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Meditation and yoga as mind-body interventions
the psychobiological effects and individual differences

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Meditation and Yoga as Mind-Body Interventions: The Psychobiological Effects and Individual Differences

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A thesis submitted in partial fulfilment of the University's requirements for the Degree of Doctor of Philosophy (PhD).

Certificate of Ethical Approval

Applicant:

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Psychological and biological effects of intensive mindfulness meditation on offenders with dangerous and severe personality disorder: A randomised controlled trial

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ABSTRACT

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? What 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. This personalised approach would not only save resources, but also help prevent harm. 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. In this chapter, we adopt a multilevel approach to evaluate extant evidence on the relationship between meditation and individual differences across four sources of variability: personality and other psychological variables, biological variables, illness severity in patients, and demographic factors.

This thesis contributes to the current literature by providing evidence that gene expression changes are a 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 synthesises heterogeneous evidence from previous studies that examined baseline participant variables that influence the response to meditation.

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DISSEMINATION

Buric, I., Farias, M., van Mulukom, V., Kurtev, S., Mee, C., Gould, L., Rahman, S., Parker, B., Brazil, I. The neural, genetic and psychological effects of meditation and yoga on prisoners with personality disorders. Poster presentation, Annual Conference of International Society for Psychoneurendocrionology, 6-8 September 2018, Irvine, USA.

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The hype and the truth about mindfulness: Can it change your life? Oral presentation, Humanist Student Society, 14th of May 2018, Southampton University, Southampton, UK.

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Buric, I., Farias, M., van Mulukom, V., Kurtev, S., Mee, C., Gould, L., Rahman, S., Parker, B., Brazil, I. The effects of meditation and yoga on prisoners with personality disorders. Oral presentation, Empowerment in the personality disorder pathway: Maximising hope, resilience and well-being for all, 5th October 2017, Durham, UK.

Buric, I. Exploring the molecular signature of meditation and yoga: How mind-body techniques change gene expression. Oral presentation, Skeptics in the Pub Birmingham, 13th September 2017, Birmingham, UK.

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research design and hypotheses. Poster presentation at Health and Life Sciences Conference, 21st April 2016, Coventry, UK.

DECLARATION

I declare that all the work within this thesis is my own work. It has not been submitted for any other degree at another university, but it will be a part of my second doctoral thesis to be submitted by September 2019 as a requirement of the joint PhD agreement between Coventry University and Radboud University.

Due to team efforts that were involved in the experimental study conducted at HMP Whitemoor described in the chapter 3 of this thesis, it is appropriate to specify what was my contribution. I developed the original research design of the experimental study as a part of my PhD application, which was later expanded to use EEG measures and risk-taking cognitive task on the recommendation of my supervisor Dr Inti Brazil. I was in charge of project management from start to end. I completed the paperwork necessary to get all ethical approvals for the prison study, and I registered the study on clincialtrials.gov. I wrote the first versions of participant information sheets, research protocol and debriefing notes, and edited all the remaining versions based on feedback from Dr Miguel Farias and Jacquie Evans. I recruited both mindfulness and yoga teachers that delivered the interventions in the prison. I ordered blood collection equipment and organised the transport of all research equipment with the help of Dr Stoyan Kurtev who also helped me to pilot the study measurements on several healthy volunteers. Two teams of two were used to collect data in the prison and they consisted of me, Dr Stoyan Kurtev and Dr Valerie van Mulukom with help of HMP Whitemoor's research team (Lloyd Gould, Sabeel Rahman and Barbara Parker and Jacquie Evans). HMP Whitemoor's research team ensured all participants whose data was used in the study received participants information sheets, completed the consent forms and received debriefing notes.

I carried out all the literature searches described in this thesis and all the statistical analysis and interpretation of the data described in this thesis. I took advice on statistical analysis and interpretation of the data from Dr Inti Brazil. The writing in this thesis is my own, but each chapter has been commented on by Dr Miguel Farias and Dr Inti Brazil. The structure of the thesis has evolved from discussions with these two supervisors.

Chapter 1: Introduction

1.1. Background

The roots of mind-body interventions stem from Eastern religions of Hinduism and Buddhism where meditation and yoga are core of the path to transformation of the self, rather than stand-alone techniques. It is believed that meditation and yoga, along with specific views of the world and prescriptions for living, can lead to entering a state of pure consciousness where the self is transcended and free from the existential constraints (Rao, 2010). Transcendental meditation was the first type of meditation that gained popularity in the West when in the 1960s an influential teacher from India, Maharishi Mahesh Yogi, started touring the world and soon thereafter gained a large following. Transcendental meditation has roots in Hinduism and it is based on the repetition of a mantra in Sanskrit and the central principle is that everything is connected through a collective consciousness and that enlightenment can be achieved by practicing transcendental meditation technique (Roth, 1994). A transcendental meditation 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). In the 1970s, scientific studies of meditation started appearing, 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 (Bai et al., 2015). The second type of meditation that gained popularity in the West is mindfulness meditation, specifically Mindfulness-Based Stress Reduction (MBSR), a secular format of mindfulness meditation that has Buddhist roots. It was developed by Jon Kabat-Zinn in the late 1970s at with aim of helping patients with chronic pain (Kabat-Zinn, 1982), but it was later applied to different clinical and non-clinical populations (Grossman, Niemann, Schmidt & Walach, 2004). MBSR has been attracting much attention from the scientific community since the 1990s and it is now the most researched mind-body intervention (MBI). There are several techniques for developing mindfulness, but the typical approach 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). MBSR is the most widespread mind-body course that is delivered 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 hatha yoga (a slow-paced type of yoga with an emphasis on breathing techniques).

Besides transcendental meditation and MBSR, many other types of meditation can be found in the scientific literature, which raises the questions what is meditation and are meditation studies comparable. However, different types can broadly be grouped 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. 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. Dividing all types of meditation into two categories is a step forward compared to the current status in research, but it is being debated whether the third category should be loving-kindness meditation (Lippelt, Commel & Colzato, 2014), or whether instead 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 realize 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 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, but there are no studies that compare these potential differences. In the same manner, certified meditation teachers will often adapt standardised meditation programmes based on their personal preferences or based on the characteristics of people that they are teaching, be it intentionally or unintentionally. Another issue is that a primary distinction between focused attention and open monitoring is easy to understand, but is it often difficult to put a meditation type in one of these categories because elements of both techniques are commonly used together in meditation programmes such as MBSR.

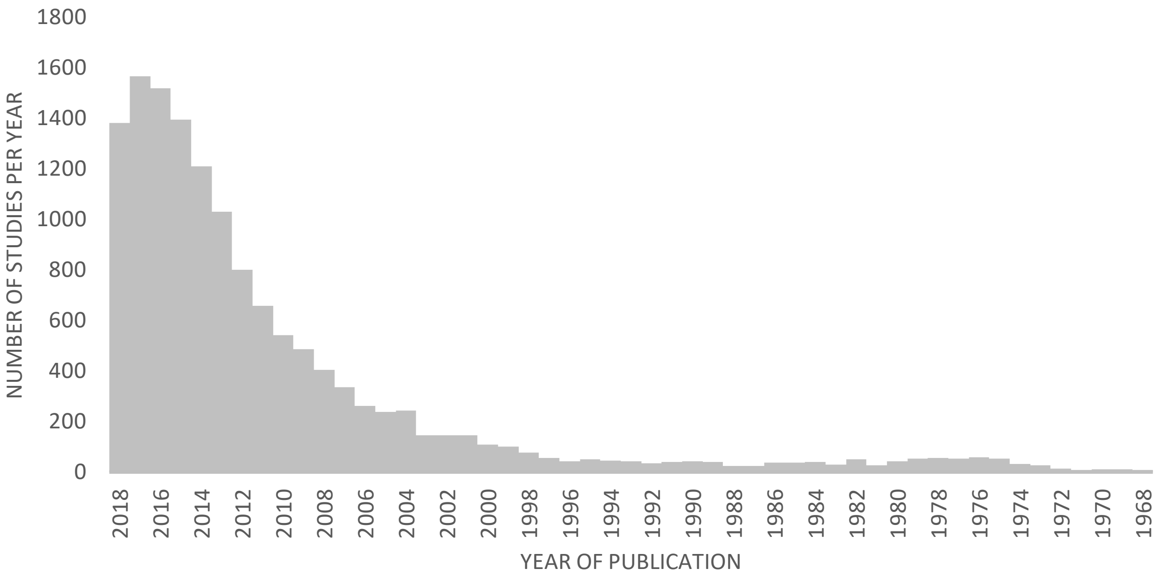

Figure 1. The increase in the number of studies related to meditation, mindfulness, yoga, Tai Chi or Qigong published from 1968 to 2018 (data obtained by searching PubMed database).

Nevertheless, the scientific interest in meditation and other MBIs such as yoga, Tai Chi or Qigong has largely gone up in the past 20 years (Figure 1.), which enabled the transition of MBIs from monasteries to the psychological mainstream. The majority of evidence is coming from mindfulness research, followed with TM, different types of yoga and Tai Chi. 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. Therefore, conclusions about the effectiveness of MBIs must be based on meta-analyses because they provide average effect sizes and often control for study quality. Meta-analyses have generally found medium effect sizes of 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 of approximately 0.5 for controlled and non-controlled studies, and in clinical and non-clinical populations. (Grossman, Niemann, Schmidt & Walach, 2004). On the other hand, meta-analysis that included 22 studies of different mindfulness-based interventions (including MBSR) and did not assess quality of the studies found larger effects sizes such as 0.70 for anxiety and 0.84 for depression across different clinical and non-clinical populations (Baer, 2003). Finally, another meta-analysis of eight MBSR randomized controlled trials looked specifically at population with chronic medical illnesses and reported effect sizes for specific mental health symptomatology (Bohlmeijer, Prenger, Tall & Cuijpers, 2010), not just general well-being. It found a small effect size of 0.26 on depression and 0.32 on psychological distress, and a medium effect size of 0.47 on anxiety. However, when low quality studies were excluded, the effects size of anxiety dropped to 0.24. Even though the effect sizes are between small and medium, they are comparable with other recognized 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 effect on various health conditions. Similar conclusions were reached in the meta-analyses of yoga, which has received less scientific attention than meditation, but nevertheless many studies are available. A meta-analysis of 12 randomised controlled trials of yoga on patients with depressive symptoms found an average effect size of -0.63 on depression, but they did not run separate analysis based on quality although they noted that nine included studies had medium to high risk of bias (Cramer, Lauche, Langhorst & Dobos, 2013). A meta-analysis of 15 randomised controlled trials of yoga on patients with cancer found large effects sizes of -0.75 for distress, -0.77 for anxiety, and -0.69 for depression. Furthermore, it was found that yoga has medium effects size of -0.51 on fatigue, 0.49 on emotional function, 0.37 on quality of life, and 0.33 on social function, and a small effect size of 0.31 on well-being (Buffart et al., 2012). Another meta-analysis of 18 randomised controlled trials of yoga on older adults found -0.57 effect size for depression and -.65 for quality of life (Patel, Newstead & Ferrer, 2012). Besides yoga, Tai Chi and Qigong are other movement-based MBIs that have been well researched. A meta-analysis of 33 studies of mixed designs and population types found moderate effect size of 0.65 for well-being, 0.66 for depression and anxiety, 0.45 for mood (Wang et al., 2010). Similarly, a meta-analysis of seven randomized controlled trails of Qigong in healthy adults found a high effect size of -0.75 on anxiety and -0.88 on perceived stress (Wang et al., 2014)

Based on the meta-analyses described above, it is clear that studies have repeatedly shown that mind-body interventions work as much as other recognized behavioural interventions, but there are many gaps in the research that need to be addressed. Most importantly, it is not clear how mind-body interventions work and for whom do they work best. Additionally, studies of 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 mind-body interventions. Mechanisms provide precise and intelligible explanation that let us fully understand the observed effects and infer causality. Without identifying mechanisms that connect mind-body interventions with benefits that people often report after consistent practice, we cannot conclude that there is a genuine causal relationship. This is a complex problem because mind-body interventions are often multifaceted, for instance the most researched meditation intervention is MBSR (Kabat-Zinn & Chapman-Waldrop, 1988) and it 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 practitioners to optimally tailor their approach to teaching meditation. So far, attempts to understand the mechanisms of mind-body interventions have been made in different disciplines. Psychologists have focused on psychological processes that strengthen with regular practice of mind-body techniques (Shapiro, Carlson, Astin & Freedman, 2006) and defined what aspects of mindfulness interventions are the most important (Lindsay et al., 2018). Neuroscientists have proposed structural and morphological changes in the brain that are observed in regular practitioners as the mechanisms by which mind-body intervention work (Lazar et al., 2005; Holzel et al., 2011; 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 mechanisms interact, which requires collaborations 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 investigate complex interactions between mechanisms.

However, even if we develop a precise understanding of the interactions among mechanisms of meditation, there will always be substantial inter-individual variation in responsiveness to meditation. The variability in responses to meditation is likely influenced by differences in participant characteristics. Surprisingly there is no extensive study on this topic and only a limited number of trials have included data on individual differences in responsiveness to meditation. 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.

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 and incarcerated populations, both of which often overlap as 65% of prisoners have personality disorders (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 and can be non-cooperative and have high drop-out rates (McRae, 2013). On the other hand, it is difficult to establish research collaborations with prisons and it takes a long time to obtain multiple ethical approvals that are mandatory to conduct a study in a prison (Reiter, 2014). Previous studies of personality disorders found positive effects of mindfulness interventions on mental health of patients with borderline personality disorders, but there are no studies on other personality disorders or studies on mind-body interventions 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 mind-body intervention 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 included a control group. Therefore, prisoners, and especially patients 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 an 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 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 clinical population

In summary, the mechanisms of MBIs, the effects of MBIs on prisoners with personality disorders and individual differences that influence the response to meditation, as three major gaps in meditation research, are the focus of this thesis.

1.2. Aims and Objectives

The specific aims of this thesis were to:

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

1.3. The structure of the thesis

Chapter 2 is related to the first aim of this thesis; it is a systematic review of 18 studies that measured gene expression related to MBIs and it included various type of research designs and populations. Chapter 2 is a slightly expanded version of the manuscript that was published in June 2017 in Frontiers in Immunology under title: *What is the molecular signature of mind-body interventions? A systematic review of gene expression changes induced by meditation and related practices* where I was the first author followed with my supervisors: Dr Miguel Farias, Dr Jonathan Jong, Dr Christopher Mee and Dr Inti Brazil.

