming some foods might reduce inflammatory gene expression, e.g., drinking 1 litre of blueberry and grape juice daily for 4 weeks changes the expression of the genes related to apoptosis, immune response, cell adhesion and lipid metabolism (van Breda et al., 2014). Similarly, a diet rich in vegetables, fruits, fish and unsaturated fats is associated with anti-inflammatory gene profile, while the opposite has been found for Western diet consisting of saturated fats, sugars and refined food products (Bouchard-Mercier et al., 2013). Similar changes have been observed in older adults after just one Mediterranean diet meal (Yubero-Serrano et al., 2012), or in healthy adults after consuming 250 ml of red wine (Di Renzo et al., 2015) or 50 ml of olive oil (Konstantinidou et al., 2009). However, in spite of this literature, only two of the studies we reviewed tested if the MBIs had any influence on lifestyle (e.g., sleep, diet, and exercise) that may have explained gene expression changes.

Another limitation is inherent to gene expression data. By themselves these do not provide much useful information unless the relationship between gene expression and psychological variables is directly explored. Only two of the reviewed studies (Creswell et al., 2012; Kaliman et al., 2014) attempted to find associations between gene expression changes and psychological constructs, such as stress reactivity and loneliness. Four other studies (Black et al., 2013; Bower et al., 2014b; Duraimani et al., 2015; Kuo et al. 2015) included psychological measures, but only to test the efficacy of their interventional programs, not to interpret observed gene expression differences. The majority of studies (56%) only included biological outcomes, which reveals a dire need for interdisciplinary collaborations in order to fully understand the interaction between molecular and psychological changes associated with MBIs.

The studies presented considerable variation, both in their type of interventions and gene expression assessment. MBIs varied from seated meditation at home to movement in groups, with lengths ranging from 4 days to 4 months: half of them used healthy adults while the other half had clinical or highly stressed samples. One interesting hypothesis to test is that the effects of MBIs will be easier to detect on populations with high levels of inflammatory gene expression at baseline (such as older adults; Creswell et al., 2012), though this remains to be tried out in future studies, as there are no present data that allow us to compare the effect sizes of gene expression changes in different population.

Another source of heterogeneity in the reviewed studies is the cell type from which gene expression data is collected. In 72% of reviewed studies data were obtained from peripheral blood mononuclear cells (PBMCs). As PBMCs consist of particular cell subtypes that have different gene expression patterns and functions, their variety could affect data interpretation. The results of studies that analysed from which cell types the observed gene expression emerged (Transcript Origin Analysis) were mixed, thus all PBMCs will have to be included in future studies.

Another aspect to bear in mind is that the biological consequences of the observed gene expression changes were not found directly, because the studies that employed circulating proteins (e.g., CRP, interleukins or cortisol) generally did not find significant results. In fact, 38% of the reviewed studies measured at least one inflammatory protein and the results were non-significant in 76% of cases and those that were significantly changed (usually TNF, CRP and IL-6) are not consistently reduced across studies. Our systematic review indicates that circulating proteins rarely change after a few months of practice, which is how long the studies usually last (46% of studies in this review lasted between 6 and 12 weeks). This suggests that as long as the study interventions consist of only a few months of practice, it will be of limited value to measure proteins. Fortunately, gene expression is more sensitive to MBIs than circulating proteins. Gene expression changes are observed after a few weeks of meditation (e.g. Creswell et al., 2012; Black et al., 2013), but they possibly emerge even after just a few days of intervention. Therefore, the conclusion that MBI techniques improve immune system function is made indirectly using bioinformatics analyses, which are based on previous studies from other areas that found associations between genes and immune outcomes (Baxevanis & Quellette, 2004).

One final methodological concern has to do with the assessment of inflammation. Throughout this review we encountered 11 different measures of inflammation. Thus, if a single inflammatory measure has decreased after an intervention, we cannot confidently conclude that the immune system is enhanced. Future studies should attempt to directly find functional consequences of observed gene expression changes. For instance, PMBC subtypes could be isolated before and after MBIs to verify if they show different *in vitro* responses.

Before widely integrating Mind Body Interventions in healthcare, more research must be done with the aim of constructing and validating a comprehensive theory of MBIs with a multi-level approach that draws connections between genetic and other data, particularly psychological and behavioural. This is the only way of advancing the literature on MBIs and responding to recent criticisms about the theoretical incongruence and lack of consistent evidence for the benefits of these techniques (e.g., Farias, Wikholm, & Delmonte, 2016). Although the studies reviewed here provide preliminary evidence that MBIs are associated with a reduced risk of inflammation-related diseases, it is unclear whether they are more effective than a range of lifestyle changes commonly recommended as a part of healthy lifestyle, such as regular exercise and a Mediterranean diet.

4. Conclusion

The results of 18 studies that used gene expression analysis in research on meditation and related mind-body interventions have overall found downregulation of NF-kB targeted genes, which can be understood as the reversal of the molecular signature of the effects of chronic stress. Even though the study designs, the population, and the types of MBI used in the studies included in this review vary, it indicates that some of the psychological and physical benefits of MBIs are underpinned by biological changes in NF-kB genes. These results need to be replicated in larger samples and with stronger research designs that control for non-specific effects of these practices and for as confounding lifestyle factors, such as sleep, diet and exercise. This research opens the doors to testing multi-level effects of MBIs, which include biological, psychological, and environmental measures, such as the study described in the next chapter.

CHAPTER 3

The neural, genetic and behavioural effects of intensive meditation and yoga on prisoners with personality disorders: a pilot randomised controlled trial

Manuscript submitted for publication

Abstract

This study was the first to test the feasibility of mind-body interventions on prisoners with different personality disorders, and to provide a preliminary evaluation of participants' response to these interventions using a combination of gene expression, neural, and behavioural measures. Thirty prisoners with personality disorders were assigned to a mindfulness intervention (n=10), a yoga intervention (n=10), or a wait-list control group (n=10) using stratified random sampling. Both mindfulness and yoga interventions were held at the same time and lasted three hours per day on five consecutive days. At baseline and after the intervention, we measured inflammation-related gene expression; resting state brain activity with electroencephalography (EEG); risk-taking and attention with cognitive tasks; event-related potentials (ERPs) related to the attention task; and stress, emotion regulation and mindfulness with questionnaires. We found that 50% of available participants were willing to be recruited, and attrition rate was 30%. Although no significant changes were found on primary or secondary outcome measures, several medium effect sizes were found in gene expression analysis (e.g. IRF1 $\eta^2 = .42$; NFKB1 $\eta^2 = .26$; STAT1 $\eta^2 = .23$; IKBKB $\eta^2 = .21$)

Intensive mindfulness and yoga are moderately feasible interventions for prisoners with personality disorders. Although the effectiveness of mind-body interventions could not be quantified due to the small sample size, we found preliminary large effects on gene expression of several inflammation related genes. This study provides a solid foundation for a larger multicentre randomised controlled trial is warranted to test if mindfulness and yoga may be an effective complementary treatment for prisoners with personality disorder.

1. Introduction

Between 10% and 15% of people have a personality disorder (Reich, Yates, & Nduaguba, 1989; Torgersen, Kringlen, & Cramer, 2001). Each of the ten types of personality disorders represent a severe expression of behaviours and thoughts relative to the way an average individual in a given culture perceives, thinks, feels, and relates. Individual with a personality disorder can cause a lot of distress to themselves and to others. Available treatments for personality disorders include different types of psychotherapy, along with psychotropic medicines for comorbid disorders. Besides cognitive-behavioural therapy, there are other available psychotherapy approaches for personality disorders such as dialectical-behaviour therapy and acceptance and commitment therapy, both of which include a mindfulness component. As an addition to usual treatments, mind-body interventions have the potential to aid in managing personality disorders by improving self-regulation and its subcomponents, such as emotion regulation (Cook-Cottone, 2015; Tang, Hölzel, & Posner, 2015), but it is currently unknown if it is feasible to conduct such studies on this vulnerable population. Nevertheless, the effects of mind-body interventions on emotion regulation (Kang, Gruber, & Gray, 2013; Menezes et al., 2015) make them promising interventions in populations who have personality disorders, which are known to display emotion regulation difficulties (Levine, Marziali, & Hood, 1997), as well as increased rates of impulsive behaviour (Steel & Blaszczynski, 1998)·

Not much is known about the effects of mind-body interventions on individuals with personality disorders. The majority of evidence focuses on borderline personality disorder, possibly because these individuals are more likely to seek treatment than those with other personality disorders, and the evidence highlights positive associations between mindfulness practice and reduced psychiatric severity and emotional reactivity (Feliu-Soler et al., 2014), as well as impulsivity (Soler et al., 2012). Additionally, observational studies found that people with more severe forms of antisocial personality disorder (ASPD) have larger deficits in trait mindfulness, and that trait mindfulness moderates the relationship between ASPD severity and aggression (Velotti et al., 2016). Others have suggested that symptoms of ASPD can be reduced through different types of meditation interventions, such as mindfulness, by targeting neurological mechanism that improve inhibitory control and empathic functioning (Holthouser & Bui, 2016), but there are no experimental studies that have directly tested this hypothesis. Furthermore, there are only case studies available for meditation and personality disorders other than borderline (Sng & Janca, 2016), and there are no studies that test the effects of yoga on any personality disorder. This gap in research is most likely due to the fact that individuals with personality disorders often remain undiagnosed and only rarely seek treatment, unless it is for comorbid disorders (McRae, 2013; Welfel & Ingersoll, 2002). The most common comorbid psychiatric disorders in people with personality disorders are substance abuse, depression and post-traumatic stress disorder (Hayward & Moran, 2008).

An indirect line of evidence for mind-body interventions and personality disorders stems from studies of prison populations. Previous studies of mind-body interventions in prisons found that 6 to 8 weeks of mindfulness meditation improved mental health in a prison environment by increasing positive mood and self-esteem, and decreasing aggression and sleep difficulties (Samuelson, Carmody, Kabat-Zinn, & Bratt, 2007; Sumter, Monk-Turner, & Turner, 2009). Even shorter meditation interventions have been found to be effective in prisons; 10 days of intensive meditation reduced substance misuse (Bowen et al., 2006), recidivism (Perelman et al., 2012), and aggressive behaviour (Suarez et al., 2014). Similarly, 10 weeks of yoga increased positive affect, reduced stress, and improved behavioural control in prisoners (Bilderbeck, Farias, Brazil, Jakobowitz, & Wikholm, 2013; Kerekes, Fielding, & Apelqvist, 2017). Other than these two yoga studies, none of the meditation studies followed a randomised procedure or included a control group, but they nevertheless provide preliminary encouraging results for the use of meditation interventions with prison populations. In addition, some research suggests that mindfulness interventions might be particularly beneficial for vulnerable populations, such as those with a high incidence of childhood trauma (Williams et al., 2014). The psychiatric morbidity figures for prisoners in the UK reveal that between a third and a fourth of this population was taken into local authority care as a child because of parental neglect or abuse (Maden, 2000), thus it is plausible that a psychologically vulnerable population like a prison sample may react better to a meditation intervention than the healthy general population. Although personality disorders are not generally linked to criminal behaviours, 65% of people in prison have personality disorders, with ASPD being the most common and present in 47% of prisoners (Fazel & Danesh, 2002) or even up to 60% according to others (Moran, 1999). ASPD is characterised by unconcern for the feelings of others, inability to experience guilt and to maintain enduring relationships, irresponsibility, disregard of social norms and laws, very low tolerance to frustration and a low threshold for aggression (American Psychiatric Association, 2013). Serving a prison sentence increases the risk for the exacerbation of personality disorders (Armour, 2012; Birmingham, 2003) and commonly comorbid psychiatric disorders (Hayward & Moran, 2008). On the other hand, staff members who work with prisoners with personality disorders face many challenges that compromise their own well-being because these patients are often resistant to treatment, and require considerable time to show therapeutic progress (He, Felthous, Holzer, Nathan, & Veasey, 2001; Kiehn & Swales, 1995; Van Beek & Verheul, 2008).

These characteristics of patients with personality disorders raise the question of feasibility of mind-body interventions in a prison setting. More specifically, it is not clear: 1) if there will be difficulties in recruiting the participants; 2) if data collection procedures and interdisciplinary outcome measures are suitable for the population of diverse personality disorders; 3) if participants will adhere to study procedures and attend assigned sessions? 4) if an external research team will have the ability to manage data collection and to implement interventions within a clinical unit of a high security prison? With the aim of answering these question, this study employed a randomized controlled design and two intervention groups (i.e., mindfulness or yoga), along with a wait-list control group in a sample of prisoners with diverse personality disorders. Besides assessing the feasibility of mind-body interventions, we provided a preliminary evaluation of participants' response to these interventions on multiple levels: genomic, neural and behavioural. The rationale for including genomic measures stems from recent studies that have found that the protective effects of mind-body interventions on physical health might be due to prominent gene expression changes (Black & Slavich, 2016; Buric, Farias, Jong, Mee, & Brazil, 2017). Different types of mind-body interventions, including mindfulness and yoga, can lower the activity of inflammation-related genes in various clinical and non-clinical populations, which reduces the risk for neurodegenerative diseases, asthma, arthritis, cardiovascular diseases, some types of cancers, and psychiatric disorders such as depression and posttraumatic stress disorder (Slavich, 2015). We wanted to test if these health-protective changes in gene expression following mind-body interventions would also be detected in a prison sample with personality disorders. Importantly, the effects of mind-body interventions extend beyond gene expression. Psychological and cognitive mechanisms of mindfulness and their neural correlates have been proposed in an overarching theory according to which mindfulness meditation includes three components that interact closely to constitute a process of enhanced self-regulation: attention control, emotion regulation, and self-awareness (Tang et al., 2015). According to this theory, all the other observed benefits of mindfulness (e.g. reduced stress or risk-taking behaviour) are a consequence of improved self-regulation. In this study, we were interested in putting this self-regulation theory to test, and to explore if it not only applies to mindfulness, but also to yoga. Thus, our choice of cognitive measures and questionnaires mainly stems from the self-regulation theory.

A systematic review found that mindfulness meditation may improve attention already in early phases of learning mindfulness techniques (Chiesa, Calati, & Serretti, 2011). Interestingly, even just five days of twenty-minute meditation training can improve executive attention when using ANT (Attention Network Test) to measure attention (Tang et al., 2007). As executive attention is an important mechanism for regulation of cognition and emotion (Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005), it is not surprising self-regulation techniques such as mindfulness can improve executive attention. Superior executive attention in meditators is also reflected in neural activity; meditators have a higher parietal P3 amplitude during the incongruent target condition (Jo, Schmidt, Inacker, Markowiak, & Hinterberger, 2016). Based on these findings, we hypothesised that executive attention would significantly improve in prisoners with personality disorders after five days of intensive mindfulness meditation practice, while no improvements were expected in the yoga and control group. Specifically, we expected that reaction times related to executive attention would decrease and that parietal P3 amplitude would increase after intervention. Besides task related EEG, we measured neural activity during rest to see if findings from previous studies that find that different types of meditation increase alpha and theta power (Cahn & Polich, 2006), and that mindfulness meditation increases theta connectivity (Wong, Camfield, Woods, Sarris, & Pipingas, 2015) also extend to patients with personality disorders.

In addition to measuring attention, we employed another cognitive task that primarily tested changes in risk-taking behaviour because it is linked with disinhibition and reoffending (Andrews, Bonta, & Wormith, 2006) and previous studies found that mindfulness meditation can reduce risky behaviour (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011). Besides risk-taking, the employed task additionally assessed decision making under ambiguity as previous studies found that ambiguity tolerance is associated with prosocial behaviour (Vives & FeldmanHall, 2018). As meditation interventions can improve some subtypes of prosocial behaviour, namely compassion and empathy (Kreplin, Farias, & Brazil, 2018), we hypothesised that there would be beneficial effects of mindfulness intervention on decision making under ambiguity.

In summary, the purpose of this study was to test the feasibility of a mindfulness intervention and a yoga intervention and to provide a preliminary exploration of multi-level outcomes in prisoners with personality disorders

2. Method

2.1. Overview of study procedures

The study was preregistered online on ClinicalTrials.gov (identifier: NCT02894203). Following the approval of five different ethics committees (University Ethics Committee, Health Research Authority, National Offenders Management Service, Cambridgeshire and Peterborough NHS Foundation Trust, and HMP Whitemoor), participants were recruited at a high-security prison within a clinical unit for prisoners with severe personality disorders that have a link between their personality pathology and the offences committed, along with a high risk of reoffending. At this unit, all prisoners attend a 5-year trauma-informed treatment program that consists of group and individual therapy, and aims to improve mental well-being, emotional self-regulation, and consequently reduce risk of reoffending. The program is delivered by a multidisciplinary team that includes prison officers, psychologists, nurses and a psychiatrist, who work closely together to carry out assessment and treatment. Interventions offered included individual therapy and group work about personality disorder awareness (0-3 months), human relationships (4-6 months), cognitive interpersonal group therapy, schema focused therapy group, affect regulation group, offence focused therapy, addictive behaviours group, and interpersonal relationships group. The prisoners were at various stages of the 5-year rehabilitation program.

Leaflets with information about the study were put in prisoners' common areas and a team of four researchers (2 internal assistants and 3 external researchers from our university lab) approached each prisoner individually to offer a participant information sheet and to answer questions about the study. During the following week, prisoners who were interested in participating were assessed for eligibility and gave written consent. To be included, inmates had to be between 18 and 65 years of age and willing to sign and informed consent form. Inmates with major neurological disorders that compromise completing the interventions or research assessments, or that had difficulty in understanding English were excluded.

Prior to randomisation, participants completed pre-intervention assessment that included questionnaires, cognitive tasks, EEG recordings and collection of blood samples (see Figure 1). Interventions commenced two weeks after the beginning of pre-intervention assessment to ensure enough time for data collection, as it took between two and three hours per participant. Following the interventions, participants completed the same set of questionnaires, cognitive tasks, neural recordings, and gave blood samples again. Post-intervention assessment began three days after the intervention and lasted for ten days. The majority of the assessment was done by fully trained assessors in two groups of two researchers (one external from the university lab and one internal research assistant), the questionnaires were administered by internal clinicians, and blood samples were collected by internal phlebotomists. Unlike other measures, blood collection was not a mandatory component of the study.

The data collection for neural and cognitive outcomes was done simultaneously in two separate rooms where two researchers tested one participant in each room. Each participant was escorted to the assigned testing room by a prison officer and searched before entrance. They were then seated in a chair and the researchers would explain the upcoming procedure that could last between 70 and 90 minutes. The assessment began with EEG setup, and after checking the impedance and reducing EEG noise, participant was positioned to sit comfortably before commencing any task. The first measure was resting state EEG (rsEEG), which required them to rest for 4 minutes with eyes closed and 4 minutes with eyes opened (the order of eyes closed/opened was randomised across participants). For the eyes closed session, participants were instructed to close their eyes, sit back, to remain still and rest without doing anything in particular, and to wait for the researchers to tell them when the 4 minutes had passed. For the eyes opened session, participants received the same instructions but were required to keep their eyes fixed on the cross on the screen or on a single area on the wall. Resting state was followed by two cognitive tasks: Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002) and Risk Ambiguity Task (RAT; Levy, Belmaker, Manson, Tymula, & Glimcher, 2012), and the stimuli for both tasks were presented on a computer screen using PsychoPy (Peirce, 2007). After the ANT, the participants were disconnected from the EEG and proceeded to perform the RAT. All the questionnaires were filled on another session during a 1-on-1 setting with a prison clinician.

In order to prevent baseline group differences in variables that might affect outcomes, participants were allocated to groups (mindfulness, yoga, or wait-list control) in equal ratios by applying stratified random sampling using a random number generator. Because important confounding variables can be unequally assigned when the sample size is small, participants were stratified by amount of therapy received (from zero to five years), dominant cluster of personality disorders (A, B, C or equally dominant A and B, and B and C), comorbid psychiatric disorder (seven had ADHD, two had major depressive disorder, and 21 had no other psychiatric diagnosis), and previous experience in meditation or yoga (five had experience in meditation, two had experience in yoga). Additionally, seven participants demanded to be in a certain group or they would not participate otherwise (one demanded to be in mindfulness group, two demanded to be in yoga group, and four demanded to be in the control group), which we accepted due to very limited number of potential participants (i.e., 59 prisoners were at the unit at the time of the recruitment). On the day before the intervention, participants received a letter informing them about the group they were allocated to, and were given instructions for the following day. Participants were encouraged to contact members of the clinical team if they had any questions or experienced difficulties during the intervention period. Members of the clinical team actively followed up participants who missed sessions.

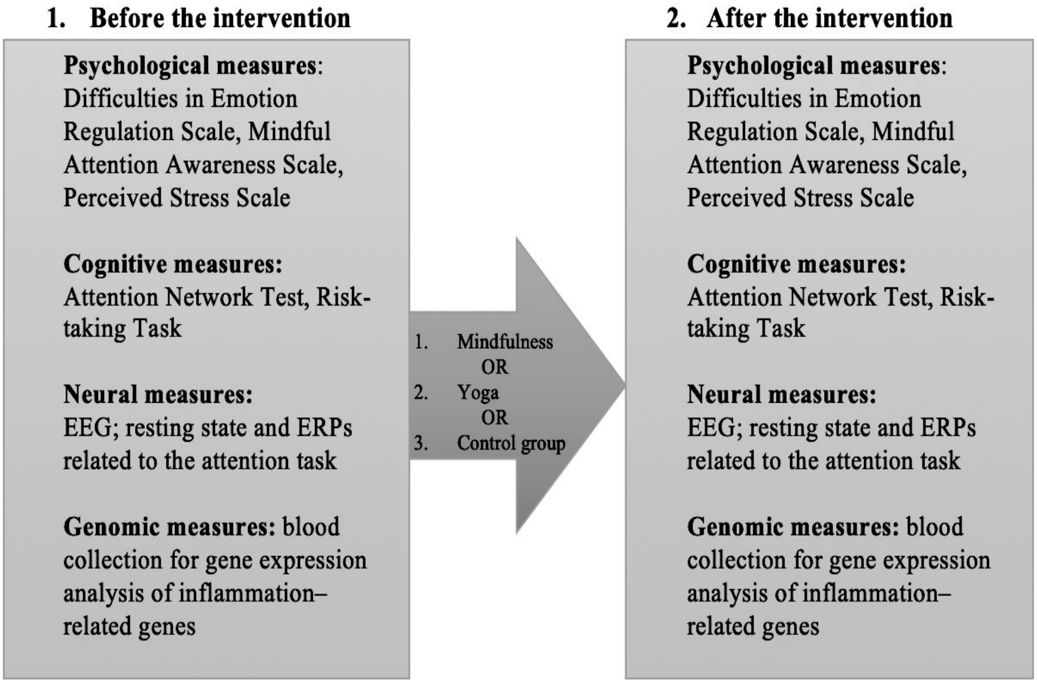

Figure 1. A graphical representation of the research design

2.2. Interventions: Mindfulness, yoga, and wait-list control group

We employed two types of intensive mind-body interventions lasting 15 hours over the course of five days. The length of the interventions was shorter than most mindfulness and yoga interventions found in the literature. Specifically, the most common mindfulness intervention is 26 hours long and spread over eight weeks, but a review of studies found that shorter interventions are just as effective, at least in terms of reducing psychological distress (Carmody & Baer, 2009). Additionally, several individual studies of mindfulness and yoga that used similar outcomes as the present study found significant effects. For instance, short mindfulness-based interventions have been found to improve attention and self-regulation (Tang et al., 2007), executive function (Zeidan, Johnson, Diamond, David, & Goolkasian, 2010) and reduce inflammatory gene expression (Kaliman et al., 2014). Similarly, short yoga-based interventions have been found to improve attention (Sethi, Nagendra, & Ganpat, 2013), reduce inflammatory gene expression (Qu, Olafsrud, Meza-Zepeda, & Saatcioglu, 2013), and affect EEG coherence (Ganpat, Nagendra, & Muralidhar, 2011). Therefore, many studies supported the effectiveness of short and intensive type of mind-body interventions, which was in our case the only option due to prisons' restrictions.

The mindfulness intervention taught skills that enable participants to cultivate awareness of the present moment in an open and non-judgmental manner. It included mindfulness of breath, mindful eating, and open monitoring, talks about the benefits of mindfulness, and daily group discussions where participants could give feedback and ask questions.

The yoga intervention was based on Hatha yoga and covered a set of beginner yoga poses with modifications provided based on the level of fitness and flexibility. Just as for the mindfulness intervention, it also included talks about the benefits of yoga and its history, and daily group discussions. Mindfulness and yoga teachers had 3 and 5 years of experience, respectively, including experience working with prison populations.

Both yoga and mindfulness interventions were five days long and consisted of a 1.5-hour long morning session and a 1.5-hour long afternoon session that were held at the same time. Similarities between interventions included the group format, size, structure, and contact hours. However, the two interventions were distinct in their content, as yoga did not include any meditation, and mindfulness did not include any yoga.

Finally, the wait-list control group followed their usual regimen, which was different than normal because the interventions were delivered during one of the four annual week-long therapy breaks within unit. In comparison with their regular routine, which follows daily therapy and work engagements, prisoners had less duties, and were socialising more than usual. All participants were offered mindfulness and yoga once the data collection was over.

4.1. Overview of measures

4.1.1. Background measures

Background measures were collected from prison files and included age, levels of psychopathy, number of psychotherapy sessions attended, personality disorder diagnosis and type of committed crime. Along with all self-report measures, these variables were used in a one-way ANOVA to test baseline differences between mindfulness, yoga, and wait-list control group. However, offence type data was available only at the group level of all recruited participants due to confidentiality reasons.

4.1.2. Genomic measures

Blood was collected for the analysis of changes in gene expression of 38 genes related to inflammation and the immune system (IL-1 signalling pathway; O'Neill & Dinarello, 2000; Subramaniam, Stansberg, & Cunningham, 2004). Venepuncture samples were collected into 10ml EDTA tubes, lysed and frozen at -80°C. Peripheral blood mononuclear cells were isolated by density gradient centrifugation. Ribonucleic acid (RNA) was extracted (QiaAmp RNA Blood Mini kit; Qiagen) and tested for suitable mass and integrity (NanoDrop One, Acclaro Sample Intelligence; Thermo Scientific). RNA was then converted to fluorescent cRNA for hybridization to IL-1 signalling pathway plate H96 (Bio-Rad Labs Ltd, UK). Gene expression data were expressed as cycle threshold (CT) values by calculating $2^{-\Delta\Delta CT}$ (Livak & Schmittgen, 2001), and referencing to the geomean of all genes because endogenous control genes that are supposed to have constant levels of expression were not stable in this case. After normalising $2^{-\Delta\Delta CT}$ to the wait-list control group median, the data were imported into SPSS and analysed by group allocation based on change scores of each normalised $2^{-\Delta\Delta CT}$.

