Contemplative Psychopharmacology: Exploring the intersection of mindfulness and pharmacologically-assisted change

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Declaration

I, Emily Thomas, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicted in the thesis.

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Impact Statement

The first empirical chapters demonstrate how the mindful state may be acutely enhanced, within the context of a one-time drug-assisted protocol. The results from the first experiment and the protocol for the second study provide a foundation for future research which may seek to combine single-session mindfulness and pharmacological substances in a well-controlled methodologically sound protocol. After replication of the initial study's results, there may also be implications for novel models of treatment, which may for example, combine a single-session of pharmacologically-assisted mindfulness with subsequent repeated sessions of behavioural treatment. Considering that a single administration of modafinil demonstrated the potential to enhance sustained attention whilst bolstering the effects of behavioural strategies on state mindfulness (and subsequent engagement in self-practice), this combined contemplative-pharmacological approach may be particularly beneficial in patients with attentional, anxiety, or affect-related difficulties. Pertinently, if a single-session of 'assisted' mindfulness was capable of helping patients engage with, and maintain practice during a subsequent mindfulness intervention, this may provide a valuable opportunity for treatment that can be mostly self-managed (i.e. with self-practice of strategies), very minimal on side-effects, less expensive (for the health system), and more empowering for the patient than the submission to daily meditation that is often standard of care. On a larger scale, what this novel therapeutic approach speaks to is an enhanced accessibility of mindfulness-based approaches, such that those who may naturally score lower on dispositional mindfulness have a more equal opportunity to access the mindful state.

Reports of psychedelics providing a good mental context for meditations, and suggested utility of meditation practices to enhance or navigate psychedelic experiences might inspire future experimental research, which may seek to explore which psychedelics are the best adjuncts to specific meditation practices. The design of future interventions may benefit from such patterns of anecdotes, paired with the small but fast-growing pool of literature indicating useful, or synergistic effects of psychedelics and meditation. One particular application may be to provide psychedelic-assisted meditation retreats for patients with specific emotional afflictions. For example, considering the proposed synergies between the mindful and psychedelic state, patients with high levels of avoidance or low motivation may benefit from such combined programs. The evidence of meditation proving as a buffer for distressing experiences or as a general navigational tool during a psychedelic trip may inspire harm-reduction approaches that could educate and/or train young persons in certain contemplative practices that may be useful in these scenarios.

In summary, these findings help affirm the bridging of contemplative and psychopharmacology research fields, with potential implications across research, clinical, and potentially societal levels.

ABSTRACT

Background

Mindfulness protocols, though beneficial for a range of indications, often involve long-term commitment and may not be accessible for those naturally low in trait mindfulness (e.g. attention-/ anxiety-related disorders). It remains unclear which 'dose' of mindfulness is necessary to produce beneficial effects, and broadly, how drugs such as nootropics and psychedelics may interact with mindfulness meditation.

Aims

The aims of this thesis are (1) to explore what dose of mindfulness is necessary to enhance state mindfulness (among other outcomes) and whether a drug can modulate, or add to the effects of a mindfulness strategy, (2) to explore how psychedelics may affect a meditation experience, and (3) to examine what role changes in mindfulness play in regards to beneficial psychological health outcomes shown after ceremonial psychedelic use.

Methods

A mixture of methodologies were applied to answer the above questions. Specifically, single-session mindfulness literature was systematically reviewed, and a double-placebo controlled study was designed and conducted to explore the potential for pharmacological enhancement of a single mindfulness strategy. A thematic analysis was conducted to explore user accounts of combined psychedelic and meditation experiences. Finally, linear multi-level models and longitudinal mediation models were used to explore the associations between changes in mindfulness capacity and psychological health over the course of a naturalistic ayahuasca study.

Results

Single-session mindfulness studies are capable of producing a variety of beneficial effects, and adjunctive modafinil appears to enhance some effects of behavioural strategies as well as participant engagement in subsequent practice. Psychedelics may also prove to be useful counterparts to meditations, and conversely, while psychedelics appear to enhance mindfulness, meditation practice can assist also in the navigation of, and potentially enhance effects of the psychedelic process.

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Glossary and Abbreviations

ACT	Acceptance and commitment therapy
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
BCT	Breath-counting task
CORE-OM	Clinical outcomes routine evaluation – outcome measure
DASS	Depression anxiety stress scale
DMN	Default mode network
DMT	N,N-Dimethyltryptamine
FFMQ	Five facet mindfulness questionnaire
HRV	Heart rate variability
KIMS	Kentucky inventory of mindfulness skills
LSD	Lysergic acid diethylamide
MAAS	Mindful attention awareness scale
MBCT	Mindfulness-based cognitive therapy
MBI	Mindfulness-based intervention
MBRP	Mindfulness-based relapse prevention
MBSR	Mindfulness-based stress reduction
MDMA	3,4-Methylenedioxymethamphetamine
PANAS	Positive and negative affect schedule
PCC	Posterior cingulate cortex
PEQ-2	Patient experience questionnaire
PFC	Prefrontal cortex
PTSD	Post-traumatic stress disorder
PVT	Psychomotor vigilance task
SMS	State mindfulness scale
TMS	Toronto mindfulness scale

Chapter 1

General Introduction

1. 1. Mindfulness Meditation: from Origins to Current Understanding

The "capacity" for mindfulness - or smriti in Sanskrit - is developed using a range of meditation techniques, rooted within Buddhist traditions (Hanh, 1976), which has occupied a central role in a system developed as a path leading to the cessation of personal suffering, for the past ~2500 years (Silananda, 1990; Thera, 1962). Mindfulness practices spread to the west with the travel of American spiritual seekers to and from India, Tibet and neighbouring countries, bringing contemplative practices to the West. Mindfulness meditation was introduced into psychological and clinical literature by studies of Jon Kabat-Zinn's original formulation into Mindfulness-Based Stress Reduction (MBSR, Kabat-Zinn et al., 1992). Since then, mindfulness and core elements of the practice have become central elements of a multitude of therapeutic approaches.

1.1.1 Defining Mindfulness

Since mindfulness emerged as an area of study, it has been closely related to clinical application and psychological research (Brown & Ryan, 2003). For example, Kabat-Zinn's frequently cited definition of mindfulness as 'intentional, non-judgmental awareness' is particularly relevant to the way in which mindfulness is applied in MBSR programs. More broadly, mindfulness is suggested to be 'an inherent capacity of mind' (e.g. Goldstein, 2002). Bishop and colleagues (2004) propose a definition of mindfulness which integrates both traditional Buddhist and contemporary definitions. This model has two components, namely: a) the self-regulation of attention (to preserve direction towards the present moment/experience), and b) assuming an orientation of curiosity, openness and acceptance towards such present experiences.

Neuroscientific investigations have aided in refining these definitions using brain imaging techniques to distinguish between various families of meditation techniques. In this context, mindfulness meditation is one of many different forms of meditation, which encompasses focused attention and open monitoring approaches (Lutz, Slagter, Dunne, & Davidson, 2008). Focused attention meditation involves directing attention to a specific object, such as the breath, a body part, or a sensation, with gentle reminders to go back to the object of attention when the mind wanders away from it. This style is most commonly learned first by novices as a way of stabilizing attention. Open monitoring forms of meditation become possible once the practitioner is able to reliably focus attention (and refocus attention after mind wandering). Open monitoring involves holding an open and curious stance to the content of the mind, without focusing on any specific stimuli, rather maintaining a state of mind, whereby new thoughts, feelings and bodily sensations can come and go without attachment to them.

Mindfulness can also be seen as a skill, which, once learned may be cultivated in many different scenarios. In this state, thoughts and emotions can be experienced in the same way as elements of the sensory experience, importantly, without responding to them in reflexive or impulsive ways (Bishop et al., 2004). This may explain the multitude of potential applications within which the practice can be of use.

1.1.2 Elements of Mindfulness

State Mindfulness. State mindfulness refers to the 'moment to moment awareness', purposeful attention, or 'skill', and is susceptible to enhancement via short-term practice (E.g.: Mahmood, Hopthrow, & Randsley de Moura, 2016). High levels of state mindfulness are associated with more pleasant affective states, less negative emotional states, and higher levels of autonomy (Brown & Ryan, 2003). Those with a greater ability to practice moment

to moment awareness also demonstrate a lower frequency of mind wandering, and a superior capacity to sustain attention (Levinson, Stoll, Kindy, Merry, & Davidson, 2014). State mindfulness has also been shown to be correlated with a greater capacity for self-regulated behaviour, and superior communication quality in a stressful context (Barnes, Brown, Krusemark, Campbell, & Rogge, 2007; Brown & Ryan, 2003).

Trait Mindfulness. Dispositional, or trait mindfulness refers to the 'innate' ability to be mindful throughout daily activities (K. W. Brown & Ryan, 2003). This capacity is believed to be more or less stable over time, though it may be entrained by long-term training or significant drug-induced states (Khoury et al., 2013; Smigielski, Scheidegger, Kometer, & Vollenweider, 2019). Trait mindfulness is associated with various elements of general and emotional well-being, such as: positive affectivity, life satisfaction, self-esteem, optimism, and self-actualisation (K. W. Brown & Ryan, 2003). Higher levels of self-regulated behaviour are found in those high greater levels of trait mindfulness, alongside lower levels of neuroticism, anxiety, and depression (K. W. Brown & Ryan, 2003). Those with greater dispositional mindfulness appear to have superior physical health, heart-rate variability, as well as better social functioning, including relationship satisfaction (Barnes et al., 2007; Bodenlos, Wells, Noonan, & Mayrsohn, 2015; K. W. Brown & Ryan, 2003; Burg & Wolf, 2012). There is also evidence of enhanced effects of MBSR programs in those that are high in trait mindfulness (Keng, Smoski, & Robins, 2011).

Conversely, for those with lower levels of dispositional mindfulness, it appears to be more difficult to regulate aspects of attention and emotion. Indeed, attentional deficit hyperactivity disorder (ADHD) and anxiety symptomology are negatively associated with trait mindfulness (Smalley et al., 2005; Yavuz, Yavuz, & Onal, 2018), paradoxically,

suggesting that those who may benefit from the benefits of mindfulness practice the most, are likely to find it most difficult to engage in them, and reap the rewards of the practice.

1. 2. Measuring Mindfulness

1.2.1 Self-Report Measures

State Measures. Key self-report questionnaires measuring state mindfulness include the state Mindful Attention Awareness Scale (State-MAAS), Toronto Mindfulness Scale (TMS), and State Mindfulness Scale (SMS). The state MAAS (K. W. Brown & Ryan, 2003) is a five-item scale which was adapted from the trait mindfulness (MAAS) measure, designed to quantify recent and present manifestations of mindful attention and awareness in day-to-day activities. This measure was designed to measure attentiveness in respect to daily activities, which, though informative does not pick up the 'meta-awareness' element of mindfulness which is key in some definitions of mindfulness (E.g.: Bishop et al., 2004). Relatedly, the state MAAS was not designed to measure mindfulness during the practice itself, or in reference to the practice.

The TMS (Lau et al., 2006) is a 13-item questionnaire, which measures mindful attention across two factors: curiosity and decentering. The TMS does measure curiosity and decentering in relation to thoughts and emotions, however does not include any questions referring to one's physical (or sensory) experience. Though items relating to curiosity likely reflect non-judgmental awareness, it may provide a narrow take on mindful awareness as a whole. Additionally, decentering is generally considered an outcome rather than a as key aspect of mindfulness, and has demonstrated only marginally adequate internal consistency (Erisman & Roemer, 2010).

The state mindfulness scale (Tanay & Bernstein, 2013) is a 21-item measure, with a subscale assessing mindfulness 'of mind', and one referencing mindfulness 'of body'. The

SMS aims to measure a quality of mind that is more consistent with Buddhist scholarship (Anālayo, 2013; Bodhi, 1993), and the definition of mindfulness formulated by Bishop and colleagues (2004), which was informed by both traditional roots and preceding mindfulness research. As such, the scale was developed with items probing "what" participants attention is focusing on, and "how" the attention is being held (for example, with deliberate attention to the present moment, and/or with curiosity). The items can be scored in relation to mindfulness practice, and the scale has revealed high internal consistency.

Trait Measures. Of the many validated measures of trait, or dispositional mindfulness, the Five Factor Mindfulness Questionnaire (FFMQ) is undoubtedly the most commonly employed (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). The FFMQ conceptualises mindfulness as a multifaceted construct, with questionnaires relating to each of five facets: observing, describing, acting with awareness, non-judging (of inner experience), or non-reactivity (of inner experience). The Kentucky Inventory of Mindfulness Skills (KIMS) is an alternative measure, which taps four of five of the FFMQ facets (Baer, Smith, & Allen, 2004). The original (trait-level) Mindful Attention Awareness Scale (MAAS, Brown & Ryan, 2003) is a unidimensional instrument, whereby respondents rate how often they have had experiences that involve automatic responding, being unaware of the present moment, or being 'mindless'. The Freiburg Mindfulness Inventory (FMI; Walach, Buchheld, Buttenmüller, Kleinknecht, & Schmidt, 2006) is another unidimensional tool, which was designed with the specific purpose of discriminating between novice and experienced meditators.

1. 3. Behavioural Approaches

1.3.1 Mind-Wandering

One construct which may be particularly interesting in terms of behavioural approaches to measuring mindfulness (or a lack thereof), is mind-wandering. It has been proposed as an *opposing construct* to mindfulness, since it is negatively correlated with dispositional mindfulness and can be reduced by mindful breathing (Mrazek, Smallwood, & Schooler, 2012). Mind-wandering is measured indirectly during a dual task, such that participants engage in a mindfulness exercise, and are probed at random intervals as to how 'on-task' their mind was at the time. Participants can also indicate themselves by pressing a particular button when their mind wandered from the mindfulness task. Mind-wandering is associated with negative mood and is a central feature of ADHD symptomology (Poerio, Totterdell, & Miles, 2013; Seli, Smallwood, Cheyne, & Smilek, 2015).

1.3.2 Breath-Based Behavioural Measures

The mindful breathing exercise (Burg & Michalak, 2011) is a behavioural measure of mindfulness, which has significant similarities with the mind-wandering task summarised above, insofar as it involves probing participants at random intervals to understand whether they were on- or off-task (having been instructed to mindfully observe and sense their breath), and provides an opportunity for self-catching instances of off-task thought between probes. Scores on this exercise are also positively associated with self-report mindfulness, and negatively correlated with rumination, negative thinking, and depression. As per the mind-wandering task and other self-report measures of mindfulness, this measure relies on the capacity and willingness of participants to honestly and accurately report internal experiences.

The breath counting task (BCT) is another breath-based behavioural measure of mindfulness, this time requiring participants to focus on counting of breaths during a mindful breathing exercise. This task involves subjects counting their breaths from one to nine (each in-out breath is a count of one) repetitively and indicating when they have reached a count of nine. Simultaneously, a respiration monitor records their breaths. In this way, breath counting accuracy can be verified, and therefore the BCT has been proposed as an 'objective' measure of mindfulness (Levinson et al., 2014). BCT accuracy is correlated with self-report mindfulness, it has sound convergent validity, differentiating between experienced and novice practitioners and has good discriminant validity, being distinct from attention and memory measures (Levinson et al., 2014). Accuracy of breath counting correlates with meta-awareness, less mind-wandering, better mood, and greater non-attachment (Levinson et al., 2014). A particular benefit of this approach is that it can be used simultaneously as a mindfulness training method and measure of mindfulness. Additionally, unlike many other measurement approaches, there is no need to interrupt the training strategy to obtain the measurement of mindful awareness.

1.3.3. Physiological Approaches

Blood Pressure (BP) is a physiological marker of stress (Pascoe, Thompson, Jenkins, & Ski, 2017), which is can be lowered by mindfulness meditation (Cernuda Martinez & Fernandez Garcia, 2021). Though it is a useful measure of exertion of the central nervous system, it is a rather crude physiological measure, which fluctuates based on factors such as physical exertion, temperature, pain or stress.

Heart rate variability (HRV), on the other hand, is considered a physiological correlate of physical *and* psychological health (Hovland et al., 2012; Stys & Stys, 1998). Measures of HRV are believed to reflect the 'integration of heart rate (HR), emotional state,

as well as higher-level cognitions required for flexible and goal-directed behaviour (Hovland et al., 2012). High levels of HRV are seen to reflect an autonomic nervous system that is flexibly capable of producing the necessary states of physiological arousal associated with emotions (Appelhans & Luecken, 2006). Relatedly, HRV has also been proposed as a biomarker for a mindful state (Krygier et al., 2013).

1. 4. The Benefits of Mindfulness Meditation

Original investigations into the therapeutic potential of mindfulness were derived from Mindfulness-based stress reduction (MBSR), group programs spanning 8-10 weeks, involving weekly 2-2.5 hour mindfulness meditation sessions, a full day of meditation, accompanied by yoga and mindfulness-related education (Kabat-Zinn, 2003). This system was originally created to combat illness-related stress, but alongside increasingly varied applications, inspired the creation of a number of 'third-wave' therapeutic approaches that hold mindfulness as a central element, such as mindfulness-based cognitive therapy (MBCT; Segal, Williams, & Teasdale, 2002), mindfulness-based relapse prevention (MBRP, Bowen et al., 2009), acceptance and commitment therapy (ACT; Hayes, Boyd, & Sewell, 2011), and dialectical behaviour therapy (DBT; Linehan, 1993).

Recent meta-analyses indicate that Mindfulness-based interventions (MBIs) appear to be helpful to combat symptomology and related clinical outcomes of psychiatric disorders – namely: anxiety, depression, pain-related conditions, and substance use disorders (Goldberg et al., 2018; Khoury et al., 2013). Though they have a wide range of potential applications, MBIs are not significantly more efficacious than evidence based treatments such as cognitive behavioural therapy (CBT), standard behavioural or pharmacotherapies (Goldberg et al., 2018; Khoury et al., 2013). Additionally, the commitment required from both participant and

facilitator is substantial, potentially creating barriers to mindfulness-based treatment (Crane & Kuyken, 2013; Lomas, Cartwright, Edginton, & Ridge, 2015).

Experimental trials have probed the processes underlying these salutary effects, whilst exploring which 'dosage' of mindfulness is necessary for beneficial effects to be demonstrated, with aims of improving accessibility and efficacy. For example, 'brief' mindfulness-based interventions have been tested that last as little as 5 minutes per session to a maximum of 30 minutes per session, with as many as 4 sessions in total. Howarth and colleagues (2019) systematically reviewed the effects of such interventions on health outcomes in general, including both clinical and non-clinical samples, finding that 93% elicited positive effects on at least one measure, despite mixed results across different indices. Significant positive findings were revealed in participants with borderline personality disorder, anxiety disorders, and depressive disorders. Though 87% of such studies were run as a single session, a range of methodological approaches, settings and outcome measures were used, thus it remains unclear how many sessions are necessary for affective, cognitive and physiological benefits within controlled contexts.

1. 5. The Neuroscience of Mindfulness Meditation

Meta-analyses of neuroimaging studies indicate that mindfulness meditation (including focused attention and open monitoring techniques), was associated with increased activation of multiple areas in the pre-motor cortex, prefrontal cortex, anterior cingulate cortex (ACC), and insula (Fox et al., 2016; Tang, Hölzel, & Posner, 2015). Clusters of deactivation were found in key areas the default mode network (DMN) such as the posterior cingulate cortex (PCC) and inferior parietal lobule (IPL): two areas suggested to play key roles in mind-wandering (Fox et al., 2016).

Changes in functional connectivity have also been shown as a result of mindfulness meditation. Specifically, experienced practitioners demonstrate stronger coupling between PCC, dorsal ACC and dorsolateral PFC, which may suggest increased cognitive control over the function of the DMN (Brewer et al., 2011). Experienced meditators also show increased connectivity between DMN regions and ventromedial PFC, which may be interpreted as default circuitry having better 'access' to internal states (Tang et al., 2015).