Chapter 3 describes the rationale, methods and results of the randomised controlled trial of mindfulness and yoga in a clinical unit for prisoners with personality disorder and it is related to the second aim of this thesis. It is written in a manuscript format and it will be submitted for publication in a peer-reviewed journal where other authors besides myself as the first one will be: Dr Miguel Farias, Dr Valerie van Mulukom, Dr Stoyan Kurtev, Dr Christopher Mee, Lloyd Gould, Sabeela Rahman, Barbara Parker, Dr Inti A. Brazil.

Chapter 4 explores the 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, individual differences due to demographic variables. Chapter 4 will be published as a book chapter in Oxford Handbook of Meditation in 2019, the other two authors are Dr Valerie van Mulukom, Dr Inti Brazil.

Chapter 5 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

2.1. 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.

2.2. 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*.

2.3. 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 2). 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.

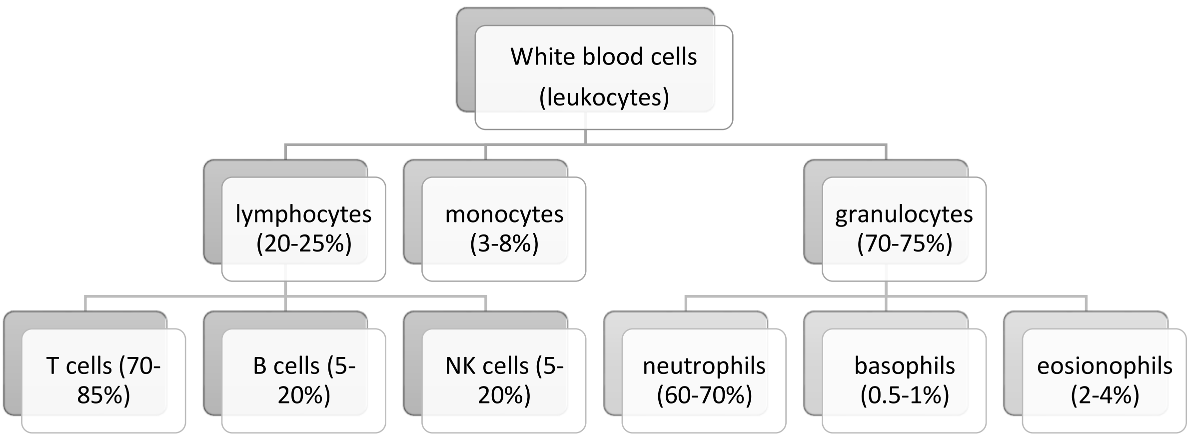

Figure 2. Types of white blood cells

2.4. 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 contextualize 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.

2.5. 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 3). 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).

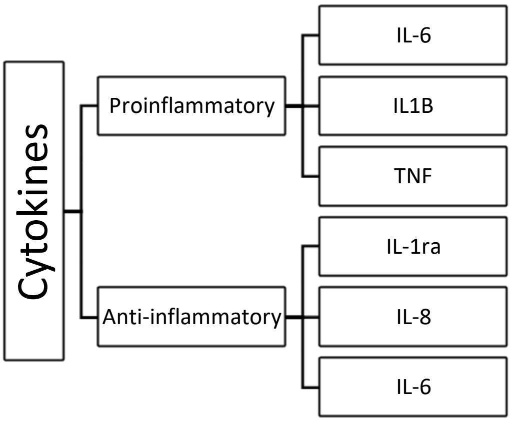

Figure 3. Pro-inflammatory and anti-inflammatory cytokines relevant for mind-body interventions

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).

2.6. Methods

2.6.1. 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 4). 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 4). 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.

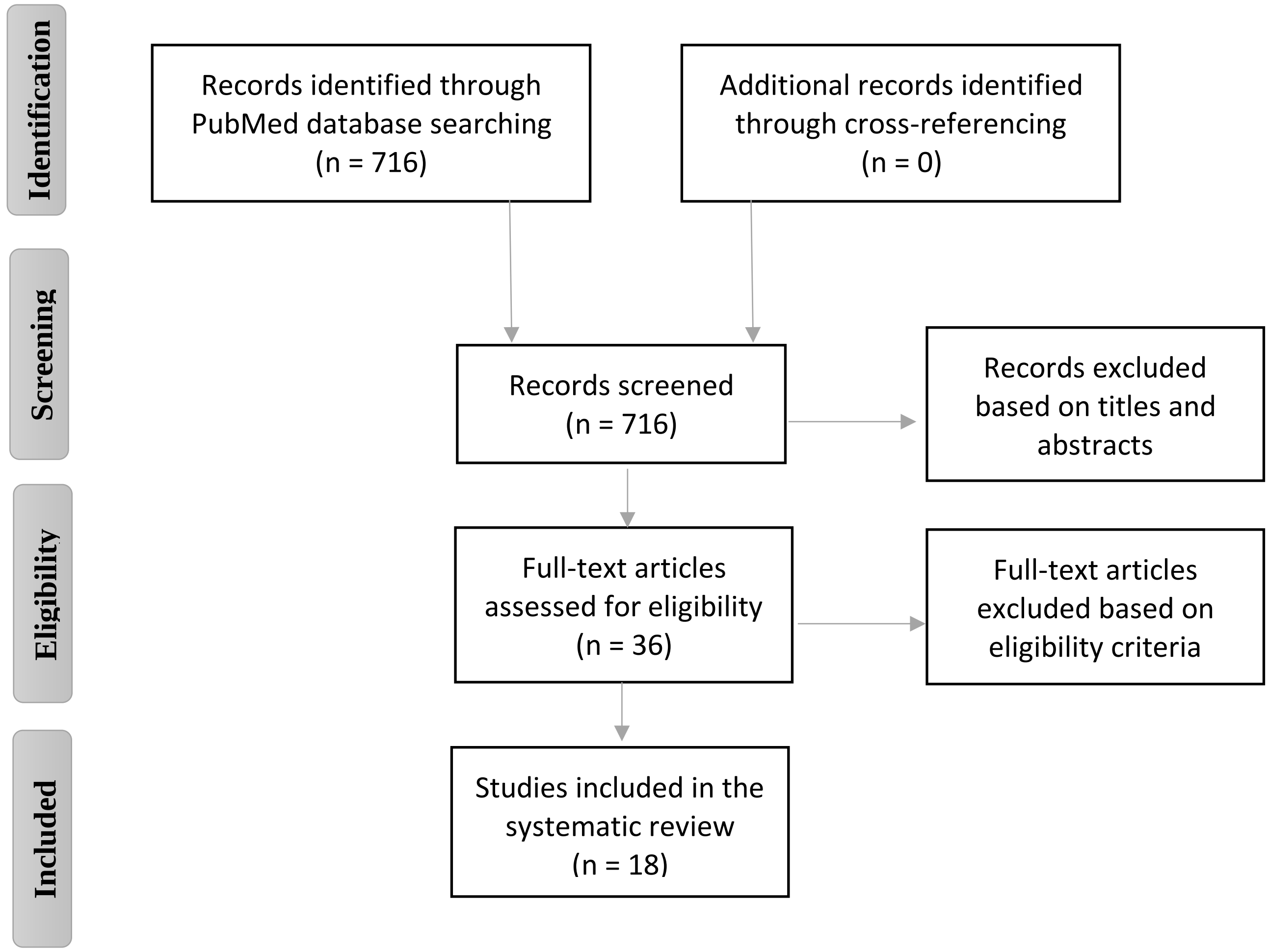

Figure 4. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart: The process of selecting relevant studies

2.7. 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).

2.7.1. Cross-sectional studies

2.7.1.1. 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 2). 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.

2.7.1.2.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.

2.7.1.3. 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.

2.7.2. Longitudinal designs

2.7.2.1. Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized 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 standardized 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.

They 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.

2.7.2.2. 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.

2.7.2.3. Tai Chi, Cellular Inflammation, and Transcriptome Dynamics in Breast Cancer Survivors With Insomnia: A Randomized 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.

2.7.2.4. Yoga reduces inflammatory signalling in fatigued breast cancer survivors: A randomized 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.

2.7.2.5. Mindfulness meditation for younger breast cancer survivors: A randomized 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.

2.7.2.6. 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.

2.7.2.7. Cognitive Behavioural Therapy and Tai Chi Reverse Cellular and Genomic Markers of Inflammation in Late Life Insomnia: A Randomized 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.

2.7.2.8. 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.

2.7.2.9. 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.

2.7.3. Rapid response

2.7.3.1. 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 visualization. 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 suggests 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 generalizable conclusions.

2.7.3.2. 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).

2.7.4. Mixed designs

2.7.4.1. 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.

2.7.4.2. 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 utilization (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.

2.7.4.3. 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.

2.7.4.4. 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.

They 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 reviewed studies*

Authors	Study type	Type of population, (experimental group sample size)	Control group type, (size)	Meditation or meditation-related type of practice	Practice frequency, training time	Gene expression technology (Bioinformatics 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 behavioural 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.,2014a	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 – (marginal), 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(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 experience	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 %	M(participants per group)=23.5 5 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 interventions lasted 8-12 weeks; 33% of interventions had only weekly meetings	44% of studies used TELiS and all found a downregulation of NF-kB	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

2.8. 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 randomized 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.

2.9. 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 small randomised controlled trial

3.1. Introduction

Between 10% and 15% of people have a personality disorder (Torgersen et al., 2001; Reich, Yates & Nduaguba, 1989). Any of the ten types of personality disorders represent an extreme of the way an average individual in given culture perceives, thinks, feels and relates to other, which causes distress to self and others. Available treatment for personality disorders include different types of psychotherapy, along with psychotropic medicines for comorbid disorders. Besides the traditional cognitive-behavioural therapy, there are other effective psychotherapy approaches for personality disorders such as dialectical-behaviour therapy and acceptance and commitment therapy that include mindfulness techniques (Linehan, 1993). As an addition to the usual treatments, mind-body interventions have the potential to aid in managing personality disorders by improving self-regulation (Hölzel et al., 2011a; Cook-Cottone, 2015). The effects of meditation and yoga on emotion regulation (Kang et al, 2013; Menezes et al., 2015) make them promising interventions with populations with personality disorders, which are known to display emotion regulation difficulties (Levine, Marziali & Hood, 1997), as well as increased rates of impulsive behaviour (Steel & Blaszczynsk, 1998). However, there is a large gap in research that addresses the effectiveness of mind-body interventions for people with personality disorders. The majority of evidence focuses on borderline personality disorder (BPD), possibly because people with BPD may be more likely to seek treatment than people with other personality disorders, and highlights positive associations between mindfulness practice and reduced psychiatric severity, emotional reactivity (Feliu-Soler et al., 2014) and impulsivity (Soler et al., 2012). Additionally, observational studies found that people with more severe form of antisocial personality disorder (ASPD) had larger deficits in trait mindfulness, and that mindfulness moderates the relationship between ASPD severity and aggression (Velotti et al., 2016). Others have suggested that symptoms of ASPD can be reduced by meditation interventions 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 mainly because people with personality disorders often remain undiagnosed and only rarely seek treatment, unless it is for comorbid disorders (McRae, 2013). The most common comorbid psychiatric disorders in people with personality disorders are substance abuse, depression and post-traumatic stress disorder (Hayward & Moran, 2008). As the general literature on meditation and yoga with healthy and clinical populations highlights its effects on stress, depression and anxiety (Kabat Zinn et al., 1992; Teasdale, Segal, Williams, et al., 2000), all of which are common problems in people with personality disorders, we can assume that mind-body interventions might benefit this population.

An indirect line of evidence for mind-body interventions and personality disorders stems from studies on prison populations. 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 characterized with 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 (He et al, 2001; Birmingham, 2018; Armour, 2012) 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 those patients are often resistant to treatment, and require a lot of time to show progress (Kiehn & Swales, 1995; van Beek & Verheul, 2008). Previous studies of mind-body interventions in prisons found that 6 to 8 weeks of mindfulness meditation improves mental health in a prison environment by increasing positive mood and self-esteem, and decreasing aggression and sleep difficulties (Samuelson, Carmody, KabatZinn, & Bratt, 2007; Sumter, MonkTurner, & Turner, 2009). Even shorter meditation interventions have been proved 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 compared to a wait-list control group (Bilderbeck et al., 2013; Kerekes, Fielding & Apelqvist, 2017). Besides the two yoga studies, none of the meditation studies followed a randomised procedure or included a control group, but they nevertheless provide encouraging results for the use of meditation interventions with prison populations. Research suggests that mindfulness interventions might be particularly beneficial to 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 (Singleton et al, 1998), thus plausible that a psychologically vulnerable sample like a prison population may react better to a meditation intervention than a general healthy population.

Overall, evidence is lacking in several respects. First, no study has yet directly tested the effects of mindfulness interventions on people with personality disorders other than borderline, the effects of yoga interventions on people with any type of personality disorders, or compared the effects of mindfulness on prisoners with a control group. This study employs a randomised controlled design and compares outcomes for both intervention groups with a wait-list control group in a sample of prisoners with diverse personality disorders who score high on psychopathy. Second, the mechanisms by which numerous benefits of meditation and yoga emerge are not clear. Recent studies have found that the protective effects of mind-body interventions on physical health might be due to prominent gene expression changes (Buric et al., 2017; Black & Slavich, 2016). 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 (Mantovani et al., 2008; Slavich, 2016). We will test if the same gene expression pattern appears in a prison sample with personality disorders. By obtaining blood samples, we can assess the effects of each intervention on this biomarker that is providing a glimpse into mind-body relationship. Psychological and cognitive mechanisms of mindfulness and their neural correlates have been proposed by Tang, Hölzel & Posner (2015) in a unifying 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. According to this, all the other observed benefits (e.g. reduced stress) are a consequence of improved self-regulation. In this study, we will put this theory to test and see if it applies to yoga as well, thus our choice of cognitive measures and questionnaires mainly stems from this self-regulation theory. We will also test changes in risk-taking behaviour because it is linked with the risk for reoffending (Andrews, Bonta & Wormith, 2006), and changes in EEG power, connectivity and event-related potentials in response to attention task in order to extend previous findings of the effects of mind-body interventions (Cahn & Polich, 2013) to the population with personality disorders.