4.1.3. Cognitive tasks and measures

Attention was measured with the Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002), which is a computer-based test to measure participants' performance in three separate components of attention. This attention model describes three components (i.e. networks) of the attention system that are functionally and anatomically distinct from other neuronal systems (Fan & Posner, 2004):

1. *Alerting* network, which controls the state of alertness and vigilance
2. *Orienting* network, which controls goal-oriented focusing of attention
3. *Executive* network, which controls the execution of responses and blocks distracting information

The ANT takes approximately 20 minutes to complete. A fixation cross was visible in the centre of the screen during the whole experiment. Cue stimuli (duration 100ms) appeared above or below the fixation cross (spatial cue), above and below the centre (double cue), in the centre (centre cue), or were not present (no cue). Cues were always valid and appeared 500ms prior to target presentation (stimulus onset asynchrony (SOA). Centre and double cues provide temporal information about the target's appearance (alerting), spatial cues additionally indicate the upcoming target's location (orienting). Target stimuli consisted of five horizontally arranged arrows or lines presented above or below the fixation cross (maximum duration 1700ms). By pressing left or right arrow key on a keyboard that was placed on the table under the computer screen, participants had to indicate the direction of the central arrow irrespective of flanking conditions that were either straight lines (neutral), arrows pointing the same direction as the central arrow (congruent flankers), or arrows pointing different directions than the central arrow (incongruent flankers). A variable fixation period after response ensured that the duration of each trial summed up to 4000ms. Subjects were instructed to respond as fast and as accurately as possible to a total of 288 trials without feedback.

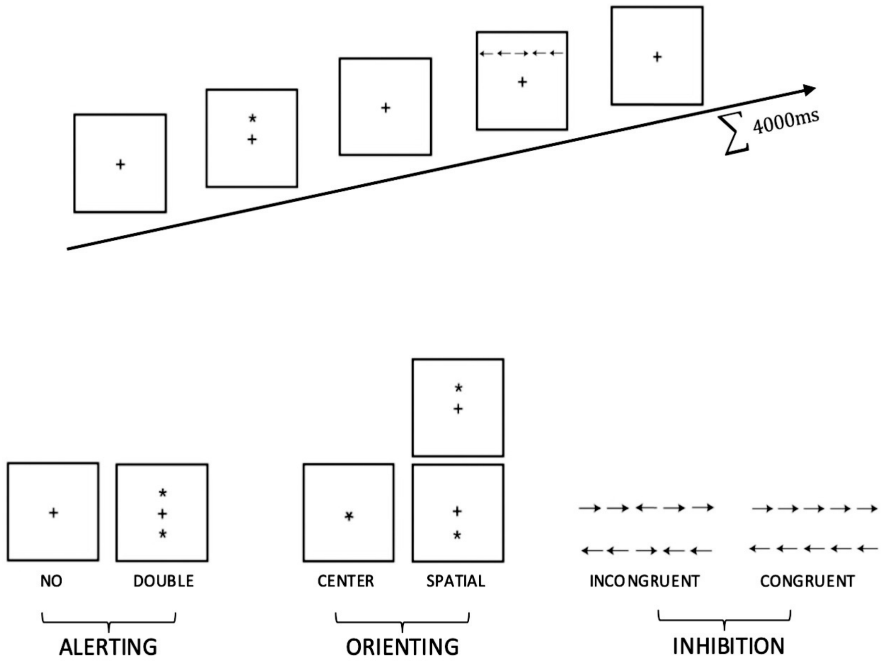

Figure 2. A schematic representation of the ANT

The raw data was organised and outliers were removed (more than two standard deviations from the mean). The data were then imported into SPSS to calculate attention network effects as reaction time (RT) differences of the following task conditions:

1) Alerting = $RT_{no\ cue} - RT_{double\ cue}$

2) Orienting = $RT_{center\ cue} - RT_{spatial\ cue}$

3) Inhibition = $RT_{incongruent} - RT_{congruent}$

Executive attention was assessed via flanker interference, and alerting and orienting networks were estimated by the effects of preceding cue conditions on the speed of response to the target-flanker display. Furthermore, change scores in alerting, orienting, and inhibition were calculated by deducting post-intervention score from the pre-intervention score.

Risk-taking behaviour and ambiguity attitudes were measured with the Risk-Ambiguity Task (RAT) that compared the preferences for risky and ambiguous monetary lotteries (Levy et al., 2012). Starting with 8 practice trials, the task consists of 90 choices grouped in blocks of 45 gain and 45 loss trials. In gain trials, participants have to choose between a certain win £5 and a lottery that can be worth £5, £8, £20 or £50 if they win, or nothing if they lose, while the probability of winning the lottery varies across trials. For example (Figure 3B), in a gain trial the participant has to choose between a certain win of £5 and a 75:25 chance of winning £20 or nothing (the size of each coloured area is proportional to the probability of receiving the outcome associated with that colour). In loss trials, monetary amounts are negative, thus participants have to choose between a certain loss of £5 and a lottery that can mean losing £0 or more than £5. For example (Figure 3A), the participant has to choose between a certain loss of £5 and equal chances of losing nothing or £8. Beside the varying probability of winning the lottery, the level of ambiguity around that probability varies randomly across the task (Figure 3C), thus the probability of winning the lottery is not always clear. Each lottery was either technically risky or ambiguous, allowing the assessment of participants' aversion to known (risky) and unknown (ambiguous) monetary risks. The main result from this task is the proportion of trials on which a participant made a risky choice (i.e. chose to gamble when the probability of winning is low) or an ambiguous choice (i.e. chose to gamble when the probability of winning is not known).

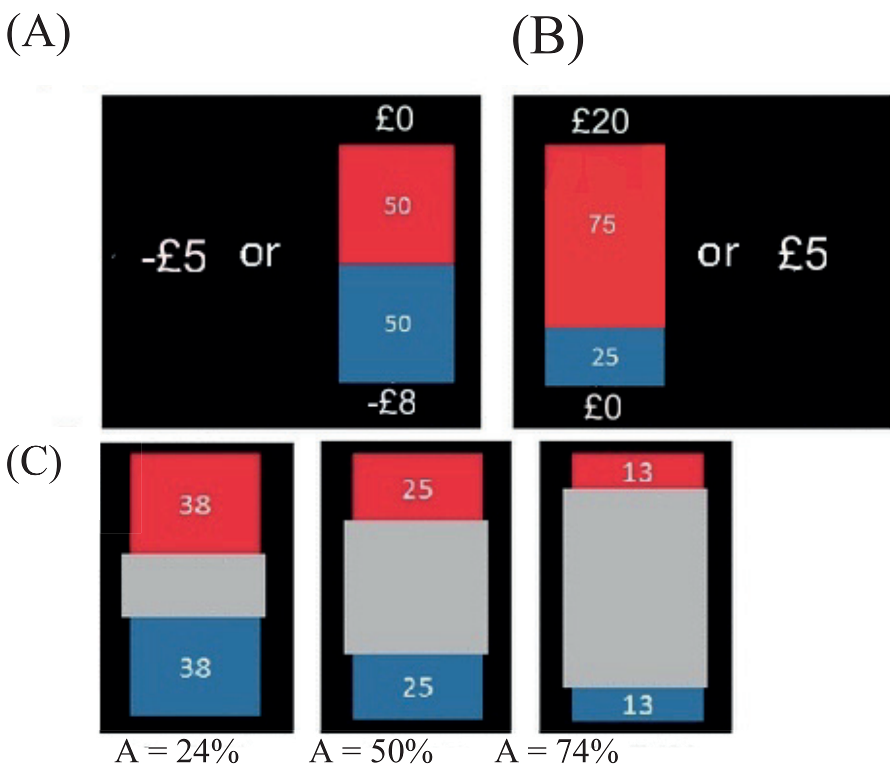

Figure 3. Examples of RAT trials: (A) loss trial, (B) gain trial, (C) different levels of ambiguity

4.1.4. Neural measures

EEG was recorded using a BioSemi ActiveTwo system with 32 electrodes with a "zero-reference" setup and arranged according to the 10–20 system. Additionally, electrooculography (EOG) and heart rate recordings were obtained. Vertical eye movements were recorded by placing electrodes above and below the left eye, another set located at the outer canthi recorded horizontal eye movements, and two electrodes on the wrist recorded heart rate. The recorded signals were digitised with a sampling rate of 1024 Hz using the BioSemi amplifier. EEG analysis was conducted with BrainVision Analyzer 2.1 (Brain Products, Munich, Germany). Ocular artefact correction was performed using an independent component analysis approach (Jung et al., 2000). The data were filtered using a 0.02-30 Hz bandpass filter combined with a 50Hz notch filter.

4.1.4.1. Event-related potential (ERPs) related to ANT

Data were submitted to baseline correction (200ms to 0ms pre-cue) and segmented relative to stimulus onset (200ms pre-cue and 1000ms post-target). Target and cue N1 were identified at P3, Pz and P4 as the first prominent negative peaks at a latency of 150ms to 250ms after onset of target stimuli. The P3 ERP component was identified at P3, Pz, and P4 as a prominent positive deflection between 300ms and 700ms after onset of target stimulus. Separate averages were created for each participant for each of the two target conditions (incongruent or congruent flankers), and the three cue conditions (no cue, central cue, and spatial cue), and every possible cue-target combination (no cue-incongruent, no cue-congruent, central cue-congruent, central cue-incongruent, spatial cue-congruent, spatial cue-incongruent). Both correctly and incorrectly responded trials were included in the EEG analysis and behavioural analyses as incorrect answers constitute less than 4% of total data. Reaction times faster than 150ms and slower than 1000ms (less than 1% of data) were removed from the behavioural data for all groups.

Analysis of attention network ERP amplitudes was conducted in conformity with behavioural analysis:

1) Alerting = target $N1_{\text{no cue}}$ - target $N1_{\text{double cue}}$
2) Orienting = target $N1_{\text{center cue}}$ - target $N1_{\text{spatial cue}}$

3) Inhibition = $P3_{incongruent\ targets}$ - $P3_{congruent\ targets}$

The ERP data were analysed in SPSS based on alerting, orienting, and inhibition change scores in voltages in electrodes P3, Pz, and P4 before and after the intervention.

4.1.4.2. Resting state connectivity

For each condition (eyes opened and eyes closed), 120 epochs with a length of 2s were created, and then filtered using a 0.02–50 Hz band-pass filter and checked for gradient artefacts (maximum voltage step of 50 μV/ms) and excessively low activity (below 0.5 μV in 100 ms intervals). The data were subsequently exported as text files for connectivity analysis in BrainWave (https://home.kpn.nl/ stam7883/brainwave.html; version 9.152.4.1), where the electrode space was rearranged and matched to the montage built into the BrainWave package, resulting in 30 usable electrodes (AF3, F7, F3, FC1, FC5, T7, C3, CP1, CP5, P7, P3, Pz, PO3, O1, Oz, O2, PO4, P4, P8, CP6, CP2, C4, T8, FC6, FC2, F4, F8, AF4, Fz, Cz). First, the data were used to test if there were changes in average neural connectivity following the interventions. This was done by filtering the data into relevant frequency bands; delta (0-4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10-12 Hz) and beta (12–25 Hz), and running a weighted phase lag index (wPLI) connectivity analysis. The wPLI quantified functional connectivity between the 30 electrodes, within each epoch, for each frequency band, for each condition, and for each participant. The wPLI expands upon standard phase lag index analysis that quantifies phase synchronisation into two different time series by examining the asymmetry of the distributions of phase differences (Hardmeier et al., 2014; Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011). Second, the data were used to test if there were differences in efficiency of neural communication following the interventions. This was done by calculating minimum spanning tree (MST) mean, which is based on recent advances in graph theory that minimise bias in comparisons between groups and experimental conditions (Stam et al., 2014). Both wPLI and MST mean data were imported into SPSS where change scores were calculated.

4.1.4.3. Power analysis

Each set of artefact-free EEG data (2s epochs) was subjected to Fast Fourier Transform (FFT) analysis with a 10% Hanning window, performed by BrainVision Analyzer. Absolute EEG band power (μV^2) for all 30 electrodes was calculated for delta (0-4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10-12 Hz) and beta (12–25 Hz) frequency bands. The data was then imported into SPSS to test if there were significant changes in power following the interventions.

4.1.5. Questionnaires

As mentioned in the introduction, the choice of outcomes was primarily based on the self-regulation theory (Tang et al., 2015):

1) Emotion regulation (Difficulties in Emotion Regulation Scale; Gratz & Roemer, 2004)
2) Perceived stress (Perceived Stress Scale; Cohen, Kamarck, & Mermelstein, 1983))
3) Mindfulness (Mindful Attention Awareness Scale; Brown & Ryan, 2003)

The Mindful Attention Awareness Scale (MAAS; Brown & Ryan, 2003) is a 15-item scale that measures dispositional mindfulness. It asks participants to rate the degree to which they are attentive to and aware of present moment experience (e.g., ‘‘I find it difficult to stay focused on what’s happening in the present’’) on a scale from 1 (almost never) to 6 (almost always). The scale shows strong psychometric properties and has been validated with college, community, and cancer patient samples. The measure takes 10 minutes or less to complete. Individual items were averaged to create a composite dispositional mindfulness score. Higher score indicates higher levels of trait mindfulness. Internal consistency (coefficient alpha) at baseline in the present sample was .69.

The Perceived Stress Scale (PSS; Cohen et al., 1983) is a 10-item scale that is the most widely scale for measuring the perception of stress. It asks participants to rate the degree to which situations in their life are appraised as unpredictable, uncontrollable and overloaded (e.g., ‘‘In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?’’) on a scale from 0 (never) to 4 (very often). The PSS was designed for use in community samples with at least a junior high school education. The questions are of a general nature and hence are relatively free of content specific to any subpopulation group. The measure takes 10 minutes or less to complete. Individual items were summed to create a stress score. Higher score indicates higher levels of stress. Internal consistency (coefficient alpha) at baseline in the present sample was .15.

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) has 36 items and contains six factors: a) non-acceptance of emotional responses, b) difficulties engaging in goal-directed behaviour, c) impulse control difficulties, d) lack of emotional awareness, e) limited access to emotion regulation strategies, and f) lack of emotional clarity. It asks the participants to rate how often the statements about emotions apply to them (e.g., ‘‘When I am upset, I become irritated with myself for feeling that way’’) on a scale from 1 (almost never) to 5 (almost always) It has high internal consistency, good test–retest reliability, and adequate construct and predictive validity. The measure takes 15-25 minutes to complete. Individual items were summed to create a composite score. Higher score indicates greater difficulties in emotion regulation. Internal consistency (coefficient alpha) at baseline in the present sample was .91.

4.2. Overview of statistical analysis

To provide a preliminary evaluation of participants' responses to mind-body interventions, data analyses were performed based on intent-to-treat (ITT) principles. Post-intervention missing data of the nine participants who dropped out was handled by running multiple imputations. A *p*-value of <0.05 was considered significant and Bonferroni correction was implemented to adjust for multiple comparisons (i.e., <.02 was considered significant in individual 2-group comparisons). The data were analysed with the IBM SPSS 24.0 software (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL). The effectiveness of interventions was tested by calculating changes scores and running non-parametric Kruskal-Wallis test for K independent samples because the assumptions for ANOVA were not met. If there was a significant difference detected, it was followed with Mann-Whitney U test and Kolmogorov-Smirnov Z test to determine specific group differences. Additionally, eta squared was used as a measure of effect size to determine the proportion of variability in outcomes that can be explained by group membership.

5. Results

5.1. Evaluation of feasibility

Within one week, we enrolled 30 participants out of 59 prisoners who were in the clinical unit for personality disorders within HMP Whitemoor on March 2017. The recruitment process was facilitated by collaborating with internal research assistants who were familiar with each prisoner. The most common reason for refusing to participate in the study were self-reported physical limitations, likely stemming from media portrayal of yoga as being for slim and flexible individuals only. The other most common reason was related to the timing of delivering interventions as it was only possible to deliver them during one of the four annual week-long therapy breaks within the unit. In comparison with their regular routine, which follows daily therapy and work engagements, during the therapy break prisoners have less duties, and also socialise and rest more than usual, thus some refused to participate in the study in order to avoid additional obligations. Finally, some potential participants refused to participate due to randomisation procedure because it prevents choosing which group to be assigned to. Similarly, 23% of recruited participants demanded to be assigned to their preferred group, which disabled a standard randomisation procedure. Nevertheless, stratified random sampling was successful as there were no differences between the three groups based on the in terms of psychopathy, type of personality disorder, perceived stress, emotion regulation, trait mindfulness, age or number of attended psychotherapy session. (Table 1). The 30 recruited participants were all male and had a mean age of 41 (SD = 8.00). All recruited participants had two or more personality disorders, which is commonly observed in clinical practice (Zimmerman, Rothschild, & Chelminski, 2005), while 90% of recruited participants had ASPD.

The data collection procedures lasted two to three hours per participant at each of the two time points and included a set of three questionnaires, two cognitive tasks, EEG recording and an optional blood sample collection. Despite the length and the complexity of measures, all participants had the capacity to complete the entire data procedures without taking a break. Participants understood the questions and tasks, the only exception being the risk-ambiguity cognitive task where some had difficulties with understanding the instructions. As blood collection was not mandatory, only 12 out of 30 participants agreed to give blood. The main reason for rejecting blood collection was a fear of misusing their blood sample and a lack of trust in anonymisation of data, which was especially evident in participants with paranoid personality disorder.

We encountered further difficulties on the first day of the interventions when four out of 30 participants decided not to attend sessions of the group they were allocated to, despite agreeing to random allocation before signing the consent form. Instead they went to their most preferred group; two participants that were allocated to yoga attended mindfulness sessions only, and two participants that were allocated to the control group attended yoga sessions only. The attrition rate was medium, which is similar to other studies of mind-body interventions (Baer, 2013). Specifically, nine (30%) dropped out of the trial before any follow-up data could be collected: five from the yoga group, three from the mindfulness group, and one from the control group. Therefore, follow-up data are available for 21 participants: five from the yoga group, seven from the mindfulness group and ten from the control group. The participants who dropped out are included in all the analyses in accordance with intention-to-treat principles, thus the final sample size is 30. All participants in the mindfulness or yoga group attended a median of six out of eight delivered sessions, and a minimum of four sessions. The two final scheduled sessions (session nine and ten) were not delivered due to a full lockdown within prison due to problems in another unit, which points to the unpredictable barriers in delivering an interventional study in a prison setting. Therefore, participants spent the final day locked in their cells instead of attending mind-body interventions. Overall, there were sufficient resources to manage the data collection and interventions within a clinical unit for personality disorders of a high security prison. The crucial component of delivering this study was a successful collaboration with internal research assistants, clinicians and other staff members.

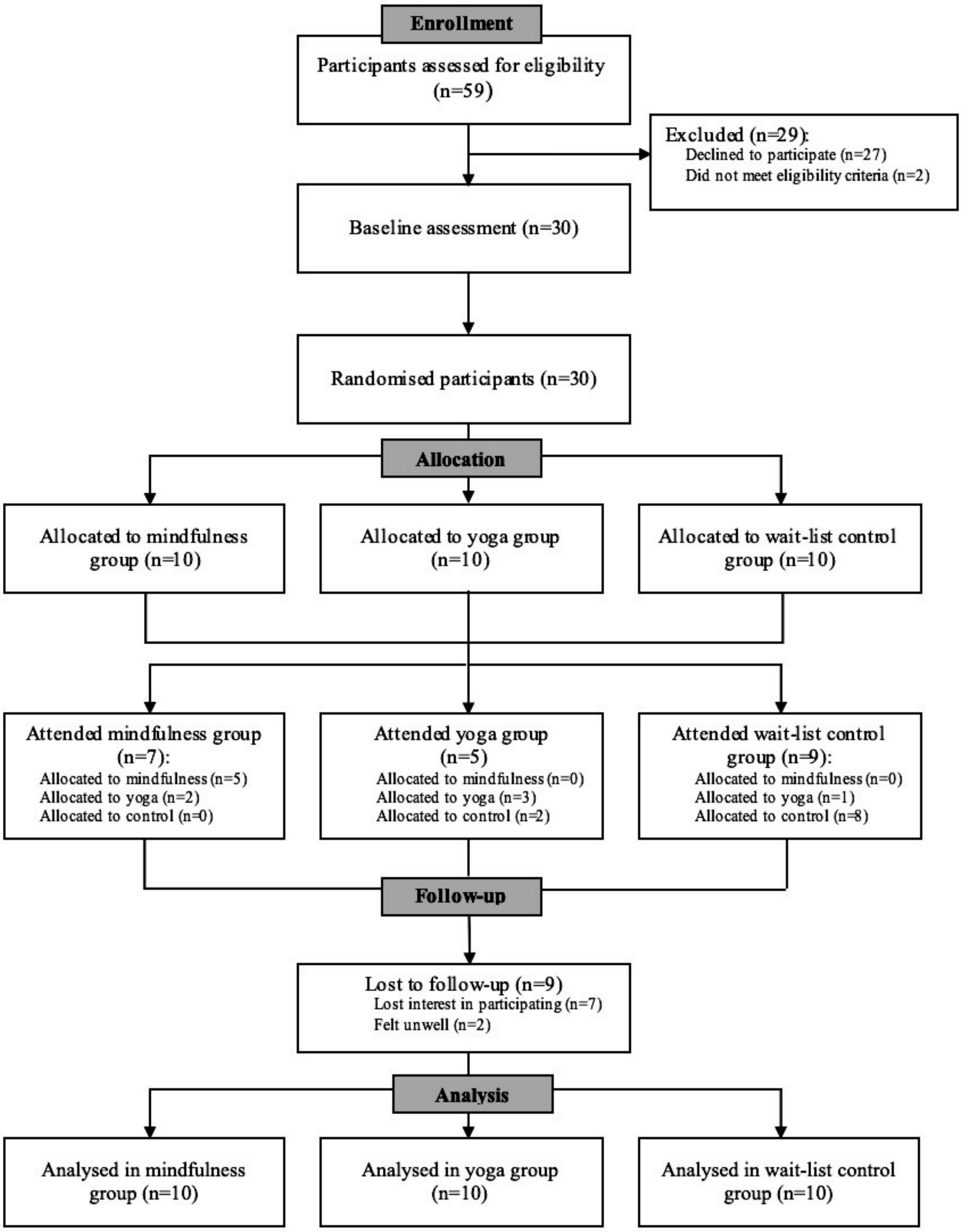

Figure 4. Flow of participants through the study

Table 1. Baseline characteristics of participants across conditions (N = 30, 10 per group)

	Mindfulness		Yoga		Control		Change
	M	**SD**	**M**	**SD**	**M**	**SD**	**Statistic, p**
Age in years	37.60	3.24	41.60	7.15	42.60	6.79	H = 4.70, p = .09
Number of psychotherapy sessions	392.10	366.90	403.20	344.55	380.40	293.68	H = .04, p = .98
Psychopathy (PCL-R)	31.75	4.12	29.32	4.99	33.16	6.98	H = .78, p = .76
Questionnaires							
PSS	24.80	6.65	25.20	6.49	26.10	4.31	H = .57, p = .75
DERS non-acceptance	17.00	3.68	16.80	5.27	19.10	6.64	H = 2.30, p = .32
DERS goal directed behaviour	13.70	4.14	16.50	2.46	16.00	5.48	H = 2.14, p = .34
DERS impulse control	14.50	3.92	15.80	4.94	17.30	6.16	H = 1.77, p =.41
DERS emotional awareness	16.90	3.84	18.30	4.90	19.10	6.21	H = 1.12, p = .57
DERS strategies	21.50	4.70	22.50	7.25	22.40	7.53	H = .07, p = .96
DERS emotional clarity	13.00	3.23	15.00	4.08	15.40	2.27	H = 2.34, p = .31
MAAS	3.13	.62	3.23	.60	3.24	.63	H = .10, p = .95
Personality disorder							
Paranoid PD	4: 4: 2 [a]		5: 3 :2 [a]		5: 2: 3 [a]		X^2 = 1.1, p = .90
Schizoid PD	0: 1: 9 [a]		2: 0: 8 [a]		0: 0: 0 [a]		X^2 = 6.22, p = .18
Schizotypal PD	0: 0: 10 [a]		2: 0: 8 [a]		1: 0: 9 [a]		X^2 = 4.54, p = .34
Anti-social PD	10: 0: 0 [a]		8: 1: 1 [a]		9: 1: 0 [a]		X^2 = 3.22, p = .52
Borderline PD	8: 1: 1 [a]		6: 3: 1 [a]		8: 1: 1 [a]		X^2 = 1.96, p = .74
Histrionic PD	2: 1: 7 [a]		1: 0: 9 [a]		2: 1: 7 [a]		X^2 = 1.75, p = .78
Narcissistic PD	4: 0: 6 [a]		3: 1: 6 [a]		4: 0: 6 [a]		X^2 = 2.12, p = .71
Avoidant PD	2: 0: 8 [a]		4: 0: 6 [a]		2: 0: 8 [a]	.	X^2 = 1.36, p = .51
Dependent PD	0: 0: 10 [a]		0: 0: 10 [a]		0: 1 :9 [a]		X^2 = 2.07, p = .36
Obsessive-compulsive PD	1: 1: 8 [a]		1: 0: 9 [a]		1: 0 :9 [a]		X^2 = 2.08, p = .72

Note: PCL-R – Psychopathy Checklist – revised; PD – personality disorder; PSS – Perceived Stress Scale; DERS – Difficulties in Emotion Regulation Scale; MAAS – Mindful Attention Awareness Scale.
[a] Frequency of definite diagnosis: probable diagnosis: no diagnosis in each group,

5.2. Preliminary evaluation of multilevel outcomes

5.2.1. Self-regulation results

In concordance with the self-regulation theory of mindfulness according to which attention control (i.e. inhibition), emotion regulation and self-awareness constitute self-regulation (Tang et al., 2015), we evaluated difficulties in emotion regulation, mindfulness, and inhibition and found no statistically significant difference after either intervention and effect sizes were zero or approaching zero (H (2,30) = 1.75, p = .43, $\eta^2 = .01$; H (2,30) = 2.06, p = .47, $\eta^2 = .00$; H (2,30) = 1.15, p = .66, $\eta^2 = .03$, respectively, Table 2).

Table 2. *The results of Kruskal-Wallis test analysis for change scores in self-report measures and cognitive tasks*

Outcome	Condition difference statistic	Significance	Effect size
Questionnaires			
Emotion regulation (DERS)	H (2, 30) = 1.75	p = .43	$\eta^2 = .01$
Non-acceptance	H (2, 30) = .95	p = .70	$\eta^2 = .04$
Goal directed behaviour	H (2, 30) = .67	p = .73	$\eta^2 = .05$
Impulse control	H (2, 30) = 2.75	p = .32	$\eta^2 = .03$
Emotional awareness	H (2, 30) = 1.50	p = .50	$\eta^2 = .02$
Strategies	H (2, 30) =.74	p = .72	$\eta^2 = .05$
Emotional clarity	H (2, 30) = 1.94	p = .45	$\eta^2 = .00$
Mindfulness (MAAS)	H (2, 30) = 2.06	p = .47	$\eta^2 = .00$
Stress (PSS)	H (2, 30) = 1.71	p = .52	$\eta^2 = .01$
RAT			
Risk .13	H (2, 30) = 2.84	p = .32	$\eta^2 = .03$
Risk .25	H (2, 30) = 2.11	p = .41	$\eta^2 = .00$
Risk .5	H (2, 30) = 1.26	p = .59	$\eta^2 = .03$
Risk .75	H (2, 30) = .71	p = .73	$\eta^2 = .05$
Ambiguity .25	H (2, 30) = 2.85	p = .44	$\eta^2 = .03$
Ambiguity .5	H (2, 30) = .14	p = .93	$\eta^2 = .07$
Ambiguity .75	H (2, 30) = 1.43	p = .61	$\eta^2 = .02$
ANT			
Alerting	H (2, 30) = 1.07	p = .61	$\eta^2 = .03$
Orienting	H (2, 30) = 1.08	p = .59	$\eta^2 = .03$
Inhibition	H (2, 30) = 1.15	p = .66	$\eta^2 = .03$

5.2.2. Risk and ambiguity results

As mindfulness and yoga can reduce the preference for risky and ambiguous monetary lotteries, which is linked with reduce risk for reoffending (Andrews et al., 2006), we analysed changes in RAT scores before and after the interventions. Results in Table 2 show that relative to the control group, neither mindfulness or yoga significantly reduced the preference for risky

(H (2, 30) = 2.84, p = .32, η^2 = .03; H (2, 30) = 2.11, p = .41, η^2 = .00; H (2, 30) = 1.26, p = .59, η^2 = .03; H (2, 30) = .71, p = .73, η^2 = .05) or ambiguous choices (H (2, 30) = 2.85, p = .44, η^2 = .03; H (2, 30) = .14, p = .93, η^2 = .07; H (2, 30) = 1.43, p = .61, η^2 = .02), and effect sizes were very low. More specifically, the proportion of trials on which a participant chose to gamble when the probability of winning is low, or chose to gamble when the probability of winning is not known, did not change following mindfulness or yoga.