Areas of the brain affected by mindfulness practice show some commonalities with areas of the brain which are affected by stimulants that are used to enhance attention, and promote vigilance, such as modafinil. For example, in rats, administration of modafinil increases activation in the ACC, and enhances extracellular dopamine in the PFC (for a review on animal and human studies, see Minzenberg & Carter, 2008).

Changes in activation of, and connectivity relating to the DMN are also commonly highlighted in investigations into other altered states of consciousness, such as the psychedelic state. For example, activity in the DMN has been shown to relate to introversion of attention, experiences of unity, transcendence of normal time and space perception, and show greater functional connectivity with networks (such as the dorsolateral PFC) that support internally directed attention (Barrett & Griffiths, 2017). Thus, there appears to be some overlap between the neurobiological changes associated with mindfulness practice and those associated with hallucinogen consumption.

1. 6. Introduction to Nootropics/ Psychedelics

Psychopharmacology seeks to implement pharmacological tools in novel ways, such as to combat mental health afflictions, reduce harm from recreational drugs, and improve quality of wellbeing (E.g.: Andersen, Carhart-Harris, Nutt, & Erritzoe, 2021; Morgan, McAndrew, Stevens, Nutt, & Lawn, 2017; Schenberg, 2018). For example, some stimulant

drugs are considered to enhance certain domains of attention, and are prescribed to aid attentional difficulties or afflictions associated with excessive sleepiness (Becker, Schwartz, Feldman, & Hughes, 2004; Nair & Moss, 2009). The rise in non-medical consumption of nootropics, inspired by attempts to leverage enhanced concentration capacities was followed by research efforts to validate claims about their enhancing effects. Though there is a lack of compelling evidence that such compounds enhance general cognitive abilities per se, they do appear to temporarily bolster elements of attention, such as focused attention (Maddalena Mereu, Antonello Bonci, Amy Hauck Newman, 2008; McLennan Battleday, 2015). Recent experimental trials have also shown promise for modafinil assisting in various mental health problems such as cocaine use disorder (Kampman et al., 2015).

Meanwhile, promising developments in recent psychopharmacological research have involved testing the efficacy of psychedelic compounds in various psychiatric disorders (e.g. treatment-resistant depression, anxiety) (Carhart-Harris et al., 2016; de Osório et al., 2015). Classic psychedelics are natural or synthetic drugs which primarily act on the serotonin system, and are known for their consciousness-altering effects, often accompanied by visual hallucinations and enhanced sensory experience. Examples include psilocybin, lysergic acid, and dimethyltryptamine (DMT). Such substances in their natural product forms – specifically decoctions of psilocybin mushrooms or ayahuasca (which contains DMT) are used traditionally for healing and ceremonial purposes, with modern-day use (outside of traditional ritual settings) motivated by a desire from users for spiritual and affective enhancement as well as clinical researchers' interests in their therapeutic potential in the treatment of psychiatric disorders. Also of note are substances such as MDMA and ketamine, which, despite different mechanisms of action, have psychedelic-like effects. These compounds also demonstrate potential for therapeutic application due to their empathogenic

and dissociative effects, respectively. For example, experimental trails indicate that MDMA may enhance the effects of self-compassion practice (Kamboj et al., 2018), and in a psychotherapeutic setting, has passed preliminary trials for safe and effective treatment of post-traumatic stress disorder (PTSD) (Mithoefer et al., 2018). Experimental trials have also provided preliminary evidence that ketamine may help treat harmful drinking behaviours (Das et al., 2019).

The resurgence in psychedelic research has built momentum at a time where novel approaches to mental health are critical. Particularly interesting are the approaches, such as mindfulness-based and psychedelic-assisted that attempt to treat causes of psychopathologies rather than symptoms, to create improvements that last longer than the acute effects of either modality. A number of researchers have noted the potential for synergy through the combination of these two methods of attaining altered states of consciousness (Eleftheriou & Thomas, 2021; Heuschkel & Kuypers, 2020; Payne, Chambers, & Liknaitzky, 2021). These two approaches work on different timescales, particularly in terms of duration of 'treatment' required before beneficial effects are seen. In addition, meditation practices are associated with general, lasting improvements in wellbeing, and mental health indices (S. L. Brown, Hughes, Campbell, & Cherry, 2020; Goldberg et al., 2018). Considering there are relatively few (controlled) studies examining the long-term effects of psychedelics, it is less clear how long positive effects last from psychedelic use, though there is evidence of sustained positive subjective effects on adaptive aspects of personality (see Griffiths, Richards, McCann, & Jesse, 2006). Correlational studies also indicate that recreational use of psychedelics is associated with lower levels of aggression, recidivism, and higher levels of engagement with nature, potentially suggesting they may have long-term beneficial effects (Gandy, 2019;

Hendricks, Clark, Johnson, Fontaine, & Cropsey, 2014; Tomlinson, Brown, & Hoaken, 2016).

1. 7. Evidence of Combinations to Date

Experimental evidence of combined contemplative and pharmacological approaches are limited to date. However, in a retreat setting, psilocybin has been administered to expert Zen meditators during a 5-day retreat, with greater beneficial effects relative to those who received placebo during the retreat (Smigielski et al., 2019). Specifically, psilocybin appeared to increase the depth and quality of the meditation experience, with neuroimaging data revealing specific changes in functional connectivity in the DMN that were related to self-referential processing. A decoupling between the prefrontal and posterior cingulate cortices was associated with the experience of ego dissolution, the extent of which predicted the magnitude of change in mood, attitudes, social and behavioural improvements at four-month follow-up.

In another study, psilocybin has been combined with different levels of 'spiritual support' (which included a mindfulness meditation component). Griffiths and colleagues (2018) found that those receiving spiritual support alongside the psychedelic had significantly more acute and enduring benefits in terms of affect, attitudes, and meaning in life at six-month follow-up. Observational studies have demonstrated that compassion-based meditation may be enhanced after consumption of MDMA, pointing to a potentially synergistic effect (Kamboj et al., 2018). Recent investigations have also demonstrated increases in mindfulness capacities after ayahuasca consumption, alongside evidence of neuroplastic changes associated with such enhancements (Sampedro et al., 2017; Soler et al., 2018, 2016). Maintaining the perspective of pharmacological enhancement to contemplative ability, it is unclear whether other drug types (i.e. non-psychedelics) may assist mindfulness

practice in a laboratory setting, and relatedly, which drugs may be suitable adjuncts to short-term mindfulness practice.

1. 8. Rationale for Thesis and Research Questions

The primary research question inspiring the present collection of work relates to how (mindfulness) meditation and pharmacological substances interact. This is explored using a multi-method approach, focusing on a) whether the effects of a brief mindfulness training can be pharmacologically modified (enhanced) and (b) the nature of the interaction between psychedelic drugs and contemplative practice/ ability. This thesis synthesises evidence from interdisciplinary methods including experimental psychopharmacology, qualitative research methods, and naturalistic study of the association between psychedelics and meditation practice/ mindfulness. As a prelude, the next chapter (chapter two) systematically reviews single-session mindfulness studies, exploring how they can alter state mindfulness, cognition, behaviour and affect. This is of special relevance to the current thesis because progress in identifying synergies between pharmacological treatments and meditation practices will partly depend on well-controlled studies of specific meditation techniques (in this case, mindfulness) that can be examined in well controlled experiments with limited 'contamination' from the multiple non-specific elements of more complex interventions. Subsequent chapters will examine specific empirical questions:

RQ1: *What are the effects of a single-session of mindfulness, combined with an attention-enhancing drug (on state mindfulness, attention and physiology) in novice participants?*

The first empirical study (Chapter three) investigates this question from a mechanistic perspective, probing whether modafinil may be a useful pharmacological target to assist first-time assisted mindfulness practice. The fourth chapter describes a pre-registered protocol for

a second empirical study that was initiated to extend the results from the first empirical study, with the aim of demonstrating increases in state mindfulness after a single session of a mindfulness task (breath counting). This study was interrupted due to the COVID-19 pandemic.

RQ2: *What are the effects of combining psychedelics and meditation?*

Chapter five explores experiences of recreational psychedelic users who have meditated under the influence of a psychedelic drug using the qualitative approach of thematic analysis.

RQ3: *Do increases in mindfulness predict or mediate the effect of ceremonial ayahuasca on psychological health and well-being?*

The final empirical chapter explores how changes in mindfulness may relate to changes in mental health and psychological well-being demonstrated after the consumption of ayahuasca in a ceremonial context. Chapter seven concludes with a discussion of key methodological issues in mindfulness research, the potential for pharmacologically-assisted mindfulness, effects of psychedelics on mindfulness capacities, and what the next steps may be in terms of pairing contemplative and pharmacological approaches, in empirically and applied contexts.

Chapter 2

States of Mindfulness: A Systematic Review Exploring Experimental Mindfulness Inductions

Key Points:

- Here, I aimed to provide an overview of single session experimental mindfulness studies, the control conditions used to highlight changes in mindfulness, and critically evaluate methodological aspects of such studies, with a primary focus on state mindfulness outcomes.
- A total of 39 studies which involved strategies between four to 60 minutes were systematically reviewed.
- Most studies demonstrated enhancements in mindfulness, alongside indications of improved adaptive affect, behaviour and cognition. Physiological results were sparse and inconclusive.
- Methodological limitations remain a critical issue in mindfulness literature, which single-session studies also fall prey to. Suggestions for future experimental research design are made.

2.1 Introduction

As the scientific exploration of mindfulness meditation continues, an increasing number of studies are published exploring its various psychological effects (Creswell, 2017). Mindfulness has been described as a concept, construct, and a process, which can be defined in a multitude of ways depending on application. Brown and Ryan (2003) define mindfulness as a receptive attention to and awareness of present events and experience. Mindfulness has been explored using a wide range of approaches, amongst increasingly varied time-frames, with many different types of behavioural comparators (Leyland, Rowse, & Emerson, 2019). As such, it is difficult to build a 'big picture', and despite informative critical commentaries

on methodologies used in mindfulness research (e.g. Davidson & Kaszniak, 2015; Van Dam et al., 2018), the research field demonstrates no particular ideal template for future experimental research.

Much focus of the past decade's research in the field has focused on the clinical application of mindfulness techniques, demonstrating potential for Mindfulness-Based Interventions (MBIs) to improve a variety of psychological (and physical) health indices (Howarth, Smith, Perkins-Porras, & Ussher, 2019; Keng et al., 2011; Khoury et al., 2013). MBIs however, often last between 6-8 weeks in duration, and involve varied central therapeutic aims and approaches. For example, Mindfulness-Based Stress Reduction (MBSR) focuses on cultivating mindfulness through close attention to present-moment experiences and events, whereas Acceptance and Commitment Therapy (ACT, Hayes et al., 2011) aims primarily to improve one's capacity to be more fully aware of one's present behaviour and values, and committing to acting in accordance with those. It is understandable, therefore, that these programmes do not exemplify the specific effects of the mindfulness strategy alone. Additionally, many randomised controlled trials (RCTs) investigating the effects of these interventions use wait-list control designs, which do not necessarily represent an accurate 'no treatment' group, since patients may halt efforts to get better whilst awaiting the planned treatment, thus accentuating treatment effects (Mohr et al., 2009).

Long-term mindfulness data predominantly only maps onto trait effects of the practice. For example, trait mindfulness has been associated with higher levels of positive affect, higher life satisfaction, greater capacity for emotion regulation, and higher levels of self-control (Baer et al., 2004; K. W. Brown & Ryan, 2003; Lakey, Campbell, Brown, & Goodie, 2007). In a similar vein, trait mindfulness has been inversely related to emotional

disturbance, negative affect, and markers of psychopathology such as dissociation and neuroticism (Baer, 2003; K. W. Brown & Ryan, 2003). Generally, mindfulness seems to encourage more flexible, adaptive responses to events, and aids in reducing reactions of the automatic or habitual nature. These studies present a promising case for a range of MBIs, however due to the long-term nature of the mindfulness interventions investigated in these studies, they cannot teach us about more isolated, specific changes that occur on a psychological or neurobiological level.

Experimental (i.e. non-clinical) mindfulness studies have sought to remedy this isolation of specific strategy effects by comparing mindfulness practice to (ideally active) control conditions. For example, 'brief' mindfulness based interventions (lasting a up to 30 minutes per session, up to a total of 100 minutes per week, and up to 4 weeks in total) have been shown to produce enhancements in affect, emotion regulation, and cognitive indices (Howarth et al., 2019). Interventions reviewed averaged 15-mintues in length, and were most commonly completed within the span of one week. Risk of bias assessments do not indicate particularly strong methodological rigor however, with only 3.5% of the 85 included studies scoring 'low' on risk of bias (Howarth et al., 2019), and in studies spanning multiple sessions, confounding variables from outside of the experimental condition may complicate the strength of conclusions drawn from predicted results.

2.1.1 The Mindfulness Induction

Single-session studies (also termed 'mindfulness inductions', as per Leyland et al., 2019) have provided an opportunity to overcome some common methodological weaknesses of mindfulness research. Mindfulness inductions are isolated experiential practices that are used without mindfulness-related theory or education (Leyland et al., 2019). This contrasts to the delivery of MBIs, which also involve activities outside of the formal mindfulness

practice, such as homework practices and group discussions. Divorcing mindfulness practice from the other components of MBI allows for optimal control over the duration of exposure to the intervention, and any control tasks, as well reducing a number of possible confounding variables which may otherwise be introduced in between sessions. Additionally, there remains uncertainty regarding the effects of different 'doses' of mindfulness, which single-session studies may help clarify. For example, in one induction protocol involving two active mindfulness groups of different lengths and one control group, only those in the shorter practice demonstrated significant enhancements in state mindfulness (Bonamo et al., 2015). Exploring single-session studies may be a way to make more clear comparisons between studies and gain an improved understanding of the effects of different lengths of inductions.

A recent review summarised the effects of single-session laboratory studies, with a focus on psychological outcomes (Jiménez, Ramos, González-Moraleda, & Resurrección, 2020). Extending Howarth and colleagues' (2019) findings, it appears that single session mindfulness inductions in a laboratory context are also capable of reducing negative mood, anxiety and distress. In contrast, Jiménez et al., (2020) found inconsistent results in a selection of reviewed studies regards to positive affect, as well as anxiety and some maladaptive attitudes. Surprisingly, only one of 19 studies included aimed to explore the association between state mindfulness and another psychological variable (Pepping et al., 2015).

2.1.2 A State of Mindfulness

The term 'state mindfulness' refers to the moment-to-moment experience of non-judgemental present-moment focus, assessed instantaneously (e.g. using the instruction to evaluate one's mental/physical state 'right now'). Although state and trait mindfulness are associated (Brown & Ryan, 2003), this does not imply that the benefits of mindfulness are

necessarily reserved for those high in trait mindfulness, as mindfulness has also been shown to be useful for participants that are typically lower scoring on trait mindfulness (Nair & Moss, 2009). Curiously, measures of state mindfulness have not been systematically included in experimental mindfulness studies. This limits the scope of conclusions that can be drawn about the effects of mindfulness, if there is no verification that changes in outcome measures are indeed accompanied by changes in state mindfulness. Considering day-to-day ratings of mindfulness are associated with greater wellbeing, higher positive affect and lower negative affect (Brown & Ryan, 2003; Lau et al., 2006), it may be important to explore how ratings of state mindfulness are affected by mindfulness inductions. Over and above verifying the effectiveness of experimental manipulations, state mindfulness scores can provide a detailed report of moment-to-moment processes, the variability of which, trait measures appear incapable of capturing (Enkema, McClain, Bird, Halvorson, & Larimer, 2020). There is preliminary evidence that state mindfulness may mediate training effects on some cognitive processes, or buffer the association between stressors and associated negative mood (Garland et al., 2015; Blanke & Lu, 2018).

2.1.3 Critical Issues Related to Mindfulness as a Construct

Like many articles on the topic, the challenges in adapting mindfulness to an experimental setting begin with its definition (Davidson & Kaszniak, 2015; Van Dam et al., 2018). Though there is a variety of definitions available, key definitions based on traditional and theoretical understanding place a particular emphasis on two elements: attention to the present moment; and the curious, open and accepting (also termed ‘non-judgemental’) approach to one’s experience in that moment (Bishop et al., 2004; Kabat-Zinn, 1994).

2.1.4 The Present Review

The aim of this systematic review was to summarise and critically evaluate the methodological aspects of single session experimental mindfulness studies that examine state mindfulness, among other psychological outcomes. It will also give an overview of behavioural 'interventions' that have been used as comparator conditions to active mindfulness conditions. Considering the plethora of applications of mindfulness interventions across health domains, the results of this review will be useful for experimental mindfulness researchers addressing a range of questions. This review will provide direction and suggestions for improving standards of experimental design in mindfulness research, and a resource which researchers can use to gain an understanding of how best they might design a methodologically rigorous experimental mindfulness study.

2.2 Method

2.2.1 Search Strategy

Searches were conducted using Ovid (covering Medline, PsychInfo and Embase), Scopus, Web of Science, The Cochrane Library, and ClinicalTrials.gov. The search included papers written in English, and published up until the original search in August 2019, and updated in October 2020. Search terms followed the three key search specifications, namely: mindfulness meditation ("mindful*"); brief induction ("induction", "brief", "single", "acute", "short", "one"); and controlled experimental laboratory design ("experiment", "laboratory", "control*", "comparison", "active").

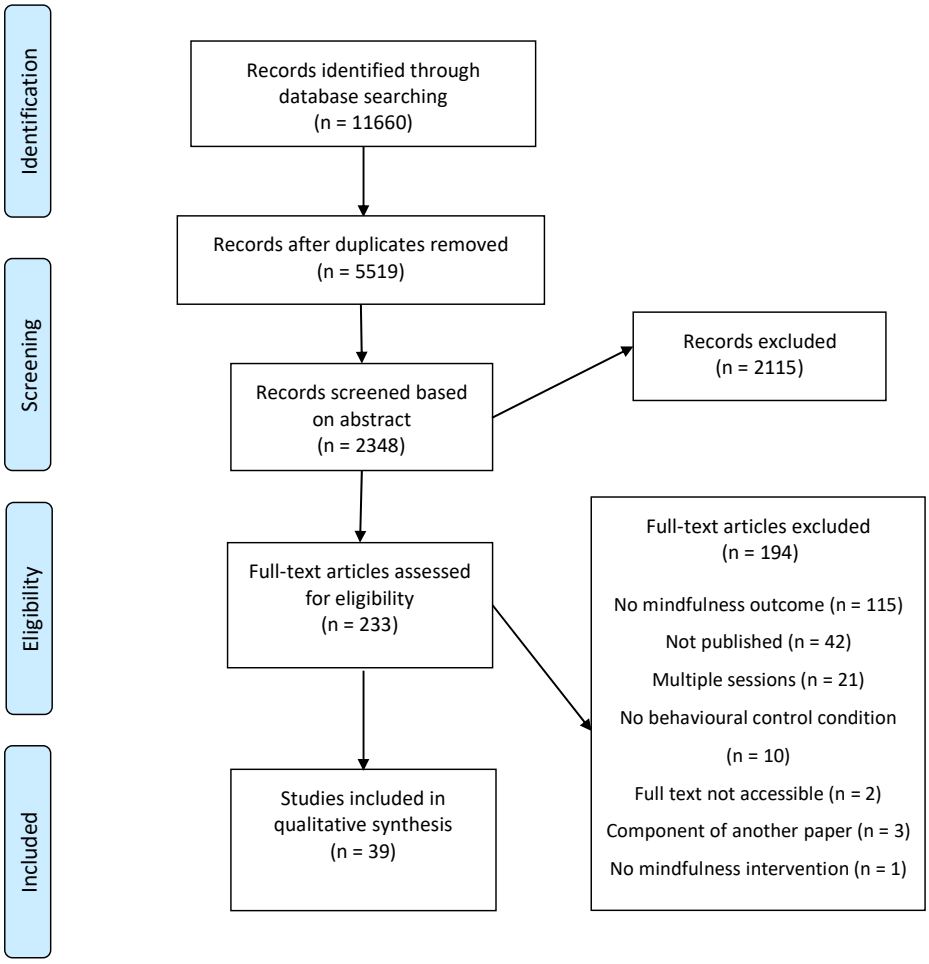
2.3 Study Selection

The search identified 11660 records (see PRISMA flow diagram, Fig. 2.1). After removing duplicates (n = 5519), titles were independently screened for eligibility by two reviewers, and abstracts of those deemed potentially relevant also screened by two reviewers.