In summary, the purpose of this study was to compare the efficacy of mindfulness, yoga and a wait-list control condition on multi-level outcomes in prisoners with personality disorders. We aimed to explore the psychobiological effects of two types of intensive mind-intervention lasting 5 days and a total of 15 hours. A review of studies that have used shortened versions of standard mindfulness interventions found that they are equally effective as interventions of standard 8-week length in reducing psychological distress (Carmody & Baer, 2009). We hypothesised that both mindfulness and yoga would be superior to control on all outcomes, and that mindfulness would be superior to yoga in measures of self-regulation. If these hypotheses are confirmed, the results will extend previous findings on the benefits of meditation and yoga to vulnerable populations, and would provide a cost-effective addition to prisoner rehabilitation.

3.2. Method

3.2.1. Participant recruitment, randomisation and group allocation

Following five different ethical approvals (The Coventry 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 programme that consists of group and individual therapy and aims to improve mental well-being, emotional self-regulation, and consequently reduce risk of reoffending. The programme 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 programme.

Leaflets with information about the study were put in prisoners' common landing areas and a team of four researchers (2 internal assistants and 3 external researchers from Coventry University) 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.

Inclusion criteria:

1. age between 18 and 65 years
2. informed consent from participant

Exclusion criteria:

1. major neurological disorders that compromise completing the interventions or research assessments
2. difficulty with understanding English

Prior to randomisation, participants completed pre-intervention assessment that included questionnaires, cognitive tasks, EEG recordings and blood samples (see section 3.2.3 and Figure 5). Interventions commenced two weeks after the beginning of pre-intervention assessment. Following the interventions, participants completed the same set of questionnaires, cognitive tasks, neural recording and gave blood samples. In order to prevent baseline group differences in variables that might affect outcomes, participants were distributed 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 interventions, participants received a letter that informs about the group they are allocated to and gives instructions for the following day. Participants were encouraged to contact members of the clinical team if they have any questions or face difficulties during the intervention period and members of the clinical team actively followed up participants who missed sessions.

3.2.2. Overview of study procedures

Both the data collection and the interventions were held in the Fens Offender Personality Disorder Service within HMP Whitemoor in England. Pre-intervention assessment began two weeks before the interventions (on 13th of March 2017) to ensure enough time to assess 30 participants. Post-intervention assessment began three days after the intervention (on 3rd of April) 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 Coventry University and one internal research assistant), only the questionnaires were administered by internal clinicians and blood samples were collected by internal phlebotomists. 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. He was then seated in a chair and the researchers would briefly explain the upcoming procedure that can last between 70 and 90 minutes. The assessment begins with EEG setup that includes measuring the circumference of the head and proper positioning of the EEG cap, adding gel and electrodes. After checking the impedance and reducing EEG noise, participant was positioned to sit comfortably before commencing with any task. The first measure was resting state EEG (rsEEG), which requires resting for 4 minutes with eyes closed and 4 minutes with eyes opened (the order of eyes closed/opened was randomised for each participant). For the eyes closed session, participants were instructed to close their eyes, sit back, try to remain still and rest without doing anything in particular, and to wait for the researchers to tell them when the 4 minutes have passed. For the eyes opened session, participants were instructed to again sit back, remain still and rest, but to also keep their eyes fixed on the cross on the screen or on a single area on the wall. Resting state was followed with two cognitive tasks: Attention Network Test (ANT) and Risk Ambiguity Task (RAT), and the stimuli for both tasks were presented on a computer screen using a Python-based software PsychoPy (Pierce, 2007). After ANT, the participants were disconnected from EEG and proceeded to RAT. All the questionnaires were filled on another session in 1-on-1 setting with a prison clinician, Blood samples were collected on a different occasion with two nurses simultaneously drawing blood from participants. Unlike other measures, blood collection was not a mandatory requirement of the study.

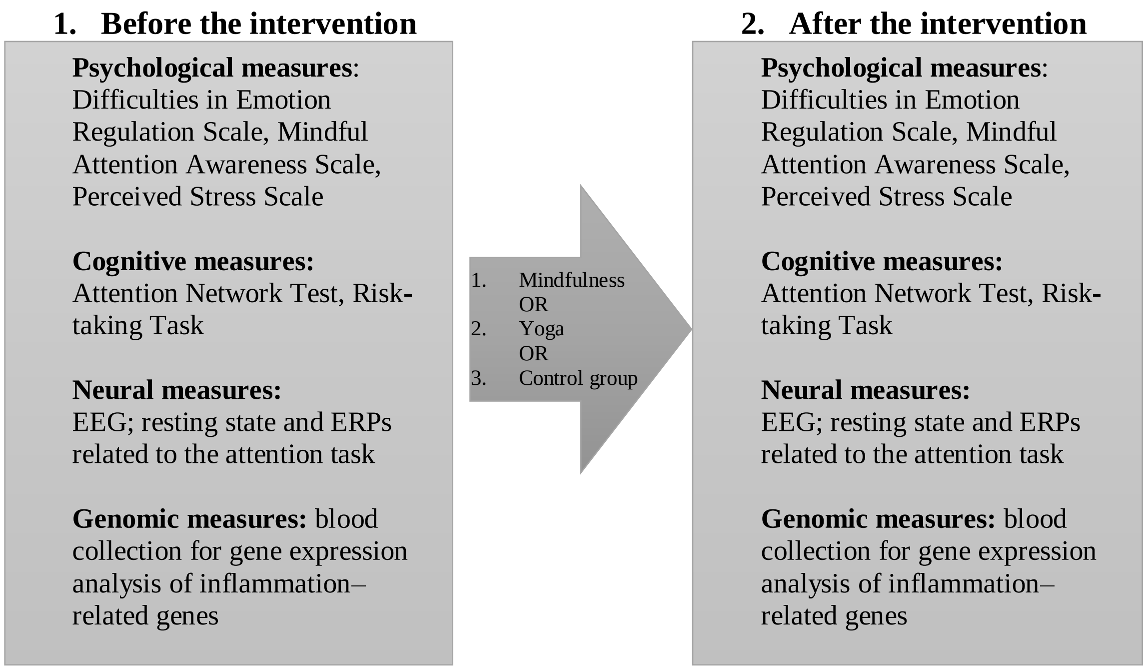

Figure 5. A graphical representation of the research design

3.2.3. Overview of study measures and statistical analysis

Intent-to-treat (ITT) principles were used for all the described analyses. 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 (<.02 was considered significant in individual 2-group comparisons). The data were analyzed with the IBM SPSS 24.0 software (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL).

3.2.3.1. Background measures

Background measures were collected from prison files and include age, levels of psychopathy, number of psychotherapy sessions attended, personality disorder diagnosis and offence type. 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, the offence type data was available only on the group level of all recruited participants due to security and confidentiality reasons, thus this was not included in the analysis to test group differences.

3.2.3.2. Biological measures

Blood samples were collected for the analysis of changes in gene expression of 38 genes related to inflammation and the immune system (i.e., 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. 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, which was processed in MS Excel by calculating $2^{-\Delta\Delta CT}$ (Livak & Schmittgen, 2001), while GAPDH was used as a housekeeping gene. After normalising

$2^{-\Delta\Delta CT}$ to the wait-list control group average, the data was imported into SPSS and analysed by group allocation based on change scores (T2 – T1) of each normalised $2^{-\Delta\Delta CT}$. Non-parametric Kruskal Wallis test for K independent samples was used 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 to determine specific group differences.

3.2.3.3. Cognitive-behavioural measures

3.2.3.3.1. Attention Network Test

Attention was measured with Attention Network Test (ANT; Fan et al., 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 (Posner & Petersen, 1990; 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.

A systematic review of previous studies found that mindfulness meditation can improve attention (Chiesa, Calati & Seretti, 2011). More specifically, the most consistent finding is that meditation improves executive attention, and this improvement is observed already in early phases of learning mindfulness techniques (Chiesa, Calati & Seretti, 2011). Interestingly, even just five days of twenty-minute meditation training can improve executive attention when using ANT to measure attention (Tang et al., 2007). As executive attention (i.e. executive network) is an important mechanism for regulation of cognition and emotion (Rueda et al., 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 et al., 2016). Based on these findings, we hypothesised that executive attention will significantly improve in prisoners with personality disorders after five days of intensive mindfulness meditation practice, while no improvements were expected in the active (i.e. yoga) or passive control group (i.e. wait-list control). Specifically, we expected that reaction times related to executive attention will decrease and that parietal P3 amplitude will increase after intervention.

The ANT takes approximately 20 minutes to complete. Briefly, 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; see Figure 6). 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, subjects 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 assured 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.

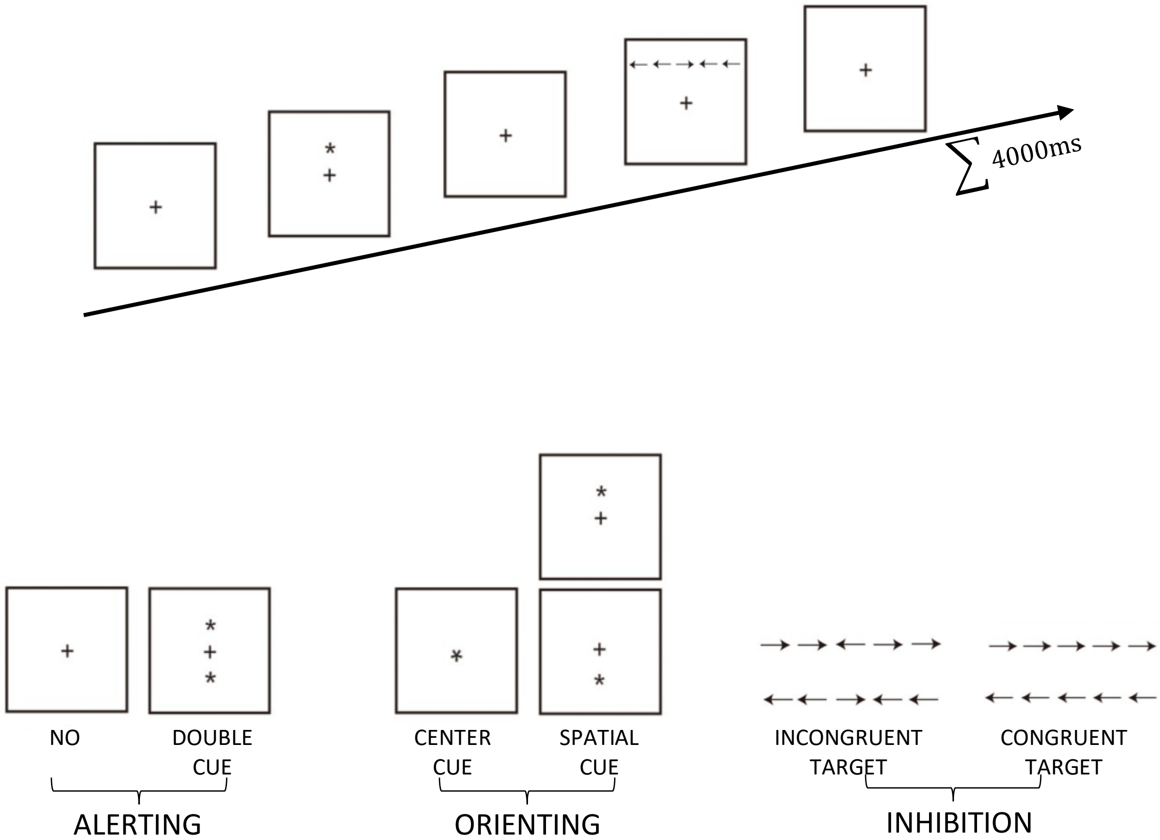

Figure 6. A schematic representation of the ANT

MS Excel was used to organise the raw data and remove outliers (i.e. those that are more than two standard deviations from the mean). The data was then imported into SPSS to calculate attention network effects as reaction time (RT) differences of the following task conditions:

alerting = $RT_{\text{no cue}} - RT_{\text{double cue}}$;

orienting = $RT_{\text{center cue}} - RT_{\text{spatial cue}}$;

inhibition = $RT_{\text{incongruent}} - RT_{\text{congruent}}$.

Executive attention is assessed via flanker interference, and alerting and orienting networks are 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. Finally, Kruskal Wallis was run with group allocation as a grouping variable (mindfulness, yoga, control) and alerting, orienting and inhibition change scores as test variables, while Mann Whitney U test and Kolmogorov-Smirnov Z were used for post-hoc analysis.

3.2.3.3.2. Risk-Ambiguity Task

Risk-taking behaviour and ambiguity attitudes were measured with Risk-Ambiguity Task (RAT) that compares the preferences for risky and ambiguous monetary lotteries (Tymula et al., 2012). Starting with 8 practice trials, the task consists 90 choices grouped in blocks of 45 gain and 45 loss trials. In gain trials, participants have to choose between a certain win of £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 7B), in a gain trial the participant has to choose between a certain win of £5 and 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 7A), 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 7C), thus the probability of winning the lottery is not always clear. Each lottery was either technically risky or ambiguous, allowing the assessment of participant’s 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).