3.2.3. ERP results

To determine if attention network ERP amplitudes changed after mind-body interventions, we ran a Kruskal-Wallis test that showed that the intervention has no preliminary effect on ERP measures of alerting (H (2,29) = 1.29, p = .55, η^2 = .03; H (2, 29) = .44, p = .81, η^2 = .06; H (2, 29) = 3.81, p = .35, η^2 = .07), orienting (H (2, 29) = 2.74, p = .27, η^2 = .03; H (2, 29) = .87, p = .72, η^2 = .04; H (2, 29) = 1.94, p = .47, η^2 = .00) or inhibition (H (2, 29) = 1.31, p = .60, η^2 = .03; H (2, 29) = .67, p = .73, η^2 = .05; H (2, 29) = 1.14, p = .68, η^2 = .03) at electrodes P3, P4 or Pz, respectively (Table 3, Figure 5).

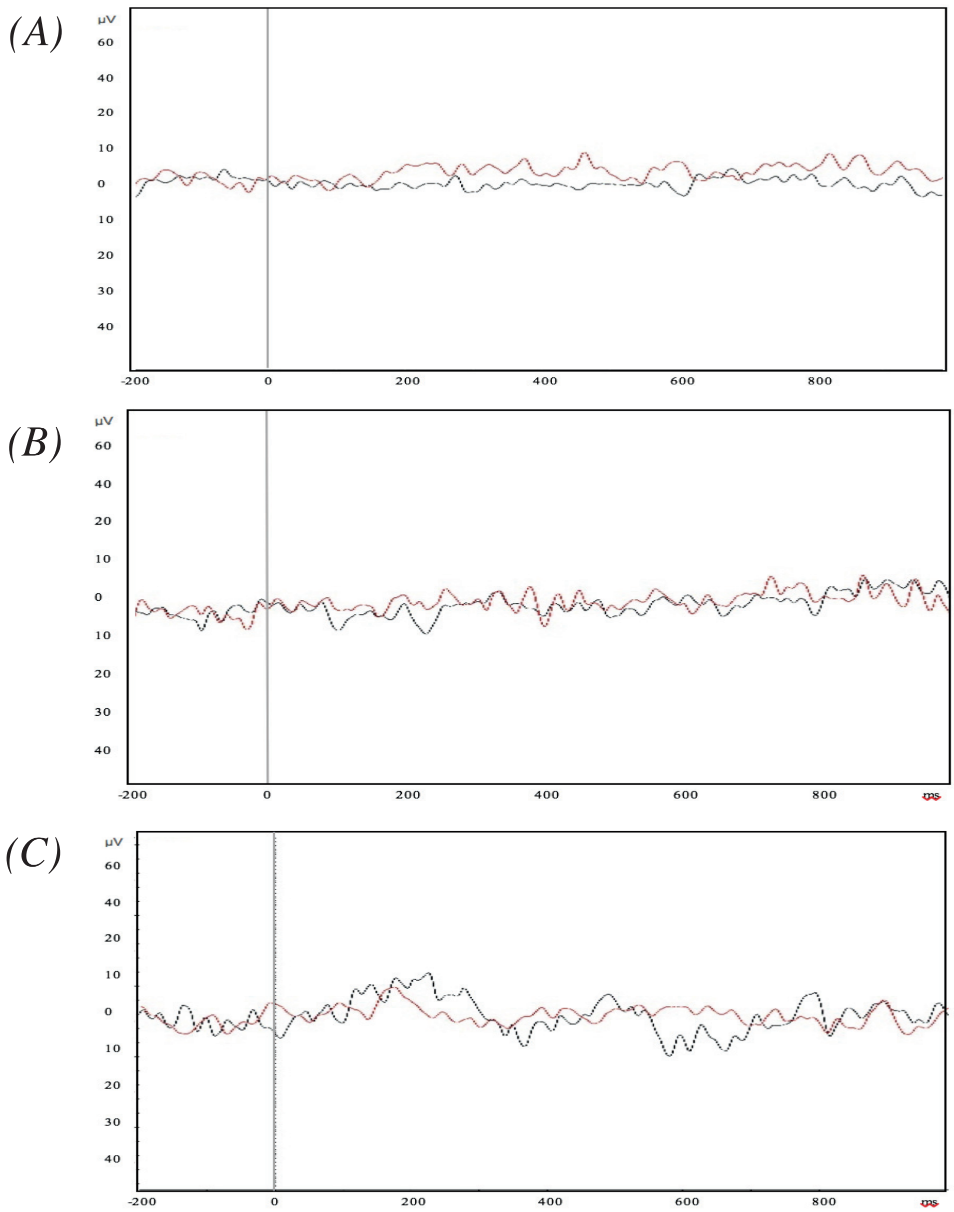

Figure 5. *Grand average waveforms for N1 and P3 at electrodes P3, P4 and Pz before (black line) and after (red line) intervention for the mindfulness group (A), the yoga group (B), and the control group (C)*

3.2.4. EEG connectivity results

To verify if there were changes in average neural connectivity following mindfulness or yoga, we analysed the difference in wPLI of each frequency band before and after the interventions. Results show that the neural connectivity remained the same in all participants regardless of group allocation (H (2, 29) = 1.21, p = .55, η^2 = .03; H (2, 29) = .31, p = .86, η^2 = .06; H (2, 29) = .86, p= .65, η^2 = .04; H (2, 29) = .92, p = .63, η^2 = .04; H (2, 29) = .57, p = .75, η^2 = .05; Table 3). Similarly, no significant differences in the efficiency of neural communications were found (H (2, 29) = .47, p = .79, η^2 = .06; Table 3).

3.2.5. EEG power results

FFT analysis of resting state EEG data found no significant difference in power in any frequency band following mindfulness or yoga compared to the control group, along with very low effect sizes (H (2, 29) = 1.92, p = .57, η^2 = .00; H (2, 29) = 3.46, p =.27, η^2 = .05; H (2, 29) = 3.04, p =.74, η^2 = .04; H (2, 29) = 1.98, p = .50, η^2 = .00; H (2, 29) = 2.71, p = .43, η^2 = .03, Table 3).

Table 3. *The results of Kruskal-Wallis test analysis for change scores in ERPs, connectivity and power analysis*

Outcome	Condition difference statistic	Significance	Effect size
ERPs			
P3 alerting	H (2, 29) = 1.29	p = .55	$\eta^2 = .03$
P4 alerting	H (2, 29) = .44	p = .81	$\eta^2 = .06$
Pz alerting	H (2, 29) = 3.81	p = .35	$\eta^2 = .07$
P3 orienting	H (2, 29) = 2.74	p = .27	$\eta^2 = .03$
P4 orienting	H (2, 29) = .87	p = .72	$\eta^2 = .04$
Pz orienting	H (2, 29) = 1.94	p = .47	$\eta^2 = .00$
P3 inhibition	H (2, 29) = 1.31	p = .60	$\eta^2 = .03$
P4 inhibition	H (2, 29) = .67	p = .73	$\eta^2 = .05$
Pz inhibition	H (2, 29) = 1.14	p = .68	$\eta^2 = .03$
Connectivity			
wPLI alpha1	H (2, 29) = 1.21	p = .55	$\eta^2 = .03$
wPLI alpha2	H (2, 29) = .31	p = .86	$\eta^2 = .06$
wPLI beta	H (2, 29) = .86	p = .65	$\eta^2 = .04$
wPLI delta	H (2, 29) = .92	p = .63	$\eta^2 = .04$
wPLI theta	H (2, 29) = .57	p = .75	$\eta^2 = .05$
MST mean	H (2, 29) = .47	p = .79	$\eta^2 = .06$
Power			
Alpha1	H (2, 29) = 1.92	p = .57	$\eta^2 = .00$
Alpha2	H (2, 29) = 3.46	p = .27	$\eta^2 = .05$
Beta	H (2, 29) = 3.04	p = .74	$\eta^2 = .04$
Delta	H (2, 29) = 1.98	p = .50	$\eta^2 = .00$
Theta	H (2, 29) = 2.71	p = .43	$\eta^2 = .03$

3.2.6. Gene expression results

To determine if prisoners with personality disorders show reduced expression of genes related to inflammation after mind-body interventions as was previously observed in studies with non-clinical and different clinical samples (Buric et al., 2017), we analysed changes in $2^{-\Delta\Delta CT}$ values and found no significant changes in the expression of any measured gene, but some effect sizes were medium and large (e.g. IRF1 η^2 = .42; NFKB1 η^2 = .26; STAT1 η^2 = .23; IKBKB η^2 = .21, Table 4).

Table 4. *Mean 2^-ΔΔCt in mindfulness and yoga group (normalized relative to the control group) and Kruskal-Wallis results of change scores (T2 – T1)*

		Mindfulness		Yoga		Control group		Test statistic	p	Effect size
		M	SD	M	SD	M	SD			
ATF2	Pre	.50	.26	.31	.25	.96	.50	H (2, 12) = .80	p =.67	η^2 = .13
	Post	1.16	.27	1.06	.39	1.16	.32			
CHUK	Pre	1.19	.06	1.23	.81	1.20	.82	H (2, 12) = .27	p =.88	η^2 = .19
	Post	1.00	.39	.65	.24	1.00	.51			
END1	Pre	.61	.27	.72	.17	.93	.31	H (2, 12) = 2.07	p =.47	η^2 = .01
	Post	.94	.43	.34	.37	1.09	.61			
F3	Pre	2.08	2.34	2.17	1.53	1.47	1.27	H (2, 12) = .63	p =.73	η^2 = .15
	Post	1.56	1.21	1.17	.47	1.44	.83			
FOS	Pre	1.73	.34	23.08	44.07	1.42	1.31	H (2, 12) = 1.47	p =.49	η^2 = .03
	Post	1.09	.24	1.37	.74	1.00	.62			
FOSB	Pre	.61	.57	.71	.60	4.84	9.30	H (2, 12) = 2.56	p =.28	η^2 = .06
	Post	2.55	1.94	2.26	1.73	1.22	.74			
FOSL2	Pre	1.20	.48	2.19	.93	.88	.48	H (2, 12) = .44	p =.82	η^2 = .17
	Post	1.84	1.72	1.36	1.32	.87	.50			
HMOX	Pre	1.06	.39	7.15	13.02	1.37	.83	H (2, 12) = .28	p =.87	η^2 = .19
	Post	.79	.36	.84	.21	.92	.22			
IKBKB	Pre	1.38	.40	1.08	1.12	1.34	.95	H (2, 12) = .12	p =.94	η^2 = .21
	Post	1.11	.59	.85	.36	1.06	.22			
IL1R1	Pre	.75	.21	.74	.11	1.46	.1.22	H (2, 12) = 2.80	p =.34	η^2 = .09
	Post	1.40	.60	1.56	.61	.95	.23			
IL1RAP	Pre	.55	.04	1.45	.89	.92	.23	H (2, 12) = 3.73	p =.16	η^2 = .19
	Post	1.41	.54	1.33	.35	1.02	.28			
IL6	Pre	1.69	.50	3.41	5.73	1.15	.81	H (2, 12) =.44	p = .81	η^2 = .17
	Post	.71	.32	.45	.37	1.09	.89			
IL8	Pre	1.89	1.40	.74	.37	.91	.48	H (2, 12) = 1.47	p = .49	η^2 = .03
	Post	1.08	.77	1.53	1.37	1.67	1.42			
IRAK1	Pre	.85	.29	.88	.26	1.15	.48	H (2, 12) = .33	p = .86	η^2 = .19
	Post	.86	.39	.85	.20	.98	.34			
IRF1	Pre	1.11	.62	1.18	.31	.96	.37	H (2, 12) = 5.78	p = .06	η^2 = .42
	Post	2.69	2.01	7.63	2.13	2.09	2.88			

JUN	Pre	1.00	.38	1.25	.94	.91	.37	H (2, 12) = 3.29	p = .20	$\eta^2 = .14$
	Post	.91	.25	.83	.36	1.74	1.30			
MAP2K3	Pre	.87	.14	1.16	.83	.84	.47	H (2, 12) = 2.95	p = .23	$\eta^2 = .11$
	Post	.67	.04	.30	.22	.98	.90			
MAP2K4	Pre	1.34	.81	2.12	1.45	1.20	.85	H (2, 12) = 1.62	p = .45	$\eta^2 = .04$
	Post	.84	.08	.94	.18	1.03	.25			
MAP2K6	Pre	1.46	.64	.89	.34	1.18	.79	H (2, 12) =.49	p = .78	$\eta^2 = .17$
	Post	1.33	.67	1.12	.22	1.04	.29			
MAP3K1	Pre	.44	.37	.50	.47	1.22	.51	H (2, 12) = 1.94	p = .38	$\eta^2 = .01$
	Post	1.05	.45	1.07	.86	1.00	.21			
MAPK14	Pre	.82	.47	1.42	.57	1.48	1.00	H (2, 12) = 1.97	p = .37	$\eta^2 = .00$
	Post	1.08	.77	1.16	.65	.82	.44			
MAPK8	Pre	.99	.81	.37	.25	.89	.37	H (2, 12) = 2.68	p = .26	$\eta^2 = .08$
	Post	.90	.48	.78	.15	1.53	1.20			
MAPK9	Pre	1.42	.87	.83	.62	1.08	.52	H (2, 12) = .08	p = .96	$\eta^2 = .21$
	Post	1.03	.42	1.10	.48	1.07	.33			
MYD88	Pre	1.29	.49	1.02	1.20	1.06	.32	H (2, 12) = 1.47	p = .48	$\eta^2 = .06$
	Post	1.92	1.61	3.05	1.40	2.11	3.35			
NFKB1	Pre	1.00	.20	.65	.24	1.26	.74	H (2, 12) = 4.35	p = .13	$\eta^2 = .26$
	Post	1.69	1.04	1.47	.67	.96	.27			
NFKBIA	Pre	.87	.31	5.48	9.05	1.08	.30	H (2, 12) = .80	p = .67	$\eta^2 = .13$
	Post	.68	.26	.81	.18	.97	.28			
NFKBIB	Pre	1.03	.45	1.14	.68	.96	.56	H (2, 12) = 2.94	p = .24	$\eta^2 = .10$
	Post	.79	.24	.69	.13	1.47	1.08			
PTGS2	Pre	.90	.86	.67	.73	.77	.42	H (2, 12) = .43	p = .81	$\eta^2 = .17$
	Post	.86	.39	.85	.20	.98	.34			
RELA	Pre	1.21	.79	.48	.13	1.06	.43	H (2, 12) =.56	p = .76	$\eta^2 = .16$
	Post	.78	.48	.39	.14	3.37	4.58			
SERPINE1	Pre	.64	.58	.75	.78	1.19	.67	H (2, 12) = 1.33	p = .52	$\eta^2 = .07$
	Post	1.03	.42	1.10	.48	1.01	.33			
STAT1	Pre	1.04	.40	.65	.32	1.06	.33	H (2, 12) = 4.03	p = .13	$\eta^2 = .23$
	Post	.83	.12	.75	.14	1.49	.82			
TNF	Pre	1.10	.17	.89	.42	1.27	.62	H (2, 12) = .67	p = .72	$\eta^2 = .15$
	Post	1.06	.17	1.03	.59	1.38	.57			
TRAF6	Pre	.90	.18	.73	.85	1.01	.41	H (2, 12) = .73	p = .70	$\eta^2 = .14$
	Post	.63	.01	.61	.03	1.03	.44			
UBB	Pre	.56	.16	.63	.31	.86	.31	H (2, 12) = .27	p = .88	$\eta^2 = .19$
	Post	.82	.60	.91	.06	1.04	.11			
UBC	Pre	.85	.84	.36	.24	1.00	.69	H (2, 12) = 2.39	p = .30	$\eta^2 = .04$
	Post	1.55	.95	.89	.18	1.10	.52			

4. Discussion and conclusions

The present study was the first one to date to test if mindfulness and yoga are feasible interventions for improving self-regulation in prisoners with personality disorders, and to explore genomic, neural and cognitive outcomes. Intensive mindfulness and yoga had shown to be safe interventions for prisoners with personality disorders. We found a solid recruitment potential in clinical units within prisons; 51% of prisoners agreed to participate. Retention rates were medium (30%) and comparable to mind-body interventions studies on other populations. Participants showed cooperation and completed all mandatory outcome measures despite their length of several hours. There were difficulties in implementing a randomisation procedure, but it is possible to overcome this and get groups that do not differ on variables that might influence the outcomes. Further difficulties are related to crossing over from one assigned group to another, which occurred in 13% of all recruited participants. We initially intended to deliver 10 1.5-hour sessions spread over five consecutive days in both mindfulness and yoga group. However, on the fifth day of the interventions, a riot occurred at another unit, which meant a full lockdown for all prisoners on that day, including our study participants. Therefore, we managed to deliver only 8 sessions (12 hours), instead of 10 sessions (15 hours). The lockdown rarely occurs within the clinical unit where the study was conducted, and it is very different from a regular day-to-day life of the prisoners because they are normally only locked in during the night. Therefore, this was a stressful event that might potentially have, to a certain degree, counteracted the beneficial effects of mindfulness and yoga.

Although previous studies found that mind-body interventions can improve aspects of self-regulation in people with borderline personality disorders (Feliu-Soler et al., 2014; Soler et al., 2012) and in prisoners (Bilderbeck et al., 2013; Kerekes et al., 2017; Samuelson et al., 2007; Sumter et al., 2009), this study found no statistically significant improvements in self-regulation following mindfulness and yoga, or in any other measured outcome. Interestingly, while all psychological, cognitive and neural measures showed very low effect sizes that are approaching zero, several genes showed markedly larger effect sizes. Most notably, a large effect size was found for the expression of gene IRF1 that encodes a protein that regulates activity of several other genes and it works as a tumour suppressor by suppressing tumour cell growth and stimulating an immune response against tumour cells. Although generally larger sample size is necessary to detect the effects of intervention, randomised control trials with small samples can still offer informative leads, and large effects can still be detected (Friston, 2012). As the effect sizes were very small for self-report measures, cognitive tasks and EEG measures, while most of the effect sizes were medium or large for gene expression, It is possible that gene expression changes are the first observable changes to emerge following mind-body intervention in personality disorders, thus future studies should not cease to explore this further despite budget requirements and more effort in data collection, storage and analysis. One final consideration concerns a possible positivity bias in the literature. All the published studies on mindfulness or yoga with prisoners or patients with personality disorders found significant positive effects of mind-body interventions. It is possible that there have been other studies that found no significant effects, but have never been published. Therefore, it might indeed be the case that our hypotheses were too optimistic based on the previous studies and that the true effect size would be small even if previously described factors were eliminated.

This study has several strengths and methodological innovations. First, although there are several other studies of mindfulness and personality disorders (Feliu-Soler et al., 2014; Soler et al., 2012) of mindfulness and prisoners (Bowen et al., 2006; Perelman et al., 2012; Samuelson et al., 2007; Suarez et al., 2014; Sumter et al., 2009) and of yoga and prisoners (Bilderbeck et al., 2013; Kerekes et al., 2017), most of these previous studies did not have a control group, and none of them included prisoners with personality disorder diagnoses. This study contributes to both forensic and psychiatric literature as the first controlled pilot trial of mindfulness and yoga in a population of prisoners with personality disorders, which is a very rarely studied clinical population despite its prevalence. We included two matched mind-body intervention groups that have the same length and the same social components, and a control group that was following their usual regimen during a therapy break. Thus, the effects of meditation were contrasted with another type of intervention and with not receiving any intervention. There was equal requirement for intervention-related activities outside sessions, and both mindfulness and yoga provided education and group support. We maximised external validity by including prisoners with various personality disorders in order to support the generalisation of the results to routine clinical practice. Last but not least, the study used an extensive array of biological and neural measures to explore the mechanisms of mind-body interventions, based on the notion that multiple levels of explanation are required to understand behavioural changes in offender populations (Brazil, van Dongen, Maes, Mars, & Baskin-Sommers, 2018).

In summary, the present study found that mind-body interventions are moderately feasible interventions for a population of prisoners with personality disorders. Preliminary evaluation of participants' responses found no statistically significant effects of mind-body interventions on genomic, neural or behavioural measures, which is expected due to small sample size. However, despite the study being underpowered to detected minimal clinically important changes, medium and large effects were found for several inflammation-related genes. This study is the essential pre-requisite that builds the foundation for a large multicentre randomised controlled trial that will determine the effectiveness of mindfulness and yoga on prisoners with various personality disorders.

CHAPTER 4

INDIVIDUAL DIFFERENCES IN MEDITATION OUTCOMES

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Abstract

Meditation generally has small to moderate effects on health and well-being, but some people experience greater benefits from meditation than others. What are the characteristics of the study participants or meditation students that lead to beneficial outcomes of meditation? In this chapter, we adopt a multilevel approach to evaluate the evidence on the relationship between participant characteristics and individual differences in meditation outcomes across four sources of variability: personality and other psychological variables, biological variables, illness severity, and demographic factors. Research in the area is sparse and has several methodological shortcomings, thus we recommend the use of multi-level models and meta-regression as ways of properly incorporating the study of individual differences with other variables.

1. Introduction

Over the past five decades, hundreds of scientific studies have accumulated evidence highlighting the positive effects of meditation (for a review see Goyal et al., 2014; Sedlmeier et al., 2012). As a consequence, meditation has gained popularity and is increasingly used as a tool to cultivate health, happiness, and general well-being. However, little attention has been paid to individual differences in responses to mediation.

As with any other kind of intervention, there is a spectrum of possible responses to meditation, from extremely positive responses at one end to adverse effects at the other. However, it is not clear what factors (e.g. personality traits) cause variation in response to meditation. By calculating the average of the responses, variation in how individual participants are affected by meditation is masked. In each study, there will be individuals who respond to meditation better or worse than the average of a group. Therefore, the individual scores illustrate the variability in responses to meditation, while the average group score masks the fact that for some people a certain meditation programme was extremely beneficial, while for others it may not have been beneficial, or even have been detrimental. Surprisingly, there is no comprehensive study on this topic and only a limited number of studies have directly tested individual differences in responsiveness to meditation. To elucidate the relationship between differences in participant characteristics and meditation outcomes, we need to identify the predictors, moderators, interactions, and correlates of the effects of meditation.

As we do not know what kind of people experience adverse effects or simply show no effects following meditation interventions, we cannot predict or improve people's responses to meditation. In other areas of health-related research, there is a shift occurring in which choices for treatment and diagnosis are tailored to the genetic, biological and cognitive characteristics of people (Cuthbert & Insel, 2013; Insel, 2014; Jackson & Chester, 2015). For instance, the treatment for many types of cancer is no longer based on the tissue type or anatomical site of origin, instead the analysis of biomarkers can predict what treatment will be optimal (Jackson & Chester, 2015). The notion that there should be individualised treatment based on patient characteristics is often called 'precision medicine' or personalised medicine. The central idea is to create new knowledge that can aid in selecting treatments that will work best for a certain person, unlike most current treatments that are designed based on the one-size-fits-all principle and benefit some individuals, while others show no improvements or even have adverse responses. The same personalised approach could be applied in meditation but, in order to get there, many years of rigorous scientific work are required to understand many participant-related factors that could influence the response to meditation. The current goal is not to provide clinical suggestions at this early stage, but rather to lay groundwork that can foster continual developments in research and inform future strategies for personalised applications of meditation. If we would be able to distinguish positive responders from null and negative responders based on their individual characteristics, then those who would benefit the most could be targeted, while a different evidence-based technique could be applied to those for whom meditation would be contra-indicated. This personalised approach would not only save resources, but also help prevent harm.

The main goal of this chapter is to examine possible sources of individual differences in the current literature and discuss the factors that have been shown to have an impact on the effects of different types of meditation. The central focus is on 26 intervention studies obtained through PubMed search that explored the effects of learning meditation on people who previously had no experience in meditation. We also consider relevant meta-analyses in addition to controlled and non-controlled interventional studies. We cover four sources of variability in individual responses to meditation that were previously identified in meditation research: i) psychological variables; ii) biological variables; iii) illness severity and iv) demographics.

2. Individual differences due to psychological variables

The majority of studies that have explored individual differences in responsiveness to meditation have focused on psychological variables. These studies used standardised psychological measures – most commonly questionnaires – through which data can be obtained quickly and efficiently. Out of many possible psychological factors that could have an impact upon the effects of meditation training, personality, stress, and mood are the most researched sources of inter-individual differences.

2.1. Stable psychological factors: The “Big Five”

Personality traits are linked to characteristic patterns of behaviour and, as such, have been a major area of interest in psychology. Personality used to be considered as stable over time and fixed after the age of 30 (McCrae & Costa, 1994), while more recently it has become accepted that personality changes across lifespan (Roberts, Walton & Viechtbauer, 2006). It has been proposed that meditation is also one of the environmental factors that can help shape personality in later life (Crescentini & Capurso, 2015). In psychology, personality is commonly described using the Big Five model that divides personality into five dimensions: Extraversion, neuroticism, conscientiousness, agreeableness and openness to experience (John & Srivastava, 1999).