Full-texts were obtained of the remaining studies (*n* = 233), and also screened by two reviewers against inclusion and exclusion criteria. Common reasons for exclusion at this stage were: lack of inclusion of a state mindfulness measure, publication in the form of study protocols, the study involving multiple sessions, and absence of a behavioural control condition. A total of 39 studies meeting eligibility criteria were included in the review.

Figure 2.1

PRISMA flow chart illustrating the identification of studies



2.3.1 Eligibility Criteria

Inclusion criteria specified that studies include adult participants (aged 18 years or over) that may or may not fall into clinical populations. Studies must have been published in

English. We sought to explore laboratory studies with randomised designs due to their scientific rigour and maximised ability to control for confounds. Other inclusion criteria specified that the mindfulness strategy be conducted in a single session, and aligned to a commonly cited modern definition of mindfulness (i.e. a receptive attention to and awareness of present events and experience, Brown & Ryan, 2003). Studies were included which had a behavioural control condition to contrast the active (mindfulness) manipulation. A state mindfulness measure must have been included amongst the outcomes.

2.3.2 Quality Appraisal

The Cochrane Handbook was searched for appropriate risk of bias assessments, alongside systematic reviews and journal articles in topical literature, but none were deemed suitable for this review considering its focus on experimental studies rather than clinical, randomised controlled trials. Additionally, studies in mindfulness literature suffer from particular methodological weakness and topic-specific challenges – elements which we found important to assess in this review. Our search for an appropriate tool led to a modification of Cochrane's Risk of Bias version 2 (RoB 2 tool; Higgins et al., 2011) items. We supplemented with questions suggested by Barnes-Holmes and Hayes (2003) to be important design features of acceptance and commitment therapy (ACT) laboratory-based component studies. The latter resulting questions are particularly suitable for evaluating single session mindfulness interventions, considering that some aspects of ACT are derived from mindfulness-based practices. This combination of items resulted in the 13 criteria outlined in Table 2.1.

Risk of bias was assessed by the first reviewer, with 25% of studies independently cross-checked by a second reviewer, and any discrepancies were resolved by a third reviewer. Each study was evaluated based on the relevant RoB 2 items, such that they would

be allocated either high, low, or unclear risk of bias. The results of the assessment can be found in Table 2.4.

Table 2.1

Overview of quality assessment criteria

Item no	Assessment question	Original suggestion/ question	Source
1	Were participants randomly assigned to their condition?	Was the allocation sequence random?	ROB-II
2	Were participants blind to the study aims/hypotheses?	Were participants aware of their assigned intervention/induction during the experiment?	ROB-II
3	Were data for the mindfulness outcome available for the majority (≥90%) of participants?	Were data for the main outcome measure available for all, or nearly all participants?	ROB-II
4	Were outcome assessors blind to participant induction conditions?	Were outcome assessors aware of the intervention received by participants?	ROB-II
5	Were results analysed in line with pre-specified analysis plans?	Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before un-blinded outcome data were available for analysis?	ROB-II
6	Were experimental groups balanced for relevant attribute variables (e.g. gender)	The experimental conditions must balance as much as possible for all relevant attribute variables (e.g., gender, psychopathology, unless the attribute(s) is the target of the analysis)	ACT guidelines
7	Were the experimental conditions balanced in all possible ways (e.g. length, level of engagement, delivery method, etc.)	The different interventions should be balanced in all possible ways, except for the critical difference you are seeking to manipulate (e.g., they should be the same length; they require similar levels of engagement with the material; … method of delivery should be identical; etc.)	ACT guidelines

Item no	Assessment question	Original suggestion/ question	Source
8	Was the matching of conditions checked and approved by independent raters?	The matching of conditions should be checked and supported by independent raters.	ACT guidelines
9	Was the primary outcome analysis informed by a (suitable) power calculation?	If the study is a group design it should be adequately powered to test the key hypotheses, especially if null results are to be meaningful.	ACT guidelines
10	Do participants articulate their understanding of the induction strategy before implementation?	Where possible and appropriate, the procedure should involve requiring participants to articulate in their own words the intervention strategy that is being provided.	ACT guidelines
11	Is the majority of the procedure automated, e.g. induction/intervention presented via audio, tasks automated	Ideally, the entire procedure, including pre-intervention baseline, intervention, and post-intervention tasks should be automated.	ACT guidelines
12	Was credibility/expectancy of intervention/induction measured?	Other questions of relevance should also be asked that might alter the interpretation of results… For example the participant might be asked to rate the likability or believability of the experimenter…	ACT guidelines
13	Was a suitable manipulation check performed to assess the application of the induction/strategy?	Ideally, some form of standardized self-report or other instrument should be developed to measure the extent to which participants understand and apply specific strategies	ACT guidelines

2.3.3 Outcome Measures

Split into four key areas:

I. State mindfulness outcomes

II. Affective outcomes

III. Behavioural outcomes

IV. Physiological outcomes

2.3.4 Data Extraction

For each study, the following data was extracted: Author(s), year of publication, sample size, mean age, gender of participants, sample size of active mindfulness group, study design, timing of mindfulness outcome, main manipulation/induction component(s), induction duration, type of control task, manipulation check, and induction effect on state mindfulness. A secondary extraction pulled the following measures: which affect measure was used, the effects of the induction on affect, any behavioural measures used, the induction effect on behaviour, any physiological measures used, and the effects of the induction on physiology.

2.4 Results

2.4.1 Methodological Overview of Studies

See Table 2.2 for an overview of study characteristics.

Table 2.2

Overview of study characteristics

Author (year)	*N (MM group)*	Mean age (% female)	Timing of MM measurement	Main manipulation/induction component(s)					Induction duration (min.)	Type of control condition	State mindfulness measure	Induction effect on state mindfulness
				Focus attn.	Mindful eating	Aware present moment	Aware breath/ body	Aware thoughts/ emotions				
Bravo et al. (2018)	299 (151)	20.84 (79.9)	Post	x			X		8	Neutral educational info	SMS	MM group sig higher on body SMS subscale compared to control
Cleirigh & Greaney (2015)	34 (18)	21.69 (35.2)	Post	x			X	X	10	Neutral educational information	TMS	Sig. higher TMS decentering in MM group compared to control
Donald & Atkins (2016)	204 (69)	21 (71)	Post		X			X	15	(1) Relaxation (2) Filler task	4-item adapted scale	Sig. higher scores in MM group compared to filler task, but not relaxation.
Eddy et al. (2015)	24 (24)	20.4 (45.8)	Post	x		X	X		15	Mind wandering	TMS	No sig. between-group difference on TMS scores
Erisman & Roemer (2010)	30 (15)	24.10 (50)	Post	x			X	X	10	Neutral educational information	TMS	Sig. higher TMS-decentering subscale in MM group compared to control
Fernando et al. (2017)	83 (nr)	21.41 (54.2)	Post	x			X	X	10	Neutral information	TMS	Sig. higher decentering in MM condition
Fisher et al. (2016)	40 (nr)	30 (100)	Post	X			X	X	10	Neutral information	5-item composite scale	No sig. between-group difference on 5-item mindfulness scale

Author (year)	*N (MM group)*	Mean age (% female)	Timing of MM measurement	Main manipulation/induction component(s)					Induction duration (min.)	Type of control condition	State mindfulness measure	Induction effect on state mindfulness
				Focus attn.	Mindful eating	Aware present moment	Aware breath/ body	Aware thoughts/ emotions				
Geisler et al. (2018)	97 (46)	22.56 (68)	Post	X		X	X		8	Relaxation	KIMS	Sig. higher scores KMIS act aware scale in the MM group compared to relaxation
Hopthrow et al. (2017)	91 (nr)	nr	Post	x	X				5	Eating two raisins in 5 min no instruction	TMS	Sig. higher TMS scores in MM group compared to control
Johnson et al. (2015)	92 (41)	23.4 (65)	Post				X	X	25	(1) Audiobook (2) Sham MM	TMS	Sig. higher scores on decentering and curiosity in MM group compared to control
Kamboj et al. (2017)	68 (34)	23.85 (50)	Post			x	X	X	11	Relaxation	TMS	No sig. between-group difference in TMS scores
Kiken & Shook (2011)	175 (nr)	19.6 (53)	Post			X	X	X	15	Mind wandering	MAAS-State	Sig. higher scores in MM group compared to control
Kohlenberg et al. (2015)	114 (43)	18.63 (65.79)	Pre + post			X	X	X	60	Nature video	SMS	Sig. main effect of time and condition
Lai et al. (2015)	70 (23)	18.86 (65.7)	Post	x				X	15	(1) Counting backwards (2) Neuro-feedback	TMS	No sig. between-group difference compared to either control condition

Author (year)	*N (MM group)*	Mean age (% female)	Timing of MM measurement	Main manipulation/induction component(s)					Induction duration (min.)	Type of control condition	State mindfulness measure	Induction effect on state mindfulness
				Focus attn.	Mindful eating	Aware present moment	Aware breath/ body	Aware thoughts/ emotions				
Lancaster et al. (2016)	194 (98)	19.03 (64)	Post	x			X		15	Relaxation	TMS	Sig. main effect: MM group higher on curiosity scale only
Lee & Orsillo (2014)	53 (14)	29.61 (79)	Pre + post	x			X		20	(1) (Music-assisted) relaxation (2) Mind-wandering	MAAS-State	No sig. between-group difference between MM and either control condition on MAAS-State
Logie & Frewen (2015)	104 (35)	18.63 (66.35)	Post	x			X		15	Reading	TMS	Sig. higher TMS scores in MM + LKM compared to control
Luberto & McLeish (2018)	86 (44)	46.03 (45.4)	Pre + post	x		X	X	X	10	Neutral educational information	SMS	Sig. main effect of time + group: MM group ^ scores
Lueke & Gibson (2016)	124 (nr)	(62.9)	Post	X			X	X	10	(1) Neutral information (2) Control attention	SMS TMS	Sig. higher scores in MM on SMS and total TMS compared to both control conditions
Lueke & Lueke (2019)	85 (46)	(58.82)	Post	x			X		10	Neutral information	SMS	Sig. higher state mindfulness in MM compared to control condition

Author (year)	*N (MM group)*	Mean age (% female)	Timing of MM measurement	Main manipulation/induction component(s)					Induction duration (min.)	Type of control condition	State mindfulness measure	Induction effect on state mindfulness
				Focus attn.	Mindful eating	Aware present moment	Aware breath/ body	Aware thoughts/ emotions				
McClintock & Anderson (2015)	70 (35)	19.1 (90)	Post	X			X		20	Distraction (concentration + imagination)	TMS	Sig. higher TMS curiosity and decentering in MM group compared to control
Noone & Hogan (2018)	65 (nr)	21.09 (73.8)	Pre + post	x		X	X		10	(1) Sham meditation (2) Mind-wandering)	MAAS - State	No between-group effects on MAAS-State
Paz et al. (2017)	104 (nr)	26.02 (45.2)	Pre + post	X		X		x	7	Neutral educational information	SMS	Sig. group x time interaction: greater increases in MM group
Reed (2018)	118 (39)	25.19 (52.5)	Post	X			X		10	(1) Mind wandering (2) No intervention	TMS	Sig. higher TMS scores in MM compared to no intervention group, but not relaxation group
Reynolds et al. (2015)	101 (26)	20.98 (64.4)	Post	x			X	X	10	Neutral information	TMS	Sig. higher TMS decentering in MM group compared to control

Author (year)	*N (MM group)*	Mean age (% female)	Timing of MM measurement	Main manipulation/induction component(s)					Induction duration (min.)	Type of control condition	State mindfulness measure	Induction effect on state mindfulness
				Focus attn.	Mindful eating	Aware present moment	Aware breath/ body	Aware thoughts/ emotions				
Ridderinkhof et al. (2017)	158 (54)	22.55 (61.4)	Post	x			X		5	Relaxation/ Mind wandering	MAAS - State	Sig. higher scores in MM compared to MW, and sig. higher scores in relaxation compared to MM
Saunders et al. (2013)	100 (50)	20.59 (59)	Pre + post			X	x	x	15	Mind-wandering	TMS	Sig. higher TMS scores in MM group compared to control
Sharpe et al. (2013)	140 (37)	20.05 (72.14)	Post	x		X	X		12	(Progressive muscle) Relaxation	TMS	No between-group effects on TMS
Stocker et al. (2019)	34 (34)	20.85 (52.94)	Post	X		X	X		4	Neutral educational information	TMS	Sig. higher TMS scores in MM group compared to control
Tan et al. (2018)	20 (10)	25.5 (65)	Post	X			X		20	Relaxation	TMS	Sig. higher TMS scores in MM group compared to control
Tan et al. (2014)	72 (nr)	23.8 (50)	Post	x			X		5	Mind-wandering	MAAS-State	Sig. higher MAAS-State scores in MM group compared to control
Taraban et al. (2017)	43 (21)	22.3 (77)	Pre + post	X					12	Mind-wandering	MAAS - State	Sig. higher MAAS-State scores in MM group compared to control

Author (year)	*N (MM group)*	Mean age (% female)	Timing of MM measurement	Main manipulation/induction component(s)					Induction duration (min.)	Type of control condition	State mindfulness measure	Induction effect on state mindfulness
				Focus attn.	Mindful eating	Aware present moment	Aware breath/ body	Aware thoughts/ emotions				
Tsai et al. (2017)	110 (54)	19.30 (100)	Pre + post			x	X	X	10	Distraction (concentration + imagination)	TMS	No between-group effects on TMS
Upton & Renshaw (2018)	153 (76)	19.87 (76.47)	Pre + post	X			X		10	Mind-wandering	SMS	No between-group effects on TMS
Vinci et al. (2014)	207 (67)	20.13 (76.3)	Pre + post	x		X	X		10	(1) Relaxation (2) Word search	TMS	Sig. higher TMS scores (curiosity + decentering) in MM group compared to control
Watford & Stafford (2015)	70 (nr)	19.31 (72.86)	Post				X	X	15	Neutral information	TMS	Sig. higher TMS decentering scores in MM group compared to control
Watier & Dubois (2016)	78 (26)	20.62 (78)	Post	x			X	X	10	(1) Attention exercise (2) Arithmetic	TMS	Sig. higher TMS scores in MM compared to arithmetic, but not attention
Weger et al. (2012)	71 (nr)	20.14 (100)	Post		X	X	x		5	Eat two raisins no instruction	TMS	Sig. higher TMS scores in MM group compared to control
Yusainy & Lawrence (2015)	110 (55)	19.52 (52.73)	Post	X			X		15	Neutral educational information	TMS	Sig. higher TMS decentering scores in MM compared to control

Note. nr – not reported, X – element explicitly stated, x - element not explicitly stated, but implied as likely considering description of strategy. SMS = State Mindfulness Scale, TMS = Toronto Mindfulness Scale, KIMS = Kentucky Inventory of Mindfulness Skills, MAAS-State = Mindful Awareness Attention Scale (State version), MM = mindfulness meditation condition, MW = mind-wandering (control) condition.

2.4.2 Participant Characteristics

Twenty-nine of the 39 studies recruited university students, of which 14 studies reported that the participants included were enrolled on a psychology course. Mean sample ages were between 18-23. Two studies reviewed included female only samples.

2.4.3 Intervention Characteristics

2.4.3 1. Type of Mindfulness. A wide variety of mindfulness strategies were used across the studies. The main induction components included across studies were: focused attention, present moment awareness, awareness of the breath/body, awareness of thoughts/emotions, and mindful eating.

Focused attention, particularly on the breath and/or body were the most common core components of strategies named in 30 of the 39 studies included. Awareness of one's thoughts and/or emotions was a key focus of inductions in 18 of studies, of which all but one study used this in combination with a grounding in awareness or focus on the breath/body. Three of the included studies used a mindful eating task as their mindfulness induction, two of which incorporated a key element of either present moment awareness, or awareness of thoughts/emotions.

2.4.4 Induction Length

The length of mindfulness strategies varied between four to 60 minutes with a mean length of 13.45 min and median length of 10 min.

2.4.5 State Mindfulness Measures

As can be seen in Table 2.2, common verified state mindfulness measures were included after the mindfulness inductions. The Toronto Mindfulness Scale (TMS, Lau et al., 2006) being the most frequently used, followed by the State Mindfulness Scale (SMS, Tanay & Bernstein, 2013), the Mindful Attention Awareness Scale (MAAS, Brown & Ryan, 2003),

and the acting with awareness scale from the Kentucky Inventory of Mindfulness Skills (KIMS, Baer et al., 2004). Two studies used four- or five-item composite scales, purportedly adapted from commonly cited mindfulness questionnaires to probing of mindful attention in a way that fit their design (Donald & Atkins, 2016; Fisher, Lattimore, & Malinowski, 2016).

2.4.6 Control Conditions

A range of control conditions were used to contrast mindfulness inductions. Generally, studies used one control condition, but in seven studies, two comparison conditions were used (Donald & Atkins, 2016; Lai, MacNeil, & Frewen, 2015; Lee & Orsillo, 2014; Lueke & Gibson, 2016; Ridderinkhof, de Bruin, Brummelman, & Bögels, 2017; Vinci et al., 2014; Watier & Dubois, 2016). See Table 2.3 for an overview of the different control conditions implemented.

Table 2.3

Examples of the types of comparison conditions used

Control condition types	**Count**
Arithmetic exercise	1
Attention (control) exercise	2
Distractor task (concentrating on imagined stimuli)	2
Eating normally	2
Filler task (e.g. count backwards, word search)	3
Listening: neutral/ educational information	13
Mind wandering	9
Neurofeedback	1
Relaxation	9
Sham mindfulness meditation	2
Watch neutral video/ reading/ audiobook	3

2.4.7 Effects on State Mindfulness

The majority of studies reviewed (33 in total) reported positive effects of the active (mindfulness) inductions on state mindfulness (i.e. increased state mindfulness). For example, mindfulness inductions were found to induce significantly higher levels of decentering (a key outcome of mindfulness practice as measured on the Toronto Mindfulness Scale; see Table 2.3), in comparison to neutral (educational) information extracts (Cleirigh & Greaney, 2015; Erisman & Roemer, 2010; Fernando et al., 2017; Johnson et al., 2015; Reynolds et al., 2015; Watford & Stafford, 2015; Yusainy & Lawrence, 2015). Only one study also reported significant group differences on the curiosity scale of the TMS (Johnson et al., 2015), though some studies reported higher 'total' TMS scores as opposed to referring to separate subscales (Lueke & Gibson., 2016; Stocker et al., 2019). In a similar vein, three studies demonstrated significantly higher mindfulness scores in comparison to neutral information, as measured by the SMS (Lueke & Lueke, 2019; Luberto & McLeish, 2018; Paz et al., 2017), with one other highlighting differences on only the 'body' not 'mind' subscale of the SMS (Bravo et al., 2018). Three studies compared a mindfulness strategy to other neutral media (reading, listening to a book, or watching a nature video), all of which found that mindfulness elicited significantly higher state mindfulness scores (Logie & Frewen, 2015; Johnson et al., 2015; Kohlenberg et al., 2015); one of which also found significant differences between reading and a second meditation condition, involving a loving-kindness strategy (Logie & Frewen, 2015).