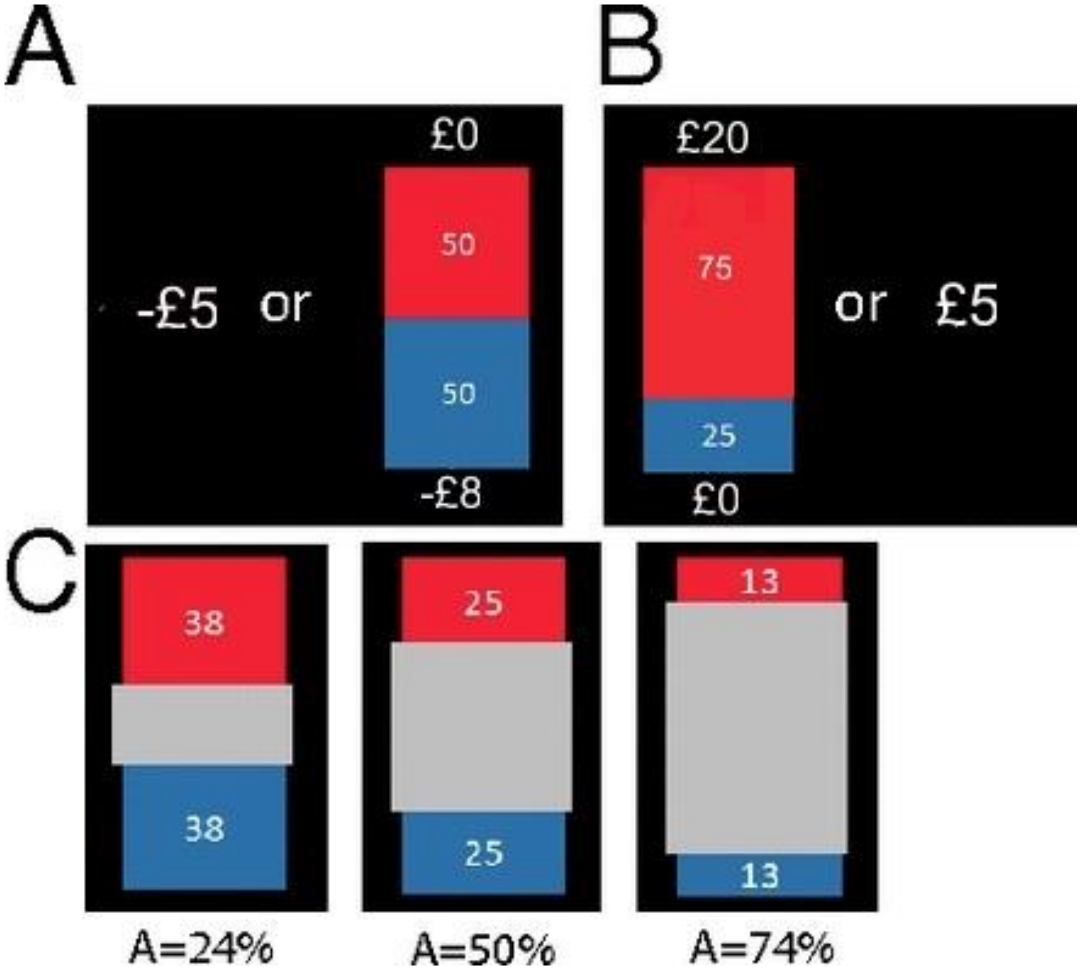

Figure 7. Examples of RAT trials: A) loss trial, B) gain trial, C) different levels of ambiguity

3.2.3.4. Neural measures

3.2.3.4.1. EEG data acquisition and pre-processing

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 digitized with a sampling rate of 1024 Hz using the BioSemi amplifier. EEG analysis was conducted with Brain Vision Analyzer 2.1 (Brain Products, Munich, Germany). Ocular artefact correction was performed using an independent component analysis approach (Jung et al., 2000). Three filters were applied: 30 Hz high cut-off, 0.02 Hz low cut-off and 50Hz notch filter. Remaining artefacts (≥50 μV gradient, >100 or <100 amplitude, >0.5 activity in intervals) were marked for later removal.

3.2.3.4.2. Event-related potentials (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 electrode sites P3, Pz and P4 as a prominent positive deflection between 300 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). Only correct responses were analysed for the behavioural data, while both correctly and incorrectly responded trials were included in the EEG analysis. Reaction times faster than 150ms and slower than 1000ms (less than 1% of data) were considered outliers and removed from the behavioural data for all groups.

Analysis of attention network ERP amplitudes was conducted in conformity with behavioural analysis:
alerting = target $N1_{\text{no cue}}$ - target $N1_{\text{double cue}}$;
orienting = target $N1_{\text{center cue}}$ - target $N1_{\text{spatial cue}}$;
inhibition = $P3_{\text{incongruent targets}}$ - $P3_{\text{congruent targets}}$.

The ERP data were analysed in IBM SPSS 24.0 software (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL) based on alerting, orienting and inhibition change scores in voltages in electrodes P3, Pz and P4 before and after the intervention. Kruskal-Wallis for K independent samples was used with group allocation as grouping variable (mindfulness, yoga, control) and alerting, orienting and inhibition change scores in P3, Pz and P4 as test variables.

3.2.3.4.3. Resting state connectivity

For each condition (EO and EC), 120 epochs with a length of 2s were created, and then filtered using a 0.02–50Hz band-pass filter and checked for gradient artefacts (maximum voltage step of 50µV /ms) and excessively low activity (below 0.5µV 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 (0-4Hz), theta (4–8Hz), alpha1 (8–10Hz), alpha2 (10-12Hz) and beta (12–25Hz), and running a weighted phase lag index (wPLI) connectivity analyses. The wPLI evaluates 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 synchronization in two different time series by examining the asymmetry of the distributions of phase differences because it additionally accounts for the magnitude of phase differences between the two-time series (Hardmeier et al., 2014; Vinck, Oostenveld, Van Wingerden, Battaglia, & Pennartz, 2011). Second, the data were used to test if there are differences in efficiency of neural communication following the interventions. This was done by calculating minimum spanning tree (MST) mean scores, 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 and used as test variables in Kruskal Wallis test for K independent samples, while grouping variable was group allocation (i.e., mindfulness, yoga and wait-list control).

3.2.3.4.4. Power analysis

Each set of artifact-free EEG data (2 s epochs) was subjected to Fast Fourier Transform (FFT) analysis with a 10% Hanning window, performed by Brain Vision 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 are significant changes in power following the interventions, which was done by calculating the change score and running a Kruskal-Wallis test for K independent samples.

3.2.3.5. Self-report measures

As mentioned in the introduction, the choice of outcomes was primarily based on the self-regulation theory by Tang and colleagues (2015):

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

Mindful Attention Awareness Scale (MAAS; Brown and 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, Kamarck & Mermelstein, 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 and Roemer, 2004) has 36 items and contains six factors: a) non-acceptance of emotional responses, b) difficulties engaging in goal-directed behavior, 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 (Gratz and Roemer, 2004). 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.

All the questionnaires were analysed in SPSS following the same procedure as previously described measures; Kruskal Wallis test with group allocation as grouping variable and mindfulness, perceived stress and difficulties in emotion regulation change scores as test variables, while Mann Whitney test and Kolmogorov-Smirnov Z were used for post-hoc analysis.

3.2.4. Mindfulness, yoga and wait-list control

The mindfulness intervention taught skills that enable participant to cultivate awareness of the present moment in an open and non-judgemental manner. It included mindfulness of breath, mindful eating and open monitoring, talks about the benefits of mindfulness and advice for practice, 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 the mindfulness intervention, it also included talks about the benefits of yoga and its history, advice for practice, 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 are the group format, size, structure, and contact hours. However, the two interventions are distinct in their content, that is yoga did not include any meditation (i.e. instructions in the *savasana* were to rest with eyes closed), 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 and resting more than usual. All participants were offered mindfulness and yoga once the data collection was over.

3.3. Results

We enrolled and randomised 30 participants out of 59 prisoners who were in the clinical unit for personality disorders within HMP Whitemoor in March 2017. On the first day of the intervention, several 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 who were allocated to yoga attended mindfulness sessions only, and two participants who 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 despite high prevalence of borderline personality disorder (73% of participants had a definite diagnosis). 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 (Figure 8). 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 analysis in accordance with intention-to-treat principles (Lachin, 2000; Gupta, 2011), thus the analysed sample size is 30. However, as blood collection was not mandatory, gene expression data is available for 12 participants only; three from the mindfulness group, four from the yoga group and five from the control group. 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 the prison.

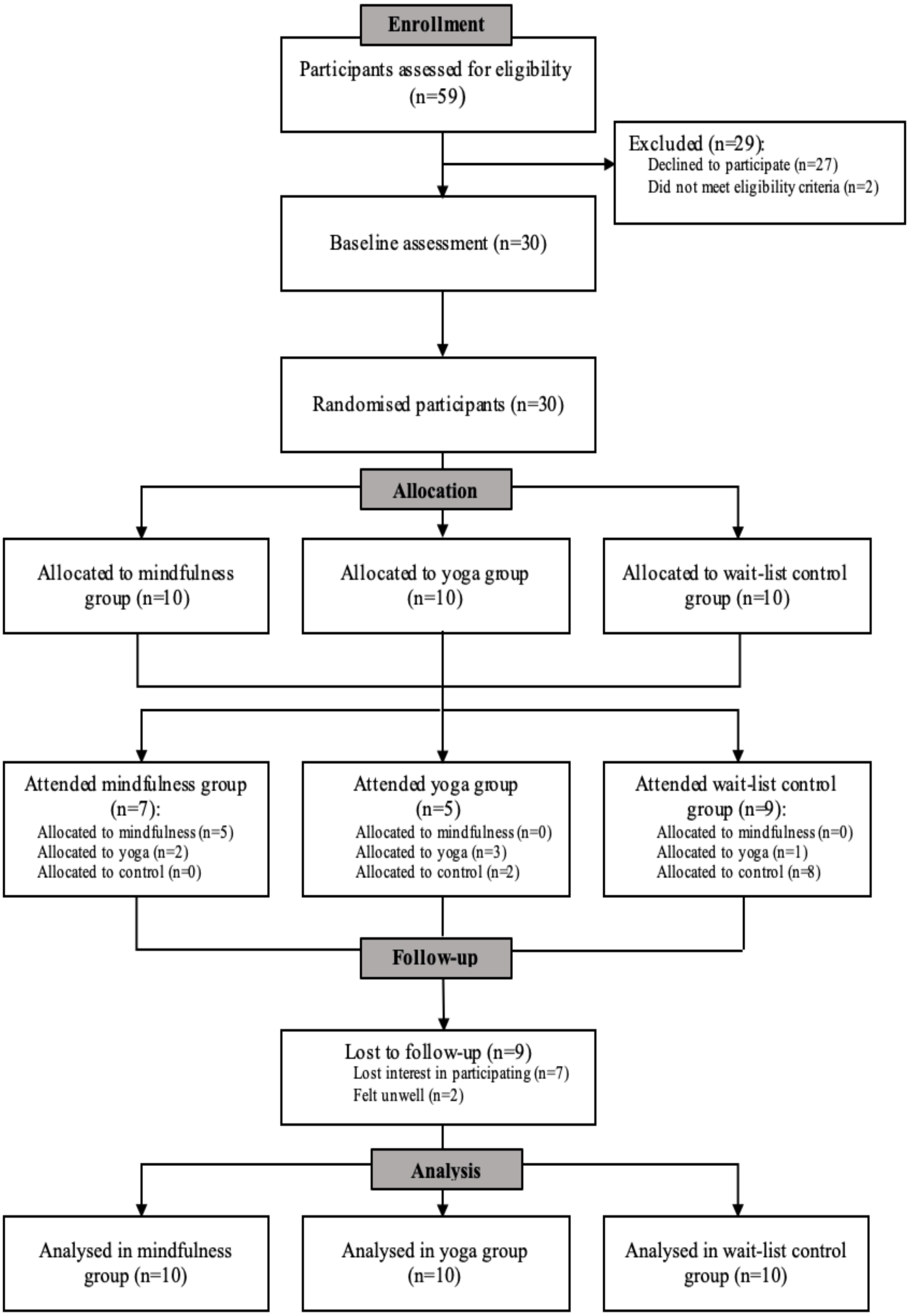

Figure 8. Flow of participants through the study

The 30 recruited participants were all male with a mean age of 41 (SD = 8.00), and 93% were white. They were at different stages of serving a life sentence for crimes that range from violent crimes, manslaughter and murder to rape and sexual assault. All recruited participants had two or more personality disorders, which is commonly observed in clinical practice (Zimmerma, Rothschild & Chelminski, 2005), while 90% of recruited participants had ASPD. The average score on The Hare Psychopathy Checklist - Revised was over 25 in all groups, which is considered the cut off for psychopathy in the UK (Skeem et al., 2011). Groups were statistically equal at baseline (Table 2), despite some participants that deliberately switched groups they were assigned to with stratified random sampling (contamination rate is 17%). Specifically, mindfulness group, yoga group and wait-list control group were not different at baseline in terms of psychopathy, type of personality disorder, perceived stress, emotion regulation, trait mindfulness, age or number of attended psychotherapy session within the 5-year Fens Service treatment programme (Table 2).

Table 2. *Baseline characteristics of participants across conditions (N = 30)*

	Mindfulness (N = 10)	Yoga (N = 10)	Control (N = 10)	Condition difference statistic
Age in years	37.60 (3.24)	41.60 (7.15)	42.60 (6.79) H	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	31.75 94.12)	29.32 (4.99)	33.16 (6.98)	H = .78, p = .76
Personality disorder				
Paranoid PD	.60 (.39) [a]	.65 (.41) [a]	.60 (.46) [a]	p = .95[b]
Schizoid PD	.05 (.16) [a]	.10 (.32) [a]	.10 (.32) [a]	p = 1.00 [b]
Schizotypal PD	.00 (.00) [a]	.25 (.42) [a]	.10 (.32) [a]	p = .29 [b]
Anti-social PD	1.00 (.00) [a]	.85 (.34) [a]	.90 (.32) [a]	p = .75 [b]
Borderline PD	.85 (.34) [a]	.75 (.35) [a]	.85 (.34) [a]	p = .89 [b]
Histrionic PD	.25 (.42) [a]	.10 (.32) [a]	.25 (.42) [a]	p = .79 [b]
Narcissistic PD	.40 (.51) [a]	.45 (.50) [a]	.40 (.52) [a]	p = 1.00 [b]
Avoidant PD	.20 (.42) [a]	.40 (.52) [a]	.20 (.42) [a]	p = .67 [b]
Dependant PD	.00 (.00) [a]	.00 (.00) [a]	.05 (.16) [a]	p = 1.00 [b]
Obsessive-compulsive PD	.15 (.34) [a]	.10(.32) [a]	.10 (.32) [a]	p = 1.00 [b]
Questionnaires				
PSS	24.8 (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

Abbreviations: PD – personality disorder, PSS – Perceived Stress Scale, DERS – Difficulties in Emotion Regulation Scale, MAAS – Mindful Attention Awareness Scale

[a] The data was coded as .0 – no diagnosis, .5 – probable diagnosis, 1.0 – definite diagnosis

[b] Fisher's Exact Test

3.3.2. Primary outcomes

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) was put to test, but it was not confirmed (Table 3). There was no statistically significant change in difficulties in emotion regulation, mindfulness and inhibition ($H(2,30) = 1.75$, $p = .43$; $H(2,30) = 2.06$, $p = .47$; $H(2,30) = 1.15$, $p = .66$; respectively) after any intervention.