It is plausible to assume that individuals high in certain personality traits, such as openness to experience, might be more inclined to try meditation. However, it is not clear how different constellations of personality traits are related to how people respond to meditation. Most studies on the topic have focussed on individual personality traits, rather than using a holistic person-centred approach that captures the pattern of relationships with multiple traits. For instance, Lane, Seskevich, and Pieper (2007) showed that participants scoring high on neuroticism experienced particularly pronounced effects of reduced perceived stress and less negative emotions after three months of mantra-based meditation practice. However, this study did not explore any other personality trait besides neuroticism. Similar results were found in a study of Mindfulness-Based Stress Reduction (MBSR) in students, which showed that those who scored high on neuroticism benefited more from MBSR than others (de Vibe et al., 2015). Individuals scoring high on neuroticism reported lower levels of mental distress and higher levels of subjective well-being as a result of the training. Notably, this study also explored if conscientiousness and extraversion moderated the response to MBSR, and found that, indeed, students who scored higher on conscientiousness experienced the greatest effect of the intervention on reducing study-related stress, but there were no effects of extraversion (de Vibe et al., 2015). A study of an Integrative Body Mind Training (IBMT), which is based on mindfulness, compared a one-week IBMT to an equally long relaxation programme in terms of improving creativity (Ding et al., 2015). This study showed that creativity improved after the IBMT training, and while the control group (who completed the relaxation training) also improved on creativity, the IBMT group outperformed them significantly. With regards to individual differences in personality, they found that psychoticism did not influence creative performance after IBMT or after relaxation. Furthermore, introversion was associated with a greater increase in creativity after the trainings in both groups, while neuroticism was associated with increases only in the meditation group. Ding and colleagues (2015) interpreted these results as an indication that introverted individuals are overall readier to engage in meditation and relaxation programmes. This interpretation is in conflict with Delmonte's (1988) findings, who found that introverted outpatients with psychosomatic and neurotic symptoms were less likely to continue practicing Transcendental Meditation (TM) regularly 3, 6, 12 and 24 months after learning the technique, suggesting they may be less likely to reap the long-term benefits of meditation. One possibility is that introverts respond more favourably to mindfulness-based programmes such as IBMT than to those mantra-based such as TM. Another explanation is that introverts may show more engagement only during the first 8 weeks of learning meditation, which is the length of the IBMT programme, and Ding and colleagues' (2015) study did not track long-term effects. Delmonte's (1988) study additionally looked at neuroticism, repression (i.e., being prone to extreme avoidance strategies such as denial), suggestibility, and locus of control (i.e., believing that events in one's own life are under personal control as opposed to external forces that are beyond control). Other than introverts, participants who scored low on repression were also less likely to practice meditation regularly at all follow-ups. Participants who scored high on neuroticism and suggestibility were less likely to practice meditation regularly at 3-month follow-up only, whereas no effect was found for locus of control at any follow-up. Further understanding of neuroticism and the response to meditation can stem from examining discomfort with emotions, which is present in people who score high in neuroticism (Bono & Vey, 2007). Distressed adults who reported more discomfort with emotion before a mindfulness intervention had less reduction in distress following the intervention (Sass, Berenbaum & Abrams, 2013). This was interpreted as them avoiding the exploration of current emotional experiences, which is an important part of mindfulness practice.

Individual differences in trait anxiety, which conceptually largely overlaps with neuroticism (Jorm, 1989), have also been a prominent topic of investigation in meditation research. However, it is important to distinguish trait anxiety/neuroticism from anxiety disorders; trait anxiety is a risk factor for developing anxiety disorders. Both seem to be linked to the effects of meditation, but there are some conflicting findings. An early meta-analysis showed that practicing different types of meditation and relaxation techniques can reduce levels of trait anxiety, and TM reduces trait anxiety the most (Eppley, Abrams & Shear, 1989). A more recent meta-analysis of 16 randomised controlled trials of TM tested if baseline trait anxiety was reduced following meditation (Orme-Johnson and Barnes, 2014). It was found that the improvements were the largest for people with high trait anxiety levels (80^{th} to 100^{th} percentile), who responded better to TM than to mindfulness-based therapy. When baseline anxiety is within the normal range, then TM and mindfulness-based intervention appear to be equally effective in reducing anxiety. However, it is not known if these participants had symptoms of anxiety that satisfied the criteria for anxiety disorders.

Two other meta-analyses of studies involving participants diagnosed with anxiety disorders and who attended mindfulness-based interventions have found conflicting results. One of these meta-analyses found that following meditation anxiety was reduced in people with anxiety disorders just as strongly as depression was reduced in those with mood disorders (Hofmann, Sawyer, Witt & Oh, 2010). The other meta-analysis found that mindfulness interventions are not helpful for individuals with a current episode of anxiety disorder, but they seem to help those with a current episode of depression (Strauss, Cavanagh, Oliver & Pettman, 2014). Differences between the results of these meta-analyses are likely due to the fact that one only included studies where participants were randomly allocated to groups and that had a control group (Strauss, Cavanagh, Oliver & Pettman, 2014), whereas the other also included pre-post designs, and included (for more than half of the eligible studies) studies without a control group (Hofmann, Sawyer, Witt & Oh, 2010).

In summary, most of the studies that explored how personality relates to meditation response are related to the Big Five personality model, especially to neuroticism and anxiety. People who score high in neuroticism or trait anxiety seem to respond better to meditation, unless they are currently experiencing an episode of anxiety disorder. Conscientious people also seem to respond better, but it is currently unknown if this is only because they are consistent with their practice. The findings for extraversion are mixed; it seems to be associated with the frequency of meditation practice, but not with any other meditation outcomes. However, these conclusions are based on just a handful of studies, and not all of them had a control group or used the same type of meditation or population. Thus, there is still a need for more studies targeting the link between personality and meditation response.

2.2. Stable psychological factors: Other personality factors

While most of the studies discussed so far were embedded in the Big Five model of personality, others have focused on alternative factors that influence personality. One such factor is *temperament*, which has been defined as “early emerging basic dispositions in the domains of activity, affectivity, attention, and self-regulation, and these dispositions are the product of complex interactions among genetic, biological, and environmental factors across time” (Shinner et al., 2012, p.2). There is a general agreement that temperament remains more stable over the lifespan than personality, and that it is evident from birth because it seems to have detectable biological correlates (Kagan, 2005).

Takahashi and colleagues (2005) explored the effects of temperament on brain activity and heart-rate variability during Zen meditation (based on counting exhales) in people who had never meditated. This study employed a psychobiological model of temperament that regards novelty seeking, harm avoidance, reward dependence and persistence as components of temperament (Cloninger, Svrakic & Brzybek, 1993). While participants were meditating, the researchers recorded brain activity through electroencephalography (EEG) and assessed heart rate variability. During Zen meditation, individuals with high levels of harm avoidance showed larger changes in power in oscillatory brain activity that range from 4 to 7 Hz, which has been associated with being mindful (e.g., Baijal and Srinivasa, 2010). Individuals with high levels of novelty seeking had larger changes in EEG power in frequencies that range from 10-12 Hz, which is associated with top-down attention (Klimesch et al., 1998). Novelty seeking was also negatively related to changes in heart rate variability, indicating deactivation of sympathetic nervous system (i.e., a part of the autonomic nervous system that prepares the body for action). Taken together, the findings support the view that there is a relationship between facets of temperament, Zen meditation, and bodily changes. However, this study focused on EEG and heart rate variability, while no psychological measures of mindfulness or cognitive measures of attention were included. Thus, it is unclear whether individuals with high levels of harm avoidance were more mindful, and if those with high levels of novelty seeking actually had a better modulation of top-down attention and higher levels of relaxation.

Mindfulness itself can also be defined as a personality trait rather than a transient state measured during meditation practice (Lau et al., 2006). From this perspective, trait mindfulness is considered to reflect the extent to which a person is oriented to the present experience in their daily life and aware of their own thoughts, emotions, and bodily sensations, without judging them or trying to change them (Baer, Smith, Hopkins, Krietemeyer & Toney, 2006). Trait mindfulness has been found to vary within populations and seems to remain relatively stable when a person has not learned how to practice mindfulness techniques (Brown & Ryan, 2003). It can be assumed that people with 'naturally' higher levels of trait mindfulness respond better to mindfulness meditation, because they find it easier to achieve a meditative state, and it may be more pleasant for them. On the other hand, it is also plausible for people who start with low levels of mindfulness to have more space for progress and to be less likely to experience a ceiling effect. The former hypothesis has been confirmed in a study that found that people who score high on mindfulness before they learn how to meditate have better long-term outcomes (following meditation) in terms of increases in mindfulness, hope, empathy, and well-being, with concurrent decreases in perceived stress and rumination (Shapiro, Brown, Tohresen & Plante, 2011). Another study found that people who are low in trait mindfulness produce more stress hormone cortisol in response to a laboratory-induced stressful situation than other participants after a 3-day mindfulness intervention, even though they report perceiving less stress (Creswell et al., 2014). The researchers suggested that a brief mindfulness intervention initially fosters greater coping efforts in people who are low in trait mindfulness, which in turn appears to increase cortisol and reduce stress appraisals. Another possibility is that mindfulness intervention does not actually reduce perceived stress in people who are low in trait mindfulness, but only their responses to questionnaires that measure perceived stress (i.e., this could be an example of a response bias).

Not all studies found that trait mindfulness influenced responses to meditation. Irrespective of initial levels of trait mindfulness, students gained similar benefits from Mindfulness Based Stress Reduction (MBSR) in a previously mentioned study that measured well-being and distress as outcomes (De Vibe et al., 2015). Similarly, a small uncontrolled study of distressed adults who received mindfulness training found no moderating effects of trait mindfulness on distress (Sass, Berenbaum & Abrams, 2013). Another study, by Jacobs et al. (2011), examined the influence of trait mindfulness on the response to meditation in experienced meditators. Their focus was on psychological functioning, which consisted of purpose in life, perceived ability to control own life, and neuroticism. After three months of intensive meditation, individuals who initially had worse psychological functioning showed the most improvement on these measures as compared to other experienced meditators. This group also showed the greatest increase in telomerase activity (i.e., an enzyme associated with longevity), which suggests that meditation reduces the risk for diseases by preventing the shortening of the ends of chromosomes that commonly occurs as we age. These findings overlap with those from studies on neuroticism and anxiety and suggest that people who are initially more mentally unwell, such as highly neurotic, anxious and insecurely attached, benefit more from meditation.

Another personality-related construct that influences the response to meditation is attachment style. This is formed in early childhood based on the relationship with the primary caregiver and is thought to influence interpersonal relationships throughout life (Bowlby, 1982). There are considered to be four main attachment styles: Secure attachment, insecure anxious-avoidant, insecure anxious-resistant, and disorganised attachment (Ainsworth, Blehar, Waters & Wall, 2015), although the main distinction that is often made is between secure and insecure attachment. An insecure attachment style is likely to be formed in cases where the caregiver does not respond consistently to the child's needs or is unavailable (Thompson & Raikes, 2003). Attachment style has been explored in the context of MBSR, where those with insecure attachment had higher baseline stress levels, and their stress levels declined dramatically in comparison to participants with secure attachment (Cordon, Brown & Gibson, 2009). Although insecurely attached individuals were twice as likely to drop out of meditation programs, those that completed them consequently had significantly lower levels of perceived stress than securely attached individuals (Cordon, Brown & Gibson, 2009). This finding converges with a study showing that introverted and neurotic people were less likely to adhere to regular meditation practice (Delmonte, 1988). It may be beneficial for teachers to recognise these traits in people who attend meditation programmes, so that an effort could be put in to keep them motivated to continue with meditation as these subgroups of individuals might also be more likely to experience benefits.

To summarise, other than the Big Five model of personality, there are some personality-related traits or temperaments that can influence the response to meditation, such as trait mindfulness, and type of attachment. Studies suggest that each of these could potentially be a predictor of the response to meditation, but at this point there are not enough studies to draw firm conclusions about any of them specifically. More studies are needed to replicate and extend these findings because of mixed results for trait mindfulness, and in the case of attachment and temperament, respectively, only one study is available. Current inconsistencies in the literature might be due to differences in population types, meditation types, or the choice of outcome measures. Importantly, personality traits are not the only factors that cause individual variability in responses to meditation. Transient factors, such as mood and stress, also seem to have some explanatory value.

2.3. Transient psychological factors: (i) Mood and stress

Mood is one of the few transient psychological factors studied in relation to meditation. In a previously mentioned study that found a link between IBMT, personality, and creativity (section 2.1.), the researchers also explored how initial mood influences creative performance following this meditation programme (Ding et al., 2015). They found that improvement in creativity after one week of meditation was predicted by higher anger/hostile mood states, and lower depression/dejection and fatigue/inertia mood states at baseline, before starting the meditation. Moreover, mood interacted with personality factors and helped explain individual variability; mood and personality explained 57% of inter-individual variability in the improvement in creativity, which suggests that initial mood is an important aspect of individual differences in meditation. Another study employed a one-off 10-minute kindness-based meditation and showed that not being in a positive mood prior to meditation leads to less relaxation, less positivity towards self, and lower stress-buffering effects after meditation (i.e., the reduction in heart rate after exposure to social stressors was slower), especially among socially anxious participants (Law, 2011). In a group of cancer patients, those with a heightened negative mood at baseline benefited the most from a mindfulness programme in terms of mood improvement and stress reduction, an effect which remained present even at a 6-month follow-up measurement (Carlson et al., 2001). Finally, one study with healthy adults found that initial mood disturbance does not influence how much people will practice compassion meditation over their 6-week course, but it was not examined if initial mood disturbance influences the response to meditation (Pace et al., 2010).

Thus, mood seems to influence the response to meditation, but it is difficult to draw a general conclusion about mood and meditation after only four studies, especially as results vary based on the type of population and assessed outcomes. Following that initial mood seems to influence how a person responds to meditation; one would predict that initial levels of stress would affect the response to meditation in a similar manner, as mood and stress normally have similar effects on behaviour (e.g., binge eating, pain, or mother-child interactions). However, this appears to not be the case in response to meditation. What has been found, instead, in a study on cancer patients who underwent MBSR, is that baseline perceived stress (i.e., levels of perceived stress before MBSR training) did not influence mood or stress levels after intervention (Carlson et al., 2001). This could be due to adverse effects experienced by stressed individuals during meditation, who may then lose motivation to practice frequently.

Based on the currently available studies, it seems that initial mood largely influences the response to meditation, while initial stress levels do not have a predictive value. However, it is possible that stress, together with mood, can influence the response to meditation indirectly; when a person is deciding whether to try meditation, current mood and stress may contribute to the generation of expectations. It is well established in health psychology that expectations about outcomes of different kinds of rehabilitations programmed influence the recovery, although the underlying mechanisms are not fully understood (Mondloch, Cole & Frank, 2001). In the next section, we will explore if positive expectations about meditation can influence the response to meditation and lead to more benefits.

2.4 Transient psychological factors (ii): Expectations and emotions

The possible impact that expectations may have on meditation outcomes is a topic that has been neglected in meditation research. One exception is Delmonte (1981, 1985, 1988) who conducted a set of meditation studies showing that positive expectations affect regularity of practice and reported benefits. Furthermore, he showed that expectations concerning the effects of meditation were not stable, but varied over time with experience. Positive expectations at baseline were predictive only of practice frequency at a 1-month follow up, but not of long-term practice frequency (Delmonte, 1981). Generally, those who ended up practicing more frequently had reported higher expectations about the positive effects of meditation at baseline. In a later study, Delmonte (1985) manipulated expectations in naïve meditators by presenting meditation as either beneficial or non-beneficial before they began a meditation course. This study demonstrated that fostering positive expectations lead to better physiological outcomes, such as lower blood pressure, lower heart rate, and lower skin conductance level. However, none of Delmonte's studies included a control group and, therefore, it cannot be ruled out that expectations could have had the same physiological effect in a non-meditation intervention. To account for this, Creswell et al. (2014) controlled for the possibility that merely having positive expectations about the outcomes of mindfulness led to perceiving more benefits in its practice. Briefly, in this study, half of the participants were randomly assigned to a brief 3-day poem analysis course, and the other half to a mindfulness course of the same length. Positive expectations about efficacy and relevance of both poem analysis and a mindfulness course were measured. During the first two days, participants in both groups had equally positive expectations that the courses were improving their cognition. On the third day however, the mindfulness group had significantly more positive expectations than the poem analysis group, demonstrating the need to take fluctuations of expectations into account in the analyses.

In addition to individual differences in expectations, emotions may be another psychological variable that may have an influence on the effects of meditation. More specifically, emotions experienced during meditation training can predict long-term continuation of meditation practice. In Cohn and Fredrickson’s (2010) study, positive emotions (amusement, awe, contentment, gratitude, hope, joy, interest, love) and negative emotions (anger, contempt, disgust, embarrassment, guilt, sadness, shame, fear) were recorded daily during 8 weeks of loving-kindness meditation training. Participants who experienced a greater amount of positive emotions during the first few weeks of training were more likely to meditate at a one-year follow-up. Even though other participants practiced just as much during the training, if they did not have an increase in positive emotions before the fifth week, they were less likely to maintain a long-term meditation practice. Interestingly, at baseline, people who became long-term meditators were no different from those who did not continue to practice meditation after the training, in terms of demographic variables, measures of mindfulness, well-being, hope, ego-resilience, savouring, self-other overlap, or symptoms of illness and life satisfaction. The only difference between those who continued to practice meditation and those that did not—aside from early positive emotions—was that continuing meditators gave and received more social support. However, it should be noted in cases like this where there are multiple comparisons (i.e., 10 variables were tested as potential differences between meditators and non-meditators), the probability of getting a false positive result is increased. Therefore, the result regarding the influence of social support on continuation of meditation practice might have occurred by chance, which can only be confirmed if future studies attempt to replicate the results. The only other study that explored the effects of emotions was done in individuals with hypertension, and it was found that the greatest reduction in blood pressure was in people who found the practice easy, and reported feeling better during meditation, and fresher and more relaxed after the practice (Seer & Raeburn, 1980).

In summary, the evidence suggests that both expectations and experienced emotions account for some of the individual differences in response to meditation. Beginning to learn and practice meditation while having positive expectations leads to more experienced benefits of meditation. Similarly, experiencing positive emotions during and after meditation appears to be important in maintaining long-term practice. The underlying mechanisms are not understood. It is possible that positive expectations foster positive emotions during meditation, although this has not been tested directly. It is crucial that researchers continue to obtain baseline measures in order to better understand the complex dynamics of the interactions between psychological variables and meditation.

3. Individual differences due to biological variables

Many have suggested that meditation, as well other mind-body interventions such as yoga or Tai Chi, should be associated with changes that extend beyond psychology (Black & Slavich, 2016; Bower & Irwin, 2016; Buric et al., 2017). This notion that meditation impacts our biology is receiving an increasing amount of attention. Several studies have explored the possibility that a blood test or a brain scan could help to assign a person to the most suitable type of meditation (Jung et al., 2012; Mascaro, Riling, Negi & Raison, 2013). The core tenet here is that, while employing this approach in practice would be expensive, if it works, it would be more objective than self-report measures commonly used in psychology research.

As our biology is constantly changing in response to the environment, the simplest method to explore whom meditation would benefit the most would be to examine the structure of our genes, which never changes. The only study that explored the relationship between genes and responsiveness to meditation compared experienced meditators with non-meditators of similar demographic characteristics (Jung et al., 2012). The meditation they investigated is called Brain Wave Vibration, which includes repetitive movements and a focus on bodily sensations. This study analysed two genes: Brain derived neurotrophic factor (BDNF), which is associated with neuroplasticity and dopamine regulation, and catechol O-methyl transferase (COMT), which is associated with regulation of dopamine, norepinephrine, and epinephrine. Surprisingly, experienced meditators who had a certain variant of BDNF gene (Val66Val) showed the same levels of perceived stress levels as non-meditators with the same gene variant. This implies that people with BDNF Val66Val gene polymorphism may not respond to meditation, at least not in terms of stress reduction. On the other hand, meditators with COMT Val158Val gene variant had lower plasma norepinephrine levels than meditators with COMT Val158Met or COMT Met158Met variants. This finding suggests that among people with the same amount of meditation experience, there will be differences in how their bodies respond to stress biologically – those with COMT Val158Val will produce lower levels of hormones associated with stress response. Moreover, experienced meditators with COMT Met158Met gene variant had even higher norepinephrine levels relative to non-meditators with the same gene variant, which suggests that this gene variant provides a disadvantage, because even if you meditate regularly your stress response will not be any better than of people with other variants of COMT gene who have never meditated before.

One must take care when considering these results and other studies on genetic variants. First, this study based its conclusions on the analysis of gene variants in only 80 meditators and 57 non-meditators, which is far from a necessary sample size in the studies of gene variants, especially if potential confounding variables are not controlled for (Moonesinghe, Khoury, Liu & Ioannidis, 2008). Studies on genetics often require much larger sample sizes (Hong & Park, 2012), thus these findings should merely be considered exploratory or hypothesis-generating. Second, even in the case when the sample size is large enough, exploring correlations of just one or a few genes with a certain outcome does not provide a full picture as many features are coded by multiple genes. Even simple characteristics, like our height, are regulated by hundreds of genes (Wood et al., 2014). Finally, genes that we inherited do not fully determine our characteristics because every gene can change its activity in response to the environment. While the genes themselves remain unchanged, the degree to which a gene is expressed (i.e., produces its own proteins) varies over time. A gene can get completely turned off (i.e., stop producing its own proteins) and will then not have an effect on the phenotype. Thus, even if a person has inherited genetic vulnerabilities, these vulnerabilities may not be expressed. Therefore, measuring gene variants and neglecting the measurement of the activity of those genes is not a reliable method for determining the influence of genetics. Even though gene activity can be determined from blood just as easily as gene variants, it is a relatively new field, and at this point there are no studies that have explored individual differences in meditation with this approach.

There are several other biological variables that can be measured from blood samples to explore individual differences, such as interleukins. Interleukins are a set of proteins considered to be the markers of the immune system's activity. An especially relevant interleukin in this context is interleukin-6 (IL-6), which shows increased concentrations in individuals with chronic stress (Carpenter et al., 2010). Also, reducing IL-6 concentration has been linked to protective effects on health (Nemeth et al., 2004). One study found that compassion meditation training decreased the levels IL-6 in response to laboratory-induced stress, but only in individuals whose practice frequency was above the median (Pace et al., 2009). However, neither baseline levels of IL-6 nor baseline levels of the hormone cortisol predicted the amount of subsequent meditation practice in this study, thus questioning the robustness of the relationship between IL-6 and meditation.

Reich et al. (2014) identified several biomarkers that can be measured in blood and predicted symptoms that were reduced the most in breast cancer patients following MBSR. More specifically, they found that reductions in gastrointestinal symptoms (dry mouth, nausea, vomiting, and lack of appetite) following MBSR could be predicted by measuring the amount of one type of white blood cells (B lymphocytes) and a protein involved in immunity against infections (interferon-γ). Moreover, psychological improvement in memory, distress and sadness following MBSR were predicted by another type of white blood cells that fights against infection (CD4 and CD8 cells), while fatigue was predicted by a protein involved in the regulation of the immune system (interleukin IL-4) and the total amount of white blood cells. Generally, participants with increased immune activity at baseline, as measured by interleukins and interferon-γ, had fewer adverse symptoms after meditation training (Reich et al., 2014).

The biological approach to individual differences does not have to stop at the analysis of various markers from blood samples. With the advances in technology, it is now possible to get access to the brain, which provides us with an additional level of explanation for understanding individual differences in meditation outcomes. Since it is known that meditation can affect the structure of the brain and its activity (see chapter Meditation and the Brain), we can assume that it might be possible to predict a person's response to meditation based on the structure or activity of their brain. This hypothesis was tested in a study that aimed to determine which type of meditation a person will prefer to practice based on their baseline brain activity (Mascaro, Rilling, Negi & Raison, 2013). In this study, participants were taught mindfulness meditation (during the first two weeks) and compassion meditation (during the last two weeks) as a part of 8-week Cognitively-Based Compassion Training (CBCT). Their brain activity was recorded with fMRI before and after intervention, during two conditions: While receiving a painful electrical stimulation, and while watching another person receive a similar type of pain. It was found that frequent practice of compassion meditation during 8 weeks of CBCT was related to increased activity in a part of the brain that is mainly associated with empathy while observing others in pain (i.e. anterior insula). On the other hand, frequent practice of mindfulness meditation during CBCT was related to decreased activity in a part of the brain that is mainly associated with emotions while receiving pain (i.e. left amygdala). Unexpectedly, activity in the insula and amygdala while receiving or observing pain was not correlated with self-reported empathy or pain aversion, thus it cannot be concluded that these self-reported psychological constructs predicted the preference for meditation type. Additionally, all participants reported to have practiced the mindfulness meditation technique less than the compassion meditation technique, which points to the possibility of biased program delivery.

In summary, BDNF and COMT gene variants, at least to some degree, seem to influence the amount of stress reduction that occurs in practitioners of Brain Wave Vibration meditation (Jung et al., 2012). However, no genes were tested besides BDNF and COMT, leaving us with a very large number of candidate genes that could help explain individual differences in meditation. Moreover, Brain Wave Vibration meditation is a rare form of meditation based on repetitive head movements, which does not overlap with common and well-researched meditation programmes such as Transcendental Meditation or those based on mindfulness. There are also indications that immune markers may have some predictive value, but a study that tested one of them (interleukin-6) found that it is not related to practice frequency of compassion meditation (Pace et al., 2010). Another study discovered that several immune markers measured from blood were associated with improvements in breast cancer patients after MBSR (Reich et al., 2014). Finally, some suggest that brain scans could be sufficient for predicting what type of meditation would be preferable for a given person, as a study found that amygdala and insula activity during pain experience and observation are indicative of practice frequency of mindfulness and compassion meditation (Mascaro, Riling, Negi & Raison, 2013). However, this belief needs to be grounded in a much larger body of empirical evidence.

While biological measures may be alluring because they are not prone to response bias such as questionnaires, currently there is only a limited amount of studies on biological measures that have been related to responsiveness to meditation. Generally, collaborations between biology and psychology in meditation research are still quite rare, but the biological approach to meditation holds the promise of opening new avenues for the future. This could be particularly useful for determining the mechanisms through which meditation could influence health and well-being in heterogeneous patient populations. Next, we will briefly review the current evidence on the usefulness of meditation in such populations.

3. Individual differences due to illness severity

Some of the most important biological and psychological findings are suggestive that the more severe the patient's condition is, the better they respond to meditation (e.g., Seer and Raeburn, 1980, or for a meta-analysis, Piet & Hougaard, 2011). However, it is unknown whether this effect is due to the possibility that particularly troubled people may have more positive expectations about meditation in the hope of finding alleviation for their symptoms. The relationship between illness severity and responding to meditation is especially evident in people with depression. A meta-analysis found that people who have had three or more or more episodes of major depression responded better to Mindfulness-Based Cognitive Therapy (MBCT) than those that experienced one or two episodes (Piet & Hougaard, 2011). Another study found that MBCT works better than usual treatment or active control only in depressed individuals who were victims of childhood abuse (Williams et al., 2014). The influence of the severity of conditions on the response to meditation has been examined in a non-psychiatric context as well. For instance, individuals with longer hypertension history and higher blood pressure responded better to Transcendental Meditation than those with shorter hypertension history or lower blood pressure (Seer and Raeburn, 1980). The only two studies that did not find a relationship between illness severity and response to meditation involved cancer patients. Disease stage and disease duration were not significant predictors of responsiveness to MBSR in this study (Carlson et al., 2001). The same was seen in individuals with hypertension, whose length of hypertension history or baseline levels of blood pressure did not influence how much their blood pressure reduced after TM (Hager & Surwit, 1978). Current research does not offer explanations as to why these two studies are so different in their outcomes.

It is clearly of great importance to conduct further research into the link between individual differences, meditation, and severity of illness. This is especially relevant for patient populations, so that the most suitable meditation practices with the best outcomes become available.

4. Individual differences due to demographic factors

Many researchers have explored whether age, gender, or education level can account for individual differences in the responses to meditation. Just as is the case with psychological variables, the effects of demographic variables vary depending on the population targeted, meditation type, and measured outcomes. A study that examined the effects of mantra-based meditation on hypertensions found that blood pressure was reduced regardless of gender or marital status (Seer and Raeburn, 1980). Similarly, a study using a mantra-based meditation and relaxation programme found that the programme reduced blood pressure and that the effects did not differ due to variability in age or sex (Hager and Surwit, 1978). On the other hand, some studies have found that demographic factors do influence the response to meditation. A large-scale study consisting of almost 600 participants who attended an 8-week mindfulness and yoga programme similar to MBSR explored associations between the likelihood that a person will attend all sessions of the programme and individual differences in demographic factors (Kabat-Zinn and Chapman-Waldrop, 1988). In this study, participants were divided into two categories – one cohort included people suffering from various chronic pain conditions (the pain cohort), or in a cohort with people with cardiovascular and gastrointestinal conditions, sleep or anxiety disorders, diabetes, or cancer (the stress cohort). It was found that, in the pain cohort, women were more likely than men to complete the whole programme, showing an effect of gender. In the stress cohort of the same study, only the level of obsessive-compulsive tendencies was a significant predictor of program completion – those with higher scores were more likely to complete the program. Age, length of pain history, medical symptoms, and other subdimensions of distress (besides the obsessive-compulsive score) were not significant predictors of completing the program, neither in the pain nor in the stress cohort (Kabat-Zinn and Chapman-Waldrop, 1988). In a study with cancer patients who underwent MBSR, women and highly educated individuals showed the greatest improvements in mood and perceived stress, while age had no predictive value (Carlson et al., 2001). Finally, in a study where college students learned mindfulness meditation, women had greater reductions in negative affect and greater improvements in trait mindfulness and self-compassion than men (Roijani et al., 2017).