A commonly used control condition was relaxation. In contrast to the above, Lancaster et al. (2016) found mindfulness to increase 'curiosity' but not 'decentering' scores on the TMS relative to relaxation. Tan et al (2018) found higher total scores on TMS in the MM group compared to relaxation, as did Geisler et al., (2018), as measured by the acting

with awareness subscale of the KMIS. Vinci et al (2014), found significantly higher scores in MM group in comparison to both relaxation and word search controls. In contrast, Donald & Atkins (2016) found those in the mindfulness condition to score higher on state mindfulness compared to those completing a filler task, but not in comparison to those completing a relaxation control condition. Lastly, Kamboj et al. (2017) and Sharpe et al. (2013) found no effects of brief mindfulness instruction in comparison to relaxation strategies on state mindfulness.

Mind-wandering and distractor tasks were also used as comparators to mindfulness strategies. For example, Reed (2018) and Saunders et al., (2013) found a main effect of group in comparison to mind-wandering, measured by the TMS; with comparable results being found in comparison to an 'imagination and concentration' distractor task, which instructed participants to concentrate on specific ideas that were presented at intervals through the time-matched task (McClintock & Anderson, 2015). Using the MAAS-State, three remaining studies highlighted differences between those that completed a mindfulness and a mind-wandering strategy (Kiken & Shook, 2011; Tan et al., 2014; Taraban et al., 2017).

One study demonstrated significantly higher scores in the mindfulness group compared to mind-wandering but not relaxation. In fact, Ridderinkhof and colleagues (2017) found their relaxation comparator to induce higher mindfulness scores at post-test compared to the mindfulness strategy. In contrast to the above, Lee and Orsillo (2014) found no significant difference between those completing a mindfulness strategy with a relaxation or mind-wandering strategy. Noone & Hogan (2018) demonstrated no significant differences in state mindfulness between those completing a mind-wandering sham meditation compared to a mindfulness meditation strategy. Three remaining studies found no differences in state mindfulness between participants that completed a mindfulness strategy in comparison to a

mind-wandering or an imagination and concentration (distraction) condition, respectively (Eddy et al., 2015; Upton & Renshaw, 2018; Tsai et al., 2017). Johnson and colleagues (2015) did not find a significant difference in state mindfulness scores after sham mindfulness vs. mindfulness meditation strategies (both which constituted a breathing exercise, but with different levels of instructional detail).

Hopthrow et al., (2017) and Weger at al., (2012) compared a mindful raisin eating exercise with eating the same number of raisins in a given time without mindfulness instruction, and found that participants in the mindfulness condition scored significantly higher on the TMS compared to controls. Lueke and Gibson's (2016) study used a second control condition involving controlling one's attention (in addition to a neutral information control), which did not elicit enhancements in state mindfulness comparable to the mindfulness condition. In contrast, Watier and Dubois (2016) showed a significant difference in state mindfulness between a mindfulness exercise and an arithmetic task but not between mindfulness and an attention exercise, which involved listening to an audio recording of information about different components of attention, and completing two attention tasks (that were likely to recruit multiple aspects of attention). Using comparatively engaging control conditions, Lai and colleagues (2015) found no significant differences between those completing a mindfulness strategy compared to counting backwards or engaging in neurofeedback.

2.4.8 Affective Outcomes

Twenty-two of the 39 studies included an affect measure, of which 21 analysed the effects of the induction on affect. Of these, 10 studies demonstrated marked improvements in positive mood, reductions in negative mood, and/or reductions in emotional reactivity. Specifically, in the context positive or negative affect manipulations, students assigned to a

mindfulness condition showed significantly higher positive affect in comparison to control participants, regardless of affect manipulation type, and more negative affect was found in mindfulness participants who experienced a negative affect induction (Watford & Stafford, 2015), and significant reductions in negative affect were demonstrated in participants either at risk of alcohol use disorder or high in trait dependency (Vinci et al., 2014; McClintock & Anderson, 2015). One study showed that positive and negative clips elicited significantly more positive and less negative affect (respectively) in a mindfulness group compared to control in participants with a high level of difficulty in emotion regulation (Erisman & Roemer, 2010). Similarly, in anxiety-provoking contexts, such as distressing or performance-related tasks, significantly less negative emotional responses were recorded by participants having completed a mindfulness manipulation in comparison to control group subjects that did not (Luberto & McLeish, 2018; Geisler et al., 2018). Finally, Lee and Orsillo (2014) demonstrated significant within-group decreases in anxiety in subjects who had elevated generalised anxiety symptoms.

2.4.9 Behavioural/Cognitive Effects

Twenty-seven studies included a behavioural task, test, or measure of recent behaviour. Sixteen showed beneficial effects of the strategy on participant behaviour or cognition. Significantly lower levels of mind-wandering, or (non-task related) distracting thoughts were found in participants after having completed mindfulness inductions between 8-12 minutes in duration, in comparison to control subjects that completed a mind-wandering or music-assisted relaxation protocol (Taraban et al., 2017; Geisler et al., 2018). Though performance on an achievement test was not affected by the induction in Geisler and colleague's study, others did show improvements in math ability after a mindfulness induction compared to control participants (Weger et al., 2012). Lee and Orsillo (2014) found

significantly better performance on an emotional Stroop task in the mindfulness group compared to thought wandering but not relaxation. Two studies showed higher performance on memory-related tasks after mindfulness instruction in comparison to listening to neutral information or completing a mind-wandering task (Lueke & Lueke, 2019; Saunders et al., 2013).

Participants completing mindfulness strategies demonstrated a higher capacity for accurate judgement in a negativity bias paradigm, in comparison to counterparts who completed a mind-wandering task (Kiken & Shook, 2011). Relatedly, Hopthrow et al., (2017) found that participants held less correspondence bias after a mindfulness strategy compared to either control group. Lower levels of age and race-related bias were also demonstrated by Lueke and Gibson (2016) as measured by a trust game task after mindfulness compared to neural information or an attention control condition.

Group decision making abilities were shown to be superior to in those who completed a mindfulness induction in comparison to participants who listened to neutral educational information (Cleirigh & Greaney, 2015). Interestingly, Kohlenberg and colleagues (2015) found significant improvements on two social connections indices after an interpersonal mindfulness exercise (including focus on other's presence, common humanity, and relational improvements) in comparison with an intrapersonal mindfulness exercise (involving focus on the breath, body sensations, thoughts and feelings), or a nature video control. Tan et al. (2014) demonstrated significantly greater mind reading abilities (i.e. mental state attribution) and more empathetic concern in those who completed the mindfulness induction compared to those who completed a mind wandering control task. In contrast, helping behaviours proved to be significantly higher in participants who ranked higher in self-compassion and completed the mindfulness strategy (Fernando et al., 2017).

In terms of behaviours relating to craving and consumption, Kamboj and colleagues (2017) found marked reductions in alcohol consumption in at-risk drinkers seven days after they completed a laboratory session involving a mindfulness strategy in comparison to a relaxation strategy. Mindfulness also increased the sensation of fullness and reduced consumption of high-reward foods in a food cue exposure task (Fisher et al., 2016).

2.4.10 Physiological Effects

Of the included studies, six collected physiological data from participants, of which three demonstrated significant group differences between the mindfulness and control condition. One study showed indications of improved self-control in participants assigned to mindfulness during the exercise compared to controls, as measured by vagal withdrawal, an index of heart rate variability (Geisler et al., 2018). Similarly, Paz and colleagues (2017) demonstrated superior physiological regulation as per greater heart rate variability in those who completed the mindfulness induction, in response to a stressor, compared to control participants. In contrast, Kamboj et al. (2017) found an upregulation of the parasympathetic nervous system in participants who completed the relaxation strategy only, rather than the mindfulness strategy, alluding to a potentially less clear relationship between heart rate variability and single-session mindfulness practice.

2.4.11 Risk of Bias

Of 39 studies reviewed, 12 were categorised ‘low risk’, the majority were classified medium risk (n = 27), and three were rated as high risk. Table 2.4 illustrates the detail of this assessment. No studies reviewed involved a process of checking the quality of matching between behavioural conditions, nor did any have participants re-explain their understanding of the strategy instructions. Only four studies pre-registered their analysis plans, and eight studies provided a power calculation for their primary outcome of interest. Credibility and

expectancy were seldom measured (n = 2), however nearly all studies included a manipulation check, and set up their studies to be predominantly automated. It was seldom reported whether the outcome assessor was blind to participant conditions, and in only three studies was this confirmed to be the case (Kamboj et al., 2017; Reynolds et al., 2015; Ridderinkhof et al., 2017).

Table 2.4

Results of the risk of bias assessment

Study	Random assignment of participants	PPT blind to hypotheses	<10% missing data for MM outcomes	Outcome assessor blind?	Analysis pre-registered?	Groups balanced for gender etc.	Conditions balanced (length, delivery method…)?	Condition matching checked?	Power calculation for primary outcome?	Participants re-explain instructions?	Majority of procedure automated?	Credibility/ expectancy measured?	Manipulation check for induction?
Bravo et al. 2018	+	+	+	/	-	/	/	-	-	-	+	-	+
Cleirigh & Greaney 2015	+	-	+	/	-	-	-	-	-	-	+	-	+
Donald & Atkins 2016	+	+	+	/	-	+	+	-	+	-	+	-	+
Eddy, et al. 2015	+	+	+	/	-	/	/	-	-	-	+	-	-
Erisman & Roemer 2010	+	/	+	-	/	+	/	-	-	-	+	+	+
Fernando et al. 2017	+	+	+	/	-	/	/	-	-	-	+	-	+
Fisher et al. 2016	+	+	+	-	-	+	+	-	-	-	-	-	-
Geisler et al. 2018	+	/	+	/	-	/	/	-	-	-	+	-	+
Hopthrow et al. 2017	+	+	+	/	-	/	+	-	-	-	/	-	+

Study	Random assignment of participants	PPT blind to hypotheses	<10% missing data for MM outcomes	Outcome assessor blind?	Analysis pre-registered?	Groups balanced for gender etc.	Conditions balanced (length, delivery method…)?	Condition matching checked?	Power calculation for primary outcome?	Participants re-explain instructions?	Majority of procedure automated?	Credibility/ expectancy measured?	Manipulation check for induction?
Johnson et al. 2015	+	+	+	-	-	+	/	-	-	-	-	-	+
Kamboj et al. 2017	+	+	+	+	-	+	+	-	-	-	+	+	+
Kiken & Shook 2011	+	+	+	/	-	/	/	-	-	-	+	-	+
Kohlenberg et al. 2015	+	+	+	/	-	+	/	-	-	-	/	-	+
Lai et al. 2015	+	+	+	/	-	/	+	-	-	-	+	-	+
Lancaster et al. 2016	+	+	+	/	-	/	+	-	-	-	+	-	+
Lee & Orsillo 2014	+	+	-	/	-	+	+	-	-	-	+	-	+
Logie & Frewen 2015	+	+	+	/	-	+	/	-	-	-	+	-	+
Luberto & McLeish 2018	+	+	+	/	-	/	+	-	-	-	+	-	+
Lueke & Gibson 2016	+	+	-	/	-	/	+	-	-	-	+	-	+

Study	Random assignment of participants	PPT blind to hypotheses	<10% missing data for MM outcomes	Outcome assessor blind?	Analysis pre-registered?	Groups balanced for gender etc.	Conditions balanced (length, delivery method…)?	Condition matching checked?	Power calculation for primary outcome?	Participants re-explain instructions?	Majority of procedure automated?	Credibility/ expectancy measured?	Manipulation check for induction?
Lueke & Lueke 2019	+	+	+	/	-	/	/	-	+	-	+	-	+
McClintock & Anderson 2015	+	+	+	/	-	+	+	-	-	-	+	-	+
Noone & Hogan 2018	+	+	+	/	-	/	+	-	+	-	+	-	+
Paz et al. 2017	+	+	/	/	-	/	+	-	-	-	+	-	+
Reed 2018	+	+	+	/	-	/	+	-	-	-	+	-	+
Reynolds et al. 2015	+	+	+	+	-	+	/	-	-	-	+	-	+
Ridderinkhof et al. 2017	+	+	+	+	-	+	+	-	+	-	+	-	+
Saunders et al. 2013	/	+	+	/	-	/	+	-	-	-	+	-	/
Sharpe et al. 2013	+	+	+	/	-	+	+	-	+	-	+	-	+
Stocker et al. 2019	+	+	+	/	-	+	/	-	+	-	+	-	+
Tan et al. 2018	+	+	+	/	-	+	/	-	-	-	/	-	+
Tan et al. 2014	+	+	+	/	-	/	+	-	+	-	+	-	+

Study	Random assignment of participants	PPT blind to hypotheses	<10% missing data for MM outcomes	Outcome assessor blind?	Analysis pre-registered?	Groups balanced for gender etc.	Conditions balanced (length, delivery method…)?	Condition matching checked?	Power calculation for primary outcome?	Participants re-explain instructions?	Majority of procedure automated?	Credibility/ expectancy measured?	Manipulation check for induction?
Taraban et al. 2017	+	/	+	/	+	+	+	-	-	-	+	-	+
Tsai et al. 2017	+	+	+	/	-	+	+	-	-	-	-	-	+
Upton & Renshaw 2018	+	/	+	-	+	/	/	-	+	-	+	-	+
Vinci et al. 2014	+	+	+	/	-	+	+	-	-	-	+	-	+
Watford & Stafford 2015	+	/	+	/	-	/	/	-	-	-	+	-	/
Watier & Dubois 2016	+	/	+	/	-	/	+	-	-	-	+	-	+
Weger et al. 2012	+	/	+	/	-	/	-	-	-	-	+	-	+
Yusainy & Lawrence 2015	+	+	+	/	-	+	+	-	-	-	+	-	+

Note. + Indicates low risk, / represents unclear level of risk, - represents high risk.

2.5 Discussion

The present review provides an overview of the effects of single-session experimental mindfulness inductions on subjective, behavioural and physiological indices. It also provides an overview of the varied control conditions used in these single session mindfulness studies. The findings indicate that even very brief instruction in mindfulness meditation can result in beneficial changes in the targeted process/attributes, such as state mindfulness. This is important because such brief experimental procedures are likely to be a common way in which *modulation* of mindfulness (e.g. through drugs or neuromodulation) would be examined and the findings suggest that mindfulness inductions are a valid way to investigate such modulation.

2.5.1 Subjective Outcomes

2.5.1.1 State Mindfulness. The majority of studies included demonstrated beneficial effects of single-session mindfulness on state mindfulness, implying that it is possible to selectively increase moment-to-moment 'felt' mindfulness after a mindfulness induction lasting as little as four minutes. These results extend previous reviews which have examined the effects of mindfulness on health outcomes (Howarth et al., 2019), cognition (Chiesa, Calati, & Serretti, 2011), and affect (Schumer, Lindsay, & David Creswell, 2018), which so far established useful applications of mindfulness across a range domains and time-frames, but did not yet explore how state mindfulness in particular is affected by brief inductions.

Though few studies appear to have measured both state and trait mindfulness across time (Enkema et al., 2020), those that have so far demonstrate positive associations between both dimensions and indices of wellbeing, and positive affect, and negative associations with negative affect, which is in line with previous literature (Gu, Strauss, Bond, & Cavanagh, 2015; Jiménez et al., 2020; Schumer et al., 2018). This may be because temporary increases in state mindfulness are a precursor to related affective and behavioural changes underlying

trait changes in mindfulness. Of the presently reviewed studies that used the Toronto mindfulness scale (TMS) to measure state mindfulness, levels of decentering were commonly found to be higher in active mindfulness group as opposed to scores on the curiosity subscale. This points to decentering as a potentially early and important component to changes in mindfulness, positive affect and well-being, such that less identification with one's internal experience may encourage less repetitive, more constructive thought patterns, for example leading to lower emotional arousal (Gu et al., 2015; Shoham, Goldstein, Oren, Spivak, & Bernstein, 2017). Decentering has been suggested as a key metacognitive process for the cultivation of mindfulness, and relatedly, healthy adaptation to experiences (Bernstein et al., 2015; Vago & Silbersweig, 2012). Experimental data using experience sampling indicates that decentering may mediate the effect of state mindfulness on reduced emotional arousal (Shoham et al., 2017). Importantly, state mindfulness measures do appear to capture a uniquely specific snapshot into subtle changes in moment-to-moment awareness.

Mindfulness practice does not always appear to enhance reported state mindfulness however. Some studies found no effects of mindfulness practice on state mindfulness, with one demonstrating significantly higher scores in those who completed the control (relaxation) strategy in comparison to the mindfulness strategy (Ridderinkhof et al., 2017). This may be because the induction was too short in length (spanning only five minutes), or it may highlight the fact that relaxation is considered to be a precursor to the process of attaining more mindful mental states (Ospina et al, 2007). Indeed some frame relaxation as a key mechanism for mindfulness meditation (Baer, 2003), and there have been varied results in other studies that compare state mindfulness after a mindfulness and relaxation strategies, despite subsequent behavioural changes in line with predictions at the time of follow-up assessments (Kamboj et al., 2017).

Null findings in regards to state mindfulness may also be explained by the measures used to quantify these differences. It is possible that certain self-report scales may be more adept at capturing the subtle changes exhibited by single-session mindfulness protocols. For example, as noted in chapter one, the State-MAAS queries mindful awareness in respect to daily activities, without any reference to the meta-awareness aspect of mindfulness (as Tanay & Bernstein (2013) describe, the *'how'* of mindful attention). It may be that distinctions between conditions would have been picked up by a more sensitive measure of mindfulness (for example, the SMS). This also holds true for shorter adapted measures as per Donald and Atkins (2016) and Fisher and colleagues (2016), whereby the measures may not have been long enough, or carefully selected enough to highlight differences between conditions (see 'Methodological comments' section for further exploration). It is also worth noting that, as per any self-reported measure of mental state, to answer accurately requires a certain level of self-awareness from participants. This may be a particularly salient challenge in contemplative science, whereby novice participants may not actually be familiar with a pure awareness, or spaciousness of mind before having practiced a mindfulness technique.

2.5.2 Affective Outcomes

This review also (secondarily) examined effects of single session mindfulness inductions on affect, and revealed mixed effects of mindfulness inductions on mood, with just less than half of studies that included an affect measure demonstrating direct affective benefits of the strategies on participant's mood. The majority of which found evidence for reductions in negative affect, followed by less severe negative emotional responses to negative mood manipulations, decreases in anxiety, and some increases in positive affect. These results align with recent reviews exploring brief mindfulness training for negative

affect (Schumer et al., 2018), though effects on positive affect and anxiety appear to remain unclear (Jiménez et al., 2020).

Emotion regulation has been proposed as a key component to the changes associated with mindfulness practice (Hölzel et al., 2011). The present results indicate that this may extend to single-session mindfulness practice, which alternative experimental research supports. For example, Arch and Craske (2006) conducted a single-session mindfulness experiment involving a mood induction. Participants who were assigned to the mindfulness condition also showed more willingness to view negatively-valenced content in comparison to those in the unfocused attention group, pointing towards a higher tolerance for negative affect, or a reduction in basal arousal, which would therefore allow for more of an increase in distress before reaching a threshold of tolerance. This is consistent with fMRI research exploring emotional reactivity and recovery from threatening stimuli, whereby those who rated higher on trait mindfulness showed less amygdala activity and more prefrontal cortical activation (which maps onto threat response regulation) compared to those who scored lower on trait mindfulness (Creswell, Way, Eisenberger, & Lieberman, 2007). Additionally, participants who completed mindfulness rather than distraction or rumination strategies have demonstrated speedier recovery from induced sad mood inductions (Broderick et al., 2005). These findings may be informative for the development of strategies for mental health that encourage mindfulness practices to recover from emotionally arousing thoughts or experiences, as well as attempting to strengthen practices in persons that are susceptible to rumination, such as those suffering from depression.