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

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

ERPs		
P3 alerting	H (2, 29) = 1.29	p = .55
P4 alerting	H (2, 29) = .44	p = .81
Pz alerting	H (2, 29) = 3.81	p = .35
P3 orienting	H (2, 29) = 2.74	p = .27
P4 orienting	H (2, 29) = .87	p = .72
Pz orienting	H (2, 29) = 1.94	p = .47
P3 inhibition	H (2, 29) = 1.31	p = .60
P4 inhibition	H (2, 29) = .67	p = .73
Pz inhibition	H (2, 29) = 1.14	p = .68
Connectivity		
wPLI alpha1	H (2, 29) = 1.21	p = .55
wPLI alpha2	H (2, 29) = .31	p = .86
wPLI beta	H (2, 29) = .86	p = .65
wPLI delta	H (2, 29) = .92	p = .63
wPLI theta	H (2, 29) = .57	p = .75
MST mean	H (2, 29) = .47	p = .79
Power		
Alpha1	H (2, 29) = 1.92	p = .57
Alpha2	H (2, 29) = 3.46	p = .27
Beta	H (2, 29) = 3.04	p = .74
Delta	H (2, 29) = 1.98	p = .50
Theta	H (2, 29) = 2.71	p = .43

3.3.3. ERP results

To determine if attention network ERP amplitudes change after mind-body interventions, we ran a Kruskal Wallis test that showed that the intervention has no effect on ERP measures of alerting (H(2,29) = 1.29, p = .55; H(2, 29) = .44, p = .81; H (2, 29) = 3.81, p = .35), orienting (H (2, 29) = 2.74, p = .27; H(2, 29) = .87, p = .72; H(2, 29) = 1.94, p = .47) or inhibition (H(2, 29) = 1.31, p = .60; H(2, 29) = .67, p = .73; H(2, 29) = 1.14, p = .68) at electrodes P3, P4 or Pz, respectively (Table 3, Figures 9, 10 and 11).

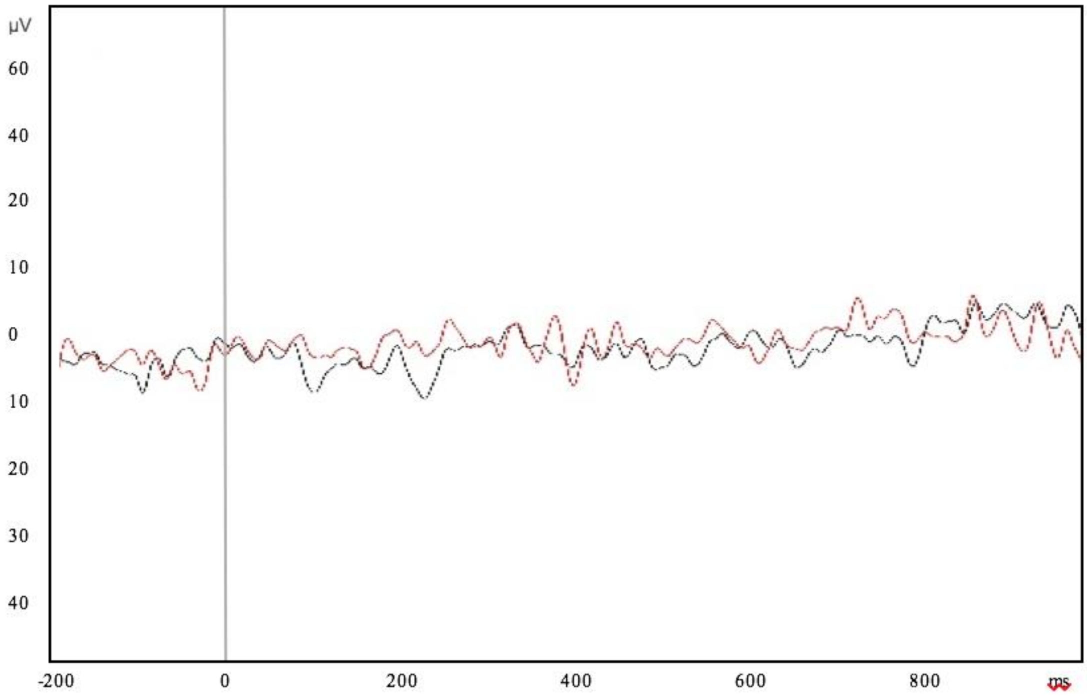

Figure 9. *Grand average waveforms for N1 and P3 at electrodes P3, P4 and Pz before (black line) and after (red line) intervention for the mindfulness group.*

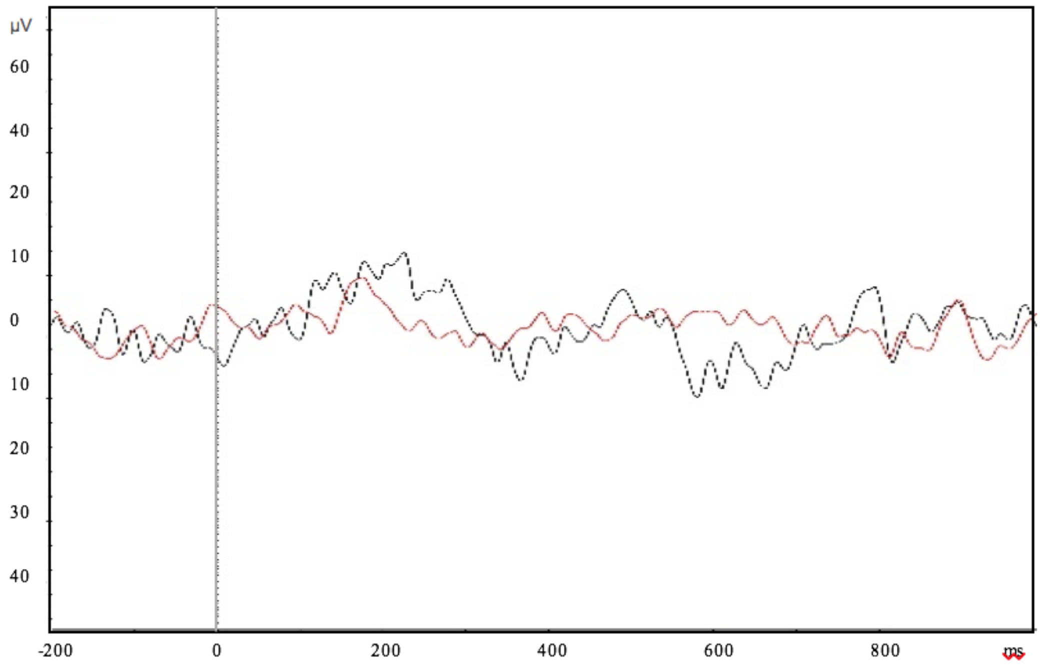

Figure 10. *Grand average waveforms for N1 and P3 at electrodes P3, P4 and Pz before (black line) and after (red line) intervention for the control group.*

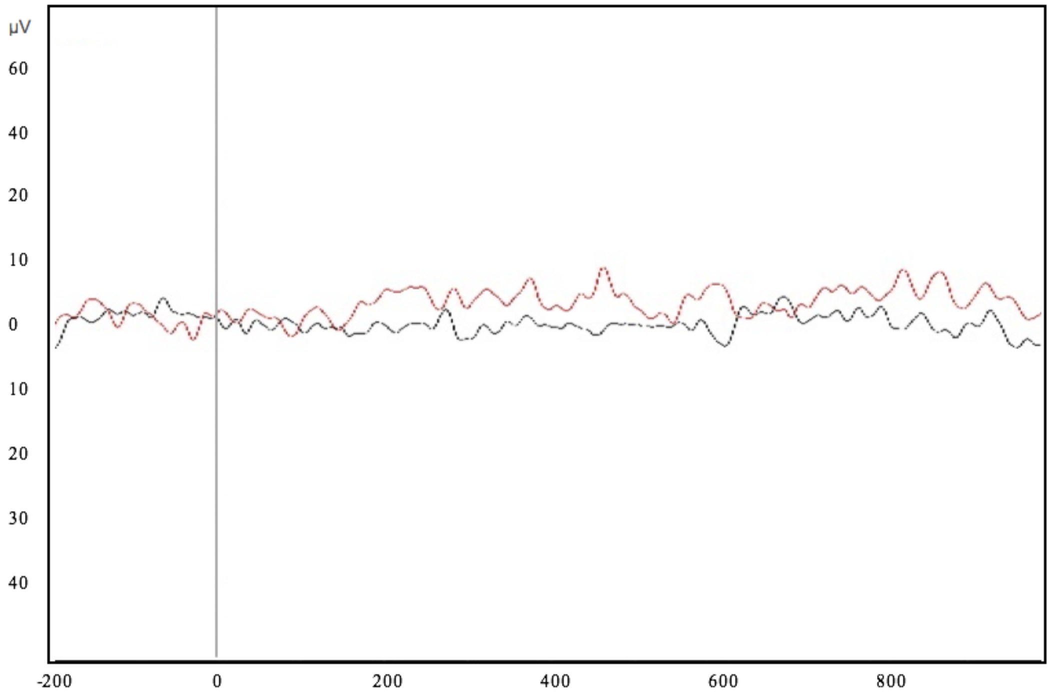

Figure 11. *Grand average waveforms for N1 and P3 at electrodes P3, P4 and Pz before (black line) and after (red line) intervention for the yoga group.*

3.3.4. EEG connectivity results

To verify if there are 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 ($H(2, 29) = 1.21$, $p = .55$; $H(2, 29) = .31$, $p = .86$; $H(2, 29) = .86$, $p= .65$; $H(2, 29) = .92$, $p = .63$, $H(2, 29) = .57$, $p = .75$; Table 2). Similarly, no significant differences in the efficiency of neural communications were found ($H(2, 29) = .47$, $p = .79$; Table 3).

3.3.5. EEG power results

FFT analysis of resting state EEG data found no significant difference in power in any frequency band following mindfulness or yoga ($H(2, 29) = 1.92$, $p = .57$; $H (2, 29) = 3.46$, $p =.27$; $H (2, 29) = 3.04$, $p =.74$, $H(2, 29) = 1.98$, $p = .50$, $H(2, 29) = 2.71$, $p =$

.43; Table 3), which is inconsistent with previous studies that generally find that different types of meditation increase alpha and theta power (Cahn & Polich, 2013).

3.3.6. Risk and ambiguity results

To determine if mindfulness or yoga can reduce the preference for risky and ambiguous monetary lotteries, which is linked with reduce risk for reoffending (Andrews, Bonta & Wormith, 2006), we analysed changes in RAT scores before and after the interventions. Results in table 3 show that relative to the control group, neither mindfulness or yoga reduce the preference for risky ($H(2, 30) = 2.84$, $p = .32$; $H (2, 30) = 2.11$, $p = .41$; $H(2, 30) = 1.26$, $p = .59$; $H(2, 30) = .71$, $p = .73$) or ambiguous choices ($H(2, 30) = 2.85$, $p = .44$; $H(2, 30) = .14$, $p = .93$; $H (2, 30) = 1.43$, $p = .61$). 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 does not change following mindfulness or yoga.

3.3.7. 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 many 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 (Table 4).

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

		Mindfulness 2^-ΔΔCt	**Yoga 2^-ΔΔCt**	**Test statistic**	**Significance**
ATF2	Pre	4.82	3.07	H (2, 12) = .14	p =.93
	Post	0.25	1.25		
CHUK	Pre	1.73	.45	H (2, 12) = .50	p =.78
	Post	.99	.65		
END1	Pre	1.43	.43	H (2, 12) = 1.33	p =.44
	Post	2.71	.30		
F3	Pre	3.84	.52	H (2, 12) = .28	p =.87
	Post	.68	.57		
FOS	Pre	3.59	1.09	H (2, 12) = 1.57	p =.46
	Post	2.06	1.27		
FOSB	Pre	.39	.05	H (2, 12) = .40	p =.69
	Post	1.37	.59		
FOSL2	Pre	3.46	.35	H (2, 12) = 1.15	p =.67
	Post	1.51	.52		
HMOX	Pre	1.17	.39	H (2, 12) = 3.09	p =.21
	Post	1.22	.66		
IKBKB	Pre	1.98	.66	H (2, 12) = .63	p =.71
	Post	1.64	.59		
IL1R1	Pre	1.08	.36	H (2, 12) = 2.87	p =.36
	Post	1.02	1.24		
IL1RAP	Pre	2.64	0.73	H (2, 12) =.40	p =.83
	Post	2.40	1.06		
IL6	Pre	.66	173.74	H (2, 12) =.20	p =.42
	Post	.33	.44		
IL8	Pre	.41	3.66	H (2, 12) = 5.48	p =.17
	Post	.43	.50		
IRAK1	Pre	1.38	.42	H (2, 12) = 1.06	p =.59
	Post	1.02	.70		
IRF1	Pre	.76	51.13	H (2, 12) = 1.04	p =.60
	Post	4.45	11.78		
JUN	Pre	3.38	.38	H (2, 12) =.21	p =.90
	Post	.78	.43		
MAP2K3	Pre	2.36	.61	H (2, 12) = 1.57	p =.46
	Post	.86	.12		
MAP2K4	Pre	3.82	0.40	H (2, 12) =.54	p =.76
	Post	1.39	0.83		
MAP2K6	Pre	2.51	.49	H (2, 12) =.34	p =.84
	Post	1.35	.88		
MAP3K1	Pre	1.27	.15	H (2, 12) =.09	p =.96
	Post	1.09	.95		
MAPK14	Pre	.74	5.18	H (2, 12) =.57	p =.75
	Post	1.34	1.70		
MAPK8	Pre	.94	.29	H (2, 12) =.26	p =.88
	Post	.62	.44		
MAPK9	Pre	3.71	.41	H (2, 12) = 2.48	p =.29
	Post	1.74	1.09		
MYD88	Pre	4.26	.35	H (2, 12) = 5.34	p =.07
	Post	4.00	5.41		

NFKB1	Pre Post	.21 .64	2.83 1.39	H (2, 12) =.57	p =.76
NFKBIA	Pre Post	1.77 .91	.61 .77	H (2, 12) = 3.46	p =.18
NFKBIB	Pre Post	2.73 .68	.47 .41	H (2, 12) =.30	p =.86
RELA	Pre Post	1.23 .39	.34 .08	H (2, 12) =.63	p =.73
SERPINE1	Pre Post	.74 1.61	.63 2.13	H (2, 12) = 1.22	p =.58
STAT1	Pre Post	1.84 1.01	.30 .49	H (2, 12) = 1.54	p =.47
TNF	Pre Post	.28 .56	4.10 .82	H (2, 12) = 2.56	p =.34
TRAF6	Pre Post	1.25 1.01	.76 .56	H (2, 12) = 2.15	p =.47
UBB	Pre Post	1.26 1.05	.38 .81	H (2, 12) = 3.75	p =.15
UBC	Pre Post	.84 1.55	.36 .89	H (2, 12) = 5.78	p =.06

3.4. Discussion and conclusions

The present study attempted to test if mind-body interventions improve self-regulation in prisoners with personality disorders, and to explore genomic, neural and cognitive outcomes. 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 (Samuelson, Carmody, KabatZinn, & Bratt, 2007; Sumter, MonkTurner, & Turner, 2009; Bilderbeck et al., 2013), this study found no improvements in self-regulation following mindfulness and yoga, neither in any other measured outcome. There are three main factors that have likely contributed to the non-significant results of this study. First, 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 and post-intervention assessment was scheduled for three days after the lockdown due to shortage of staff over the weekend. The lockdown rarely occurs within the clinical unit where the study was conducted, and it is very different than a regular day-to-day life of the prisoners because they are normally only locked up at certain time during the day and overnight, while they attend psychotherapy sessions, fulfil their duties or socialise during their association period. Therefore, we can assume that the lockdown has influenced the results of this study because it was stressful day that may have counteracted the beneficial effects of mindfulness and yoga. Second, 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., 2013). 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 feasibility of short and intensive type of mind-body interventions, which was in our case the only option due to prisons' restrictions and participants' therapy commitments. Furthermore, it is likely that even if the final two sessions were delivered, we would not observe changes in any of the measured variables because patients with personality disorders are often resistant to treatment, thus a longer intervention might be necessary to observe changes in this population. Third, it is also possible that the sample size was too small to detect the effects of the interventions. We aimed to recruit 60 participants and to dynamically allocate them to meditation, yoga or control group in equal ratios. The required sample size was calculated based on a meta-analysis of 163 published meditation studies with healthy individuals, which showed a mean effect size of 0.28 (Cohen's d) (Sedlmeier et al, 2012). The calculations for a 3 x 3 design showed that to achieve an effect size of .28 (with a power level of .90 and probability level of .05) we need to use a sample size of 60 (i.e., 20 participants x 3 groups). Therefore, the results could be due to Type II error because more participants were needed to observe statistically significant differences between mindfulness, yoga and wait-list control group. Finally, another consideration is regarding the positivity bias. All the published studies on mindfulness or yoga and prisoners or patients with personality disorders found significant positive effects of mind-body interventions. It is possible that there have been other studies that have 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.