In summary, age and level of education do not seem to influence people's responses to meditation in a consistent way. In contrast, gender does seem to be one factor for which differences have been found across studies. Note, however, that studies on how demographic factors are associated with meditation outcomes are relatively scarce. There are still other factors that need to be examined, such as ethnicity and socio-economic status, which may be explored in future studies.

5. Conclusions

In this chapter we have provided an overview of the current state of research concerning the potential of psychological, biological, and other factors in accounting for individual differences in the effects of meditation. The majority of studies were related to psychological individual differences that may influence responses to meditation. Psychological factors that were investigated include neuroticism, anxiety, conscientiousness, mindfulness, attachment style, mood, emotions, and expectations. Of these, trait anxiety/neuroticism and expectations have shown consistent effects over several studies. People high in anxiety generally show more positive effects of meditation, as do people who expect positive outcomes. Important biological factors seem to be related to BDNF and COMT gene polymorphisms, and biomarkers of immune activity such as IL-6. Other than psychological and biological factors, there is some evidence that illness severity, particularly in individuals with recurrent depression and hypertension, is associated with better meditation outcomes. Finally, the findings concerning demographic factors suggest that age and level of education do not seem to have an effect on meditation outcomes, while gender does seem to have an impact.

The paucity of work in the area needs to be underlined. This review is based on 26 studies obtained by doing a database search using relevant keywords, and it is possible that some relevant studies were not included. The heterogeneity of the outcome measures that have been used in the area also makes comparability across studies difficult. Overall caution needs to be exercised about the conclusions that can be drawn from this work.

In the majority of the studies examined in this chapter, researchers have assessed their target population using group-comparison designs (i.e., experimental group, active and passive control groups). In these cases, within-group variation has been treated as statistical nuisance; noise or error that needs to be separated from the actual effect. However, as we have seen throughout this chapter, meditation may not just show an effect at the group level, but may also have an effect on the individual level. One way of measuring individual differences (such as within-group variation) is through multilevel modelling, which also allows for the examination of condition-based or group differences (Hoffman, 2007). Such models are also known as hierarchical linear models. The central tenet of this type of modelling is that in cross-sectional studies, individuals (i.e., level 1 measurements) are nested within groups (i.e., level 2 measurements), and in longitudinal studies, measurements on given occasions (level 1) are nested within individuals (level 2). These models allow for individual variance to be taken into account as well as group variance. Moreover, individual differences in within-person variation and within-person covariation over time can be examined simultaneously (Hoffman, 2007), making this approach very useful in longitudinal setups. Several meditation studies have already used multilevel modelling to assess, for example, if the day of measurement influenced the effect of loving-kindness meditation (Carson et al., 2005), or whether the duration of meditation practice and positive emotions differed within persons and between persons (Fredrickson et al., 2017). In one study using Zen meditation, multilevel modelling revealed that individual differences had a significant effect on the meditation outcomes (Christian et al., 2016). Thus, we recommend this statistical method for future studies investigating individual differences in meditation.

In this chapter, we have discussed meta-analyses that tested individual differences through moderator analysis or meta-regressions of meditation outcomes (e.g. Orme-Johnson and Barnes, 2014 that included 16 studies testing if baseline anxiety influences meditation outcomes). This is because a meta-analysis uses pooled estimates of several studies, which is more precise than a single estimate obtained from an individual study. However, the results that are based on study level (i.e., group average data) are not optimal to answer questions about individual differences, due to heterogeneity between the results of the studies. The common sources of heterogeneity across studies include differences in the participant inclusion and exclusion criteria between studies, differences in how meditation is taught or the presence of different types of control group. Meta-regression is a technique that can be used to address such questions, but its downside is that it may not be representative of the true relationship in the data at the individual level because it is calculated using summary values from each study. For instance, imagine a meta-analysis of 60 studies that examined the effects of mindfulness on working memory, and that it has already been established that working memory capacity is affected by age. The effect of participant age on outcomes of meditation may be investigated with a meta-regression by including the mean age of the patients in each study, but this estimate would be biased because it is based on the average age of the sample included in each study, thus neglecting variability within each study. The solution to this problem is to obtain data for each participant of every included study and to use these data as a starting point instead of the group average of every study. This kind of meta-analysis is called *individual patient data meta-analysis* (Lau, Ioannidis & Schmid, 1998; Stewart & Clarke, 1995), and it is considered to be the gold standard given its superior statistical power relative to meta-regression (Stewart & Clarke, 1995; Lambert, Sutton, Abrams & Jones, 2002). In summary, meta-analysis can be a valuable tool when the goal is to investigate intervention effects, such as the effects of meditation on stress. However, individual patient data meta-analysis is optimal when the goal is to investigate which individual differences modify the effects of an intervention, such as when determining whether older people experience less stress reduction following meditation. Therefore, we invite researchers to conduct individual patient data meta-analysis, as the effect of participant characteristics on outcomes of meditation may otherwise not be detected.

Whilst the majority of studies discussed in this chapter investigated psychological variables, this does not necessarily mean that these factors are the most important ones or that they will have the biggest explanatory value. Also, if the impact of individual differences on meditation outcomes can be examined at multiple levels (e.g., biological and psychological), then interactions among these levels could be explored. We propose that researchers should shift their central focus from group average to individual differences, because much of the variance which would otherwise go unnoticed (or indeed be treated as error) can be examined that way.

We would like to end with a suggestion that may be useful for meditation teachers or therapists using meditation interventions. As shown above, individual expectations help to improve meditation outcomes, which leads us to suggest the use of motivation-enhancing procedures, such as giving clear examples of the positive effects of meditation based on the available scientific literature. Similar procedures have already been applied in the context of psychotherapy. For instance, there is a stronger effect of cognitive therapy for depression when it aims to enhance people's expectations of its positive effects — this has been shown to improve retention and engagement in therapy (Constantino, Ametrano & Greenberg, 2012). We further suggest that it would be useful to monitor individual expectations either informally through dialogue or, ideally, systematically with a questionnaire before starting the meditation teaching. One such questionnaire that can be applied in the context of meditation is the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000), which only takes a few minutes to complete. The statements applied to meditation would read like this (meditation students would rate each statement from 0 to 100%):

1) At this point, how successfully do you think this meditation course will be in raising the quality of your functioning?
2) How confident would you be in recommending this meditation course to a friend who experiences similar problems?
3) By the end of the meditation course, how much improvement in your functioning do you think will occur?
4) At this point, how much do you really feel that the meditation course will help you to improve your functioning?
5) By the end of the mediation course, how much improvement in your functioning do you really feel will occur?

These suggestions are only a starting point, as more research needs to be done in order to develop refined recommendations. Further research on this topic is valuable to meditation teachers and clinicians alike, because it could be used to adapt meditation sessions to make them more effective and reduce the risk for adverse effects. Furthermore, taking sources of individual differences into account could reduce attrition rates in clinical treatments and research projects that are testing the long-term effects of meditation. Meditation is a promising technique for both clinical and non-clinical populations, with potentially large implications for some individuals. Therefore efforts should be made to shed light on individual differences so that we may be able to more accurately predict whom meditation may benefit the most.

CHAPTER 5

THE EFFECTS OF PARTICIPANT CHARACTERISTICS ON MEDITATION INTERVENTION OUTCOMES: A META-ANALYSIS

Manuscript submitted for publication

Abstract

Meditation interventions typically show small to moderate effects on health and well-being, but we know little about why these effects vary across individuals. This is the first meta-analysis to investigate the relationship between baseline participant characteristics and the outcomes of meditation. A systematic search yielded 50 eligible studies with 7782 participants. We found that a higher baseline level of psychopathology and depression were associated with deterioration in mental health after a meditation intervention. On the other hand, participants with higher scores on interpersonal variables, motivation, medical conditions, and mindfulness showed higher levels of positive outcomes. Higher well-being and stress were simultaneously associated with moderate increases in negative and positive meditation outcomes. Participant demographics, psychological traits, and self-concept, and length of meditation practice did not significantly influence the response to meditation. Overall, we found that meditation interventions affect participants differently, and identified some of the individual characteristics that should be considered when using meditation as an intervention.

1. Introduction

Meditation is generally practiced with the aim of achieving positive changes, whether physical, mental health, or of a moral-spiritual character. Its contemporary focus in the West is very much on health and well-being, but similar concerns on how to use meditation techniques to live a better life have been reported over two thousand years ago in various traditions, such as in Daoism (Roth, 1996). The science of meditation has just turned 50 years old. Before the 1970s, we can only find a handful of scattered studies focusing on meditation experts (nuns, monks or gurus). This changed quickly from 1970 when the first study on the psychophysiological effects of Transcendental Meditation was published, focusing on relatively naïve practitioners who had been meditating for less than one year (Wallace, 1970). Although studies using naïve practitioners instead of selected religious experts have become the norm, the field is still ripe with universalist expectations that meditation will affect all individuals in the same way. In reality, the effectiveness of meditation practices varies among individuals; while many reap benefits and become dedicated long-term practitioners, others sense no noticeable effects or might even experience unwanted, unpleasant, or adverse effects (Cebolla et al., 2017; Lindahl et al., 2017; Schlosser et al., 2019; Van Dam et al., 2018). Such variability in meditation effects has been noticed as early as the 5th century in Buddhist sources, where it is mentioned that there is a possibility of a 'meditation malaise' that includes feeling dull, confused, restless, or sunken (Ahn, 2008).

In 1977 the American Psychiatric Association issued a statement on meditation strongly recommending the need to undertake research that evaluates the possible usefulness, indications, and contraindications of meditation (American Psychiatric Association, 1977). Over 40 years have passed and we still have not achieved a body of research allowing us to tell which type of individuals may benefit the *most* and the *least* from meditation interventions. One example of the wide-reaching problems driven by the lack of insight into individual differences in meditation research concerns its clinical implications. Meta-analyses focusing on mindfulness-based interventions (MBIs) have shown that patients with some psychiatric conditions using these techniques experience a level of symptom reduction equivalent to that of other evidence-based treatments, such as psychotherapy or biomedical treatment (Goldberg et al., 2018; Hofmann & Gómez, 2017; Veehof et al., 2016). Despite this evidence, the British National Institute for Health and Care Excellence (NICE) recommends MBIs in only two specific cases: for individuals with a history of three or more episodes of depression (Pilling et al., 2009), and for treating fatigue in patients with multiple sclerosis (Perry et al., 2014). This rather restrictive recommendation is understandable as the majority of current evidence is based on reports of mean group changes, but pays no attention to how individuals might react differently to MBIs or other meditation-based practices. With the rapid expansion of meditation-based interventions for the treatment of various disorders, it now becomes imperative to move beyond group-level data in order to predict individual effects. If there is variability in the valence and intensity of meditation effects across individuals, the task at hand is to assess this variability so clinicians and therapists know when and with whom to use these techniques and when to avoid them.

As it happens with other types of psychological interventions, there are three groups of characteristics that are likely to lead to variability in responses to meditation interventions: participant, intervention, and teacher characteristics (Baer et al., 2019). The focus of this paper is on participant characteristics because there has been no comprehensive analysis of participant factors in relation to the efficacy of meditation-based interventions. The lack of studies in this area is not surprising given the universalist assumption guiding studies on meditation techniques for five decades, which can be simply be stated as ‘meditation works in the same way for everyone’. This assumption explains why, thus far, participant characteristics as sources of variability in the response to meditation have not been examined directly through a meta-analysis, but only briefly explored as moderating factors in meta-analyses that examine the effects of meditation on specific dependent variable in a specific population (e.g., age as a moderator of the effect of meditation on reducing trait anxiety in adults, see Khoury et al., 2015; Orme-Johnson & Barnes, 2013; Zoogman et al., 2015). Moreover, this assumption is at odds with current endeavors in science and clinical practice that recognize the importance and urgency to develop interventions that are tailored to the individual's needs (i.e. are personalized) (Cuthbert & Insel, 2013), particularly in populations that tend to be less responsive to the established interventions (Brazil et al., 2018). The central idea behind personalized medicine is to move beyond the one-size-fits-all principle. One way in which we can move meditation research in the direction of individualized treatment is to first explore carefully how participant characteristics might affect meditation interventions.

2. Aims of the study

The overarching goal of the present study was to lay the groundwork that can foster continual developments in research and inform future strategies for personalized applications of meditation. Our first aim was to examine the relationship between participant characteristics and responses to meditation through a meta-analysis. Thus, our focus is different from previous meta-analyses that have examined the overall effects of meditation on well-being and health-related outcomes across different populations or whether meditation works as an intervention (e.g., Khoury et al., 2015; Orme-Johnson & Barnes, 2013; Sedlmeier et al., 2012; Zoogman et al., 2015). These previous studies targeted average effects at the group level, which means that individual variations in meditation outcomes are masked. Instead, we focused on the demographical and personality characteristics of the participants and how these are related to varying meditation outcomes. In order to carry out this meta-analysis, we identified studies of meditation-based interventions that measured at least one variable pertaining to participant characteristics and reported how these characteristics were linked to meditation outcomes.

We based some of our hypotheses on the findings from previous meta-analyses that examined participant characteristics as moderators of their main outcome measure for the effect of meditation. We expected to find that demographic variables had no effect on the outcomes of meditation as previous meta-analyses found that age, gender and ethnicity did not moderate various outcomes of meditation in clinical and non-clinical samples (Khoury et al., 2015; Orme-Johnson & Barnes, 2013; Zoogman et al., 2015). Furthermore, we expected that participants with higher trait anxiety would show a more positive impact of meditation, as a previous meta-analysis found that the reduction in trait anxiety following meditation was greater in people with high anxiety levels (Orme-Johnson & Barnes, 2013). Finally, as one meta-analysis found that people with three or more or more episodes of major depression responded better to Mindfulness-Based Cognitive Therapy (MBCT) than those with one or two episodes (Piet & Hougaard, 2011), we hypothesized that participants with higher depression levels at baseline would experience a more positive impact from meditation. We did not have further specific hypotheses about other participant characteristics and their effect on meditation outcomes, as many of these characteristics are still unknown and the present study is the first to systematically explore the literature in order to uncover them.

Our second aim was to test for moderators of the relationship between participant characteristics and meditation outcomes. We included six moderators: sample size, sample type, research design, study quality, meditation type, and length of meditation. These moderators were chosen based on the results of previous meta-analyses focusing on meditation, which often show smaller effect sizes in studies with larger samples, in non-clinical samples, in randomized controlled trials, and in studies of high methodological quality (Sedlmeier et al., 2012). Effect sizes often vary for different types of meditation and different lengths of meditation interventions (Kok & Singer, 2017), thus we wanted to test these moderators in the context of participant characteristics and meditation. Given that concerns have been raised about the methodological quality of meditation studies (Chiesa & Serretti, 2009; Goyal et al., 2014), we also examined the methodological rigor of the studies included in our analysis.

3. Methods and Materials

3.1. Selection of studies

We searched the databases Psych INFO, MEDLINE, PsycARTICLES on March 2019 using the following search terms: (meditation OR mindfulness) AND (moderator OR predictor OR individual differences OR interaction). In order to locate studies that were not detected with the initial database search, we contacted 58 experts to enquire if they were familiar with additional studies that met our eligibility criteria, and we hand searched references of the 79 articles that met our eligibility criteria (Figure 1). Following the removal of duplicates, 2000 records were screened.

A total of 50 articles met the following inclusion criteria:

1) The sample contained participants that were 18 years of age or older;
2) Both clinical and non-clinical samples were allowed;
3) There should be at least 10 participants per group (Hedges, 1982);
4) Studies had to include a meditation intervention, baseline measures of participants' characteristics, and at least one meditation outcome;
5) All types of meditation or meditation-based interventions that included meditation as a core component were eligible;
6) Research designs could be experimental or quasi-experimental;

7) Articles should have been published in English in peer-reviewed journals

Exclusion criteria:

1) Meta-analyses, review papers, commentaries, doctoral theses, and conference proceedings;
2) Studies that only used non-standardised tasks and/or questionnaires;
3) Studies with outcomes that cannot be categorised as having positive or negative impact on mental health

3.2. Quality assessment

We assessed the methodological quality of the studies using the National Institutes of Health Study Quality Assessment Tools: Quality Assessment of Controlled Intervention Studies and Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (National Heart, Lung and Blood Institute, 2014). Each tool consists of eight to 14 questions that are answered with yes, no or not reported/cannot determine/not applicable, where the latter two suggest a potential flaw in the study design or implementation. The questions examine components of internal validity, such as if study used random sequence generation, included blinding of outcome assessment or showed selective reporting of statistical results. We had to modify two out of three quality assessment tools, as some items were not applicable to meditation research. Specifically, in the Quality Assessment of Pre-Post Studies with no Control Group, we excluded two items: *Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?* and *If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?* In the Quality Assessment of Controlled Intervention Studies, we excluded one item: *Were study participants and providers blinded to* *treatment group assignment?* because it is dubious whether one can truly blind participants to a meditation intervention (Davidson & Kaszniak, 2015). The responses were coded as 1 if the answer was *yes* or as 0 if the answer was *no* or *not reported*.

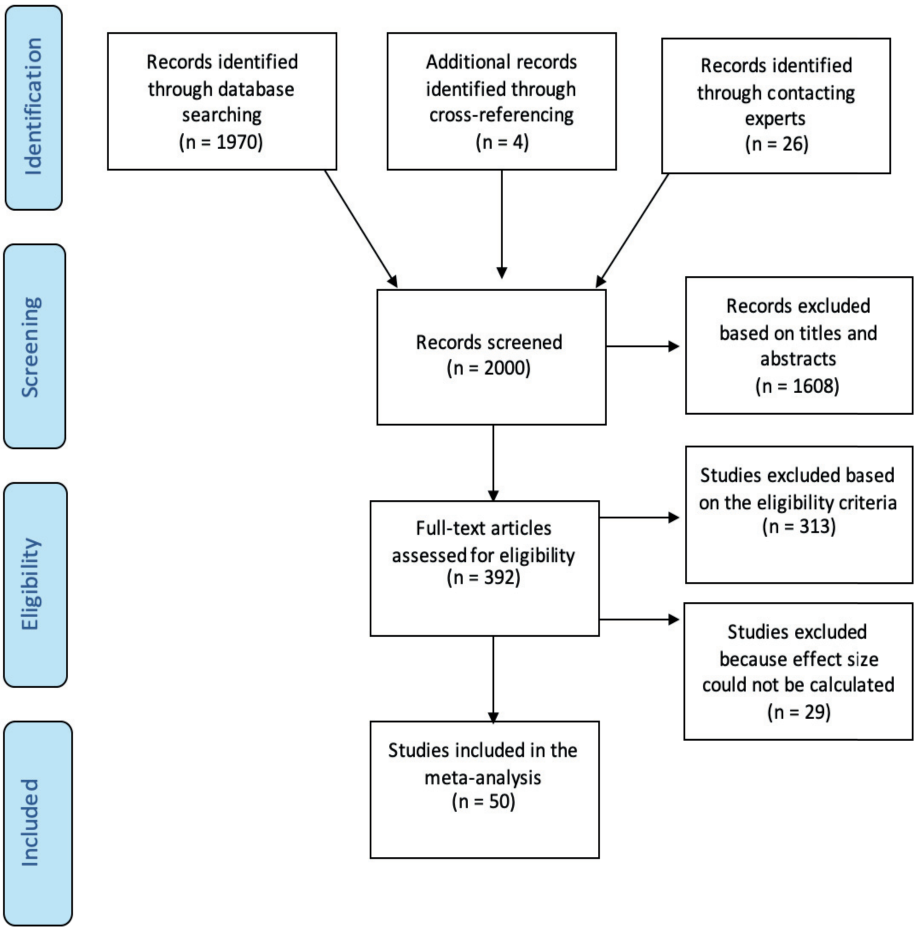

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart: The process of selecting relevant studies

3.3. Study characteristics

There was a total of 7782 participants across 50 articles (full references of included articles can be found in appendices). Studies showed moderate quality based on the National Institutes of Health study quality assessment tools (see Table 3). Median length of meditation interventions was 56 days. Out of the 50 included studies, mindfulness meditation was used in 68% of the studies, while 14% of the studies employed transcendental meditation, and other techniques (mainly compassion or breathing meditations) were used in 18% of studies. Furthermore, 56% of the studies had a pre-post design studies without a control group, while 44% were randomised controlled trials. Randomised controlled trials used active control groups in 58% of cases, which included psycho-education or various forms of attention control, such as reading or listening to a story.

Healthy adults were examined in 56% of the 50 eligible studies. The most common clinical populations were patients with chronic medical conditions, such as cancer, hypertension or arthritis (24%). The most prevalent mental disorders were anxiety (18%) and depression (18%), followed by substance abuse (14%), and studies that targeted more than one mental disorder (14%). Studies were published between 1978 and 2018, though the majority (72%) were published in the past ten years, which suggests a growing interest in examining the effects of participant characteristics.

3.4. Procedure for data extraction and categorisation

The lead author (IBu) reviewed titles, abstracts, and full texts. An extraction sheet was used to specify relevant information for each study: sample size, meditation type, meditation length, type of research design, quality assessment, examined participant characteristics, outcomes, and the relationship between participant characteristics and outcomes. Two authors

(IBu and JMAD) independently extracted data on participant characteristics and meditation outcomes. Inter-rater agreement was high (r = .89) and disagreements were discussed until consensus was reached.

Data extraction yielded 99 variables for participant characteristics and 76 outcome variables (see Table 1 and Table 2). Given that many sources of individual differences in mediation outcomes still remained to be uncovered, we first explored whether 'themes' could be found within the pool of extracted outcomes variables by clustering participant characteristic variables into thematic categories. Each category consisted of at least four studies. We began by forming categories that were present across most studies, such as *well-being, psychopathology, psychological traits*, and *medical conditions.* If there were four or more studies within one category that were thematically similar, this led to the formation of a separate category. For example, studies categorized under *anxiety* were initially part of the *psychopathology* category until, from the classification process, 4 or more studies assessing anxiety emerged. We found thirteen conceptually distinct categories of participant characteristics (Table 1). A second researcher (JMAD) also conducted the clustering in order to control for subjectivity bias. Inter-rater agreement was high (r = 0.93) and all discrepancies were settled before proceeding with the analyses.

Following this, we classified all meditation outcomes into two types: positive or negative (Table 2). They were classified as *positive* when an increase in scores had a positive impact on mental health (e.g. emotion regulation), and into *negative* when an increase in scores meant a deterioration in mental health (e.g. stress). Studies with outcomes that could not be classified as positive or negative were excluded from the analyses; this led to the exclusion of two studies with EEG measures.

Finally, we considered the moderators. As three out of our six moderators were categorical, they were coded as follows: sample type was coded as 'non-clinical' or 'clinical';

meditation type was coded as 'mindfulness', 'transcendental meditation', or 'other type of meditation'; type of research design was coded as 'RCT' if the study was a randomized controlled trial, or as 'non-RCT' if another experimental design was employed.

Table 1. *Participant characteristics that were measured in the 50 eligible studies, categorised across 13 Categories*

Category	Number of studies	Measured baseline participant characteristics
Psychological Traits	11	absorption, social desirability, cooperativeness, persistence, novelty seeking, harm avoidance, reward dependence, repressive/defensiveness, hypnotic responsivity, Big Five (extraversion, neuroticism, openness to experience, conscientiousness, agreeableness), sensory imagery
Anxiety	7	state anxiety, social anxiety, trait anxiety, bodily symptoms of anxiety
Self-concept	9	locus of control, low self-esteem, perceived self, self-concept, self-transcendence, self-directedness, self-efficacy, self-compassion, perceived behavioural control
Interpersonal	9	positive life experiences, social support received, social support given, insecure attachment, history of interpersonal violence, childhood abuse, life experience stressors, sexual trauma, combat-related trauma
Demographics	13	age, gender, marital status, employment, education
Depression	9	depression symptoms, history of recurrent depression, number of depression episodes, fatigue
Motivation	8	therapist's assessment of patient's motivation, therapist's prediction of leaving preterm, expectancy, motivation for spiritual growth, considered meditation, considered therapy, attitudes about meditation, intentions to practice meditation, subjective norms
Psychopathology	4	obsessive-compulsive behaviour, alcohol consumption, posttraumatic stress disorder severity, psychological maladjustment, severity of substance use
Mindfulness	7	trait mindfulness, curiosity, decentering, non-judgement
Belief system	4	irrational beliefs, spirituality, religiosity, implicit religiousness/spirituality, religious affiliation
Medical conditions	6	headaches, length of time since cancer diagnosis, pain/stress diagnosis, diastolic blood pressure, hypertension history, number of comorbid pain conditions, baseline pain
Stress-related factors	7	cortisol, IL-6, lymphocyte subsets, mitogen-stimulated subsets, pain catastrophizing, discomfort with emotion, sexual distress
Well being	12	psychological detachment from work, sleep quality, sleep duration, well-being, pain self-efficacy, minutes of physical activity per day, distress tolerance, relaxation level, mood, positive and negative affect, positive emotions, experience in group therapy, psychological functioning, physical functioning, mental health

Note: The second column represents the number of studies per category and its sum is bigger than the total number of included studies (N = 50) as almost all studies had outcomes that were included in more than one category.

Table 2. *Outcomes of meditation interventions that were measured in the 50 eligible studies, categorised as positive or negative*

Category	Number of studies	Measured baseline participant characteristics
Positive outcomes	65	meditation practice frequency at home, meditation session attendance, implicit religiousness/spirituality, religion, coherence, sleep duration, mindfulness, visual imagery (during meditation), pleasantness (during meditation), curiosity, positive affect, well-being, ambiguity tolerance, quality of life, responding to hypertension treatment, executive attention, focusing, health, pain control
Negative outcomes	65	heart-rate variability, skin conductance, perceived pain, pain interference, drop-out rate, perceived stress, PTSD severity, depression, trait anxiety, social anxiety, somatic anxiety, work hours, distress (during meditation), distress, negative affect, discomfort with emotion, worry, fatigue, anger, frequency of substance abuse, rumination, catastrophizing,

Note: The second column represents the number of studies per category and its sum is bigger than the total number of included studies (N = 50) as almost all studies had multiple outcomes. An outcome is categorised as positive if its increase has a positive impact on mental health or as *negative* if its increase meant deterioration in mental health.

3.4. Data handling and statistical analysis

A summary of data extraction and analysis can be found in Figure 2. Following data extraction and categorisation of variables, effect sizes were calculated as Pearson's *r* using Meta-Calc (Rosenberg, M. S., Adams, D. C., & Gurevitch, J., 2000). If there were insufficient data to calculate effect sizes in the published studies, we contacted the authors. Similarly, for studies that included statistical corrections that reduced comparability across studies (e.g. including age as a covariate in all analysis), authors were contacted to obtain original data in order to calculate the uncorrected effect sizes. There were 79 studies that met our eligibility criteria, but as the data could not be retrieved from its authors for 29 studies we had to exclude them, leaving a total of 50 studies.