2.5.3 Cognitive and Behavioural Outcomes

Similar to the affective results outlined above, just over half of the studies reviewed indicated that a mindfulness induction was helpful for a specific behaviour or cognitive

capacity. Reductions in mind-wandering were demonstrated, as well as improvements on attention, memory and mathematic tests. Decreases in bias of judgement were also found, implying a greater potential for accurate judgement after mindfulness. In regards to social behaviour and cognition, group decision making abilities appeared to be enhanced by mindfulness practice, as well as feelings of social connection, mind-reading capability, empathy, and helping behaviours.

These results align with theorisation of attention regulation as key to mindfulness practice (Hölzel et al., 2011), as well as experimental and neuroimaging data relating mindfulness practice to conflict monitoring and attention orienting capabilities (Tang et al., 2015). A recent review and meta-analysis explored the effects of mindfulness inductions specifically on cognition, finding a small global effect across all domains of cognition, which included memory, attention, executive functions, and higher-order functions (Gill, Renault, Campbell, Rainville, & Khoury, 2020). However, in separate analyses significant effects were only found for higher-order functions. Though this contrasts to literature assuming attentional functions as the primary component of change (e.g.; Holzel et al., 2011), the evidence for higher-order functions supports the idea that reducing cognitive bias may be an important target, or component of positive change related to mindfulness practice (Vago & Silbersweig, 2012).

If biases in attention and emotional processing are important in the practice of mindfulness, it may hold potential applications around potentially pathological, or risky behaviour such as drinking, drug use or gambling (Bowen et al., 2009; Kamboj et al., 2017; Khanna & Greeson, 2013). Relatedly, Lakey and colleagues (2007) found those higher in trait mindfulness were less likely to have problems with gambling, with risk-taking performance partially mediating this relationship. A weakening of ‘habitual responding’ that

has been associated with mindfulness practice (Wenk-Sormaz, 2005) may also play a part in this beneficial role of mindfulness. Lastly, it is possible that enhancements in emotional processing support more healthy and less risky behaviours by way of enhancing interpersonal connectedness (K. W. Brown, 2005), and reductions in perceived rejection (Creswell et al., 2007).

2.5.4 Physiological Outcomes

A small number of studies included in this review included physiological measures, of which half found no direct effects of the induction. Though preliminary, results point towards less effortful self-control during mindfulness exercise (Geisler et al. 2018), and improvements in physiological regulation in response to a stressor (Paz et al., 2017). These results align with previously summarised results regarding improvements in attentional and emotion regulation as a result of short-term mindfulness practice. Results were not consistent however, with one study showing upregulation of parasympathetic activity after a relaxation but not mindfulness strategy (Kamboj et al., 2017). These results imply that a similar set of physiological processes may be engaged in early state mindfulness compared to relaxation training, since both types of training have been found to elicit reductions in physiological reactivity compared to a wait-list control group (Ortner et al., 2007).

2.5.5 Methodological Comments on the Reviewed Studies

Though our findings point towards beneficial effects of mindfulness (particularly on affective, cognitive, and behavioural domains), there remain improvements in design and methodology which can help create more valid and reliable findings in future investigations. For example, the reviewed studies were seldom pre-registered. Though not limited to research in the area of mindfulness, the pre-registration of empirical studies is beneficial in that the process encourages having clear a priori hypotheses, analyses plans, and reduces the

likelihood of publication bias. It is worth noting however that the open science movement is gaining traction throughout experimental psychology, and it is hoped that the majority of future mindfulness research will be pre-registered.

Another common methodological issues is the design of appropriate control conditions that are well-matched with the mindfulness inductions. Though experimental conditions were often balanced (on at least one structural element, such as time), condition matching was not checked in any of the reviewed studies allowing for a large element of subjectivity from the researcher in terms of what constitutes well-matched conditions. The variety of control conditions implemented speaks to the lack of consensus regarding optimal behavioural conditions for mindfulness strategies, despite theoretical commentaries making related suggestions (e.g. Davidson & Kaszniak, 2015). Considering relaxation control conditions can elicited higher mindfulness scores than (active) mindfulness strategies (e.g. Ridderinkhof et al., 2017), it would be difficult to infer that the control conditions used to date are perfectly operationalised to differentiate between mindfulness and non-specific strategy factors. One promising approach to somewhat rectify the challenge with comparator tasks is to use two control conditions, such that specific elements of the mindfulness strategy could be controlled for. An example would be Donald and Atkins (2016) using a relaxation strategy to control for any relaxing effects of the mindfulness condition, alongside a filler task as a no-treatment control, which sought only to keep participants mildly engaged in a task that was unlikely to elicit any particular mindfulness-related effects.

It seems noteworthy that among a variety of validated state mindfulness measures, two studies included used adapted scales, which compromised of different questions from other mindfulness questionnaires. In one case (Donald & Atkins, 2016), questions were adapted from validated trait mindfulness scales (i.e. Baer et al., 2006; Brown & Ryan, 2003),

which had been used in a previous study in an expanded form (see Reb & Narayanan, 2014). The second study to use a composite scale did not provide any information as to the source of the questions. Though this may call to question the inclusion of the two studies, it was preferred to maintain a maximally objective approach to the review of the studies, and considering they met inclusion criteria (and there was no pre-defined plan to exclude studies based on methodological rigor), this variety in measurement of state mindfulness exemplifies the heterogeneity of methods found in the literature to date.

In this selection of studies, there were also no instances of studies reporting that they requested participants to re-explain the instructions (to verify comprehension), which creates uncertainty about what the participants were actually practicing during the strategy period. Whilst the vast majority of studies kept the participants blind to the study hypotheses, blinding of the outcome assessor was seldom specified. However, the common methodological strength of double-blinding is generally much less common in studies of psychotherapeutic procedures. This allows for some researcher-associated expectation effects. Indeed, researcher allegiance, or preference for one intervention over another appears to be an important predictor of intervention effect (Gaffan, Tsaousis, & Kemp-Wheeler, 1995). Lastly, credibility of the strategy, and expectancy of its usefulness were seldom reported, which stands as another opportunity for improvement of future research, since participant expectancy and perceived credibility may threaten the internal validity of studies by altering participant behaviours (Hardy et al., 1995). Relating to the importance of utilising an appropriately matched control condition, it is important that a control condition would also create a positive expectation that the intervention or task will be useful (Mohr et al., 2009).

With the consideration that different types of control conditions produce different effects on outcomes of RCT studies (Cuijpers, Van Straten, Warmerdam, & Smits, 2008), in an attempt to make the most appropriate comparisons in this review, studies have been summarised based on the control conditions used. It is noted, however that the heterogeneity of study designs complicates the comparison of findings across studies.

2.5.5.1 Matters of Experience. In the reviewed studies, there was a mixture of experience levels of participants, though the majority recruited novices or those with very little experience with mindfulness, it is an important factor to consider in future research. Neuroscientific explorations of mindfulness have demonstrated that different areas of the brain are recruited depending on experience, which maps onto the different cognitive processes recruited at different stages of experience with the practice (Tang et al., 2015). Therefore, making comparisons across studies which included participants with greatly varying levels of experience may not produce accurate conclusions.

2.5.6 Implications

Mindfulness inductions appear to have beneficial effects on state mindfulness, affect (regulation), and some behavioural and cognitive capacities. These strategies could have numerous therapeutic applications, due to their ease of accessibility, low cost, and wide variety of domains that can be targeted. For example, brief mindfulness instruction may help manage cravings, strengthen emotion regulation, and improve memory. With further (methodologically rigorous) examination of mindfulness inductions (via well-controlled randomised experiments), it will be possible to make clearer suggestions as to how brief mindfulness strategies may be implemented in clinical settings.

2.5.7 Strengths and Limitations

2.5.7.1 Strengths. A key strength of this review were the methods used to implement the review. Double screening, and checking inter-coder reliability was checked at every stage, with the aim of reducing the subjective element of the review process. Carrying out second-rater checks on the risk of bias assessment was another such approach to attempt to maintain the highest level of methodological rigor. Another strength pertains to the novelty of this collection of studies. This is the first review to explore effects of mindfulness inductions on state mindfulness. Though state mindfulness measures are often used as manipulation checks for strategies, there has been no focus on how moment-to-moment changes in mindfulness capacities change as a result of inductions. Measures of trait mindfulness have predominantly been explored in experimental studies, with novel long-term methods such as ecological momentary assessment demonstrating the capacity for state mindfulness measures to highlight a variety and subtlety of experience that trait measures are not capable of (Enkema et al., 2020). Additionally, this review culminates studies with a large variety of aims, tasks, and measures for comparison, to obtain a big picture view of what we know so far about the effects mindfulness inductions.

2.5.8 Limitations

As has been demonstrated by meta-analyses, publication bias can challenge the strength of an effect between strategies and control conditions (Schumer et al., 2018). Additionally, considering the majority of studies included here used student samples, these results may not generalise to wider populations. In fact, Schumer and colleagues (2018) found that student samples showed significantly weaker effect sizes for mindfulness vs. control condition comparisons than community samples did, highlighting the importance of sample recruitment. Additionally, in many of the studies included, experience with meditation was not necessarily an exclusion criteria for participation. This may be a

noteworthy confound, considering that meditation experience is associated with changes in cognition, brain structure and function (Tang et al., 2015), and that experience of meditation and skill in related meta-cognition may change the way that participants understand (and therefore report) their experience (Varela & Shear, 1999). Since we focused on laboratory studies here, the findings are not necessarily generalizable to clinical work or applied settings, but they are important for directing experimental research.

2.5.9 Future Research

Future studies should include state mindfulness measures, to a) ensure that manipulation is targeting mindfulness; b) to help explore how state mindfulness changes within short time frames; and c) to obtain more information around the processes involved in changes to health indices that are measured (e.g. state mindfulness may mediate changes in wellbeing). Great care should be taken when selecting a behavioural control condition with which to match mindfulness strategies, such that they should be credible, produce a positive expectation of usefulness, and be well-matched to the mindfulness condition on non-specific elements (such as duration and method of engagement). It would be beneficial for future studies to use appropriately large sample sizes, provide power calculations for these values, and ensure understanding of instructions by participants to instil greater methodological rigor. Lastly, future studies may seek to recruit using community samples, as opposed to primarily student samples to enable making more generalisable conclusions.

Chapter 3

Stimulating Meditation: A Randomized Controlled Experiment Combining Modafinil and Mindfulness Training.

Work presented in this chapter gave rise to the following publication:

Thomas, E. M., Freeman, T. P., Poplutz, P., Howden, K., Hindocha, C., Bloomfield, M., & Kamboj, S. K. (2021). Stimulating meditation: a pre-registered randomised controlled experiment combining a single dose of the cognitive enhancer, modafinil, with brief mindfulness training. *Journal of Psychopharmacology, 35*(6), 621-630.

Key Points:

- This randomised double-blind placebo-controlled experimental study aimed to test whether a single dose of modafinil may augment mindfulness training
- Seventy-nine participants completed a laboratory-based experimental session in which they were randomised to placebo or modafinil, and a mindfulness or relaxation strategy. Self-report measures of (state and trait) mindfulness and affect; behavioural measures of sustained attention and mind-wandering; and physiological measures were recorded.
- Results indicated that modafinil acutely increased state mindfulness and enhanced sustained attention. Though no differential between-group strategy effects were found on state mindfulness, those assigned to mindfulness demonstrated significantly greater parasympathetic activation post-strategy. No strategy or drug effects were found on mind-wandering, though participants assigned to modafinil engaged in significantly more strategy practice in the week following the experimental session.

3.1 Introduction

Mindfulness, a meditation practice derived from the Buddhist contemplative tradition, can be viewed as a form of cognitive (attentional) training. Although definitions of mindfulness vary and emphasise different underlying psychological processes (e.g. experiential acceptance, interoceptive discernment, insight, compassion), most definitions acknowledge the centrality of *attention* and its regulation as a foundational skill (Bishop et al., 2004; Kabat Zinn, 1994). Neuropsychological definitions of attention include a capacity to sustain, switch and inhibit the allocation of information processing resources to a particular internal or external object (Posner & Petersen, 1990). An example of an internal object of attention is the breath, and mindful breathing is a prototypical mindfulness exercise intended to increase attentional regulation. This typically involves a combination of an extended singular focus on the breath within a single session (sustained and focused attention), cognitive control of unrelated thoughts (executive function/inhibition) and refocusing of attention to the breath when the mind wanders (attentional switching). Although novices often struggle with mindfulness exercises, and typically experience frequent 'task-unrelated thoughts' (mind-wandering), long-term training is associated with enhanced performance on attentional tasks (Lutz et al., 2008) and reduced mind-wandering (Mrazek, Schooler & Smallwood, 2012). This improved performance is thought to reflect enduring structural and functional changes in brain regions that, for example, subserve interoceptive attention, i.e. attention towards sensations arising from the body (Farb, Segal & Anderson, 2013).

Mindfulness is increasingly used as a (component of) psychological treatment(s) for a variety of mental and physical health problems. Research trials of mindfulness-based interventions (MBIs) have demonstrated the strongest evidence for preventing relapse to

depression, although other indications also show promising responses to MBIs (Goldberg et al., 2018). MBIs modelled on mindfulness based stress reduction (Kabat-Zinn et al., 1992) typically involve weekly, two hour-long group sessions over the course of several weeks, as well as ongoing daily practice. In addition to studies demonstrating the efficacy of this format of MBIs for depression, addiction and pain (e.g. Goldberg et al., 2018), single-session experimental studies, in which mindfulness is administered in order to temporarily increase *state* mindfulness, have also been employed to examine the effects of relatively isolated *components of* mindfulness. Some such studies have attempted to match mindfulness training with active control conditions such that differences in credibility, expectancy, and other demand characteristics are minimised (e.g. Kamboj et al, 2017). These studies suggest that temporary adaptive changes in behaviour, affect and cognition can be attributed to the use of specific mindfulness strategies (Arch & Craske, 2006; Erisman & Roemer, 2010; Mrazek, Smallwood & Schooler, 2012).

The nature of MBIs, both in terms of their short-term demands (prolonged within-session practice), and their relatively extended duration (typically spanning ~8 weeks), might not be optimal for some individuals. Abbreviated treatments might be more accessible to a wider range of patients. As revealed in the previous chapter, the number of single session studies utilising mindfulness has greatly increased in recent years, with all 39 included studies being completed in the past 10 years, and mindfulness inductions lasting as little as four minutes on one occasion only. In accordance with other reviews exploring the effects of short-term mindfulness studies (Howarth et al., 2019; Leyland et al., 2019), this trend alludes to the promising potential nature of much shorter MBIs, which, due to this condensed format, may be significantly easier to engage in for many individuals. In our aforementioned review,

77% of studies demonstrated significant group effects on at least one domain of the mindfulness measure used in comparison to a control group.

Notably, obstacles other than length and repeated practice might prevent initial engagement with MBIs. Indeed, the specific focus of MBIs on self-regulation of attention represents a potential barrier in patients for whom attentional and motivational difficulties are an inherent symptom of their (affective or attentional) disorder (Barnhofer et al., 2009; Eysenck et al., 2007). In addition, negative correlations have been documented between trait mindfulness and attention deficit-hyperactivity disorder (ADHD) symptoms (Keith et al., 2017), implying that those who suffer from attentional difficulties start off at a disadvantage when it comes to trying to implement mindfulness-related skills. A similar pattern emerges with severity of depressive symptoms, whereby they display negative correlations with trait mindfulness, and positive correlations with mind-wandering (Deng et al., 2014). One approach to overcoming such obstacles may be to employ biological strategies (e.g. cognition enhancing drugs) to support the basic attentional capacities required for mindfulness.

Additionally, short-term experimental studies provide a valuable opportunity to examine and potentially isolate specific processes involved in mindfulness. For example, using a single-session protocol it is possible to gain a better understanding of the effects of certain types of mindfulness strategy on relevant outcomes since it is easier to control for many extraneous factors, and the ‘dose’ of mindfulness can be carefully controlled. This contrasts to studies examining the effects of mindfulness-based programs (MBPs) which span multiple weeks, and will have various homework components that participants may or may not engage with outside of formal practice hours (e.g. MacCoon et al., 2012). This variability in potentially mindfulness-inducing tasks, and frequency of engagement over the course of MBPs makes it difficult to parse out the effects of specific mindfulness strategies

or tasks. As noted in chapter three, mindfulness inductions have investigated the effects of brief (single-session) mindfulness strategies on elements of attention, memory, affect, behaviour and physiology, by isolating and testing specific mindfulness strategies.

Findings from cognitive neuroscience suggest two primary modes of consciousness, which correspond to descriptions of distinct, established forms of meditation: focused attention and open monitoring (Lutz et al., 2008; Ricard et al., 2014). These studies have thus enabled meditation techniques and accompanying mental states to be increasingly defined in terms of underlying psychological and neurobiological processes. Pharmacological studies may represent an additional approach to studying these processes. For example, stimulants, such as methylphenidate or modafinil, which are used (on and off-label respectively) to treat symptoms of ADHD, modulate brain activity and/or connectivity in regions involved in arousal/alerting, attention and executive function. In particular, in healthy volunteers at rest, modafinil enhances functional connectivity between regions of the salience network such as the insula and anterior cingulate cortex, areas which have been defined as key for the processing of, and attentional response to salient internal and external stimuli (Cera et al., 2014). Components of this network are also activated during mindfulness, with the anterior cingulate frequently cited as demonstrating neuroplasticity as a result of training (see Tang, Hozel & Posner, 2015). Behaviourally, the effects of modafinil (improvements in executive functioning, aspects of attention, learning and memory; Battleday & Brem, 2015) resemble improvements in cognition that have been described in studies of mindfulness (see Chiesa, Calati & Seretti, 2010). As such, stimulant drugs might also acutely *mimic* aspects of the attentional state(s) attained through mindfulness (particularly focused attention) training. It is also possible that such stimulants might acutely *augment* the efficacy of mindfulness

training. Modafinil in particular would appear to be a useful drug in this regard, especially given its limited side effects and low abuse potential (Battleday & Brem, 2015).

Here, using a randomised double-blind, placebo controlled experimental design, we examined the effects of acute behavioural and pharmacological strategies that were selected to target focused attentional processes, i.e. state mindfulness and its behavioural-attentional correlates. This was achieved by employing a parsimonious mixed within-between subjects design (e.g. Kamboj et al., 2015; Kamboj et al, 2018) in which assessment of a pharmacological effect is separated from that of a behavioural manipulation, while also allowing their combined effects to be tested. We assessed state mindfulness, positive and negative affect, and autonomic activity (indirectly), to determine the extent to which modafinil's effects paralleled those of mindfulness meditation, and whether modafinil and mindfulness interact additively or synergistically (Moss et al., 2016). Our pre-registered hypotheses were that, compared to an active relaxation control, brief mindfulness training would increase state mindfulness, improve sustained attention and decrease mind-wandering. We also predicted that compared to placebo, modafinil would have similar directional effects to brief mindfulness training on these outcomes. In addition, we examined the possibility of additive or synergistic effects between strategy and drug by testing the interaction between these variables, although the absence of previous research in this area precluded strong *a priori* predictions. As such, tests of interaction effects should be considered exploratory, designed to steer future research.

3.2 Methods

The study received ethical approval from the University College London Research Ethics Committee. Hypotheses, methods and analysis plans were pre-registered on the open science framework (OSF; https://osf.io/34xn9).

3.2.1 Study Design

This study employed a 2 (drug) x 2 (strategy), factorial, between-subjects design with additional within subject factors of time and day (see below), in a double-blind, randomised experiment. Both a matched placebo drug control and a well-matched active control for mindfulness (i.e. relaxation) were used. This resulted in four experimental groups: placebo-relaxation, modafinil-relaxation, placebo-mindfulness, and modafinil-mindfulness.