Despite the described limitations, this study also has strengths and methodological innovations. First, although there are other studies of mindfulness and personality disorders (Soler et al., 2012; Feliu-Soler et al., 2014), of mindfulness and prisoners (Samuelson, Carmody, KabatZinn, & Bratt, 2007; Sumter, MonkTurner, & Turner, 2009; Bowen et al., 2006; Perelman et al, 2012; Suarez et al, 2014), and of yoga and prisoners (Bilderbeck et al., 2013; Kerekes, Fielding & Apelqvist, 2017), only the latter yoga studies had a control group. This study contributes to both forensic and psychiatric literature as the first controlled 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 passive control group that was following their usual regimen. 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. Additionally, the study used a vast array of biological and psychological measures to understand the mechanisms of mind-body interventions, which required interdisciplinary collaborations.

Although the present study found no significant effects of mindfulness or yoga on prisoners with personality disorders, it is important for future studies to replicate and extend these findings in larger samples and longer interventions. Personality disorders are an important population to study due to their high prevalence in the general population, and clinical units within prisons provide an opportunity to work with this population that is normally not available.

4.1. Background

Since the introduction of eastern meditation techniques in western countries, a predominant view has been that meditation may only lead to positive transformations, from overcoming mental health problems to having a better understanding of life. Over the past few decades, hundreds of scientific studies have accumulated evidence highlighting the positive effects of meditation (for a review see Goyal et al., 2014 or 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, the problem is that science is generally based on calculating group averages with the aim of finding general principles, while individual differences in response are treated as noise. In reality, group averages represent a small subset of individuals (Borkenau & Ostendorf, 1998), or they can even be artefacts that represent nobody (von Eye, 2009) and where the average responder does not even exist. For instance, neuroimaging studies that look for general principles of brain function average brain maps of multiple individuals and use the average brain map to conclude about other individuals although such pattern in brain activity may never been detected at the level of the individual (Dubois & Adolphs, 2016). The focus on individual variability instead of averages has already led to important implications in personalised medicine by tailoring pharmacotherapy based on traits that cause variations in responses.

As with any other kind of intervention, there is a spectrum of possible responses to meditation, from extremely positive responses on one end to adverse effects on the other. However, it is not known which traits cause variation in response to meditation. By calculating the average of the responses, individual variation in how individual participants are affected by meditation is masked. For instance, in a study exploring psychological changes after learning meditation, the usual practice is to report the average score of the group as whole, and compare it with a score of a control group that did not learn meditation. Within the meditation group, there are individuals who responded 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 meditation programme was extremely beneficial, not beneficial, or even detrimental. While there is always variation within groups in psychology studies, it is striking that the presence of individuals showing either negative or no responses to meditation are systematically overlooked within many meditation studies.

Only a limited number of studies have included data on individual differences in responsiveness to meditation. To elucidate the relationship between differences in participant characteristics and meditation outcomes, we need to identify predictors, moderators, interactions, and correlates of the effects of meditation.

One of the central challenges lies in the heterogeneity of measured outcomes in meditation research; there is no consensus on what a beneficial outcome of meditation is. Even studies that are testing the same form of meditation often use different tasks and questionnaires to measure their outcomes. A meta-analysis of 163 meditation studies found 21 distinct categories of measured outcomes, such as emotion regulation (i.e., the ability to monitor, evaluate and respond to emotions effectively, Thompson & Calkins, 1996), personality, perception, stress, or empathy (Sedlmeier et al., 2012). In recent years several theories that focus on underlying processes that lead to observed benefits of meditation have been developed, though they are mainly related to mindfulness techniques. The most notable theory postulates that the central outcome of mindfulness is improved self-regulation, (consisting of three components: attention, emotion regulation and self-awareness), and that all the other observed benefits are simply a consequence of improved self-regulation (Tang, Hölzel & Posner, 2015). If researchers agree that these are the central outcomes of meditation then studies would be easily comparable, allowing for better comparisons.

The main goal of this chapter is to examine 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 studies obtained through PubMed search that explored the effects of learning meditation in people who previously had no experience in meditation. Besides controlled and non-controlled interventional studies, but we also touch upon relevant meta-analyses that examined moderators of outcomes. We cover four sources of variability in individual responses to meditation that were previously identified in meditation research: i) personality and other psychological variables; ii) biological variables; iii) illness severity and iv) demographics.

4.2. Individual differences due to psychological variables

Research on meditation stems from psychology in the 1960s, while other scientific disciplines, such as neuroscience or molecular biology, have only begun approaching this subject more extensively over the past two decades. Therefore, it is not surprising that 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, which have an advantage that they can be obtained quickly and efficiently. The caveat of psychological measures is that they are prone to response bias, such as lying to present oneself in a socially desirable manner or to please the researchers. Out of many possible psychological factors that could impact the effects of meditation training, it seems that personality, stress, and mood are the most researched sources of inter-individual differences.

4.2.1 Stable psychological factors: personality traits

Personality traits give rise 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 interventions, such as meditation, can shape personality towards a healthier profile (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, but it is not clear how different personality types respond to meditation. In a study investigating one of the personality dimensions, Lane, Seskevich and Pieper (2007) showed that neurotic participants 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. In a study of Mindfulness-Based Stress Reduction (MBSR) in students, similar results were found: those who scored high on neuroticism benefitted more from MBSR than others (de Vibe et al., 2015). Individuals scoring high on neuroticism reported lower levels of mental distress and increased 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 students who scored higher on conscientiousness experienced the greatest effect of the intervention on reducing study-related stress, while there were no effects of extraversion (de Vibe et al., 2015). People who score high on conscientiousness are generally more likely to regularly take good care of their health and to live longer (Bogg & Roberts, 2004), so it is possible that they gain more benefits from meditation merely because they practice consistently. A study of an Integrative Body Mind Training (IBMT), which is based on mindfulness, compared IBMT to a relaxation programme in terms of improving creativity (Ding et al., 2015). In this study, participants were examined on various personality and mood measures (extraversion/introversion, neuroticism and psychoticism), before and after one week of IBMT or relaxation training. They 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 does not influence creative performance after IBMT or after relaxation, which is unexpected because a facet of conscientiousness is commonly measured as the inverse score on a psychoticism scale (Bogg & Roberts, 2004). Furthermore, introversion was associated with greater improvement in creativity after the trainings in both groups, while neuroticism was associated with improvement only in the meditation group (Ding et al., 2015). Therefore, unlike neurotic participants, introverted participants can similarly improve their creativity whether they choose to practice meditation or relaxation. Neurotic participants have better creative performance only if they practice meditation, perhaps because it reduces judging difficult thoughts and emotions that are common in neurotic people, unlike relaxation that merely attempts to induce pleasant experiences. Ding and colleagues (2015) interpreted these results as an indication that introverted individuals are overall readier to engage in meditation and relaxation programmes, which is conflict with Delmonte’s (1988) findings. His study with outpatients with psychosomatic and neurotic symptoms found that introverts were less likely to continue practicing transcendental meditation regularly after three, six, 12 and 24 months after learning the technique, meaning 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 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 own life are under personal control as opposed to external forces that are beyond control). Besides introverts, participants who score low on repression were also less likely to practice meditation regularly at all follow-ups. Participants who score 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.

Individual differences in trait anxiety, which is conceptually largely overlapping 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 responding to meditation, but there are some conflicting findings. An early meta-analysis showed that it was possible to reduce levels of trait anxiety by practicing different types of meditation and relaxation techniques, but that transcendental meditation reduces trait anxiety the most (Eppley, Abrams & Shear, 1989). A more recent meta-analysis of 16 randomized controlled trials of transcendental meditation tested if baseline trait anxiety influences the reduction in trait anxiety following transcendental meditation (Orme-Johnson and Barnes, 2014), and found that the improvements were largest for people with high anxiety levels (80^{th} to 100^{th} percentile), who responded better to transcendental meditation than to mindfulness-based therapy. When baseline anxiety is within normal range, then and mindfulness-based intervention appear to be equally effective in reducing anxiety (Orme-Johnson and Barnes, 2014). However, it is not known if these participants had symptoms of anxiety that satisfy the criteria for anxiety disorders. Two other meta-analyses, on studies involving participants diagnosed with anxiety disorders and who attended mindfulness-based interventions, have found conflicting results. One meta-analysis found that anxiety is reduced in people with anxiety disorders just as strongly as depression is reduced in those with mood disorders following meditation (Hofmann, Sawyer, Witt & Oh, 2010). The other meta-analysis found that mindfulness interventions are not helpful for patients 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 meta-analyses are likely due to the fact that one meta-analysis only included studies where participants are randomly allocated to groups and that have 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 influences the response to meditation are related to the Big Five personality model, especially to neuroticism/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 influence how much a person practices meditation, but not to other outcomes. However, these conclusions are based on just a handful of studies, and not all of them have a control group or use the same type of meditation or population, thus this is just the beginning of understanding how major personality traits can influence the response to meditation.

4.2.2. 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 factors 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” (Shiner et al., 2012, p.2).

Takahashi and colleagues (2005) explored the effects of temperament on brain activity and heart-rate variability during Zen meditation (a meditation based on counting exhales) in people who had never meditated before. This study employed a psychobiological model of temperament that regards novelty seeking, harm avoidance, reward dependence and persistence as components of temperament, and which overlaps conceptually with the Big Five model of personality (De Fruyt, Van De Wiele & Van Heeringen, 2000). During Zen meditation, individuals with high levels of harm avoidance had higher power in frequencies that range from 4 to 7 Hz, which is associated with being mindful (Aftanas & Golocheikine, 2001). Individuals with high levels of novelty seeking had higher power in frequencies that range from 10-12 Hz, which is associated with endogenous, or top-down, attention (Shaw, 1996), and they also demonstrated a shift in heart rate variability that indicates an activation of parasympathetic nervous system (i.e., a part of the autonomic nervous system that relaxes the body and conserves energy). Reward dependence and persistence did not influence the response to Zen meditation - neither in terms of brain activity nor heart rate variability. However, this study focused on EEG and heart rate variability, while no psychological measures of mindfulness or cognitive measures of attention were included, so it is unclear whether individuals with high levels of harm avoidance really were more mindful, and whether individuals with high levels of novelty seeking indeed had a better modulation of endogenous attention and higher levels of relaxation.

Mindfulness itself can also be defined as a personality trait rather than a transient state measured during mindfulness 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 own thoughts, emotions, and bodily sensations, without judging 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 that people who start with low levels of mindfulness have more space for progress and are 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 during a stress. 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 influences responses to meditation. Irrespective of initial levels of trait mindfulness, students gained similar benefits from MBSR in a previously mentioned study that measured well-being and distress as outcomes (De Vibe et al., 2015)

Jacobs et al. (2011) studied the influence of current psychological functioning on the response to meditation in experienced meditators, who attended an intensive three-month meditation programme based on mindfulness techniques. In addition to trait mindfulness, the researchers also measured purpose in life, perceived ability to control own life, and neuroticism, and grouped these variables in an analysis to represent 'psychological functioning'. After three months of intensive meditation, meditators 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, seem to benefit more.

Another, possibly less conventional, personality-related construct that influences the response to meditation is attachment style. According to attachment theory, attachment style 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 generally, the main distinction that is made is between secure and insecure attachment. An insecure attachment is likely to be formed in cases where the caregiver does not respond consistently to 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, while post intervention their stress level 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 MBSR consequently had significantly lower levels of perceived stress than securely attached individuals (Cordon et al., 2009). This finding converges with the previously mentioned study that showed that introverted and neurotic people are also less likely to adhere to regular meditation practice (Delmonte, 1988) because insecurely attached individuals are more often introverted and neurotic (Hagekull & Bohlin, 2003; Shaver & Brennan, 1992). It may beneficial for teachers to recognise these trait 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 summarize, temperament, trait mindfulness, and type of attachment are the only explored personality-related traits outside of the Big Five model that can influence the response to meditation. More studies are needed to replicate and extend these findings because there are several studies with mixed results and in the case of attachment, 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.

4.2.3. Transient psychological factors: Mood and stress

Mood seems to be another important psychological variable related to individual differences in meditation outcomes. In a previously mentioned study that found a link between IBMT, personality, and creativity, 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., slower hear-rate reduction after a laboratory-induced social stressors), 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 mindfulness program 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 (Pace et al., 2010). In sum, mood certainly seems to influence the response to meditation, but it is difficult to make 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) does not influence mood or stress levels after intervention (Carlson et al., 2001), which might 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.