When studies used different measures of the same construct (e.g. two pain scales) or of the same category (e.g. several measures within well-being; see Table 1), the effects were averaged across measures. Similarly, in studies that had several follow-ups, the effects were averaged across all post-intervention time-points. When studies included three or more groups, the meditation intervention group was compared against the combination of other groups (for a similar procedure see (Hoppenbrouwers et al., 2016)).

Effect sizes were imported into MetaWin, normalised through Fisher's z-transformation, and examined using random-effects model (Rosenberg, M. S., Adams, D. C., & Gurevitch, J., 2000). Heterogeneity of scores between and within studies was assessed with the *Q* statistic (Cochran, 1954). Publication bias was evaluated using funnel plots combined with Rosenthal's fail-safe N approach (Orwin, 1983). A funnel plot shows the mean effect size of eligible studies converted to Fisher's z on the X-axis and standard errors on the Y-axis, along with the expected distribution of studies in the absence of bias (Sterne et al., 2006). If studies were symmetrically distributed around the mean effect size, this shows there is no publication bias. Conversely, the fail-safe N indicates the number of unpublished studies with non-significant results that would be required to make the mean effect size non-significant (Egger et al., 1997). As a rule of thumb, if the fail-safe N is larger or equal to 5n + 10, where n is the number of studies, then the results are considered to be robust (Rosenberg, 2005). As this meta-analysis includes 50 studies, the fail-safe N had to be larger than 260 for the results to be considered robust. Note that a category was only included in an analysis if the outcome measures required for that particular analysis were available for at least 4.

In addition to testing the overall effect of participant characteristics on meditation outcomes, and examining effect sizes for each category of participant characteristics, we conducted moderator analyses. Three categorical moderators were examined with subgroup analyses, while three continuous moderators were examined with meta-regression. The interpretation of the effect sizes is based on established guidelines by which the effects were considered small if r = .1, medium if r = .3 and large if r = .5 (Cohen, 2013). Significance was determined based on bootstrapped 95% confidence intervals.

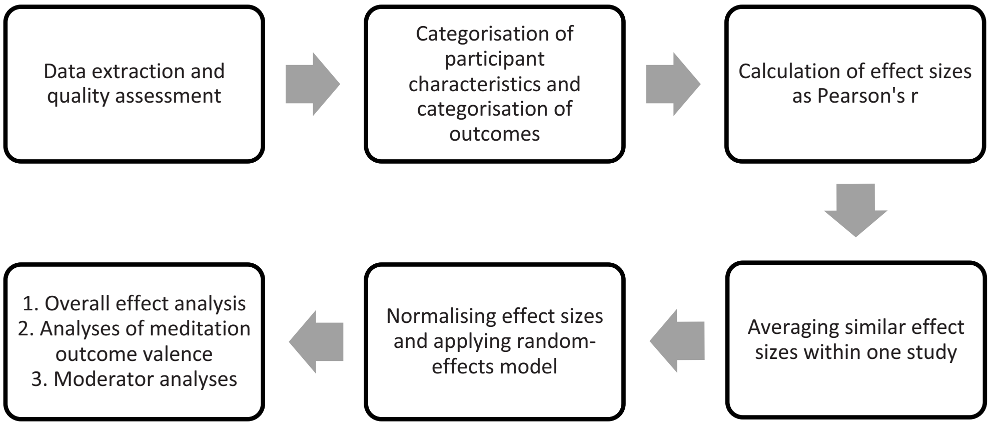

*Figure 2***.** Schema for conducting data extraction and analysis. First, the relevant data were extracted from the 50 eligible studies and the quality of each study was rated. Second, we categorised all independent variables (i.e., participant characteristics) and dependent variables (i.e., outcome measure of meditation intervention), which resulted in thirteen categories of independent variables and two categories of dependent variables. Third, all extracted effect sizes were converted into Pearson's *r*. Fourth, multiple effect sizes within one study were averaged when they were related to the same construct or the same category, when the effect sizes represented two or more follow-ups, or when studies included three or more groups. Fifth, effect sizes were normalized through Fisher's z transformation and a random-effects model was applied in all analyses. The general analysis shows the effect of participant characteristics on meditation response. Subgroup analyses were used to show the effect for each category of participant characteristics on meditation response, to examine how each category differs between two types of outcomes (i.e., positive and negative), and to test categorical moderators: sample type, research design, and meditation type. Finally, a meta-regression was conducted to test for continuous moderators: sample size, study quality, and length of meditation.

4. Results

4.1. Overall analysis

In order to determine if participant characteristics had an overall impact on the efficacy of meditation interventions, we conducted a meta-analysis that included all variables collapsed across positive and negative health outcomes. The summary of the extracted data can be found in Table 3. The mean effect size for the overall analysis was $r = 0.11$ (*CI* 0.07, 0.15), showing a small effect of participant characteristics on the response to meditation interventions. The funnel plot is symmetrical (Figure 3) and Rosenthal's fail-safe number pointed out that 2574 studies with null-results are needed to make the main effect found in the overall meta-analysis statistically non-significant, which is above the recommended threshold of 260. However, heterogeneity within studies was high and statistically significant, while heterogeneity between studies was low and statistically non-significant (Table 6). The results for the tests of heterogeneity indicated methodological, statistical, or clinical diversity among the studies included in the meta-analysis.

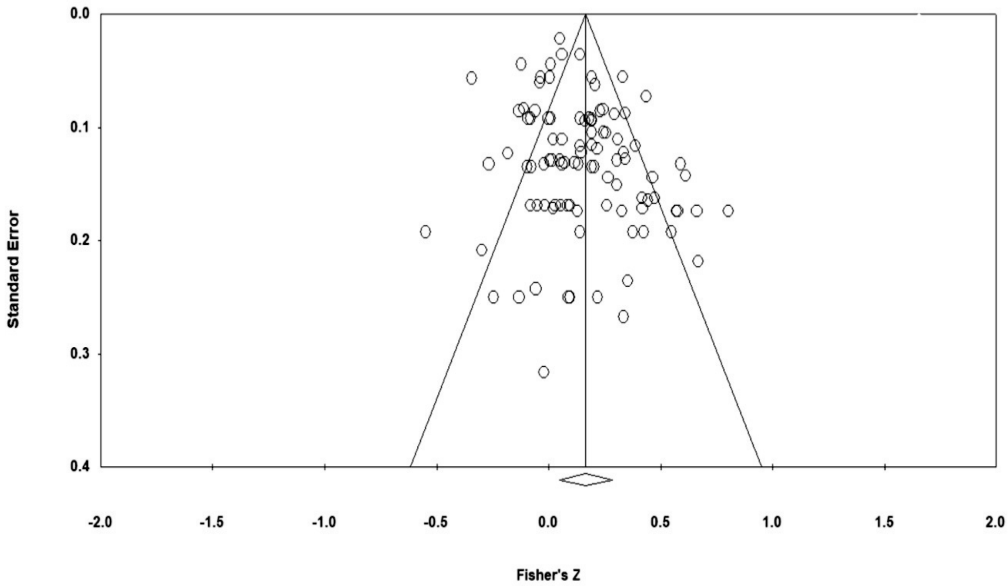

*Figure 3***.** The funnel plot shows the overall mean effect size of eligible studies converted to Fisher’s z on the X-axis and standard errors on the Y-axis, along with the expected distribution of studies in the absence of bias.

Table 3. *Summary of the results of all included studies showing authors of each study, examined participant characteristic and outcomes of meditation, effect size (ES) converted to Pearson's r, sample size, research design type, sample type, meditation type and length, and study quality estimated with tools by National Institutes of Health (ranging from 0 to 1)*

Authors	Participant characteristics	Outcomes	ES	Sample size	Design type	Sample type	Meditation type	Meditation length (days)	Study quality
Azam, Katz, Mohabir, & Ritvo, 2016	having headache	heart-rate variability	0.37	77	RCT	healthy adults	loving-kindness meditation	1	0.83
Brotto, Basson, Smith, Dricoll, & Sadownik 2015	trait anxiety	change score in pain	0.02	63	non-RCT	women with vulvodynia	mindfulness	56	0.7
	depression	change score in pain	0.13	60	non-RCT	women with vulvodynia	mindfulness	56	0.7
	number of comorbid conditions	pain induced by a cotton swab at 6mo follow-up	-0.18	69	non-RCT	women with vulvodynia	mindfulness	56	0.7
	sexual distress	change score in pain	0.05	63	non-RCT	women with vulvodynia	mindfulness	56	0.7
Cohn & Fredrickson, 2010	social support received	continued meditation practice at 8 weeks	0.19	95	RCT	healthy adults	loving-kindness	365	0.69
	daily positive emotions during the week before learning meditation	continued meditation practice at 8 weeks	0.24	95	RCT	healthy adults	loving-kindness	365	0.69
Cordon Brown & Gibson, 2009	insecure attachment	Drop-out rate	0.29	131	non-RCT	healthy adults	Mindfulness-Based Stress Reduction	75	0.9
Crandall, Cheung, Young, & Hooper, 2019	intentions to practice mindfulness and subjective norms	practicing mindfulness	0.3	85	non-RCT	healthy adults	mindfulness	14	0.9
	perceived behavioral control	practicing mindfulness	0.06	85	non-RCT	healthy adults	mindfulness	14	0.9
	age, gender, employment status	practicing mindfulness	0.02	85	non-RCT	healthy adults	mindfulness	14	0.9

Crescentini, Urgesi, Campanella, Eleopra, & Fabbro, 2014	implicit religiousness/spirituality	implicit religiousness/spirituality	0.4	30	non-RCT	healthy adults	mindfulness	70	0.5
Day, Halpin, & Thorn, 2016	expectations/motivation	pain interference	0.34	21	RCT	chronic headache pain	Mindfulness-Based Cognitive Therapy	56	0.54
	expectations/motivation	home practice	0.15	21	RCT	chronic headache pain	Mindfulness-Based Cognitive Therapy	56	0.54
Delmonte, 1981	age	deciding to learn meditation after tm lecture	0.25	94	non-RCT	healthy adults	transcendental meditation	16	0.6
	expectations	deciding to learn meditation after tm lecture	0.33	64	non-RCT	healthy adults	transcendental meditation	16	0.6
	perceived self	deciding to learn meditation after tm lecture	0.32	70	non-RCT	healthy adults	transcendental meditation	16	0.6
Delmonte, 1985	expectations (positive rationale group)	skin conductance	0.42	40	non-RCT	healthy adults	transcendental meditation	1	0.7
Delmonte, 1988	extraversion	becoming a regular meditator at 12mo	0.02	37	non-RCT	outpatients with psychosomatic and neurotic symptoms	transcendental meditation	104	0.7
Dobkin, Zhao, & Monshat, 2017	not depressed	stress	0.30	63	non-RCT	patients with various chronic illnesses	Mindfulness-Based Stress Reduction	56	0.7
	not depressed	coherence (average comprehensibility, manageability, meaningfulness,	0.10	63	non-RCT	patients with various chronic illnesses	Mindfulness-Based Stress Reduction	56	0.7
Felleman, Stewart, Simpson, Heppner, & Kaerny., 2016	gender	PTSD severity	0.16	116	non-RCT	PTSD veterans	Mindfulness-Based Stress Reduction	56	0.8
	PTSD severity	PTSD severity	0.19	116	non-RCT	PTSD veterans	Mindfulness-Based Stress Reduction	56	0.8
Gawrysiak et al., 2016	distress tolerance	perceived stress	0.32	327	non-RCT	healthy adults	Mindfulness-Based Stress Reduction	56	0.9
Greenberg et al, 2018	self-compassion	change in depression symptoms	-0.02	13	RCT	patients with depression	Mindfulness-Based Cognitive Therapy	56	0.62
Greeson et al., 2011	having a religious affiliation	change in depression symptoms	-0.04	279	non-RCT	healthy adults	Mindfulness-Based Stress Reduction	56	0.9

Greeson et al., 2015	having a religious affiliation	change in depression symptoms	0.01	322	non-RCT	healthy adults	Mindfulness-Based Stress Reduction	56	0.9
	Age	change in depression symptoms	-0.04	322	non-RCT	healthy adults	Mindfulness-Based Stress Reduction	56	0.9
	mindfulness	change in depression symptoms	0.19	322	non-RCT	healthy adults	Mindfulness-Based Stress Reduction	56	0.9
	mental functioning	change in depression symptoms	0.19	119	non-RCT	healthy adults	Mindfulness-Based Stress Reduction	56	0.9
Geschwind, Peeters, Huibrs, van Os, & Wichers, 2012	number of depressive episodes	depression symptoms HSRD scale	0.21	260	RCT	adults with history of depression	Mindfulness-Based Cognitive Therapy	56	0.77
Heide, Wadlinton, & Lundy, 1980	hypnotic responsivity	trait anxiety	0.2	58	RCT	healthy adults	mantra meditation	7	0.77
	hypnotic responsivity	perceived benefit from meditation	0.19	58	RCT	healthy adults	mantra meditation	7	0.77
Herdt, Bührlen, Bader, & Hänny, 2012	therapist's assessment of the patients' motivation	number of attended sessions	0.43	51	non-RCT	psychiatric patients	Mindfulness-Based Cognitive Therapy	63	0.8
	having participated in group therapies earlier	completed sessions 1-3	0.21	74	non-RCT	psychiatric patients	Mindfulness-Based Cognitive Therapy	63	0.8
Hülsheger, Feindholt, & Nübold 2015	Age	work hours	-0.13	140	RCT	healthy adults	mindfulness	10	0.46
	Age	sleep duration	0.00	140	RCT	healthy adults	mindfulness	10	0.46
	Age	mindfulness	-0.06	140	RCT	healthy adults	mindfulness	10	0.46
	trait mindfulness	mindfulness	0.19	140	RCT	healthy adults	mindfulness	10	0.46
	sleep duration	sleep duration	0.23	140	RCT	healthy adults	mindfulness	10	0.46
Jazaieri, Lee, Dolfin, & Gross, 2016	low social anxiety	social anxiety during MBSR	0.30	47	RCT	patients with social anxiety disorder	Mindfulness-Based Stress Reduction	56	0.54
Kabat-Zinn and Chapman-Waldrop, 1988	Gender in pain cohort	completing the program	0.12	500	non-RCT	patients with stress or pain-related conditions	Mindfulness-Based Stress Reduction	56	0.6
	type of pain/stress diagnosis	completing the program	0.14	784	non-RCT	patients with stress or pain-related conditions	Mindfulness-Based Stress Reduction	56	0.6
	gender (total population)	being a no-show vs being a drop-out	0.06	784	non-RCT	patients with stress or pain-related conditions	Mindfulness-Based Stress Reduction	56	0.6

Kharlas & Frewen, 2016	mindfulness	distress during meditation	-0.12	508	non-RCT	healthy adults	mindfulness	1	0.6
	mindfulness	visual imagery during meditation	0.13	508	non-RCT	healthy adults	mindfulness	1	0.6
	sensory imagery	distress during meditation	0.01	508	non-RCT	healthy adults	mindfulness	1	0.6
	sensory imagery	pleasantness during meditation	0.25	508	non-RCT	healthy adults	mindfulness	1	0.6
Lee & Bowen, 2015	Conscienti-ousness	curiosity	0.01	63	non-RCT	prisoners with addiction disorders	mindfulness	56	0.7
Logie & Frewen, 2015	curiosity	negative affect during referential processes	0.15	70	RCT	healthy adults	mindfulness	1	0.69
	curiosity	positive affect during referential processes	0.14	70	RCT	healthy adults	mindfulness	1	0.69
Ly et al., 2014	low depression symptoms	depression symptoms	0.40	37	RCT	patients with major depressive disorder	mindfulness	56	0.92
Mak et al., 2019	discomfort with emotion	well-being	0.04	216 1	RCT	healthy adults	mindfulness	28	0.85
	ambiguity tolerance	well-being	0.03	216 1	RCT	healthy adults	mindfulness	28	0.85
	gender	well-being	0.04	216 1	RCT	healthy adults	mindfulness	28	0.85
	religion	well-being	0	216 1	RCT	healthy adults	mindfulness	28	0.85
	discomfort with emotion	distress	0.05	216 1	RCT	healthy adults	mindfulness	28	0.85
	ambiguity tolerance	distress	0.03	216 1	RCT	healthy adults	mindfulness	28	0.85
	gender	distress	0	216 1	RCT	healthy adults	mindfulness	28	0.85
	religion	distress	0	216 1	RCT	healthy adults	mindfulness	28	0.85
Michalak et al., 2016	childhood abuse	depression change in meditation group (observer rated)	-0.29	26	RCT	patients with chronic depression	Mindfulness-Based Cognitive Therapy	56	0.61
Nguyen-Feng et al., 2016	history of interpersona l violence	worry	-0.33	314	RCT	healthy adults	mindfulness	1	0.61

Nguyen-Feng, Greer, & Frazier, 2017	history of interpersonal violence	depression, anxiety, stress	-0.11	147	RCT	healthy adults	mindfulness	28	0.77
Oken, Goodrich, Klee, Memmott, & Proulx, 2018	gender age education	health-related quality of life	0.01	121	non-RCT	stressed adults	mindfulness	42	0.69
	depression	health-related quality of life	-0.08	121	non-RCT	stressed adults	mindfulness	42	0.69
	mental health, affect, sleep quality	health-related quality of life	0	121	non-RCT	stressed adults	mindfulness	42	0.69
	life stressors	health-related quality of life	0.14	121	non-RCT	stressed adults	mindfulness	42	0.69
	perceived stress	health-related quality of life	0.01	121	non-RCT	stressed adults	mindfulness	42	0.69
	neuroticism	health-related quality of life	0.18	121	non-RCT	stressed adults	mindfulness	42	0.69
	expectancy	health-related quality of life	-0.09	121	non-RCT	stressed adults	mindfulness	42	0.69
	self-efficacy	health-related quality of life	-0.09	121	non-RCT	stressed adults	mindfulness	42	0.69
	mindfulness	health-related quality of life	0	121	non-RCT	stressed adults	mindfulness	42	0.69
Pace et al., 2010	affect	amount of practice (high vs low)	0.36	30	non-RCT	healthy adults	compassion meditation	42	0.8
	affect	amount of practice (high vs low)	0.5	30	non-RCT	healthy adults	compassion meditation	42	0.8
Pace et al., 2009	IL-6	amount of practice (high vs low)	0.14	30	non-RCT	healthy adults	compassion meditation	42	0.8
	gender	amount of practice	0.12	61	RCT	healthy adults	compassion meditation	42	0.85

		(high vs low)							
	depressive symptoms	amount of practice (high vs low)	0.07	61	RCT	healthy adults	compassion meditation	42	0.85
Park & Park, 2012	self-directedness	heart-rate variability	-0.10	58	non-RCT	healthy adults	paced breathing	1	0.8
	harm avoidance	heart-rate variability	-0.08	58	non-RCT	healthy adults	paced breathing	1	0.8
Prins, Decuypere, & Van Damme, 2014	pain catastrophizing	rating pain during painful stimuli	0.26	51	RCT	healthy adults	mindfulness	1	0.62
Reich et al., 2014	lymphocyte subsets	fatigue	0.32	17	RCT	breast cancer patients	Mindfulness-Based Cognitive Therapy	42	0.77
Rohsenow Smith, & Johnson, 1985	anxiety	anxiety difference	0.58	36	RCT	adults with heavy drinking problems	cognitive-affective stress management	1	0.23
	irrational beliefs	anger difference	0.52	36	RCT	adults with heavy drinking	cognitive-affective stress management	1	0.23
	social support	anxiety difference	0.13	36	RCT	adults with heavy drinking	cognitive-affective stress management	1	0.23
	alcohol consumption	anxiety difference	0.52	36	RCT	adults with heavy drinking	cognitive-affective stress management	1	0.23
	locus of control	anxiety difference	0.32	36	RCT	adults with heavy drinking	cognitive-affective stress management	1	0.23
	mood	anxiety difference	0.67	36	RCT	adults with heavy drinking	cognitive-affective stress management	1	0.23
Rojiani, Santoyo, Rahrig, Roth, & Britton, 2017	women	negative affect	0.31	77	non-RCT	healthy adults	mindfulness	84	0.7
	men	mindfulness	0.67	77	non-RCT	healthy adults	mindfulness	84	0.7
Roos, Bowen, & witkiewitz, 2017	Substance use severity	Number of substance use days	0.1	80	non-RCT	substance use disorders	Mindfulness-Based Relapse Prevention	56	0.92
	depression	Number of substance use days	0.05	80	non-RCT	substance use disorders	Mindfulness-Based Relapse Prevention	56	0.92
	anxiety	Number of substance use days	-0.07	80	non-RCT	substance use disorders	Mindfulness-Based Relapse Prevention	56	0.92
Rosenzweig et al., 2010	type of pain diagnosis	psychological distress	0.33	133	non-RCT	patients with chronic pain	Mindfulness-Based Stress Reduction	56	0.7
	type of pain diagnosis	quality of life	0.26	133	non-RCT	patients with chronic pain	Mindfulness-Based Stress Reduction	56	0.7
Sass, Berenbaum, & Abrams, 2013	low discomfort with emotion	psychological distress	0.58	24	non-RCT	healthy adults	mindfulness	56	0.7

Seer & Raeburn, 1980	diastolic blood pressure	responding to treatment	0.40	41	RCT	patients with hyper-tension	transcendental meditation	5	0.61
	feeling relaxed	responding to treatment	0.44	41	RCT	patients with hyper-tension	transcendental meditation	5	0.61
Shapiro, Brown,	mindfulness	rumination	-0.5	30	RCT	healthy adults	mindfulness	56	0.69
Thoresen, & Plante, 2011	mindfulness	mindfulness	0.29	30	RCT	healthy adults	mindfulness	56	0.69
Smith et al., 1978	trait anxiety	trait anxiety	0.22	19	RCT	adults with anxiety	transcendental meditation	180	0.85
	trait anxiety	continued practice of meditation for 6 months	0.10	22	RCT	adults with anxiety	transcendental meditation	180	0.85
	age	trait anxiety	0.09	19	RCT	adults with anxiety	transcendental meditation	180	0.85
	gender	continued practice of meditation for 6 months	0.16	22	RCT	adults with anxiety	transcendental meditation	180	0.85
	considered therapy	trait anxiety	-0.24	19	RCT	adults with anxiety	transcendental meditation	180	0.85
	considered therapy	continued practice of meditation for 6 months	0.30	22	RCT	adults with anxiety	transcendental meditation	180	0.85
	self-concept (averaged)	trait anxiety	-0.13	19	RCT	adults with anxiety	transcendental meditation	180	0.85
	self-concept (averaged)	continued practice of meditation for 6 months	0.06	22	RCT	adults with anxiety	transcendental meditation	180	0.85
	social desirability	trait anxiety	0.10	19	RCT	adults with anxiety	transcendental meditation	180	0.85
	social desirability	trait anxiety	-0.01	19	RCT	adults with anxiety	transcendental meditation	180	0.85
Takahashi et al., 2005	novelty seeking	heart-rate variability	-0.06	20	non-RCT	healthy adults	other types of meditation	1	0.5
Tamagawa et al.,2015	anxiety	class attendance	0.26	38	non-RCT	distressed breast cancer patients	Mindfulness-Based Cancer Recovery	56	0.8
	married/cohabitating vs single	home practice	0.20	38	non-RCT	distressed breast cancer patients	Mindfulness-Based Cancer Recovery	56	0.8
	depression	meditation home practice	0.09	38	non-RCT	distressed breast cancer patients	Mindfulness-Based Cancer Recovery	56	0.8
	social support	meditation home practice	0.10	38	non-RCT	distressed breast cancer patients	Mindfulness-Based Cancer Recovery	56	0.8
	months since cancer diagnosis	meditation home practice	-0.05	38	non-RCT	distressed breast cancer patients	Mindfulness-Based Cancer Recovery	56	0.8

	low self-esteem	class attendance	0.03	38	non-RCT	distressed breast cancer patients	Mindfulness-Based Cancer Recovery	56	0.8
	repressive/defensiveness	class attendance	-0.02	38	non-RCT	distressed breast cancer patients	Mindfulness-Based Cancer Recovery	56	0.8
	low well-being	class attendance	0.05	38	non-RCT	distressed breast cancer patients	Mindfulness-Based Cancer Recovery	56	0.8
Watier & Dubois, 2016	low mindfulness	executive attention	0.19	78	RCT	healthy adults	mindfulness	1	0.62
Weinstein & Smith, 1992	absorption	somatic anxiety difference	0.55	52	non-RCT	adults with anxiety	focused attention meditation	1	0.8
	absorption	focusing difference	-0.53	52	non-RCT	adults with anxiety	focused attention meditation	1	0.8
Zalta et al., 2018	combat or military sexual trauma	PTSD severity	0.41	191	non-RCT	PTSD patients	cognitive processing, mindfulness, yoga and psycho-education	31	0.9
	combat or military sexual trauma	health	0.22	191	non-RCT	PTSD patients	cognitive processing, mindfulness, yoga and psycho-education	31	0.9
	gender	PTSD severity	0.1	191	non-RCT	PTSD patients	cognitive processing, mindfulness, yoga and psycho-education	31	0.9
Zautra et al., 2008	history of recurrent depression	catastrophizing	0.24	144	RCT	patients with rheumatoid arthritis	mindfulness	56	0.54
	history of recurrent depression	pain control	0.15	144	RCT	patients with rheumatoid arthritis	mindfulness	56	0.54
Zuroff & Schwarz, 1978	expectancy	anxiety difference	-0.26	60	RCT	healthy adults	transcendental meditation	63	0.62
	psychological maladjustment	anxiety difference	0.06	60	RCT	healthy adults	transcendental meditation	63	0.62
	locus of control	anxiety difference	0.53	60	RCT	healthy adults	transcendental meditation	63	0.62
	social desirability	anxiety difference	-0.2	60	RCT	healthy adults	transcendental meditation	63	0.62

4.2. Analyses based on thematic categories

Which categories of participant characteristics are associated with meditation efficacy?

Subgroup analyses were conducted to show whether effect sizes varied across the thirteen categories of participant characteristics. We found that six out of 13 categories had significant effect sizes. Based on bootstrapped 95% confidence intervals, the statistically significant categories of participant characteristics were: anxiety, psychopathology, well-being, depression, stress-related factors, and medical conditions (see Table 4).

Table 4. *The Results of Meta-Analysis Showing the Mean Effect Size (ES) for Each Category of Participant Characteristics and the Corresponding 95% Confidence Intervals (CI)*

Participant characteristics category	Number of samples	Number of ES	Mean ES	Bootstrapped 95% CI
Psychological Traits	11	15	.06	-.08, .18
Anxiety	7	7	**.19**	.03, .37
Self-concept	9	10	.13	-.02, .28
Interpersonal	9	10	.09	-.10, .24
Psychopathology	4	4	**.20**	.08, .41
Belief system	4	5	.07	-.01, .24
Well-being	10	13	**.20**	.11, .31
Motivation	8	10	.17	-.01, .34
Depression	9	11	**.15**	.08, .22
Stress-related factors	7	8	**.15**	.06, .32
Demographics	12	18	.01	-.09, .09
Mindfulness	7	11	.06	-.03, .16
Medical conditions	6	7	**.20**	.04, .32
Overall	103	129	**.11**	.07, .15

Note. Significant results are marked in bold. Mean ES reported as Pearson's *r*. The analysis contained 103 independent samples, exceeding the number of included studies (N = 50) because more than one participant characteristic (e.g. anxiety and gender) was used in most studies. The number of effect sizes exceeds the number of samples because more than one participant characteristic from the same category was used in some studies (e.g. gender and age belong to the demographics category).