3.2.2. Participants

Eighty participants were recruited from UCL and the local community through online and paper-based adverts. The sample size was calculated (Gpower; Faul et al., 2007) for a repeated measures (three time-point) within-between subjects interaction based on an effect size for state mindfulness reported by Tanay and Bernstein (2013). Specifically, we assumed a small-medium effect (f=0.175), a correlation between repeated measure of r=0.5, power=0.8 and α=0.05. This indicated that N=80 was required.

Participants were randomly and evenly (n=20/group) allocated to placebo-relaxation, modafinil-relaxation, placebo-mindfulness, modafinil-mindfulness, with equal numbers of men (n=10) and women (n=10) per group. Two participants' data could not be included. One did not complete the laboratory session (n=1; relaxation-placebo group). This participant did not report any adverse response in the period following drug administration, however, while listening to the strategy instructions, they became distressed and requested the session be terminated. No significant within-session adverse reactions to drug or strategy were reported. Another participant misreported screening information, which came to light after testing was completed (n=1; relaxation-placebo group). Due to practical constraints, only one of these participants was replaced, resulting in a final sample of n=79 (placebo-relaxation: n=9 men, n=10 women).

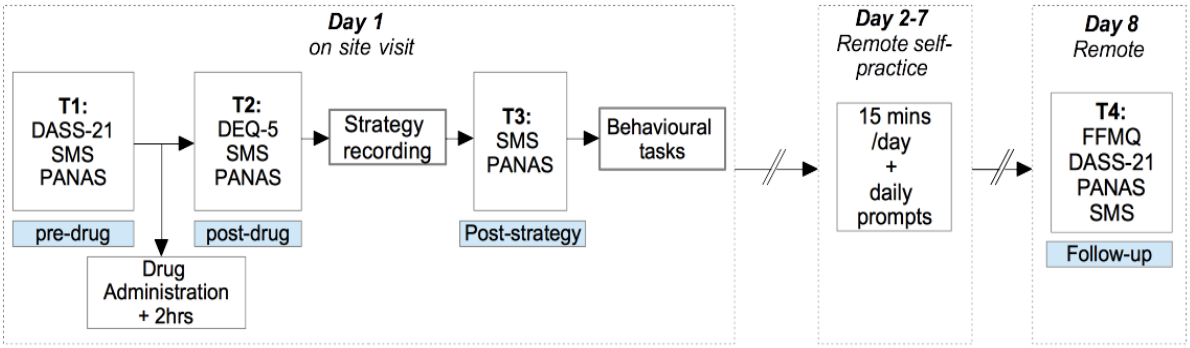
Participants were required to be 18-50 years old. Exclusion criteria were: presence of mental health, substance use or other relevant medical disorders, contraindications to modafinil use, pregnancy and current breastfeeding. In addition, participants were excluded if they engaged in recent regular meditation practice (within the last six months), and/or had >20 hours lifetime total meditation experience. Participants were compensated for their time (£25). All provided written informed consent. All experimental procedures and outcome assessments were conducted under blinded conditions. Participants were blinded to the drug condition, and were unaware that there were two strategy conditions. Experimenters were blinded to both drug condition and strategy condition.

3.2.3 Procedure

Participants who passed a telephone-screening to verify eligibility criteria attended the laboratory session. The order of tasks in the lab session is outlined in Figure 3.1. Briefly, after consenting, participants were fitted with an ECG device, and completed baseline demographic and mood/trait measures (FFMQ, DASS-21). They also completed the pre-drug (time-point 1: T1) state measures (SMS, PANAS; see below). They then swallowed capsules containing either modafinil or placebo with water, followed by a 2hr rest/drug absorption period, during which they either watched low arousal nature documentaries, relaxed or read. After the drug absorption period, participants completed the post-drug (time-point 2: T2) questionnaires (SMS, PANAS), before listening to a recording of the strategy instructions to which they were randomly assigned. Immediately after this, they completed the mind-wandering task, and then the post-strategy (time-point 3: T3) questionnaires (SMS, PANAS). The psychomotor vigilance task was completed last. A remote follow-up assessment was completed after a week, including the day eight questionnaires: SMS, PANAS, FFMQ and DASS-21.

Figure 3.1

Procedural flowchart showing the order of tasks and questionnaires across the experiment



DASS-21 = Depression, Anxiety + Stress scales; PANAS = Positive and Negative Affect scale; SMS = State mindfulness scale; DEQ-5 = Drug Experience Questionnaire; FFMQ = Five Facet Mindfulness questionnaire

3.2.4 Drug Preparation

In the active drug groups, 200 mg of modafinil (Glenmark Pharmaceuticals Europe Limited, UK) was administered orally with water. The dose of modafinil used here was based on studies demonstrating enhanced cognitive effects after a single dose (Turner et al., 2003). Modafinil tablets were reformulated by over-encapsulation into opaque gelatine capsules with additional skimmed milk powder (Marvel, Premier Foods, UK) filler. Matched placebos were identical opaque capsules filled only with milk powder. Integrity of double blinding was tested by eliciting independent treatment guesses from participant and researcher.

3.2.5 Strategy Instructions

Strategy instructions were presented via headphones with the volume set to a level that minimized audio leakage. The recordings were deployed using a randomization procedure that was concealed from the experimenter, thus ensuring blinding to strategy condition. The audio instructions were presented in two segments. The first was an explanation of the strategy and brief practice, after which credibility and expectancy were

assessed (see below). This was followed by the main strategy practice. Details on strategy development, along with sample instructions are provided in the Appendix (section 8.1).

Mindfulness: the mindfulness strategy instructions were developed specifically for this study, with scripts designed to be brief and widely comprehensible. They were intended to promote attention to the breath (e.g. Williams and Penman, 2011) through repeated encouragement to 'notice' the breath and the experience of breathing, and to return to the breath when the mind wandered (i.e. when attention drifted from the focus on the breath). These instructions were consistent with focused attention-type meditation rather than open monitoring (Lutz et al., 2008). The instructions deliberately avoided the use of the term "mindfulness" to conceal the overt aims of the strategy and reduce expectancy effects (Kamboj et al., 2017), and instead referred to 'focused breathing' throughout the experiment.

Relaxation: the relaxation strategy instructions were designed to be closely matched to the mindfulness strategy in terms of method of administration, duration, and complexity of language (reading level). This strategy encouraged breath *control*, through deep regulated breathing, along with muscle relaxation. As with the mindfulness instructions, participants were instructed to return to performing the regulated breath exercise when they noticed their mind wandering. For participants randomized to this strategy, the strategy was referred to as "regulated abdominal breathing" in the audio recording.

3.2.6 Self-report Questionnaires

The abbreviated (two-item) versions of the patient health questionnaire (PHQ-2; Gilbody et al., 2007) and generalised anxiety disorder Scale (GAD-2; Spitzer et al., 2006) were used as brief screening tools to identify significant low mood and anxiety symptoms prior to the experimental session. Those scoring a total ≥ 3 on either pair of questions were excluded at screening. The depression, anxiety and stress scale (DASS-21; Lovibond &

Lovibond, 1995) was used as a baseline measure of mood/anxiety disorder symptoms and was re-administered at 1-week follow-up. Trait mindfulness was assessed using the brief (15 item) five facet mindfulness questionnaire (FFMQ; Baer et al., 2006) at baseline and follow-up.

3.2.6.1 State Measures. A primary outcome was (change in) *state* mindfulness. Of the available state mindfulness measures, the 20-item State Mindfulness Scale (SMS; Tanay & Bernstein, 2013) was the most relevant for the current study as the items clearly relate to attentional processes (*awareness of* activities of the mind and body). Participants rated each SMS item (e.g. "*I noticed pleasant and unpleasant thoughts*"; "*I felt aware of what was happening inside of me*"; "*I noticed physical sensations come and go*.") on a five-point scale in relation to their experience in the previous 10 minutes. The SMS was completed at three time-points within the experimental session: pre-drug (T1) post-drug (T2), and post-strategy (T3).

State affect was assessed using the Positive and Negative Affect Schedule (PANAS; Watson, Clark & Tellegen, 1988) which consists of two subscales listing 10 positive and 10 negative adjectives. Participants rated each adjective in relation to their *current* experience, from 1 (very slightly or not at all) to 5 (extremely). Participants completed the PANAS immediately after the SMS, at T1, T2 and T3.

Finally, drug related subjective effects were assessed using the 5-item drug effects questionnaire 5 (DEQ-5; Morean et al., 2013): *feel* (the effect of the drug), *high*, *dislike*, *like*, and *want more*. These were rated using a modified 5-point scale from: "not at all" (1), to "extremely" (5).

3.2.6.2 Behavioural Measures

3.2.6.2.1 Mind-wandering Task . Mind-wandering (a shift in attention to task-unrelated thoughts) may be a cognitive-behavioural marker of (absence of) mindfulness. Mrazek and colleagues (2012) demonstrated that a brief mindfulness exercise increased sustained attention and reduced mind-wandering compared to active (relaxation) or no task (reading) controls (Mrazek, Schooler & Smallwood, 2012). We therefore adapted the task described by Mrazek et al., (2012) to assess 'probe-caught' and 'self-caught' mind-wandering occurrences. Participants were instructed to perform the strategy (mindfulness or relaxation) that they had previously received instructions on, and to press a mouse key if their mind wandered from the strategy. Both self-caught (mouse clicks in the absence of a probe) and probe-caught (mouse clicks within 1 sec after an audio probe) instances were recorded. Probes were presented with a pseudo-random inter-probe interval of 40-80 seconds (average interval 60 sec), and a total of 15 probes were presented over the course of the 16-minute task.

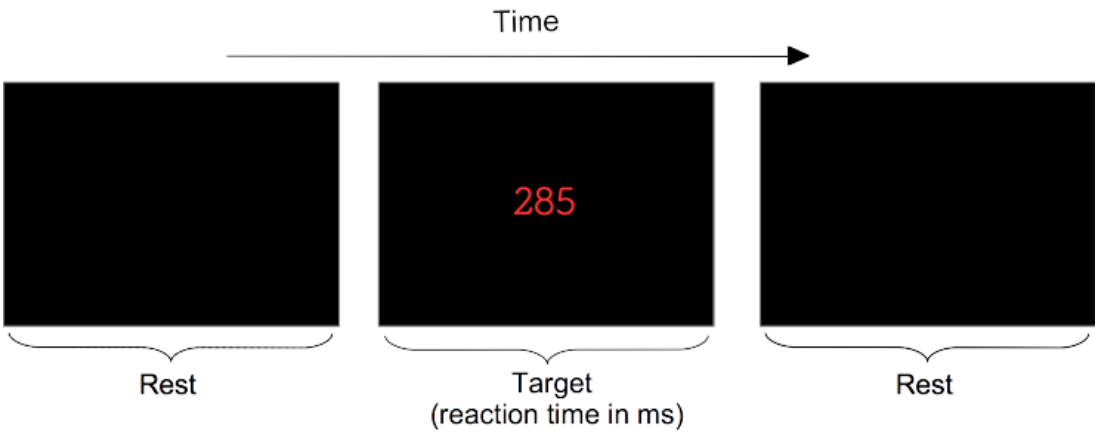
3.2.7 Psychomotor Vigilance Task (PVT)

Performance on the PVT has previously been shown to be sensitive to both modafinil (Dignes & Weaver, 2003) and mindfulness training (Kaul et al., 2010; Wong et al., 2018). The version of the task used here (PC-PVT 2.0) is described in Khitrov et al (2014). Participants were instructed to attend to the computer screen, and click the mouse as quickly as possible, when they see a visual stimuli appear. This is the reaction time, which displays as a timer (in milliseconds) in the middle of the screen in red numbers. When a click is made after the number appear, they remain on the screen briefly, then the next trial begins. If a click is made before the numbers appear, 'FS' appears on the screen to indicate a false start. The visual stimuli were presented at random intervals, and the data analysed as mean reaction times. As recommended (Khitrov et al, 2014), a high performance gaming mouse

(Harpoon RGB gaming mouse, Corsair) was used to ensure accurate response (reaction time) recording. See Figure 3.2 for an illustration of a PVT trial.

Figure 3.2

An illustration of the psychomotor vigilance task



3.2.8 Blood pressure

Blood pressure was assessed at baseline, post-drug, and post-strategy using a commercial wrist-worn blood pressure monitor. Alongside the subjective measures, we took three blood pressure and heart rate measurements at baseline, pre-drug (T1), post-drug (after 2 hr; T2), and after the strategy instructions (T3).

3.2.9 Heart rate variability (HRV)

A Firstbeat ECG device (Bodyguard 2, Firstbeat Technologies) was attached at the beginning of the testing session, and recorded inter-beat (RR) interval data throughout the session. Data extraction and processing took place offline. Three 5 min intervals corresponding to pre-drug (T1), post-drug (T2) and finally, *during* strategy instructions (T3) were used. As in our previous study (Kamboj et al., 2017), the root mean square of successive differences (RMSSD) was used to index HRV.

3.2.10 Control Measures

3.2.10.1 Credibility & Expectancy Questionnaire. Devilly and Borkovec's (2000) questionnaire was adapted to assess credibility of the strategies after an explanation of each strategy but before the main instructions. Credibility was determined from the average of three questions that inquired about how logical, successful and recommendable each strategy was in relation to "helping you to calm your mind". Expectancy was based on a single question relating to how much each strategy was 'felt' to be potentially helpful (in calming the mind). Each question was rated on a 1 ("not at all") to 9 ("very much").

3.2.10.2 Compliance Check. Following Arche & Craske (2006), at the end of the study, participants completed a manipulation check, which asked them to which extent they closely followed the audio instructions for the strategy. This is recorded on a 0 (very untrue) to 7 (very true) scale.

3.2.10.3 Treatment Guesses. To determine whether the integrity of the blind was retained, participants and the researcher independently guessed whether the participant received placebo or modafinil. Responses were entered directly onto the computer-based survey at the end of the experimental session, such that participants and experimenter were unaware of each other's response.

3.2.11 Follow-up

Participants were invited to practice the strategy that they had learned for the seven days after the experimental session, after which they completed an online follow-up assessment that included the FFMQ, DASS-21, SMS, and PANAS.

3.2.12 Statistical Analyses

Statistical analyses were conducted using SPSS (version 25; IBM). The analysis plan was pre-specified on the OSF (https://osf.io/34xn9). Minor departures from this were

required because of an incorrect specification of the role of the two between-subjects factors in the analysis section of pre-registration document. Thus, instead of a single between-subjects factor, 'group', with four levels, the primary analyses (should have) involved *two* between-subjects factors (2 x 2; below). Additional exploratory analyses on drug effects on amount of practice and on drug x day (baseline, follow-up) were also conducted.

Data were checked for accuracy and univariate outliers (i.e. scores with studentised residuals ≥ 3). Outliers were winsorized in accordance with recommendations of Tabachnick and Fidell (2001), namely replaced by $x_{(highest\ non\text{-}outlier)}$ (or $x_{(highest\ non\text{-}outlier)}+1$ if outcome values included 0). Distributions were inspected for normality and considered to be normal unless visual inspection or distribution parameters (skewness/standard error or kurtosis/standard error ratios >3) indicated a deviation. Deviation from normality was evident for PVT reaction times and PANAS-negative scores, and hence these were $\log_{10}$ transformed, which successfully reduced skewness and/or kurtosis. Analyses and reported *F* and *p* values relate to transformed data for these outcomes, although for ease of interpretation untransformed means are presented in the results.

Outcomes assessed at a single time-point were analysed using univariate factorial ANOVA (mind-wandering, PVT, and strategy practice) or independent samples t-test (strategy compliance ratings, DEQ scores), with false discovery rate adjustments as appropriate. Continuous variables measured at each within-session time-point (state mindfulness, HRV, and affect) were analysed using factorial repeated measures ANOVA, with time (pre-drug, post-drug and post strategy: T1, T2, T3 respectively) as a within-subjects factor. 'Long-term' effects (between baseline and 1 week, i.e. day 1 to day 8) on mood (DASS-21) and *trait* mindfulness (FFMQ) were analysed in separate 2 × 2 × 2

analyses. No *a priori* predictions were specified for affect (PANAS), HRV, or any of the longer-term effects, therefore these analyses remained exploratory.

Where Mauchly's test indicated significant departures from sphericity, degrees of freedom were adjusted using Greenhouse-Geisser correction. Where non-integer *df*s are reported, this reflects such adjustment; in other places, departures from expected integer *df*s reflect occasional missing data, which was excluded list-wise from analyses. An alpha threshold of 0.05 was used and two-tailed tests are reported. All post hoc tests of significant ANOVA effects were Bonferroni corrected to maintain a family-wise error rate of 0.05. Effect sizes associated with post hoc comparisons are expressed as Cohen's *d*, with appropriate correction for repeated measures correlations for within-subjects comparisons across two time-points (Dunlap et al., 1996). Means ± standard deviations are reported in the text and tables, and means ± standard errors (SE) are indicated in figures.

3.3 Results

3.3.1 Participants

Baseline demographic and trait measures are summarised in Table 3.1. The values are within the ranges expected of a normative sample.

Table 3.1

Means and standard deviations for baseline measures

	Placebo		Modafinil	
	Relax[1]	Mindful	Relax	Mindful
Age	26.68 (7.19)	24.35 (5.39)	23.80 (3.71)	26.20 (5.60)
DASS (dep)	8.11 (5.10)	6.90 (5.13)	7.00 (6.10)	8.80 (6.72)
DASS (anx)	5.47 (4.89)	4.80 (3.27)	6.20 (5.06)	7.16 (5.47)
DASS (stress)	9.37 (4.81)	9.20 (4.27)	12.20 (5.80)	13.60 (7.21)
FFMQ	46.95 (7.01)	51.05 (5.70)	50.50 (6.93)	49.60 (5.63)

Note. [1] n=19 (9 men, 10 women); other groups n=20 (10 men, 10 women). FFMQ = Five facet mindfulness questionnaire; DASS = Depression, anxiety, and stress scales

3.3.2 Subjective State Measures

3.3.2.1 State Mindfulness Scale. No main effect or interactions involving strategy were found (p values ≥0.125), indicating that, contrary to our hypothesis, the mindfulness strategy did not produce the intended larger increase in state mindfulness relative to relaxation. However, as shown in Figure 3.2, and in line with our hypothesis that modafinil would increase state mindfulness, those receiving modafinil showed a significantly greater increase in state mindfulness between T1 and T2 compared to those who received placebo (time × drug interaction: $F(1.8,137) = 6.268$, $p = .003$, $\eta p^2 = .077$).

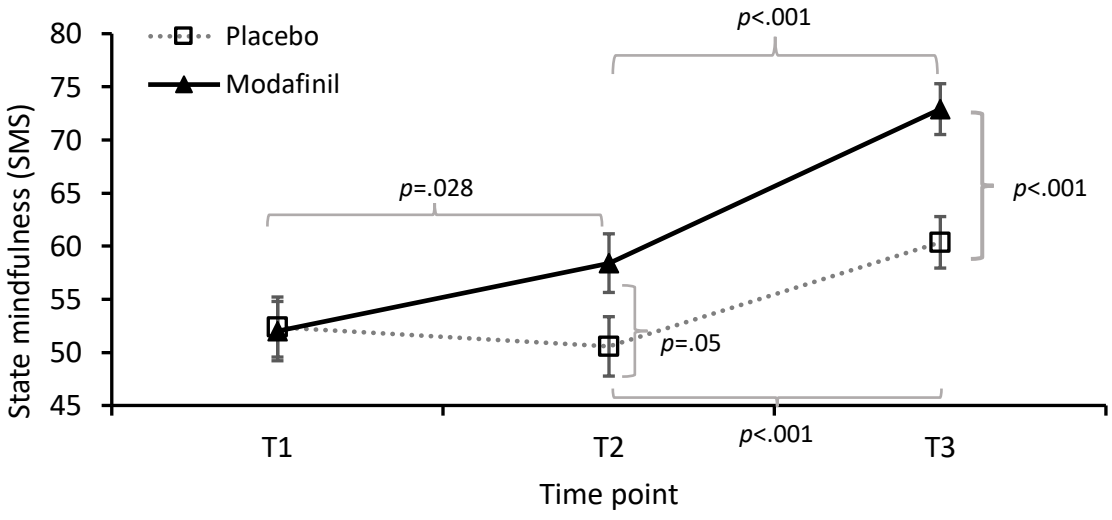
Collapsing across strategy, pairwise Bonferroni corrected tests comparing state mindfulness at T1 and T2 separately for each of the drug conditions, showed no change in the placebo conditions ($p > 0.99$), but a significant, small increase following modafinil (p =

0.028, d = 0.344). The effect of time between T2 and T3 was significant (p < 0.001) and of moderate magnitude in the placebo conditions (d = 0.633), whereas in the modafinil group, the T2 to T3 increase was large (p < 0.001, d = 0.821).