4.2.4. Other psychological variables: expectations and emotions

It follows from the principles of placebo effects that initial expectations of meditation can significantly affect outcomes. Somehow however, this topic has been neglected in meditation research since the 1980's. Back then, Delmonte (1981; 1985; 1988) 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 are not stable, but vary over time as more experience is obtained; baseline positive expectations are 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. Another study by Delmonte manipulated expectations in naïve meditators by presenting meditation as either beneficial or non-beneficial before they began a meditation course (Delmonte, 1985). 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 (Delmonte, 1985). However, none of Delmonte's studies included a control group, and therefore alternate explanations – such as that expectations could have the same physiological effect in a non-meditation intervention – cannot be ruled out. These issues can be overcome by including group differences in expectations as a covariate in the statistical analysis of the main outcome, as was done in a study that explored stress reactivity and mindfulness (Creswell, 2014). This way, the author could control for the possibility that merely having positive expectations about the outcomes of mindfulness leads to perceiving more benefits. 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 mindfulness course were measured. During the first two days of courses, 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 analysis.

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 (Cohn and Fredrickson, 2010). 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—is 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 with patients 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 meditation (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.

4.3. 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 our genes, which never change as they are inherited. 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 is a less common meditation that 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 have 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. While these results may seem strong and definite, there are more than a few remarks to be made on this study and to studies on genetic variants in general. 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), 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 genes are generally team players: Even simple characteristics like our height are regulated by more than 40 genes. 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 in this case, it does not have an effect on the phenotype. Therefore, even if a person has inherited the worst possible genes, they will not necessarily determine his or her fate, and therefore measuring gene variants and neglecting the measurement of the activity of those genes is not a reliable method. 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 that 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) since it is increased by chronic stress (Carpenter et al., 2010), and its reduction has protective health effects (Nemeth et al., 2004). One study found that compassion meditation training decreases the levels IL-6 in response to laboratory-induced stress, but only in those whose practice frequency was above the median (Pace et al., 2009). However, neither baseline levels of IL-6 nor baseline levels of cortisol can predict the amount of subsequent meditation practice, which was the only outcome tested to be under influence of an individual difference. (Pace et al., 2009).

Reich et al. (2014) identified several biomarkers that can be measured in blood and predict 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), 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 to explore individual differences in meditation on. Since it is known that meditation can affect structure of the brain (Hölzel et al., 2011b) and its activity (Davidson et al., 2003), 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 recent 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 (anterior insula) while observing others in pain. 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 (left amygdala) while receiving pain. Unexpectedly, activity in the insula and amygdala during 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 predict 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 or simply the popularity of mindfulness programs in the west. In summary, BDNF and COMT gene variants seem, at least to some degree, 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 around 20,000 potential gene candidates that could 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. 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, there is hope that a brain scan might be sufficient to predict what type of meditation would be preferable for a given person, as a study found that amygdala and insula activity are indicative of practice frequency of mindfulness and compassion meditation (Mascaro, Riling, Negi & Raison, 2013).

While biological measures may be alluring because they are not prone to response bias such as questionnaires, currently there is still only a limited amount of studies on biological measures that have been related to responsiveness to meditation. Generally, collaborations between biology and psychology are still quite rare, but the biological approach to meditation certainly has promising applications for the future.

4.4. Individual differences due to illness severity in patients

Important findings that overlap with biological and psychological influences on meditation come from studies that have found that the more severe the patient's condition is, the better the response to meditation. However, it is not known whether this effect is due to particularly troubled people having more positive expectations of meditation in the hope of alleviation of their symptoms. The relationship between illness severity and responding to meditation is especially evident in people with depression. A 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). 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, patients 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 whose disease stage and disease duration were not significant predictors of responsiveness to MBSR (Carlson et al., 2001) and patients with hypertension whose length of hypertension history or baseline levels of blood pressure did not influence how much their blood pressure reduced after transcendental meditation (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 for this to be investigated further, especially for patient populations, so that the most suitable meditation practices with the best outcomes become available.

Table 5. *A summary of the reviewed studies on individual differences and meditation*

Authors	Population type (N)	Control group	Meditation type	Meditation duration	Individual Differences	Outcomes	The relationship between individual differences and outcomes
Carlson et al., 2001	Cancer patients (89)	None	Mindfulness	7 weeks	Mood, stress, disease stage and duration, age, education, gender	Perceived stress, mood	Increase in positive mood and reduction in perceived stress was greater in participants with higher negative mood at baseline. Reduction in perceived stress was greater in participants with higher education. No effect of baseline stress, age, disease stage or duration
Cohn & Fredrickson, 2010	Health adults (95)	None	Loving-kindness	8 weeks	Positive emotions during the day, mindfulness, well-being, self-efficacy, ego-resilience, savouring, social support, self-other overlap, symptoms of illness, life satisfaction	Practice frequency	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. 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 initial positive emotions—is that continuing meditators gave and received more social support
Cordon, Brown & Gibson, 2009	Healthy adults (131)	None	MBSR	8 weeks	Attachment, age	Perceived stress, drop-out rate	Greater drop-out rate in insecurely attached participants, but the insecurely attached participants that finished MBSR had greater stress reduction than securely attached. No effect of age
Creswell et al., 2014	Healthy adults (66)	Cognitive training	Mindfulness	3 days	Trait mindfulness	Perceived stress, cortisol, cardiovascular response to stress	Reduction in perceived stress and increase in cortisol was greater in participants who score higher on trait mindfulness. No effect on cardiovascular response.

De Vibe et al., 2015	Healthy adults (288)	Wait-list	MBSR	8 weeks	Neuroticism, conscientiousness, extraversion, mindfulness	Mental distress, well-being	Reduction in mental distress and increase in well-being was greater in participants high in neuroticism. Reductions in stress were the greatest in participants high in conscientiousness. No effect was found for mindfulness and extraversion.
Delmonte 1985	Healthy adults (40)	None/ resting (same participants)	TM	1 hour	Expectations	Blood pressure, heart rate, blood volume, skin conductance, skin temperature, EMG	Reduction (from baseline to meditation) in systolic and diastolic blood pressure, heart rate and skin conductance was greater in participants who had positive expectation. No significant difference in EMG, blood volume, and skin temperature.
Delmonte, 1981	Healthy adults (94)	None	TM	1, 3, 5 and 7-month follow-up	Perceived self, expectations, age	Choosing to learn TM after introductory session, Frequency of meditation	Those who chose to learn meditation after an introductory session were older, initially had more negative perceived-selves, and had higher expectations. High practice frequency was related to positive perceived-self at 1 month follow-up and high expectations at 3, 5 and 7-month follow-up. Younger participants responded more positively to the introductory session and they meditated more frequently, had more positive perceived-selves, and were more likely to report an improved perceived-self compared with their initial pre-talk scores, than older subjects.
Delmonte, 1988	Outpatients with psychosomatic and neurotic symptoms (37)	None	TM	3, 6, 12 and 24-month follow-up	Introversion, neuroticism, sensitization-repression, suggestibility, locus of control	Practice frequency	Participants who score high on introversion and low on repression were less likely to practice meditation regularly at all follow-ups. Participants who score high on neuroticism and suggestibility were less likely to practice meditation regularly at 3-month follow-up only. No effect was found for locus of control.

Delmonte, 1988	Outpatinets with psychosomatic and neurotic symptoms (37)	None	TM	3,6, 12 and 24 months	Neuroticism, introversion, sensitisaton, suggestibility, locus of control, repression-sensitisation	Practice frequency	Participants high in neuroticism were less likely to practice regularly after 3 months. Participant high in extraversion were more likely to practice after 3,6,12 and 24 months. Participants high in repressing were more likely to practice after 3,6,12 and 24 months. Participants high in suggestibility were less likely to practice at the 3 months. Locus of control is not significant for any time point.
Ding et al., 2015	Healthy adults (84)	Relaxation	IBMT	1 week	Introversion, neuroticism, psychoticism, tensions/anxiety. depression/dejection, anger/hostility, fatigue/inertia, confusion/bewilderment, vigour/activity	Creativity	Increase in creativity was greater in introverted and neurotic participants. No effect was found for psychoticism. Increase in creativity was greater in participants who scored lower on depression and fatigue, and in those who scored higher on anger/hostility and vigour/activity.
Hager & Surwit, 1978	Patients with borderline hypertension (30)	Blood pressure biofeedback	Meditation-relaxation	4 weeks	Age, gender, blood pressure, use of medication, length of hypertension history	Blood pressure	No effect of any variable.
Jacobs et al., 2011	Experienced meditators (60)	Wait-list	Shamatha	3 months	Psychological functioning (measured as trait mindfulness, perceived control and purpose in life)	Telomerase, psychological functioning	Increase in psychological functioning and in telomerase was greater in participants with initially low psychological functioning

Jung et al., 2012	Experienced meditators (80) vs non-meditators (57)	None	Brain wave vibration	1 session	BDNF gene, COMT gene	Plasma norepinephrine, epinephrine, dopamine, perceived stress	Experienced meditators who have BDNF Val/Met or BDNF Met/Met allele have lower levels of perceived stress than people with those alleles who do not meditate. Experienced meditators who have BDNF Val/Val have the same levels of perceived stress as people with those alleles who do not meditate. Experienced meditators who have COMT Met/Met or COMT Met/Val allele have higher norepinephrine than experienced meditators with COMT Val/Val allele. No effect for epinephrine and dopamine.
Kabat-Zinn & Chapman-Waldrop, 1988	Patients with pain or stress symptoms, various diagnosis (598)	none	Mindfulness	8 weeks	Gender, age, length of pain history, symptoms, distress	Completing the programme	In the pain cohort, women were more likely than men to complete the whole programme. In the stress cohort, only the level of obsessive-compulsive tendencies (distress subscale) was a significant predictor of program completion. 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.
Lane, Seskevich & Pieper, 2007	Healthy adults (133)	None	Mantra-based	3 months	Neuroticism	Stress Negative emotions	Reduction in stress and negative emotions was greater in participants high in neuroticism
Law, 2011	Healthy adults (113) – doctoral thesis	Visualisation	Loving-kindness	10 minutes	Mood, social anxiety	Relaxation, positivity towards self, perceived stress	Increase in relaxation, positivity and stress buffering effects was greater in participant who were in a positive mood prior to meditation, especially among socially anxious participants
Mascaro, Rilling, Negi & Raison, 2013	Healthy adults (29)	Health education	Cognitively-Based Compassion Training (mindfulness and compassion)	8 weeks	fMRI Self and Other pain task	Practice frequency	Practice frequency of compassion meditation was related to increased activity in anterior insula while observing others in pain. Practice frequency of mindfulness meditation was related to decreased activity left amygdala while

							receiving pain.
Orme-Johnsons and Barnes, 2014	Meta-analysis of RCTs, clinical and non-clinical populations (1295)	Varies	TM and mindfulness	Varies	Anxiety Age	Anxiety	Reduction in anxiety was greater in anxious participants. No effect was found for age.
Pace et al., 2010	Healthy adults (32)	None	Compassion	6 weeks	Perceived distress Cortisol IL-6	Practice frequency	No effect of baseline perceived distress, cortisol or IL-6 on practice frequency
Piet & Hougaard, 2011	Meta-analysis; patients with recurrent depression currently in remission (593)	Varies (all RCTs)	MBCT	8 weeks	Number of depressive episodes	Risk of relapse	Patients with three or more depressive episodes show greater reduction in symptoms of depression
Reich et al., 2014	Cancer patients (41)	Wait-list	MBSR	6 weeks	B lymphocytes, interferon-γ, IL-4, total number of lymphocytes, lymphocyte subsets	Gastrointestinal symptoms (dry mouth, nausea, vomiting, and lack of appetite), memory, distress and sadness, fatigue	Gastrointestinal symptoms following MBSR were predicted by B lymphocytes and interferon-γ. Psychological improvement in memory, distress and sadness were predicted by CD4 and CD8, and fatigue was predicted by IL-4 and the total amount of white blood cells. Generally, participants with increased interleukins and interferon-γ at baseline had fewer symptoms after meditation training
Rojiani et al., 2017	Healthy adults (77 undergraduate students)	None	Mindfulness	12 weeks	Gender	Mindfulness, mood, self-compassion	Reductions in negative affect and improvements in mindfulness and self-compassion were greater in women than in men.
Seer & Raeburn, 1980	Patients with hypertension history (41)	Placebo meditation and wait-list	TM	5 weeks	Length of hypertension history, blood pressure, emotions during and after meditation, perceiving meditation practice as easy, gender, marital status, history of	Blood pressure	Reduction in blood pressure was greater in participants who had longer hypertension history and higher diastolic blood pressures. Reduction in blood pressure was greater in participants who were feeling more relaxed at baseline and in those who were experiencing pleasant emotions during and after meditation practice and found the practice easy No effect for gender, marital status or history of taking

					hypertensive medication		antihypertensive medication.
Shapiro, Brown, Tohresen & Plante, 2011)	Healthy adults (30)	Wait-list	MBSR	8 weeks	Trait mindfulness	Train mindfulness, well-being, hope, empathy, perceived stress, rumination, forgiveness, self-compassion	Increase in mindfulness, well-being, hope and empathy, and decrease in perceived stress was greater in participants with higher baseline mindfulness immediately after MBSR, and at 2 and 12-month follow-up. Increase in self-compassion was greater in participants with higher baseline mindfulness immediately after MBSR, but not at follow-up. All the other measures were non-significant.
Strauss, Cavanagh, Oliver and Pettman, 2014	Meta-analysis of RCTs, patients with current episode of depression or anxiety disorder (578)	Varies	Mindfulness	Varies	Primary diagnosis	Symptoms of illness	Mindfulness interventions reduce symptoms in patients with current episode of depression, but not in those with a current episode of an anxiety disorder
Takahashi et al. (2005)	Healthy adults (20)	Relaxation (the same participants served as a control group)	Zen	1 session	Novelty seeking, harm avoidance, reward dependence and persistence	EEG power analysis and heart-rate variability (nuLF, nuHF and LF/HF)	Participants with high levels of harm avoidance had higher theta power. Participants with high levels of novelty seeking had higher alpha power and higher nuLF and LF/HF. Reward dependence and persistence did not influence the response to Zen meditation neither in terms of brain activity nor heart rate variability.
Williams et al., 2014	Patients with recurrent depression currently in remission (274)	TAU or cognitive psychological education + TAU	MBCT +TAU	8 weeks	History of childhood trauma	Risk of relapse	The risk of relapse was lower in participants who score above the median on history of childhood trauma if they attend MBCT instead of cognitive psychological education or just TAU.