Outcome valence: Do the effects of participant characteristics vary depending on whether mental health outcomes are negative or positive?

Next, we tested whether each of the identified categories was linked to negative and/or positive effects on mental health after mediation. The mean effect size for participant characteristics on the negative effects of meditation was r = 0.12. The largest effect sizes were for stress-related factors (r = 0.25), well-being (r = 0.24), depression (r = 0.22), and psychopathology (r = 0.21), while the smallest were for demographics (r = 0.03), interpersonal (r = 0.03), and mindfulness (r = - 0.04) variables. Only four categories out of 12 had statistically significant effect sizes: Psychopathology, well-being, depression, and stress-related factors. There were less than four studies available for medical conditions for this particular analysis, thus this variable was not examined (see Table 5).

The mean effect size for participant characteristics on the positive effects of meditation was r = 0.11 (*CI* 0.06, 0.15). Six out of 10 categories were significant: motivation (r = 0.23), medical conditions (r = 0.19), well-being (r = 0.19), interpersonal (r = 0.17), mindfulness (r = 0.15), and stress-related factors (r = 0.10), (see Table 5). The results were not carried out for three categories – anxiety, psychopathology, and belief system – because there were less than four studies available. The analyses also revealed that the diversity in outcome measures was a large source of heterogeneity, as the Q statistic decreased when the data were split into studies with positive and negative outcomes (see Table 6). Therefore, although the overall analysis indicated that there was homogeneity of effect sizes across studies, this was not the case once the total sample was divided into sub-classes based on the different types of outcomes of meditation. Rosenthal's fail-safe N was large for both positive and negative outcomes (510 and 457, respectively), suggesting that the results are robust.

Table 5. The *Results of the Meta-Analysis showing effect size (ES) of each category of participant characteristics on positive and negative outcomes, with corresponding 95% confidence intervals (CI)*

Participant characteristics category	**Negative outcomes**			**Positive outcomes**		
	Number of ES	Mean ES	CI	Number of ES	Mean ES	CI
Psychological traits	7	.08	-.09, .29	8	.04	-.18, .18
Anxiety	5	.20	.00, .44	N/A	N/A	N/A
Self-concept	5	.18	-.10, .43	5	.08	-.05, .22
Interpersonal	6	.03	-.23, .25	4	**.17**	.12, .21
Psychopathology	4	**.21**	.08, .42	N/A	N/A	N/A
Belief system	4	.08	-.03, .35	N/A	N/A	N/A
Well-being	5	**.24**	.09, .50	8	**.19**	.09, .30
Motivation	4	.06	-.26, .41	6	**.23**	.05, .38
Depression	6	**.22**	.14 .30	5	.06	-.03, .13
Stress-related factors	4	**.25**	.09, .60	4	**.10**	.03, .26
Demographics	7	.03	-.04, .11	11	.00	-.19, .11
Mindfulness	5	-.04	-.25, .13	6	**.15**	.08, .21
Medical conditions	N/A	N/A	N/A	4	**.19**	.07, .32
Overall	65	**.12**	.06, .18	63	**.11**	.06, .15

Note. N/A: analysis is not possible because less than four studies were available. Mean ES reported as Pearson's *r* with significant results marked in bold. The number of effect sizes exceeds the number of samples because more than one participant characteristic from the same category was used in some studies (e.g. gender and age belong to the demographics category).

4.3. Moderator analyses: Categorical

Research design: Do participant characteristics have a larger effect in randomized controlled trials?

Types of research designs were coded as categorical variables to differentiate between randomised controlled trials and other research designs. The effect size in RCTs (r = 0.11, *CI* 0.06, 0.77) was almost identical to other study types (r = 0.11, *CI* 0.06, 0.15). The Q statistic was significant, indicating a large amount of heterogeneity based on study design. More specifically, there was a high amount of heterogeneity within and between the samples in RCTs, which suggests that included RCTs showed more diverse effect sizes, while studies employing a non-RCT design had less variability in the effects of participant characteristics (see Table 6). Large fail-safe numbers support the robustness of these results.

Sample type: Do participant characteristics have a larger effect in clinical or non-clinical samples?

To test if participant type moderated the relationship between participant characteristics and meditation outcomes, we differentiated between clinical and non-clinical samples. Although the effect size was larger for studies with clinical (r = 0.14, *CI* 0.10, 0.19) than non-clinical samples (r = 0.08, *CI* 0.03, 0.13), both types showed significant effects of participant characteristics on meditation outcomes. The heterogeneity statistic was significant when studies were split based on the sample type, which suggests that sample type was a source of heterogeneity (Table 6). Unexpectedly, the effect sizes of participant characteristics in studies with non-clinical samples varied significantly, while the effect sizes of studies with diverse clinical samples were consistent. Large fail-safe numbers support the robustness of these results.

Table 6. *The Results of the Meta-Analysis showing Effect Size (ES), Confidence Intervals (CI), Overall Heterogeneity (Q), Heterogeneity Within Studies (Q_w), Heterogeneity Between Studies (Q_b) and Fail-Safe Ns for the Overall Analysis, Subgroup Analyses and Moderator analyses*

	ES	95% CI	Q	Q_w	Q_b	Fail-safe N
Overall analysis	**.11**	.07, .15	**197.99**	**179.97**	18.01	2574
Negative outcome analysis	**.12**	.06, .18	82.58	**70.74**	11.84	457
Positive outcomes analysis	**.11**	.06, .15	74.62	63.28	11.34	510
Moderator analysis 1: research design			**220.02**	**219.96**	0.06	2874
RCT	**.11**	.06, .77	**124.71**	**111.20**	**13.52**	780
non-RCT	**.11**	.06, .15	88.80	88.62	0.18	515
Moderator analysis 2: sample type			**225.48**	**221.15**	**4.33**	2948
clinical	**.14**	.10, .19	86.51	75.85	**10.66**	909
non-clinical	**.08**	.03, .13	**127.59**	**127.47**	0.12	435
Moderator analysis 3: meditation type			**219.90**	**215.08**	4.82	2872
mindfulness	**.09**	.06, .13	**121.83**	**121.07**	0.75	1216
transcendental	**.18**	.05, .27	18.15	16.80	1.36	44
other	.16	.02.,.32	23.31	18.52	**4.78**	25
Moderator analysis 4: length of meditation	.11	.08, .14	**216.42**	**216.13**	0.07	2822
Moderator analysis 5: sample size	**.11**	.08, .14	**225.31**	**219.24**	**6.07**	2945
Moderator analysis 6: study quality	**.11**	.08, .14	**217.95**	**212.35**	**5.59**	2846

Note. Q statistic represents a composite measure of heterogeneity between (Q_b) and heterogeneity within studies (Q_w). Rosenthal's fail-safe N represents the required number of unpublished studies with non-significant results that would make the mean effect size non-significant, which should be over 260 in the case of a meta-analysis of 50 studies.

Meditation type: Do participant characteristics have a larger effect in mindfulness meditation?

Types of meditation were coded as categorical variables to differentiate between mindfulness, transcendental meditation, and other types of meditation. The lowest effect size was for mindfulness (r = 0.09, *CI* 0.06, 0.13), followed by other types of meditation (r = 0.16, *CI* -0.02, 0.32), and the largest for transcendental meditation (r = 0.18, *CI* 0.05, 0.28). However, participant characteristics had a significant effect on outcomes in studies that employed mindfulness or transcendental meditation, while this was not found for other types of meditation. Heterogeneity was significant only in studies that used mindfulness, while studies of transcendental meditation and other types of meditation show more consistent effect sizes, but also low fail-safe numbers, which suggests that these results are not robust (see Table 6).

4.4. Moderator analyses: Continuous

Meta-regression was conducted to examine three continuous moderators: sample size, length of meditation intervention, and study quality. We first tested whether sample size moderated the effect size of participant characteristics. Meta-regression confirmed that participant characteristics had a smaller effect on meditation outcomes when studies had larger samples (p = 0.01). Next, we investigated whether the frequency of meditation intervention or practice moderated the effect size of participant characteristics. Meta-regression results showed that the effect size of participant characteristics was not affected by the frequency of meditation practice (p = 0.79), which varied from 1 to 365 days. The third question concerned the moderating effect of the methodological quality of the study (for scores see Table S1 in the Supplement). Meta-regression showed that quality of the study moderated the effects of participant characteristics on meditation response, so that studies with higher quality had lower effect sizes (p = 0.02). Fail-safe N confirmed that the results are rigorous for all three meta-regressions, but Q statistics point to significant heterogeneity, which indicates large variability in effect sizes (see Table 6).

5. Discussion

The present meta-analysis shows that participant characteristics play a significant role in shaping responses to meditation. Here we focused on participant characteristics as sources of variability in responses to meditation, though we acknowledge that contextual factors, such as characteristics of the meditation teacher or group processes, can also play a role. We found that six categories of participant characteristics were significantly related to meditation outcomes. Small to medium effect sizes were found for well-being, psychopathology, medical conditions, stress-related factors, depression and anxiety. On the other hand, mindfulness, motivation, demographics, interpersonal, belief system, self-concept and psychological traits variables had no significant effect on the overall meditation outcomes.

The second set of results concerned the impact of participant characteristics on negative and positive health outcomes. Psychological traits, self-concept and demographics were the only non-significant categories for the overall analysis and for the positive/negative subgroup analyses. This suggests that the response to meditation is not significantly impacted by participants' personality traits as operationalized in, for example, the Big Five theory of personality, nor to self-concept variables such as self-esteem or locus of control. In line with our findings, demographic variables have previously been found to not have a significant effect on the effect of meditation on health. For example, there was no effect for age and gender on psychological outcomes of various types of meditation in clinical and non-clinical samples (Sedlmeier et al., 2012). Similarly, there was no effect of age on outcomes of mindfulness-based interventions in non-clinical (Khoury et al., 2015) or clinical populations (Goldberg et al., 2018). It is important to note, though, that the similar results found in previous meta-analyses were based on a more restricted set of studies, while our meta-analyses included a much larger dataset obtained through a targeted search of all studies that examined the role of participant characteristics on meditation responses.

In contrast, two categories were significantly related to meditation outcomes in all analyses: well-being and stress-related factors. We found that participants with higher baseline levels of well-being showed moderate increases for both negative and positive meditation outcomes. Similarly, participants with higher baseline levels of stress showed moderate increases in negative outcomes, and small increases in positive outcomes. These results suggest that meditation has contrasting, even opposing effects for individuals with higher well-being and higher stress levels. One possible explanation for the effects of well-being is that self-report measures mask cognitive biases in answering items, such that individuals with lower insight into their emotions, thoughts and behavior, or with a high tendency to show social desirability, might rate themselves high on well-being measures. Another possibility is that learning meditation may reveal unwanted or less desirable aspects of the self, which are difficult to deal with and, as a consequence, lead to less positive outcomes. Some authors have argued that mindfulness-based types of meditation, where one learns to observe in a non-judgmental way one's thoughts and emotions, can be a difficult process for some or take longer to process than the usual time of the interventions (Creswell et al., 2014; Farias & Wikholm, 2015).

There was another unexpected and somewhat counter-intuitive result. Subgroup analysis revealed that baseline levels of depression were only significantly related to negative outcomes. In other words, a meditation practice or intervention is more likely to lead to negative outcomes for an individual reporting a higher level of depression. We need to qualify this result by looking at the individual studies that led to this result. Three out of the nine included studies in this category were conducted with participants with a diagnosis of current major depression episode (Ly et al., 2014) or a history of major depression (Geschwind et al., 2012; Zautra et al., 2008), while the six remaining studies included different clinical populations that often exhibit symptoms of depression, such as chronic pain conditions (Brotto et al., 2015), breast cancer survivors (Tamagawa et al., 2015) or substance use disorders (Roos et al., 2017). This suggests that it is not depression per se, but depression as a comorbid factor that might interact negatively with meditation. This claim seemingly contradicts prior meta-analytic findings showing that individuals with a current episode of depression can benefit from a meditation-based intervention (Strauss et al., 2014). However, Strauss and colleagues (2014) did not directly examine if there was a relationship between the extent of depression symptoms that are present before the meditation intervention and the outcomes after the intervention, thus there remains a possibility that their data would show results similar to ours if the same research question was examined.

Overall, these results highlight the possibility that some individuals can react negatively to meditation, which contradicts previous reports that adverse events are either non-existent or very infrequent in mindfulness-based interventions, happening in about only 1% of participants (Wong et al., 2018). The negative effects of mind-body interventions have been an uncomfortable and neglected topic within meditation research, though recently some studies have suggested that unwanted, unpleasant, or adverse experiences in meditators are relatively common, with suggestions that the prevalence for these effects may be as high as 25 to 32% (Cebolla et al., 2017; Schlosser et al., 2019). The prevalence and relevance of these negative effects are underestimated. Two recent meta-analyses of mindfulness-based therapeutic interventions found that only 9 trials out of 47 (19%) (Goyal et al, 2014) and 36 trials out of 231 (16%) (Wong et al, 2018) reported adverse effects. There are also criticisms concerning the use of unreliable methods to address these negative effects (Lindahl, Britton, Cooper & Kirmayer, 2019), and a tendency to frame these effects as difficulties during meditation which will eventually transform themselves into positive experiences (e.g., Chen, Qi, Hood & Watson, 2011).

In this respect, our results indicate that individuals with baseline characteristics of high depression and psychopathology are more likely to *not* benefit from meditation than others without these characteristics. This finding supports the work of clinicians who have been calling for the careful screening of participants before engaging with meditation-based interventions, particularly aiming to protect those who are at higher risk of mental health problems (Lustyk et al., 2009). Other than screening, clinicians should be encouraged to monitor the whole range of meditation-related experiences, in order to understand how difficult or negative experiences are appraised, the level of distress or functional impairment, and their duration, so that additional support may be provided.

Looking at the other side of the spectrum, subgroup analysis revealed that motivation, medical conditions, and interpersonal characteristics were significantly related to only positive outcomes. These results point at various interesting possibilities. First, it indicates that those suffering from medical problems may particularly benefit from meditation. It would be interesting for future studies to look at the processes that potentially mediate this relationship, such as self-regulation, or detachment from anxiety related to the medical condition. Second, it shows that interpersonal characteristics play a significant role in shaping meditation outcomes. A closer look at the studies involved shows that most of them focused on negative interpersonal factors, such as abuse, violence, and sexual trauma. This is in line with some research suggesting that individuals with a history of childhood trauma are more likely to benefit from a meditation-based intervention, when being treated for recurrent depression (Williams et al., 2014). Thirdly, motivational factors, such as positive attitudes and expectations of meditation, were associated with positive outcomes. This is an expected finding as it can be assumed that individuals who begin learning meditation with higher motivation and expectations of achieving benefits actually do show more benefits. Nevertheless, this is an important result to consider, since few meditation studies have controlled for this variable. Those who have, though, have found that positive expectations of meditation outcomes play a significant role in the results of studies (Creswell et al., 2014).

We took a deeper look into the data by examining several moderators: research design, sample type, meditation type, length of meditation intervention, sample size and study quality. The effects of participant characteristics on meditation outcomes were statistically significant concerning the type of research designs (RCTs or non-RCTs), the types of samples (clinical or non-clinical), and whether a study employed transcendental meditation or mindfulness. However, we did not find a significant effect of participant characteristics in studies that employed other types of meditation interventions. The likely reason for this is that only 9 out of the total of 50 studies used meditation interventions other than mindfulness or transcendental meditation, and these studies included various types of meditation (e.g., paced breathing or compassion meditation) and showed somewhat inconsistent results — as indicated by the large confidence intervals.

The results of meta-regression showed that participant characteristics have the same effect on the outcomes of meditation regardless of the length of meditation intervention, which ranged from 1 day to 1 year. This suggests that future studies could successfully study the effects of participant characteristics using brief meditations interventions because predictors of short-term and long-term outcomes of meditation are similar. On the other hand, participant characteristics had a smaller effect on meditation outcomes when studies had larger samples and higher methodological quality.

One critical consideration is the large amount of variation in measures of individual differences in meditation research. To deal with this, we created categories based on previous research. There is are inherent ambiguities in this process; for example, some could argue that ‘experience in group therapy’ should not belong to the category ‘well-being’, but in the interpersonal category. We have dealt with this problem following standard protocols of inter-rater reliability and discussion. We also acknowledge that this meta-analysis is the first one of its kind, which means that further work is required to validate its results and develop clear clinical recommendations. One suggestion for a future meta-analysis is include individual level data, instead of group averages that were used here. We found that overall, the quality of studies was moderate. Studies typically maintained fair or good quality by consistently and clearly stating the objectives and describing the interventions, recruiting participants representative of the target population, using valid and reliable measures, and avoiding high drop-out rates.

6. Conclusions

This meta-analysis has shown that participant baseline characteristics significantly influence the response to mindfulness and Transcendental Meditation interventions. Although more work is needed to validate these results and develop clinical recommendations, our results lead us to suggest that it should be mandatory to actively monitor the experiences of individuals undertaking meditation interventions, particularly individuals with high levels of psychopathology and depression who are more likely to experience a deterioration of their condition or other adverse effects. We are not categorically stating that difficult or unexpected experience during meditation is necessarily psychopathological or abnormal, but the meaning and consequences of such experiences need to be controlled for and examined in a dialogue with the affected individual. We hope that the societal interest in meditation and in its health promoting possibilities, coupled with the growing awareness of personalized medicine, will engage clinicians, researchers, and meditation teachers in a dialogue that openly addresses for whom and when meditation is indicated or contra-indicated.

Chapter 6

General Discussion

1. Summary

The aim of this thesis was to expand the current knowledge on MBIs by providing an integrative multi-level assessment that allowed for: a) addressing their biological correlates; b) comparing the potential benefits of different MBIs on neuro-cognitive and psychobiological outcomes with a vulnerable population; c) examining the variability of meditation outcomes based on participant characteristics. This thesis addressed three specific questions: 1. Are there robust changes in gene expression following MBIs that might be considered mechanisms for their benefits?; 2. Is the administration of MBIs feasible in a clinical prison setting and can prisoners with personality disorders benefit from MBIs?; 3. How do participant characteristics influence meditation outcomes? To carry this out, I used a variety of techniques from psychology, biology, and cognitive neuroscience, as well as meta-analytical methods and systematic reviews.

The first question was examined in a systematic review of peer-reviewed studies using gene expression as one of the outcomes of MBIs, including meditation, yoga, Tai Chi and Qigong. The main finding was that there was a general anti-inflammatory gene expression pattern across different MBIs, which indicates that gene expression is a mechanism that helps to explain why people experience that MBIs improve their health. Chronic inflammation can be found in the basis of many leading causes of mortality, such as cardiovascular diseases, dementia, some types of cancer, depression or PTSD, thus finding ways to tackle is a top priority. It remains unknown if other behavioural interventions can affect chronic inflammation in a similar manner.

The second question was explored through a randomised controlled trial that tested the feasibility and effectiveness of an intensive 5-day mindfulness or yoga intervention on prisoners with personality disorders. Thirty participants were randomised to either mindfulness, yoga or wait-list control group. Multilevel assessments included EEG connectivity, spectral power

analyses and ERPs, difficulties in emotion regulation, mindfulness, stress, inflammatory gene expression, behavioural risk-taking and attention. Non-significant statistical effects were observed across almost all measures, but five out of 35 analysed inflammation-related genes that showed medium effects in terms of gene expression. However, these results are considered preliminary due to a small sample size. Both mindfulness and yoga interventions were not particularly feasible due to difficulties in recruitment, adherence, preventing attrition of participants, and delivering the interventions. Most notably, the programme of the fifth day of the interventions was not delivered due to a lockdown in a nearby prison unit, which resulted in a lack of staff members that were necessary to deliver the interventions safely. More studies with bigger sample sizes are necessary to determine whether intensive MBIs offer benefits for prisoners with personality disorders.

The third question that is related to individual differences in meditation was explored in chapters 4 and 5. The narrative review (chapter 4) provided an overview of 26 studies that explored individual differences in responding to meditation through the assessment of the relationship between participant characteristics and meditation outcomes. The majority of studies were focused on psychological individual differences that influence the response to meditation, including neuroticism, anxiety, conscientiousness, mindfulness, attachment style, mood, emotions, and expectations. Important biological factors were BDNF and COMT gene polymorphisms, biomarkers of immune activity such as IL-6 and amygdala and insula activity. Other than specific psychological and biological factors, studies suggested that illness severity might also influence the response to meditation, while demographic factors do not. Next, a quantitative approach was employed by conducting a meta-analysis that quantifies the size of the effects of participant characteristics on meditation outcomes (chapter 5). The analysis of fifty eligible studies found that although the overall effect of participant characteristics on the response to meditation was small, several types of participant characteristics had moderate effects: medical conditions, well-being, and psychopathology. It was also found that people with higher baseline scores related to psychopathology and depression were more likely not to benefit from meditation. On the other hand, people with higher scores on interpersonal variables, motivation, medical conditions, and mindfulness were more likely to benefit from meditation. Several participant characteristics did not affect the response to meditation: demographics, psychological traits, and self-concept.

2. General discussion of main findings

The studies in this thesis addressed several important gaps in the research of MBIs. First, gene expression changes were elucidated as one potential mechanism of health benefits that are associated with regular practice of mind-body techniques such as meditation, yoga, Tai Chi or Qigong. Unexpectedly, all MBIs showed an anti-inflammatory gene expression pattern, which is the opposite of chronic stress, although some of the MBIs include a physical component, while others are mainly sedentary (e.g., sitting down in a quiet environment while focusing one's attention). This raises the question of whether the supposed beneficial effects of MBIs on gene expression can be obtained with behavioural interventions that do not include a specific mind-body component, such as nutritional or exercise interventions. This is an important question because people who do not respond well to meditation or other MBIs might reap the same health benefits by engaging in another lifestyle modification that they find more enjoyable and thus can maintain motivation for long-term practice more easily. Unfortunately, only a handful of studies have examined the effects of nutritional or exercise interventions on gene expression (Dijk et al., 2009; van Breda et al., 2014; Gjevestad, Holven & Ulven, 2015; Bouchard-Mercier et al., 2013; Yubero-Serrano et al., 2012; Di Renzo et al., 2015; Konstantinidou et al., 2009) so it is too early to make a conclusion before more studies are conducted. Ideally, we would see comparative effectiveness research that identifies the best behavioural interventions in terms of gene expression within a specific target population. However, there are many other questions regarding MBIs and gene expression that need to be answered. From the analysed studies of MBIs, it was observed that the amount of inflammatory proteins often does not change from pre- to post-intervention, which would be expected as the activity of genes that code for those proteins increases. This suggests that posttranscriptional regulatory mechanisms might be degrading the mRNAs before they get to the ribosomes and translate into proteins. Additionally, it is not clear when this anti-inflammatory gene expression pattern emerges because studies normally take blood samples only before and after interventions. It is also unclear for how long the change in gene expression can be maintained if one stops practicing MBIs. Therefore, besides conducting comparative research, future studies should explore posttranscriptional regulatory mechanisms, such as miRNAs, and also have multiple time points of sample collection during the interventions, along with several long-term follow-ups to track gene expression changes over time.

In our small randomised controlled trial with prisoner, the findings from the systematic review about MBIs and gene expression were used to select a subset of 35 inflammation-related genes that were more likely to change expression following MBIs. This study addressed another gap in the research of MBIs; it was the first to examine the feasibility and the preliminary effects of mindfulness and yoga interventions in incarcerated offenders with various personality disorders. It was found that mindfulness and yoga were only moderately feasible interventions, but in comparison with a wait-list control group, no effects of mindfulness or yoga were found in most of the applied measures (EEG connectivity, power, ERPs, attention, risk-taking, perceived stress, emotion regulation, and mindfulness) other than medium effects of gene expression of several inflammation-related genes. This was contrary to our hypotheses, as we expected positive effects on all measures, which was observed in previous studies on non-clinical and different clinical populations. It is likely that these results were driven by various factors: first, we did not manage to deliver the last day of the interventions due to a full lockdown in the prison. This was not only a stressful day for our participants that are normally locked up at certain times during the day and overnight, but it also reduced the intended length of our interventions by 20%. A second factor pertains to the type of population; it is possible that patients with personality disorders might not respond to short intensive MBIs, but might require longer interventions for changes to be observed. Although conducting studies in prisons brings many challenges, especially if it is a clinical population that requires additional ethical approvals and there is the risk of a high dropout, it is important to conduct further studies on this population with longer MBIs, potentially of a less frequent practice than we used.

The final gap that was addressed in this thesis concerned the lack of understanding of individual differences in responses to meditation. Based on the results from chapters 5 and 6, it was discovered that meditation affects people differently based on their characteristics. Although contextual factors certainly play a role, such as characteristics of the meditation teacher or group processes that occur among meditation students, we focused on participant characteristics as sources of variability in responses to meditation. This meta-analysis was exploratory and its findings should be used to generate hypotheses of future studies. It is important to note that the fifty studies that were eligible for inclusion in the meta-analysis did not cover the whole array of participant characteristics that could potentially influence the response to meditation (e.g. cognitive variables like attention or working memory). The first step towards developing more precise clinical recommendations is to conduct methodologically rigorous studies of meditation interventions that test various participant characteristics as moderators. The second step could be to conduct a meta-analysis that would include individual level data, instead of group averages that were used in the last study of this thesis. This section concludes the discussion on three specific gaps in MBI research that were addressed in this thesis. In the upcoming sections, the focus will first be on methodological flaws of MBI studies, followed by a presentation of a novel interdisciplinary MBI research framework.

Despite the fact that there has been a substantial research interest in MBIs over the past two decades that resulted in thousands of published studies, the interpretation of these studies has been challenging due to their methodological limitations. This problem became apparent during the quality assessment of 50 studies that were included in the meta-analysis on chapter 5. The biggest problem with the quality assessment of studies that use MBIs was the lack of transparent reporting that would enable the assessment of all aspects of study quality. It is generally recommended to adhere to the Consolidated Standards of Reporting Trials (CONSORT), that has an extension for social and psychological interventions (Montgomery et al., 2018). This checklist covers many important aspects of interventional studies, including eligibility criteria for participants or sample size calculation, but some characteristics that determine the quality of MBI studies are not included, such as teacher's qualifications and experience. Developing a reporting guideline that is specific to MBIs could improve the quality of research in the field and, in turn, contribute to estimating the effectiveness of MBIs more accurately. Furthermore, the same MBI study can get different quality scores based on the type of applied quality assessment tool used. Based on a recent review, there are six commonly used quality assessment tools for randomised controlled trials and two for non-randomised interventional studies (Zeng et al., 2015). Some of these general tools neglect aspects of MBI studies that contribute to their quality, thus it is important to attempt reaching a consensus on which tool is best suited for MBIs or to develop a MBI-specific quality assessment tool.