Complementary post hoc tests at each level of time showed that state mindfulness was marginally higher at T2 in the modafinil versus placebo group (p =0.053, d = 0.45), with the divergence between drugs being more pronounced at T3 (p < 0.001, d = 0.83). Collectively these results suggest that modafinil enhances the effects of behavioural interventions that either encourage relaxation or mindfulness. See Figure 3.3.

Figure 3.3

Estimated marginal means (± SE) for drug × time effects on state mindfulness (State Mindfulness Scale; SMS).



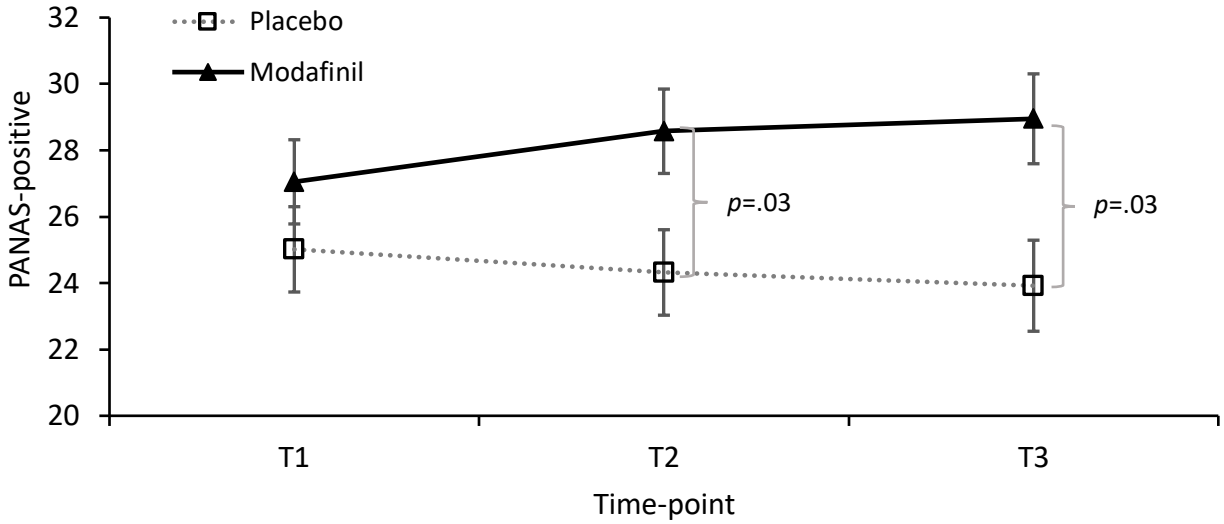
Note. All p values are Bonferroni corrected.

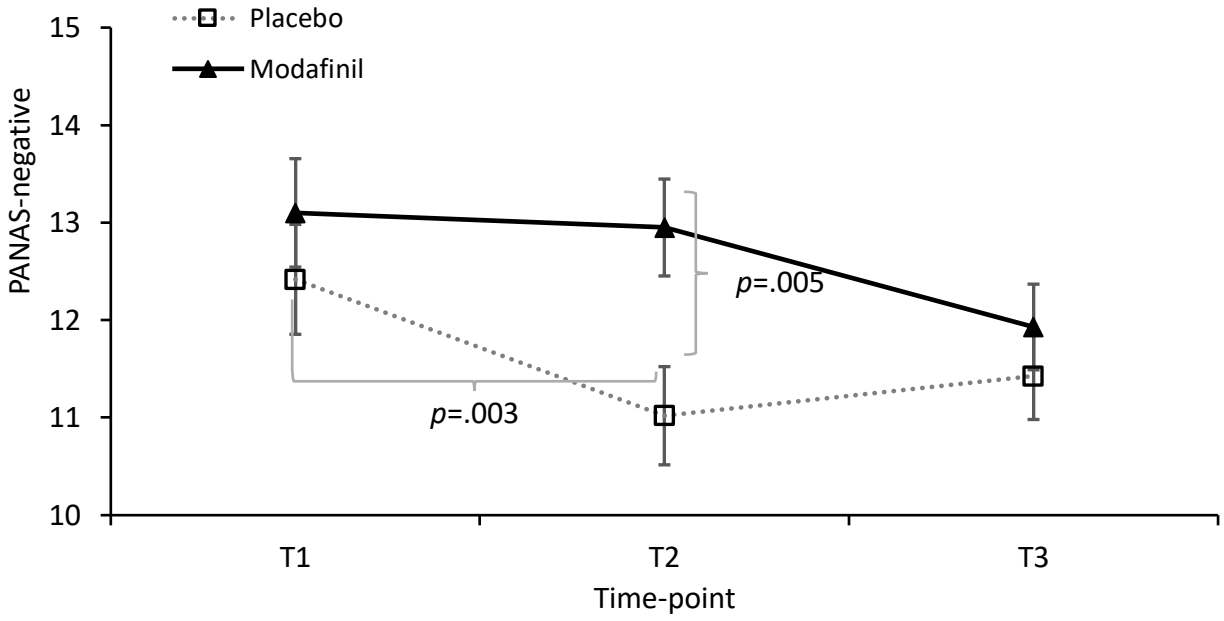
3.3.3 Positive and Negative Affect

As illustrated in Figure 3.4, there were no significant two or three-way interactions for PANAS-positive scores *(F* values ≤ 2.263, p values ≥ 0.083) and no main effect of strategy ($F(1,75)=0.195$, $p=.660$). However, although the time × drug interaction did not reach significance ($F(1.76, 131.71)=2.623$, $p = 0.083$), there was a main effect of drug ($F(1,75)=5.077$, $p = 0.027$, $\eta_p^2=0.063$). Given this effect and the presence of a marginal interaction, exploratory Bonferroni corrected pairwise comparisons were performed to explore the effect of drug at each level of time. These suggested that positive affect scores were higher following modafinil compared to placebo at T2 ($p = 0.021$, $d = 0.536$) and T3 ($p = 0.011$, $d = 0.595$). To determine if change in positive affect differentially affected change in state mindfulness in the two drug conditions, correlations between ΔPANAS-positive (T2-T1) and ΔSMS (T2-T1) were performed for each drug. However, these did not suggest a differential association ($r_{placebo(37)}=0.562$, $p < 0.001$; $r_{modafinil(38)}=0.442$, $p=.004$).

Figure 3.4

Time by drug effects for (a) positive affect (mean PANAS-positive affect scores ±SE), (b) negative affect (PANAS-negative ± SE).





Note. for PANAS-negative, raw scores are shown for ease of interpretation, although statistical analyses reported in the text were performed on log transformed PANAS-negative scores. *p* values are Bonferroni corrected.

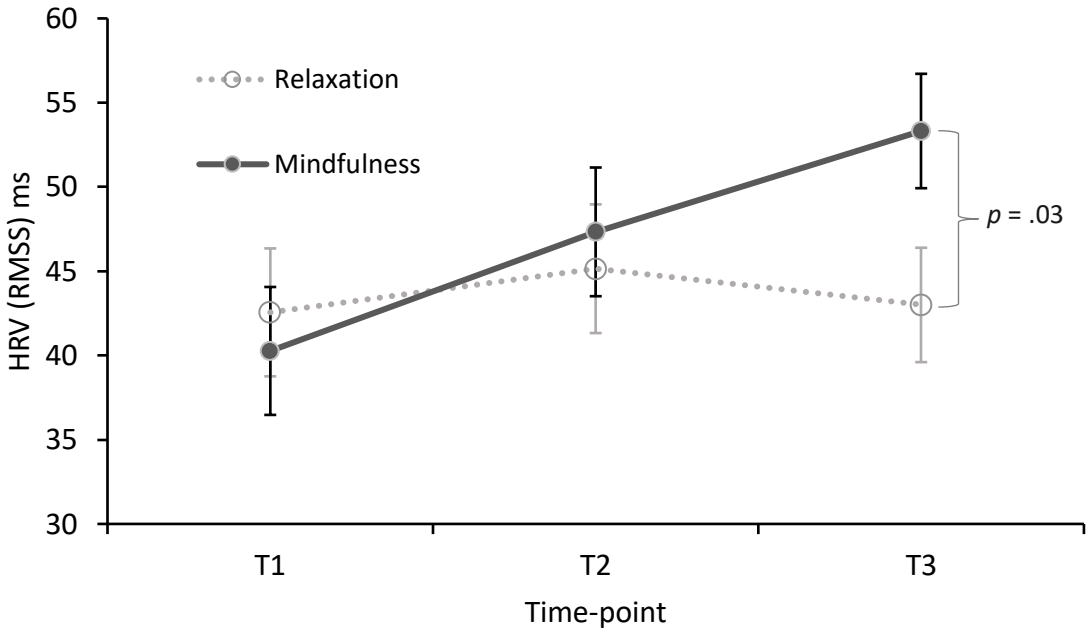
On the PANAS-negative subscale there were no interactions involving strategy (*F* values ≤2.425, *p* values ≥0.092; NB, analysis of PANAS-negative was performed on log transformed values). However, a main effect of time ($F(2,150)=5.736$, $p = 0.004$, $\eta_p^2 = 0.113$) was found under a time × drug interaction ($F(2,150)=3.143$, $p = 0.046$, $\eta_p^2=0.04$; Fig. 3.4b). Post hoc tests of drug and time at each level of time and drug respectively showed a significant and moderate-sized reduction in negative affect between T1 and T2 in the placebo group ($p = 0.003$, $d = -0.60$). A small decrease ($d = -0.291$) between T2 and T3 in the modafinil group was not significant ($p = 0.086$). PANAS-negative scores were significantly lower in the placebo versus modafinil group at T2 ($p = 0.005$, $d = -0.646$), although scores converged at T3 ($p = 0.382$; Figure 3.4b).

3.3.4 Physiological Indices: Heart Rate Variability

There was no main effect and no interactions involving drug on the RMSSD measure of HRV (*F* values ≤ 1.776; *ps* ≥0.173). However, a significant main effect of time ($F(2, 136)=5.612$, $p = 0.005$, $\eta p^2 = 0.076$) was found under a time × strategy interaction ($F(2,136)=4.743$, $p = 0.010$, $\eta_p^2 = 0.065$). This was due to a strategy difference in HRV at T3 (collapsed across drug), with mindfulness producing higher HRV than placebo, as illustrated in Figure 3.5.

Figure 3.5

Strategy × time effect on heart rate variability (RMSSD).



Note. The *post hoc p* value for the mindfulness versus relaxation comparison at T3 is Bonferroni corrected. Values are means ± SE.

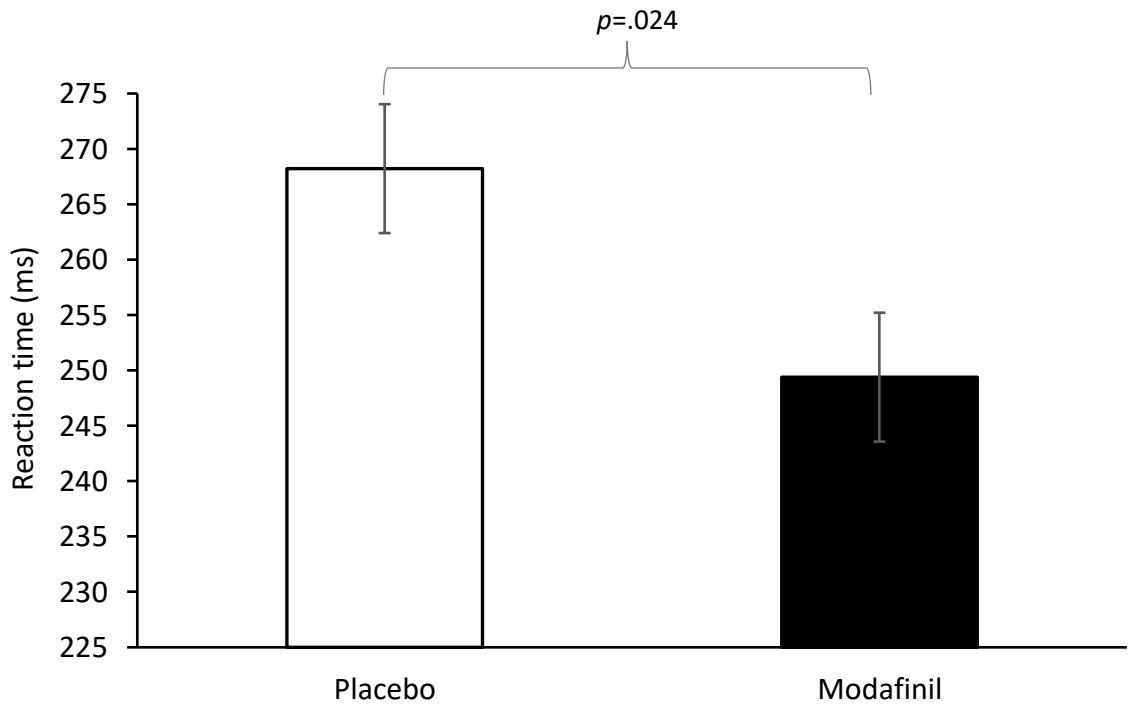
Since measurement at T2 preceded strategy instructions, the apparent increase in HRV between T1 and T2 in the mindfulness conditions cannot be attributed to the mindfulness strategy. Focusing instead on the effect of time between T2 and T3, Bonferroni corrected post hoc tests revealed that the increase in HRV in the mindfulness group failed to reach significance (p = 0.074, d = 0.30). However, the difference between relaxation and mindfulness at T3 was significant (p = 0.031, d = 0.519). In line with previous research (Hou et al., 2005) modafinil had no effect (no main or interaction effects involving drug) on systolic (values $F \leq 0.697$, $ps \geq 0.407$) or heart rate (F values ≤ 2.091, $ps \geq 0.127$).

3.3.5 Sustained Attention

As predicted, a factorial drug × strategy ANOVA (on log transformed reaction times) showed a main effect of drug on psychomotor vigilance task (PVT) reaction times ($F(1,70)=5.295$, $p = 0.024$, $\eta p^2=0.07$). As illustrated in Figure 3.6, this reflected faster reaction times in the modafinil relative to placebo group. There was no drug × strategy interaction ($F(1,70)=0.014$, $p = 0.907$) and the effect of Strategy did not reach statistical significance ($F(1,70)=3.823$, $p = 0.055$), although the relaxation group had marginally faster reaction times (251.5 ± 36.2 ms) than the mindfulness group (266.1 ± 36.2 ms).

Figure 3.6

Mean reaction times (±SE) for the psychomotor vigilance task.



Note. Untransformed data is displayed for ease of interpretation.

3.3.6 Mind-wandering Task

For both self-caught mind-wandering events (mean across conditions: 4.18 ± 2.89) and probe-caught events (16.81 ± 13.32), there were no main effects of strategy or drug and no two or three-way interactions involving drug and strategy (all F values ≤ 3.034, p values >0.086).

3.3.7 Control Measures

3.3.7.1 Expectancy, Credibility and within-session Strategy Compliance. As expected for closely matched strategies, average credibility ratings for relaxation (6.21 ± 1.53) and mindfulness (6.54 ± 1.23) were not significantly different ($t(77)=1.050$, $p = 0.297$). Similarly expectancy was similar for relaxation (5.79 ± 1.45) and mindfulness (6.10 ± 1.45; $t(77)=0.935$, $p = 0.353$). Compliance did not differ for relaxation (6.03 ± 1.06) and mindfulness (6.08 ± 1.05; $t(77)=0.208$, $p = 0.836$).

3.3.8 Blinding and Subjective Drug Effects

Twenty-eight participants (of n=39) in the placebo groups correctly guessed their treatment (72%); in the modafinil group 17/40 (43%) guessed correctly ($\chi^2(1, n=79)=1.764$, $p = 0.184$). Researchers guessed at chance levels for placebo (59% correct) and modafinil (50%; $\chi^2(1, N=79)=0.641$, $p = 0.423$). Overall this indicated that double blinding was preserved, although participants in the modafinil groups provided higher ratings for the '*feel*' item of the drug effects questionnaire ($p_{(FDR\text{-}adjusted)}=0.035$; Table 3.2).

Table 3.2

Subjective drug effects (drug effects questionnaire scores)

	Placebo	Modafinil	*t*-value; uncorrected *p*	Fdr adjusted p^*
Feel	1.59 (0.88)	2.23 (1.14)	2.762 .007	.035
High	1.21 (0.52)	1.60 (0.98)	2.223 .029	.073
Dislike	1.33 (0.62)	1.43 (0.78)	0.577 .566	.566
Like	1.92 (1.18)	2.43 (1.28)	1.813 .074	.123
More	2.05 (1.32)	2.30 (1.29)	0.850 .398	.498

Note. * Benjamini-Hochberg Adjusted *P* value

3.3.9 Follow-up

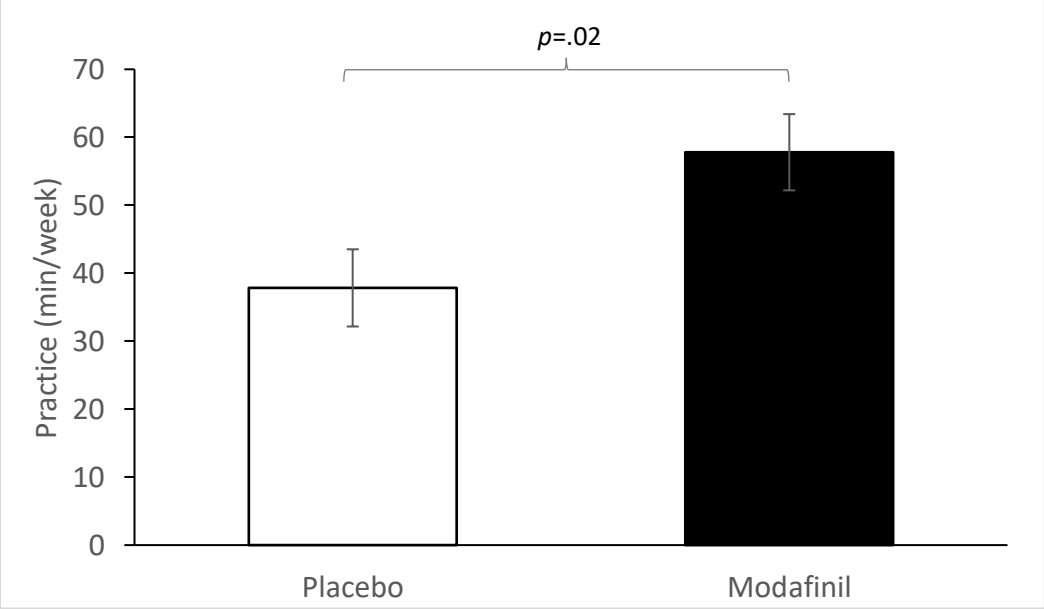
3.3.9.1 Engagement with Self-practice. The majority of participants (*n*=73; 92.4%) indicated that they engaged in at least some strategy practice during the follow-up period (≥1 occasion), with the mean minutes of practice for the whole sample at 47.82 (± 35.49) min. The drug × strategy effect on total minutes of practice during the 7-day follow-up period was not significant $F(1,75) = 0.251$, $p = 0.618$) and the strategy main effect was also non-significant ($F(1,75) = 0.354$, $p = 0.553$). Additionally, there were no significant strategy or drug effect on the number of strategy practice occasions in the follow-up period (overall mean across conditions: 5.1 ± 3.1; *F* values ≤2.521, *ps*≥0.117). However, there was a significant main effect of Drug ($F(1,75) = 5.613$, $p = 0.02$). During the follow-up,

participants in the placebo group practiced *either* strategy for a total of 35.78 ± 32.53 min (mean + SD) compared to 54.78 ± 34.71 in the modafinil group, representing 53% more time spent on strategy practice in the modafinil group (see Figure 3.7).