Abbreviations: BDNF – brain-derived neurotrophic factor, CD – cluster of differentiation (i.e., type of white blood cells), COMT – catechol-O-methyltransferase, EEG – electroencephalography, EMG – electromyography, fMRI – functional magnetic resonance imaging, IL – interleukin, LF/HF – low frequency power/high frequency power, MBCT – Mindfulness-Based Cognitive Therapy, MBSR – Mindfulness-Based Stress Reduction, TAU – treatment as usual, TM – transcendental meditation.

4.5. Individual differences due to demographic factors

Many researchers have explored demographic variables to see if 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 is reduced regardless of gender or marital status in another (Seer and Raeburn, 1980). Similarly, a study of a mantra-based meditation and relaxation programme found that it 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 some 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, individual variation on demographic variables such as age, gender, and level of education do not seem to influence people's responses to meditation in a consistent way. Note, however, that studies on this topic are relatively scarce. There are still many other factors that need to be examined, such as individual differences in ethnic background, which may be explored in future studies.

4.6. Quality assessment

Methodological quality was assessed using the Study Quality Assessment Tools by National Heart, Lung and Blood Institute. More specifically, three assessment tools were used based on the type of research design: Quality Assessment of Controlled Intervention Studies, Quality Assessment of Pre-Post Studies with no Control Group and Quality Assessment of Systematic Reviews and Meta-Analyses (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,* whereas 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. Modifications were made in two out of three quality assessment tools; some items were dropped out because they cannot be answered with a *yes* in meditation research. More 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 not possible to blind participants.

The 26 studies were graded and categorised based on their scores as *good, fair* or *poor*. A study would be graded as *good* if it met at least 80% of criteria listed within the quality assessment tool, which would suggest that it has the least risk of bias, and results are considered to be valid. A study that meets at least 50% of criteria indicated *fair* confidence in the validity of study results, which may change with further studies because it is susceptible to some bias deemed not sufficient to invalidate its results. Finally, a study that meet less than 50% of criteria indicated *poor* confidence in the validity of the results, a significant risk of bias, and a greater likelihood that further studies might show contradictory evidence. Studies rated as poor were not excluded because no studies of better quality that examine the same individual difference were available, thus in this case poor quality studies have to be considered.

The examination of methodological quality of the studies shows that the majority of studies are of fair quality (61%), almost a third of the studies (31%) are of good quality, and the remainder (8%) was of poor quality. The most consistent flaw across studies was not blinding the assessors to participants intervention assignment in studies that had a control group, which can be easily overcome in future studies by having a different researcher doing the assessment than the one that is in charge or randomisation or the delivery of intervention. Studies with control groups were generally using valid and reliable measures, adhering to intervention protocols and managed to avoid high drop-out rates. Studies with control groups maintained fair or good quality by consistently 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.

Table 6. *Quality Assessment of Meta-Analyses*

Authors	**1. Is the review based on a focused question that is adequately formulated and described?**	**2. Were eligibility criteria for included and excluded studies predefined and specified?**	**3. Did the literature search strategy use a comprehensive, systematic approach?**	**4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?**	**5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?**	**6. Were the included studies listed along with important characteristics and results of each study?**	**7. Was publication bias assessed?**	**8. Was heterogeneity assessed? (This question applies only to meta-analyses.)**	**Total answered with *yes* (out of 8)**
Orme-Johnsons and Barnes, 2014	Y	Y	Y	N	N	Y	Y	Y	6
Piet & Hougaard, 2011	Y	Y	Y	Y	Y	Y	Y	Y	8
Strauss, Cavanagh, Oliver and Pettman, 2014	Y	Y	Y	N	N	Y	Y	Y	6

Table 7. *Quality Assessment of Pre-Post Studies with no Control Group*

Aurhors	**1. Was the study question or objective clearly stated?**	**2. Were eligibility/selection criteria for the study population prespecified and clearly described?**	**3. Were the participants in the study representative of those who would be eligible for the intervention in the population of interest?**	**4. Were all eligible participants that met the prespecified entry criteria enrolled?**	**5. Was the sample size sufficiently large to provide confidence in the findings?**	**6. Was the test/service/intervention clearly described and delivered consistently across the study population?**	**7. Were the outcomes prespecified, clearly defined, valid, reliable, and assessed consistently across all participants?**	**8. Were the people assessing the outcomes blinded to the participants' interventions?**	**9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?**	**10. Did the statistical methods examine changes in outcomes from before to after the intervention? Were statistical tests done that provided p values?**	**Total answered with *yes* (out of 10)**
Cordon, Brown & Gibson, 2009	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	9
Delmonte, 1981	Y	N	Y	Y	NP	Y	N	N	N	Y	5
Delmonte, 1985	Y	Y	Y	Y	N	Y	Y	N	Y	N	7
Delmonte, 1988	Y	Y	Y	Y	N	Y	Y	N	Y	N	7
Jung et al., 2012	Y	Y	Y	Y	N	N	Y	N	Y	Y	7
Kabat-Zinn & Chapman-Waldrop,1988	Y	Y	Y	N	Y	Y	Y	N	N	N	6
Lane, Seskevich & Peiper, 2007	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	9
Pace et al., 2010	Y	Y	Y	Y	NP	Y	Y	N	Y	Y	8
Rojiani et al., 2017	Y	N	Y	Y	Y	Y	Y	N	Y	Y	8
Takahashi et al., 2005	N	N	Y	NP	N	Y	Y	N	Y	Y	5

Table 8. *Quality Assessment of Controlled Intervention Studies*

Authors	1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	3. Was the treatment allocation concealed (so that assignments could not be predicted)?	4. Were the people assessing the outcomes blinded to the participants' group assignments?	5. Were the groups similar at baseline on important characteristics that could affect outcomes?	6. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	7. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	8. Was there high adherence to the intervention protocols for each treatment group?	9. Were other interventions avoided or similar in the groups)?	10. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	11. Did the authors report that the sample size was sufficiently large to detect a difference in the main outcome with at least 80% power?	12. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	13. Were all randomized participants analyzed in the group to which they were originally assigned?	Total answered with *yes* (out of 13)
Carlson et al., 2001	Y	Y	NP	NP	Y	Y	NA	Y	Y	Y	N	Y	Y	9
Cohn & Friedrickson, 2010	Y	NP	NP	NP	Y	NP	NP	NP	Y	Y	NP	Y	NP	5
Creswell et al., 2014	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	11
De Vibe et al., 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13
Ding et al, 2015	Y	Y	N	N	NP	NP	NP	Y	Y	Y	N	Y	Y	7
Hager & Surwit, 1978	Y	N	N	N	Y	N	Y	Y	Y	Y	N	Y	Y	8
Jacobs et al., 2011	Y	NP	NP	NP	N	Y	Y	Y	Y	Y	N	Y	Y	8
Law, 2011	Y	NP	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	9
Mascaro et al., 2013	Y	NP	NP	N	NP	N	Y	Y	Y	Y	N	Y	N	6
Reich et al., 2014	Y	NP	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	9
Seer & Raeburn, 1980	Y	NP	N	Y	NP	NP	NP	Y	Y	Y	N	N	Y	7
Shapiro et al., 2011	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	10
Williams et al., 2014	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12

4.7. Discussion and conclusions

In this chapter, we have provided an overview of the current state of affairs concerning the potential of psychological, biological and demographic factors in accounting for individual differences in the effects of meditation. This information is valuable to meditation teachers and clinicians alike because they could use it to adapt their 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. Additionally, researchers could conduct studies with high-responders only and overcome the need for large samples to get sufficient statistical power to detect effects of meditation.

The majority of studies discussed in this chapter investigated psychological variables, but that does not necessarily mean that these factors are the most important ones or that they will have the biggest explanatory value. The next natural step is to conduct a meta-analysis because it would provide effect sizes of each individual difference and inform future studies in a more precise manner. However, a meta-analysis of such data is a rather complex task, mainly due to several sources of heterogeneity. More specifically, outcome variables vary because meditation researchers rarely base their choice of outcomes on theoretical frameworks. A previous meta-analysis managed to summarise the outcomes of previous meditation studies in 21 distinct categories (Sedlmeier et al., 2012), which suggests that multiple meta-analyses would have to be conducted (e.g. effect size of each individual difference on each outcome category) and that there would a discrepancy in the number of available per outcome category. Furthermore, there is a lot of heterogeneity in the research designs, population types or types of meditation in meditation research, but an initial meta-analysis of individual differences should keep their eligibility criteria wide to include all studies that explored this topic, but account for study quality. An additional problem in conducting a meta-analysis on this topic is that some eligible studies might be missed because it is difficult to conduct a comprehensive search because individual differences are often secondary analysis that is not mentioned in the title or in the abstract, but this can be overcome, at least to some degree, by contacting experts in the field.

A central issue with the current studies on meditation is that conclusions are limited due to low comparability among studies, as they measure different outcomes, use different meditation programmes and different populations. One potential remedy for this problem would be to use a common theoretical framework, which would reduce variability in measured primary outcomes. For instance, if future studies of individual differences in mindfulness meditation would adopt the self-regulation theory (Tang, Hölzel & Posner, 2015) and measure attention, emotion regulation and self-awareness as primary outcomes, then we could eliminate the possibility that inconsistent results across studies are due to differences in chosen outcome measures. This approach would enable a clearer understanding of individual differences in meditation because it would reduce the number of possible sources of conflicting results among studies that are testing the same type of meditation on the same type of populations (i.e., inconsistent results are then likely due to nuances in the procedure or in the research design).

One suggestion for future studies is that they should aim to link the effects of meditation to individual differences at multiple levels (e.g., biological and psychological), and explore interactions among these levels. We invite researchers to shift their central focus from group average to individual differences, and to aim for larger samples that would enable the use of complex modelling. 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—eventually, we may be able to predict whom meditation would benefit the most.

5. General discussion

5.1. Main findings

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? What participant baseline characteristics influence the response to meditation?

The first question was examined in a systematic review of all studies that have been published in a peer-review journals and used gene expression as one of the outcomes of different MBIs, including various types of meditation, yoga, mindfulness, Tai Chi and Qigong. The surprising finding was that there was a general anti-inflammatory gene expression pattern across different MBIs, despite the fact that some of the MBIs include a physical component, while others are mainly sedentary. This raises the question if the supposed beneficial effects of MBIs on gene expression can be obtained with behavioural interventions that do not include a 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 at this point in time before more studies are conducted. Ideally, we would see comparative effectiveness research that would identify best behavioural interventions in terms of gene expression in a specific target population. However, there are many other questions to be answered as well. 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 protein increases. This suggest that posttranscriptional regulatory mechanisms might be degrading the mRNAs before they get to the ribosomes and translate to 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 not clear for how long can the change in gene expression 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 Chapter 3, the effectiveness of intensive 5-day MBIs on prisoners with personality disorders was explored with a randomised controlled trial. Non-significant effects were observed across all measures: EEG connectivity, power and ERPs; difficulties in emotion regulation; mindfulness; stress; inflammatory gene expression; risk-taking and attention. 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 impossible to discern the cause of the non-significance as there are multiple causal factors that likely interact. More specifically, 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 and overnight, but it also reduced the intended length of our interventions for 20%. A final potential causal factor is related to the type of population as patients with personality disorder might not respond to short intensive MBIs, but might require longer interventions for the 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 bring a high risk of dropping out, we encourage researchers to conduct further studies on this population with longer MBIs of a smaller intensity and to conduct assessments at several time-points during the interventions in order to observe when they are starting to respond.

Finally, chapter 4 provided an overview of studies that explored individual differences in responding to meditation and categorises them for clarity. It was observed that the majority of studies are related to psychological individual differences that influence the response to meditation. Psychological factors that were found to influence the response to meditation are neuroticism, anxiety, conscientiousness, mindfulness, attachment style, mood, emotions and expectations. Important biological factors seem to be BDNF and COMT gene polymorphisms, biomarkers of immune activity such as IL-6 and amygdala and insula activity. Besides specific psychological and biological factors, studies suggest that illness severity might also influence the response to meditation, while demographic factors do not. However, this review does not provide us with a possibility to conclude which individual differences contribute the most and, therefore, cannot provide specific advice for future studies. It is necessary to conduct a large meta-analysis that would actually be a series of small meta-analyses due to several sources of heterogeneity, such as population types and choice of outcomes of meditation. We also invite researchers to explore any individual differences that might influence the response to meditation, and ideally to also test interactions between individual differences and to measure the effects of meditation on multiple levels (e.g. biological, psychological, and neural), and explore interactions among these levels. However, a study that would test many variables and their interactive effects in creating a response to meditation would be difficult to conduct because they would need much larger sample sizes than are usual in meditation research. Another issue with the current studies on meditation is that conclusions are limited due to low comparability among studies, as they explore different types of meditation and measure different outcomes. To start working towards a remedy for this problem, we again invite researchers to use a common theoretical framework. Such a framework would reduce variability in measured primary outcomes and could be used to categorise different types of meditation into focused attention and open monitoring. For instance, a recent theory of mindfulness postulates that the central outcome of mindfulness is improved self-regulation, which consists of three components: attention, emotion regulation and self-awareness (Tang, Hölzel & Posner, 2015). All other commonly reported beneficial outcomes, such as stress reduction, are considered to be a consequence of improved self-regulation (Tang, Hölzel & Posner, 2015). Employing a theoretical approach would increase comparability between meditation studies and lay ground for a more precise meta-analysis.

5.2. Conclusions

In summary, this thesis addressed several gaps in the research of MBIs. It elucidated gene expression changes 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. Generally, all examined MBIs show an anti-inflammatory gene expression pattern, which is the opposite of chronic stress. Further studies are necessary to replicate this finding and to examine if similar pattern appears after other behavioural interventions. Furthermore, a study from this thesis was the first to examine the effects of mindfulness interventions on personality disorders other than borderline, and the first to examine the effects of yoga on any personality disorder. In comparison with a wait-list control group, no significant effects of mindfulness or yoga were found on prisoners with various personality disorders in any of the applied measures: EEG connectivity, power, ERPs, attention, risk-taking, perceived stress, emotion regulation, mindfulness or inflammatory gene expression. The final gap that was addressed was related to the lack of understanding of baseline participant characteristics that influence the response to meditation. Findings from previous studies that examined this question were synthesised across four categories: personality and other psychological variables, biological variables, illness severity in patients, and demographic factors, which lays ground for a comprehensive meta-analysis of individual differences in responsiveness to meditation.

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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 infomation 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

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. Perceived Stress Scale

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Appendix 3. Difficulties in Emotion Regulation

Appendix 4. Mindful Attention Awareness Scale

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