Researchers that conduct studies on MBIs face challenges towards achieving the gold standard of methodological quality that mirrors double-blind placebo-controlled interventions. Normally, this approach is used in biomedical research to test the effectiveness of a novel drug by comparing experimental, placebo and wait-list control groups, while neither the participants or people administering the drug are aware of group assignment. Within the context of MBIs, this would require constructing a sham MBI that would be delivered to participants in the placebo group. This means, for example, that participants would be led to believe that they are learning how to meditate, when instead they are doing something similar, which is not meditation. Although quite rare, similar approaches have been attempted (e.g., Zeidan, Johnson, Gordon & Goolkasian, 2010), but it is difficult to achieve intervention credibility when people are exposed to MBIs through the media or through interpersonal experiences. It certainly would be impossible to achieve blinding of the MBI instructor, but blinding of data collectors or outcome adjudicators is possible and a solid first step towards higher methodological rigour of randomised controlled trials of MBIs. This form of blinding is crucial to ensure unbiased assessment of outcomes even if a study is using outcomes that are more objective than self-reports, which was clearly demonstrated in a randomised controlled trial that tested two medical treatments in patients with multiple sclerosis. In particular, neither active treatment regimen was superior to placebo when assessed by blinded neurologists, but there was an apparent benefit of both treatments in comparison to placebo when non-blinded neurologists performed the assessments (Noseworthy et al., 1994). Therefore, although subjective self-report outcomes are the most at risk of bias, some forms of more objective outcomes often involve a degree of subjectivity that makes them at risk of bias as well.

Other than the lack of blinding of data collectors, another common downside of randomised controlled trial of MBIs was the preference of wait-list control groups over active control groups. This preference is easy to understand because wait-list control groups cost less and require less logistics within the research project. However, the lack of control groups is one of the main reasons why systematic reviews and meta-analysis show low confidence in evidence for the effects of MBIs (e.g. Goyal et al., 2014). Active control groups are necessary because they can discern the effects of MBIs that go beyond non-specific benefits of MBIs, such as placebo effect, attention from the researchers or teachers, interactions with other participants or demand characteristics. Other than matching in non-specific benefits, the active control group and experimental group should be equal in length, practice time, and both should have highly trained and confident instructors. Therefore, an ideal active group against which the effects of an MBI would be compared should be the same as that MBI across all aspects. In reality, this is hard to achieve and thus not all active control groups provide the same amount of rigour. With the aim of providing an optimal comparison condition for the most researched MBI (MBSR: Mindfulness Based Stress Reduction), researchers created the Health Enhancement Program that has identical group format, amount of practice, and instructor's expertise and confidence (MacCoon et al., 2012). More specifically, the Health Enhancement Program consists of listening to music, nutrition education, functional movement and physical activity. Interestingly, research shows that the benefits from the Health Enhancement Program are comparable to those from MBSR in terms of reduction in anxiety, general distress, hostility, and medical symptoms, while MBSR is superior only in terms of pain tolerance (MacCoon et al., 2012). These findings support that it is crucial to use active control groups when testing the effectiveness of MBIs because many observed benefits do not emerge due to the practice of mind-body techniques, but rather due to many non-specific factors that are a part of the intervention. Future studies should not only focus on using active control groups, but also on developing optimal comparison conditions for standardised MBIs other than MBSR.

As well as the need for methodological improvements, the MBIs literature would also benefit from developing clearer theoretical frameworks. Most frameworks used are unidimensional; they encompass only a portion of the mechanisms that explain how MBIs work to create observed benefits. One exception is a framework that includes neural and psychological mechanisms of mindfulness (Tang, Hölzel & Posner, 2015). This framework proposes that the central psychological mechanism of mindfulness is improved self-regulation, which consists of three components: attention, emotion regulation and self-awareness (Tang, Hölzel & Posner, 2015). Furthermore, the proposed corresponding neural correlates of the three components of self-regulation are: anterior cingulate cortex and the striatum that are involved in attention control; multiple prefrontal regions, limbic regions and the striatum that are involved in emotion regulation; and the insula, medial prefrontal cortex, posterior cingulate cortex and precuneus that are involved in self-awareness (Tang, Hölzel & Posner, 2015). However, this model does not sufficiently capture the multi-level framework that is needed to understand the effect of MBIs. Below I propose an extension of this framework that explains mechanisms of MBIs on multiple levels, including psychological, neural and molecular, and that also considers interactions among these levels.

4. The psychoneurogenomic framework of MBIs

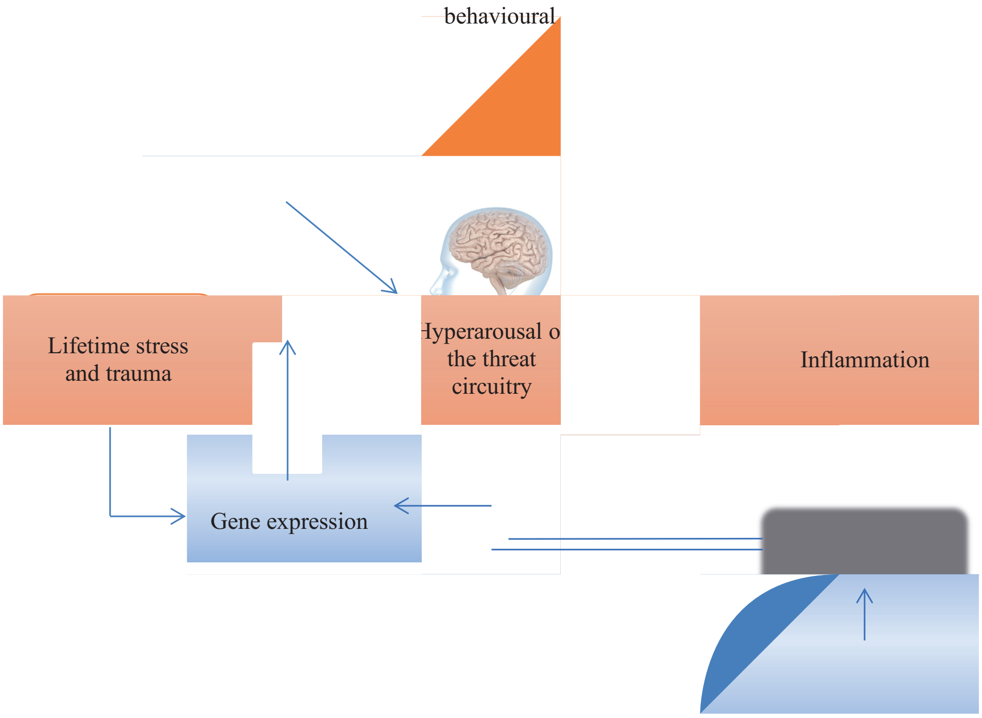

Figure 1. An interdisciplinary MBI research framework that takes into account multilevel interactions, and combines psychology, neuroscience and genomics.

The proposed model consists of eleven hypotheses that are based on findings from previous studies. The first set of hypotheses (H1-H4, Figure 1) is related to the factors that determine the arousal of the threat circuitry and, consequently, the stress response, thus a brief overview of the stress response is warranted to begin with. When there is a perceived threat in the environment, be it a psychological or physical stressor, the brain's threat circuitry becomes activated and initiates a chain of molecular reactions that constitute the stress response (Rodrigues, LeDoux & Sapolsky, 2009). This reaction begins when amygdala detects a threat and causes the release of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus, which in turn causes the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH travels through the bloodstream to adrenal glands that then synthesise and release cortisol and other glucocorticoids from their cortex. Glucocorticoids circulate around the body and go back into the brain where they bind to glucocorticoid (GR) and mineralocorticoid receptors (MR). MRs are sensitive to circadian changes in glucocorticoids, while GRs need a higher amount of glucocorticoids for activation and shut down the stress response. This hypothalamic-pituitary-adrenal (HPA) axis is a classic negative feedback loop — production of glucocorticoids feeds back to the brain and then their production declines, which ultimately stops the stressful reaction. However, when stress is severe or chronic, the brain undergoes structural changes that are not adaptive in terms of mental and physical health. Namely, changes in prefrontal cortex, hippocampus and amygdala lead to the hyperarousal of the threat circuitry, so now more things are perceived as a threat and the stress response is easily triggered (Davidson & McEwen, 2012, McEwen & Gianaraos, 2011, McEwen & Morrison, 2013). Lifetime stress and trauma are known to affect function and structure of the brain, including the regions that regulate stress reactivity (Rodrigues, LeDoux & Sapolsky, 2009). Therefore, the level of arousal of the threat circuitry is largely determined by lifetime stress and trauma that remodel the brain (H1). However, the consequences of the same lifetime experiences can vary across individuals based on their genetic predispositions, because the inherited genetic structure also determines the structure and activity of the brain (H2) and it makes some individuals more susceptible to perceiving threats. Importantly, the activity of the inherited genes is influenced by the environment through changes in gene expression, and studies suggest that lifetime stress and trauma can change gene expression in the hypothalamus and amygdala, which are central components of the threat circuitry (H3 and H4; McGowan et al., 2009).

The next set of hypotheses (H5-H7, Figure 1) is related to the bidirectional communication between the neural and the immune system. The hyperarousal of the threat circuitry continuously upregulates the components of the immune system that generate inflammation (H5; Slavich & Irwin, 2014). The main molecular indicators of inflammation are proteins called cytokines that can travel from the immune system back to the brain (H6; Irwin & Cole, 2011). While inflammation is beneficial when it is short-term and in response to physical danger, chronic stress leads to prolonged inflammation that is detrimental to health (Slavich, 2015). More specifically, it increases the risk for viral infections and inflammation-related diseases such as anxiety, depression, asthma, cardiovascular disease, stroke, and cancer, neurodegenerative disorders (Furman et al., 2019). Therefore, the brain can initiate inflammation (H5) and the immune system can feed back to the brain through cytokines (H6) and regulate the function of the central nervous system and its effects on the behaviour and health (H7).

The final set of hypotheses (H8-H11, Figure 1) describes how mind-body interventions can get under the skin and influences mental and physical health outcomes. Based on the previously described framework that posits that self-regulation is the core psychological mechanism of mindfulness interventions (Tang, Hölzel & Posner, 2015), I hypothesise that not only mindfulness, but also other behavioural interventions will improve self-regulation (H8), reduce activity in the threat circuitry (H9), and change gene expression of inflammation-related genes (H10), which ultimately determines the levels of inflammatory proteins (i.e., cytokines; H11). As studies suggest that different mind-body interventions have the same molecular mechanisms in terms of gene expression (Buric et al., 2017), I argue that self-regulation is the core psychological mechanism of all mind-body interventions. By boosting self-regulation with mind-body interventions, a previously hyper-aroused threat circuitry can become normalised, which in turn reduces inflammation and protects health.

3.1. Advantages offered by the psychoneurogenomic framework of MBIs

MBIs cannot be fully understood by relying exclusively on psychological methods. Instead, an interdisciplinary approach is mandatory to address the blind spots. Neuroimaging and genomic techniques can advance our understanding of underlying mechanisms of MBIs that can potentially be used as biomarkers for prevention and treatment. These novel ideas can be examined by implementing longitudinal experimental studies using prospective genomic, neuroimaging and behavioural data in testing the effectiveness of various behavioural interventions. These studies would address several important research questions stemming from the proposed framework (Figure 1). Some key questions that need to be answered in order to elucidate the major components of the model are:

1) Is the change in arousal of the threat circuitry related to improvements in self-regulation?
2) Is the change in self-regulation following mind-body interventions related to changes in gene expression?
3) Do some mind-body interventions target self-regulation better than the others?

The main challenge in applying this framework is that a study that would test many variables and their interactive effects in creating a response to MBIs would be difficult to conduct because they would need much larger sample sizes than are usual in meditation research. This challenge, however, does not outweigh the potential benefits. By using this psychoneurogenomic framework, we can not only observe how the person becomes recalibrated to facilitate adaptation to interventions, but also compare the effectiveness of different behavioural interventions and lay ground for tailored treatment. This framework could transform intervention science, showing how environmental circumstances foster changes in gene expression and neural plasticity that results in adaptive behaviour.

4. Closing remarks

The work presented in this thesis made a significant contribution by elucidating molecular mechanisms of MBIs, by testing the feasibility and the effects of mindfulness and yoga in a rare clinical population that, and by describing participant characteristics that influence the response to meditation. The thesis emphasises the importance of applying interdisciplinary research approaches in order to gain a deeper understanding of MBIs. Based on the findings from this thesis and other previous studies, I presented a novel research framework that has the potential to explain human behaviour and health through multilevel research of MBIs and other interventions that target inflammation.

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Appendices

Appendix 1. Abbreviations

BMI	Body mass index, calculated as the body weight divided by square of the body height
CBT	Cognitive behavioural therapy, the most common approach in psychotherapy
CREB	cAMP response element-binding protein, a transcription factor that regulates genes involved in neuroplasticity and memory
CRP	C reactive protein, a protein produced by the liver that can be measured from the blood as an indicator of inflammation
CTRA	Conserved transcriptional response to adversity, a molecular signature of stress
FeNO	Fractional exhaled nitric oxide, a measure of airway inflammation
GR	Glucocorticoid receptor, a transcription factor that affects inflammation and cellular proliferation
GSEA	Gene Set Enrichment Analysis, a type of bioinformatics analysis of the genes that change expression
HPA	Hypothalamus-pituitary-adrenal (axis), the key circuitry involved in the stress response
IBD	Inflammatory bowel disease, a term that include Crohn's disease and ulcerative colitis, which are chronic inflammatory disease of the colon and/or small intestine

IBS	Irritable bowel syndrome, a chronic inflammatory condition that brings symptoms such as cramps, bloating, diarrhoea or constipation
IL	Interlukin, a protein that regulates immune responses
IPA	Ingenuity Pathway Analysis, a type of bioinformatics analysis of the genes that change expression
IRF	Interferon related transcription factor, regulates anti-viral responses
KKM	Kirtan Kirya Meditation, a form of meditation that includes singing a mantra and finger gestures (mudras)
MAP	Mindful awareness practices, a standardised 6-week mindfulness intervention
MBCT	Mindfulness based cognitive therapy, an approach that combines CBT and mindfulness
MBI	Mind-body intervention, an umbrella term for meditation, yoga, mindfulness, Tai Chi, Qigong and relaxation response
MBSR	Mindfulness Based Stress Reduction, a standardised 8-week mindfulness intervention
miRNA	Micro RNA, a small non-coding RNA molecule that can interfere with the expression of a gene after it is transcribed
mRNA	Messenger RNA, a large family of RNAs that transport genetic information from DNA to ribosomes

NF-kB Nuclear Factor Kappa B, a transcription factor regulating a large number of genes related to immune response, cell survival, differentiation, and proliferation

PBMC Peripheral blood mononuclear cells, blood cells that have a round nucleus: lymphocytes and monocytes

RR Relaxation response, it refers to any practice that can elicit a physiological response that is the opposite of the stress response.

RT qPCR Real time quantitative polymerase chain reaction is a laboratory technique that detects gene expression

SK&P Sudarshan Kirya and related practices include yoga poses, breathing exercises and meditation

SNS Sympathetic nervous system, activates fight or flight response when stress is detected

TELiS Transcription Element Listening System, a type of bioinformatics analysis of the genes that change expression

TLR Toll like receptor, protein that plays a role in the immune system

TM Transcendental meditation

TNF Tumour necrosis factor, a prototypical pro-inflammatory cytokine that plays a central role in inflammation, immune system development, and apoptosis.

TOA Transcript origin analysis, a bioinformatics analysis that determines the cellular origin of detected gene expression changes

TSST	Trier Social Stress Test, a behavioural test of stress reactivity that consists in giving a speech and doing arithmetic operations in front of judges

Appendix 2. References for all studies that were included in the meta-analysis (Chapter 5)

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Data management

The prison study from Chapter 3 was pre-registered. Clinicaltrials.gov identifier is NCT02894203:

https://clinicaltrials.gov/ct2/show/NCT02894203

The full gene expression dataset can be found at the Gene Expression Omnibus:

https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE134703

https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GPL26947

The rest of the data (questionnaires, cognitive tasks and EEG outcomes) related to the prison study from Chapter 3 can be found at the Open Science Framework:

https://osf.io/28kbj/?view_only=13e44dba17c34df5a5874137a5c4d331

All relevant data regarding the meta-analysis of individual differences in meditation from Chapter 5 can be found at the Open Science Framework:

https://osf.io/nquwa/?view_only=53d1a09611c945cf8e115386e6898741

English summary

There is considerable evidence for the effectiveness of mind-body interventions (MBIs) in improving mental and physical health in various clinical and non-clinical populations, but there are several gaps that remain poorly understood. The aim of this thesis was to expand the literature on MBIs by answering three major questions: Are changes in gene expression a mechanism of MBIs? Do MBIs work for prisoners with personality disorders? Do participant baseline characteristics influence the response to meditation?

To answer the first question related to gene expression as mechanisms of MBIs, we searched PubMed throughout September 2016 to look for studies that have used gene expression analysis in MBIs (i.e., mindfulness, yoga, Tai Chi, Qigong, relaxation response, and breath regulation). Due to the limited quantity of studies, we included both clinical and non-clinical samples with any type of research design. Eighteen relevant studies were retrieved and analysed. Overall, the studies indicate that these practices are associated with a downregulation of nuclear factor kappa B (NF-kB) pathway; this is the opposite of the effects of chronic stress on gene expression and suggests that MBI practices may lead to a reduced risk of inflammation-related diseases. However, it is unclear how the effects of MBIs compare to other healthy interventions such as exercise or nutrition due to the small number of available studies. More research is required to be able to understand the effects of MBIs at the molecular level.

To answer the second question related to the effects of MBIs on prisoners with personality disorders, we recruited thirty prisoners with personality disorders who score high on psychopathy and have more than two personality disorders. They were assigned to a mindfulness intervention (n=10), to a yoga intervention (n=10), or to a wait-list control group (n=10) using stratified random sampling. Both mindfulness and yoga interventions were held at the same time and lasted three hours per day on five consecutive days. At baseline and after the intervention, we measured inflammation-related gene expression; resting state brain activity with electroencephalography (EEG); risk-taking and attention with cognitive tasks; event-related potentials (ERPs) related to the attention task; and stress, emotion regulation and mindfulness with questionnaires. Thirty participants were included in intention-to-treat analysis. We expected that both yoga and mindfulness will improve self-regulation (i.e., executive attention, emotion regulation and self-awareness), reduce stress and risk-taking

behaviour, downregulate inflammatory-related gene expression and increase alpha and theta power. By using intent-to-treat analysis, we found no significant effects of interventions on any of these measures ($p>.05$). We found that mind-body interventions do not benefit prisoners with personality disorders and we assume that non-significant results are likely due to several methodological factors; a lockdown on the final day of the interventions, the length of the interventions and insufficient statistical power.

The third question is related to individual differences in responding to meditation. While meditation classes, in particular mindfulness meditation classes, have become increasingly popular and more readily available, their outcomes vary. Some people reap benefits of the classes and become dedicated long-term practitioners, while others see no effect or might even experience adverse effects. If we would be able to distinguish positive responders from null and negative responders based on their individual characteristics, then those who would benefit the most could be targeted, while a different evidence-based technique could be applied to those for whom meditation would be contra-indicated. Surprisingly, there is no comprehensive study on this topic and only a limited number of studies have included data on how different people respond to meditation. The thesis synthesizes heterogeneous evidence from previous studies that examined baseline participant variables that influence the response to meditation; first as a narrative review and then as a comprehensive meta-analysis. Overall, we found that a higher baseline level of psychopathology or depression was associated with deterioration in mental health after a meditation intervention. On the other hand, participants with higher scores on interpersonal variables, motivation, medical conditions, and mindfulness showed higher levels of positive outcomes. Higher well-being and stress were simultaneously associated with moderate increases in negative and positive meditation outcomes. Participant demographics, psychological traits, and self-concept, and length of meditation practice did not significantly influence the response to meditation.

This thesis contributes to the current literature by providing evidence that gene expression changes are mechanisms of health benefits associated with MBIs. Furthermore, it suggests that prisoners with personality disorders do not respond to short and intensive MBIs and it synthesizes heterogeneous evidence from previous studies that examined baseline participant variables that influence the response to meditation.

Nederlandse samenvatting

Er is aanzienlijk bewijs dat laat zien dat interventies gericht op lichaam en geest (mind-body-interventies of MBI's) effectief de mentale en fysieke gezondheid kunnen verbeteren in verschillende klinische en niet-klinische populaties. Het is echter nog onvoldoende bekend waarom MBI's tot deze verbetering kan leiden. Ook is het niet duidelijk hoe dit soort behandelingen een effect kunnen hebben op (neuro)biologische processen in het lichaam, en welke rol individuele verschillen hierbij spelen. Dit proefschrift levert een belangrijke bijdrage aan de kennis omtrent MBI's door drie belangrijke vragen te beantwoorden: Kunnen MBI's leiden tot veranderingen in genexpressie? Kunnen MBI's worden ingezet als interventie bij gedetineerden met persoonlijkheidsstoornissen? En zijn persoonlijke eigenschappen van invloed op het effect van meditatie?

Om te onderzoeken of MBI's kunnen leiden tot verandering in genexpressie is in september 2016 een literatuuronderzoek gestart, waarbij gezocht is naar studies die gebruik hebben gemaakt van analyses van genexpressie bij MBI's (o.a. mindfulness, yoga, Tai Chi, Qigong, ontspanningstherapie en ademhalingstherapie). Vanwege het beperkte aantal studies is besloten om zowel klinische als niet-klinische doelgroepen mee te nemen in het onderzoek. In totaal werden achttien relevante onderzoeken gevonden en geanalyseerd. Over het algemeen gaven deze onderzoeken aan dat MBI's gerelateerd zijn aan een verminderde regulering van het netwerk waarin transcriptiefactor kappa B (NF-κB) betrokken is. Dit effect is tegenovergesteld aan de gevolgen van chronische stress op genexpressie en geeft aan dat MBI's mogelijk leiden tot een verminderd risico op ontstekingsreacties. Het is echter onduidelijk hoe de effecten van MBI's zich verhouden tot andere gezondheidsinterventies, zoals lichaamsbeweging of voeding, vanwege het beperkte aantal beschikbare onderzoeken. Er is daarom meer onderzoek nodig om de effecten van MBI's op moleculair niveau beter te begrijpen.

Om de tweede vraag over de effecten van MBI's op gedetineerden met persoonlijkheidsstoornissen te kunnen beantwoorden, zijn dertig gedetineerden met tenminste drie persoonlijkheidsstoornissen en een hoge score op psychopathische kenmerken gerekruteerd. Ze werden willekeurig toegewezen aan een mindfulness-interventie (n = 10), een yoga-interventie (n = 10) of een wachtlijstcontrolegroep (n = 10). Mindfulness- en yoga-interventies werden tegelijkertijd gehouden en duurden drie uur per dag gedurende vijf opeenvolgende dagen. Er zijn verschillende voor- en nametingen uitgevoerd. Zo is er gekeken naar de mate van genexpressie van ontstekingsfactoren en is, met behulp van elektro-encefalografie (EEG), de hersenactiviteit in rusttoestand gemeten. Daarnaast is risico-gedrag en aandacht gemeten met behulp van cognitieve taken en is de hersenactiviteit tijdens de aandachtstaak bestudeerd. Verder zijn er vragenlijsten gebruikt om stress, emotieregulatie en mindfulness in kaart te brengen. Dertig deelnemers werden geïncludeerd in de analyses. Naar verwachting zouden zowel yoga- als mindfulness-interventies leiden tot verbeterde zelfregulatie (dat wil zeggen executieve aandachtsprocessen, emotieregulatie en zelfbewustzijn), verminderde stress en verminderd risicogedrag, verlaagde genexpressie van ontstekingsfactoren en een verhoogde alfa- en theta activiteit in de hersenen. Echter, volgens de resultaten van dit onderzoek profiteerden gedetineerden met persoonlijkheidsstoornissen niet van de interventies en werden er op geen enkele van de uitkomstmaten significante verschillen gevonden tussen de voor- en nameting. Mogelijk is een aantal methodologische factoren van invloed geweest op de resultaten, zoals een lockdown op de laatste dag van de interventies, de lengte van de interventies en de beperkte statistische power van het onderzoek.

Het derde vraagstuk dat is onderzocht in dit proefschrift betreft de rol van individuele verschillen op de effectiviteit van meditatie. Hoewel meditatielessen, met name mindfulness-meditatielessen, steeds populairder en toegankelijker zijn geworden, lopen de effecten ervan uiteen. Sommige mensen hebben baat bij de lessen (de 'positieve respondenten') en worden langdurige en toegewijde beoefenaars, terwijl anderen geen effect of zelfs nadelige effecten ervaren. Als we positieve respondenten zouden kunnen onderscheiden van niet- en negatieve respondenten op basis van hun individuele eigenschappen, dan zouden MBI's kunnen worden ingezet bij degenen die er het meeste baat bij hebben. Een andere evidence-based techniek zou kunnen worden ingezet bij degenen die geen positief effect ervaren als gevolg van meditatie. Verrassend genoeg was er nog geen uitgebreide studie over dit onderwerp en zijn er slechts een beperkt aantal studies die hebben onderzocht hoe verschillende mensen reageren op meditatie. In hoofdstuk 3 van dit proefschrift zijn de bevindingen van eerdere studies die de invloed van individuele eigenschappen van deelnemers op het effect van meditatie onderzochten beschreven en geanalyseerd. Hieruit bleek dat de aanwezigheid van psychopathologie of depressie samenhing met een verslechtering van de geestelijke gezondheid na een meditatie-interventie. Deelnemers met hogere scores op interpersoonlijke variabelen, motivatie, medische aandoeningen en mindfulness lieten juist meer positieve effecten zien. Een hogere score op welzijn en stress hing zowel samen met een toename van negatieve als positieve effecten van meditatie. Demografische kenmerken, psychologische eigenschappen, zelfbeeld, en de duur van de meditatiebeoefening hadden geen significante invloed op het effect van meditatie.

Dit proefschrift draagt bij aan de huidige kennis door te laten zien dat MBI's geassocieerd zijn met veranderingen in genexpressie die leiden tot verbetering van de gezondheid. Daarnaast suggereert het dat gedetineerden met persoonlijkheidsstoornissen niet reageren op korte en intensieve MBI's en presenteert het een uitgebreide samenvatting en analyse van bevindingen uit eerdere studies die de rol van individuele kenmerken op het effect van meditatie onderzochten.

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About the author

Ivana Buric was born in Split, Croatia in 1991. She studied psychology at undergraduate and graduate level at University of Zagreb, Croatia where she graduated among top 1% of her generation. She defended her master's thesis in 2014 titled "Integration of approaches as a new framework for research on stress vulnerability and resilience: Genetic, epigenetic and neural mechanisms of the hypothalamic-pituitary-adrenal axis reactivity".

It was during the recovery from a traffic accident in 2013 that Ivana developed a strong interest in techniques that can counteract the effects of stress. She was dealing with chronic pain, anxiety and attention deficits, and after experiencing the benefits of mind-body techniques she became curious about how these benefits emerge and if they are related to gene expression changes.

In 2015 Ivana was funded by Erasmus+ to do a research internship in molecular biology at University of Exeter, where she got her first research experience and gained skills in gene expression and epigenetics. Later in 2015, Ivana started a dual PhD programme at Coventry University (United Kingdom) and Donders Institute for Brain, Cognition and Behaviour, Radboud University (Netherlands), which was funded by a studentship from Coventry University. Here Ivana received training in cognitive neuroscience, which she then combined with psychology with molecular biology in the research of mind-body techniques. She defended the first part of her doctoral thesis at Coventry University in December, 2018. She currently works as a lecturer at Univerity of Split, Croatia and as a mindfulness instructor.