3.3.9.2 Trait Mindfulness and Negative Affect. Tests of within-subjects effects (i.e. interactions involving time and drug and/or strategy) showed that there were no longer-term changes (Day 1 to Day 8) in trait mindfulness (FFMQ, F values ≤ 1.567, p values ≥0.215), state mindfulness (SMS, F values ≤ 1.086, p values ≥0.301) or negative affect (DASS-21-depression, F values < 1).

Figure 3.7

Total time (min/week) spent practicing in week following lab session (mean ± SE)



3.4 Discussion

3.4.1 Overview and Contextualisation of Results

In this study, increases in state mindfulness described in some previous studies of behavioural mindfulness training (e.g. Tanay & Bernstein, 2013) were found to be mimicked using an acute pharmacological intervention. Specifically, 200 mg modafinil caused a significant increase in state mindfulness prior to any behavioural training (from T1 to T2), and bolstered the beneficial effects of both behavioural strategies from T2 to T3 on state mindfulness. Exploratory analysis also suggested that participants administered a single dose of modafinil spent 53% more time practicing their assigned strategy in the seven days after in-lab training relative to placebo. Additionally, modafinil improved participants' performance on the sustained attention (psychomotor vigilance) task. However, contrary to hypotheses, there was no evidence of an effect of modafinil on mind-wandering.

In contrast to the hypothesised pharmacological effects, which were confirmed (on state mindfulness and sustained attention), there was no effect of Strategy on sustained attention performance, mind-wandering or on state mindfulness: both strategies showed equivalent increases in SMS scores between T2 and T3. We observed higher post-strategy parasympathetic activation (reflected in higher HRV) in the mindfulness condition (in both drug conditions), and although this was not hypothesised *a priori*, increased heart rate variability has been suggested as a potential biomarker for mindful states (Krygier et al., 2013). Finally, there was no evidence of synergistic effects of modafinil and mindfulness, as indicated by the lack of any drug × strategy interactions.

One rationale for examining interactions between mindfulness and modafinil is that modafinil (or related drugs), might have utility as temporary adjuncts to mindfulness-based treatments (e.g. in early phases of treatment), especially in patients who might otherwise fail to engage in such therapies. For example, people with low levels of trait mindfulness may

find the required exercises especially challenging and hence may not expect to benefit from such treatment. Indeed, mindfulness-based relapse prevention for substance use disorder (for example) has lower rates of compliance relative to standard cognitive-behavioural relapse prevention (e.g. Bowen et al, 2014). In addition, patients whose cognitive resources are depleted due to high levels of rumination or worry obtain less benefit from mindfulness-based interventions (Banerjee, Cavanagh & Strauss, 2018), while those with impairments in executive function and inhibitory control deficits may find it difficult to adhere to treatment (see Witkiewitz et al, 2019). Adjunctive pharmacological interventions that counteract such barriers by, for example, lowering the threshold for attaining focused attentional states, might therefore enable wider benefits of mindfulness to be realised. Our results provide the first indication that modafinil has the potential to augment state mindfulness, warranting further investigation of this strategy in people who might benefit from mindfulness-based strategies, but initially find it difficult to engage.

3.4.2 Pharmacologically-assisted Mindfulness within a Neuroscientific Context

Neuroimaging studies of modafinil have demonstrated decreases in BOLD signal in the anterior cingulate cortex (ACC), which were associated with improved performance on cognitive tasks (Rasetti et al., 2010), and considered to be a reflection of increased efficiency of information processing due to the drug's catecholaminergic effects. Evidence of modulation of function of the ACC by modafinil has also been demonstrated in patient populations (e.g.: Green et al., 2005). Considering the importance of this region for mindfulness (Holzel et al., 2017), and evidence that it is particularly highly recruited in early stages of practice (Tang, Hozel & Posner, 2015), it is conceivable that enhanced connectivity and/or efficiency may have contributed to the increased levels of state mindfulness, demonstrated both before and after the behavioural strategies were completed.

Our finding of enhanced engagement in self-practiced strategies in the seven days following the lab session is indicative of modafinil's potential as a complement to behavioural strategies such as mindfulness and relaxation. Interestingly, participants did not significantly differ in the number of occasions they applied themselves to practice, but those in the modafinil groups maintained longer self-practice sessions in the week following the laboratory visit. Enhanced self-practice in those who were received modafinil could partly be explained by having a 'facilitated' initial experience of their assigned strategy. Having an 'assisted' experience during the lab session might have encouraged adherence to practice sessions during the follow-up period. Indeed it has been shown that participant's experience of a behavioural strategy can likely effect their likelihood of adhering to following sessions (Van Cappellen, Catalino, & Frederickson, 2020). Increasingly, pharmacological-augmentation models of behavioural therapies are being accepted and implemented. A recent example is 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for PTSD (Mithoefer et al., 2018), which uses the drug-assisted session to allow patients to more easily tolerate distress and remain within a desirable range of anxious activation, potentially allowing for greater extinction learning during exposure to distressing memories. Though the application is different, modafinil in this case may temporarily enhance executive functions such as response inhibition (e.g. Turner, Clark, Dowson, Robbins, & Sahakian, 2004), thus facilitating the engagement in focused attention. It is also plausible that participants without particular deficiencies in attentional capacities, but that score naturally low on trait mindfulness may benefit from the acute enhancement of sustained attention capacities (Turner et al., 2004), making it easier to access a state that feels less difficult, and alongside potentially greater activation of reward circuitry associated with mindfulness practice (Kjaer

et al., 2002), a more positive association created with the process, therefore enhancing the time that participants engage in unassisted self-practice.

The challenge for pharmacological enhancement of contemplative practices is to identify suitable (efficacious, safe and acceptable) drugs that acutely modulate the psychological processes that underlie therapeutic mindfulness and related contemplative practices. Because of the overlapping descriptions of altered conscious experiences produced by psychedelics and (to a much lesser extent and/or less frequently) meditation practices, recent studies have examined the possible co-facilitation between psychedelic drugs and meditative practices (e.g. Griffiths et al., 2018; Smigielski et al., 2019). Indeed, there is a strong clinical rationale for using meditative techniques to *prepare* patients for therapeutic psychedelic experiences (see chapter five). Foundational mindfulness techniques (i.e. focused attention exercises) that create the cognitive context for 'insight-oriented' practices (i.e. open monitoring; see Lutz et al., 2008 - might also help to create a suitable internal state (i.e. a 'set') conducive to a pleasant psychedelic experience, while also reducing the chances of 'challenging' experiences. This idea has some parallels to the notion that combining modafinil with mindfulness might increase the acceptability of mindfulness exercises by generating a suitable 'attentional context' for simulating and/or enhancing a focused attention form of meditation.

Unlike psychedelics, which reliably produce a unique state of consciousness that closely resembles the peak transcendent experiences reported by highly experienced meditators, the effects of modafinil reported here were, unsurprisingly, subtle. As such, the contexts in which psychedelics and drugs like modafinil might be used adjunctively as enhancement strategies for mindfulness-based treatments are likely to be quite different. For example, psychedelics might be reserved for instances of treatment-resistance that are

maintained by cognitive rigidity and which require a fundamental shift in perspective that cannot be achieved using behavioural procedures (like mindfulness) alone. A recent example of this would be the use of a single ketamine administration to support a mindfulness-based behavioural modification program for patients with cocaine dependence (Dakwar et al., 2019). On the other hand, attention-modulating drugs such as modafinil might be suitable adjunctive treatments when patients have a specific cognitive phenotype that would interfere with engagement with mindfulness techniques. This might be the case, for example, when attentional impairments are a core symptom of a disorder (e.g. attention deficit-hyperactivity disorder; Smalley et al., 2009), or are secondary to worry (e.g. in generalised anxiety) or rumination (in depression; Banerjee et al, 2018). Considering the negative correlation between ADHD and trait mindfulness (Deng et al., 2014; Keith et al., 2016), it would appear that there is a great amount of potential for applying 'assisted mindfulness' in certain patient populations.

3.4.3 Future Research

In the current study we examined a specific, isolated aspect of mindfulness meditation (focused attention), in the absence of the multiple and complex meditation strategies typically used in clinical interventions. This was necessary to minimise the additional 'noise' generated by the other components of mindfulness interventions, which engage a variety of psychological/psychophysiological processes other than focused attention (e.g. interoception, affect labelling, self/other-affiliation, distributed attention). However, these component processes may also be amenable to pharmacological manipulation, allowing them to be interrogated using pharmacological probes. For example, the β-adrenoceptor agonist, isoproterenol, which enhances interoceptive awareness (through increased cardiac contractility and heartbeat detection) has been used to test the idea that interoceptive acuity is

especially well-developed in experienced meditators (it is not; Khalsa et al., 2019). Considering the research on psychedelics referred to above, other studies have shown that MDMA, which has pro-affiliation effects, may bolster the efficacy of another set of contemplative techniques: compassionate-oriented practices (Kamboj et al., 2015, 2018). As such, the current study builds on the small but growing literature in contemplative science in which pharmacological agents are either used as experimental probes to interrogate the specific psychological processes implicated in meditation practices (isoproterenol, oxytocin), or tested as potential adjunctives to therapeutic meditation (MDMA, classic psychedelics).

Future research could also employ techniques such as fMRI to investigate if the effects found here are mediated by mechanisms such as changes in functional connectivity in areas of the brain relevant to self- and biologically-relevant stimuli, such as the salience network. There is evidence that modafinil can enhance functional connectivity in areas such as the insula – an area that is key in the processing of sensorimotor and interoceptive stimuli, as well as the control of motivation (Cera et al., 2014).

3.4.4 Strengths and Limitations

This was an experimental study examining the potential of modafinil to mimic or enhance a specific component of behavioural training in healthy volunteers. Strengths include the randomised controlled nature of the design, pre-registration of research questions and analyses, and the close matching of behavioural strategies used.

It is possible that the relatively small effect on state mindfulness and absence of enhancement of strategy effects observed with modafinil reflected our recruitment of participants with intact attentional performance. Future studies may seek to examine these effects in other populations, who might be expected to have impaired capacity to engage in

mindfulness training (e.g. those with high levels of rumination, worry, substance use, or poor performance on working memory or attentional tasks).

One of the challenges of studying the effects of specific mindfulness (and indeed, other psychological treatment) techniques is the design of control interventions that are equivalent in complexity, credibility, and expectancies, while also being relatively inert. While we succeeded in the first three aims, the relaxation strategy did not appear to be inert, at least in relation to increasing state mindfulness. It is likely that this is because the active relaxation control instructions were insufficiently distinct from the mindfulness instructions. This problem of effectively matching and blinding active primary interventions and active controls is not unique to experimental studies. Active controls for clinical mindfulness interventions - even those that appear to target different mechanisms of change compared to mindfulness - can produce equivalent increases in mindfulness (McCoon et al., 2012; see Levinson et al, 2014). As such, the design of suitable controls remains a priority in this area of research.

3.4.5 Conclusion

This study demonstrates that modafinil has potential as an adjunct to attentional aspects of mindfulness training. In particular, since modafinil increases state mindfulness, it may be a useful preparatory treatment prior to the use of behavioural mindfulness training. Additionally, modafinil increased psychomotor vigilance (acutely) and the duration of time practicing a psychological strategy by 53%. Future studies should aim to translate these findings to clinical samples, particularly in those with cognitive patterns (rumination, worry) or neuropsychological phenotypes (impaired working memory, executive function and/or attentional abilities) that may ordinarily limit the effectiveness of or engagement with mindfulness.

Chapter 4

Study Protocol: A Double-blind Randomised Controlled Trial Exploring the Effects of Modafinil and Breath-counting in Healthy Participants

4.1 Introduction

4.1.1 Background

The evidence demonstrating the therapeutic potential for mindfulness meditation is growing, with numerous forms of therapy now incorporating an element of mindfulness practice (Creswell, 2017). The evidence is most robust when considering longer-term mindfulness-based training, such as mindfulness-based stress reduction (MBSR, Kabat-Zinn, 1990). However, much like other long-term behavioural therapies, attrition rates are found to be as high as 38% (Arch et al., 2013), and current data demonstrate limited effectiveness for persons with a current diagnosis of anxiety (e.g. Strauss, Cavanagh, Oliver, & Pettman, 2014). Motivational and attentional difficulties may be a barrier to successful engagement, as well as cognitive patterns which seem naturally counter to the approach of mindfulness (e.g. avoidance is a common mechanism for (maladaptive) coping in anxiety and depression, which sits in opposition to present moment awareness of one's thoughts and experience). Additionally, symptoms of attentional disorders, anxiety and depression correlate negatively with trait mindfulness (Smalley et al., 2009, Keith et al., 2017), demonstrating that persons suffering from associated psychopathologies essentially start off at a disadvantage compared to a healthy sample before beginning a mindfulness or other contemplative practice.

How, then, may we build a bridge between mindfulness meditation and its myriad benefits and those who most require assistance in those domains? One solution is to combine behavioural and pharmacological approaches: just as combinations of pharmacotherapy and psychotherapies have proven to be more effective than one approach alone (Moss et al.,

2016), a pharmacologically-assisted introduction to mindfulness meditation may help provide the attentional and motivational mind-set required for novice mindfulness practice (see chapter 3). Indeed, it has been demonstrated that contemplative practice and serotonergic drugs such as MDMA may have an additive effect on mindfulness-related capacities such as self-compassion (Kamboj et al., 2018), and that mindfulness-related abilities such as acceptance can be useful to prepare for psychedelic experience (Watts & Luoma, 2020), suggesting 'assisted mindfulness' approaches may be a valuable option.

Though early investigations have been conducted exploring the combination of certain meditative techniques with psychedelics (e.g.: Smigielski, Scheidegger, Kometer, & Vollenweider, 2019), to the author's knowledge, our empirical study summarised in the previous chapter was the first to experimentally manipulate mindfulness and a pharmacological agent within a laboratory context, to explore their separate and interactive effects. In this randomised controlled experiment, we compared the effects of a mindfulness strategy (in contrast to a relaxation control strategy) and modafinil (versus placebo) on measures of state mindfulness, sustained attention and physiological indices.

We demonstrated that modafinil (compared to placebo) increased state mindfulness, and improved engagement with strategy practice in the following week (measured by time spent completing self-practice). We found that behavioural strategies produced only limited differential effects - predominantly on heart rate variability - indicating increased parasympathetic activity following brief mindfulness training, but equivalent increases in state mindfulness between the two strategies. These results suggest that an adjunctive approach between modafinil and mindfulness is worthy of further exploration. They also demonstrate the methodological difficulties that are prevalent in mindfulness research (as summarised in chapter two), including operationalising mindfulness (i.e. as a purely

subjective, self-reported state), and the challenging task of choosing appropriate behavioural control condition for mindfulness tasks. The systematic review in the second chapter illustrates how varied the approach to operationalising and measuring mindfulness is to date in the literature, which is an indication that historically there has not been a single guiding empirical approach to tackling these issues. Neither has there been a consensus on objective changes (i.e. biomarkers) that accompany mindful states. Although neuroimaging might be considered a potentially valuable approach to obtaining objective indices of mindful states, the existing evidence suggests that there are no consistent or *specific* mindfulness related changes in oscillatory activity in the brain (Lomas, Ivtzan, & Fu, 2015). For example, although a number of EEG studies have shown increased alpha and theta during mindfulness, these may largely reflect changes in alertness rather than most aspects of mindfulness. Equally, neuroimaging technologies are generally expensive, and not necessarily conducive to testing large samples.

A significant advance in this respect was made by Levinson and colleagues (2014). In four separate studies with >400 participants, where they provided a convincing and experimentally convenient approach to tackling the objective measurement of mindfulness states using a breath counting task. This task operationalises mindfulness as ‘present moment awareness’, and acts as both a task to train mindfulness and measure it simultaneously. This involves the participant tracking the number of breaths they take (breath counting), while mechanical changes during respiration (i.e. the abdomen rising and falling) are monitored objectively. Accuracy of counting (i.e. levels of correspondence between objectively measured breath count and participant-reported counts) correlates with self-report measures of mindfulness, and could differentiate novice from experienced meditators, even when controlling for sustained attention and working memory task scores. Training with the breath

counting task was also associated with decreased mind-wandering, more positive affect, as well as improved indices of meta-awareness and non-attachment (Levinson et al., 2014). Reliability and validity have also been reproduced in an Asian undergraduate sample (Wong, Massar, Michael, & Lim, 2018), generalising the original studies by Levinson et al (2014) which were completed with local university or Buddhist community members in the USA. Wong and colleagues (2018) also found the BCT to be associated with sustained attention and self-reported mindfulness, alongside demonstrating good test-retest reliability.

Thus, for this second empirical study, we employed a breath counting task very similar to that of Levinson and colleagues (2014), using a similar experimental design to the experimental study reported in chapter three. The key difference apart from using the validated and objective measure of mindfulness (breath counting) to supplement the self-report measure of state mindfulness, was the use of an arithmetic task as the behavioural control condition. As explored in chapter two, it is desirable for behavioural control tasks to a) be active, such as to control for the effect of engaging in a task, b) match the mindfulness strategy on non-specific factors (such as duration), and c) not contain elements of, or be likely to instigate a state of mindfulness. An arithmetic task was chosen as the behavioural control since it would be feasible to match the breath counting task on structural elements, such as form of the task (including the requirement for a behavioural response) and its duration. An arithmetic task could also be adapted to create a similar level of engagement as the mindfulness strategy, and it may also instigate a positive expectation of usefulness for cognitive training. A similar task has been used as an active control condition in a single-session mindfulness experiment, and enabled differential effects on state mindfulness to be detected relative to the mindfulness condition, and an attention task (Watier & Dubois,

2016), thus we believe it to be less likely to unintentionally produce mindfulness-like effects, allowing differential strategy effects to emerge more clearly.

4.1.2 Hypotheses as Published on the Open Science Framework

H1 - Modafinil will increase state mindfulness and sustained attention, and decrease mind-wandering compared to placebo.

H2 - A mindfulness intervention (i.e. breath counting task) will enhance state mindfulness, sustained attention, parasympathetic activity (increased RMSSD, HRV) and decrease mind-wandering compared to the arithmetic control task.

H3 - Modafinil and the mindfulness intervention (breath counting task), when combined, will have additive effects on: state mindfulness, sustained attention and mind-wandering.

H4 - Participants who receive modafinil will spend longer self-practicing the task they learnt in the week after the lab session compared to those who received placebo.

On the basis of the results presented in chapter two, the elements of these hypotheses pertaining to mind-wandering, should be considered exploratory rather than confirmatory. Although the results from chapter two do not support strong (confirmatory) hypotheses in favour of reducing mind-wandering following modafinil or mindfulness, we believe that the theoretical basis for these hypotheses is sufficiently strong as to re-examine it in a new sample.

4.2 Methods

4.2.1 Pre-registration of Study

Methods, hypotheses and analysis plans were pre-registered via Open Science Framework before any data was collected for this study (osf.io/8pwa6).

4.2.2 Study Population

We will recruit participants from the university and local community.

Considering we aim to recruit 'healthy' participants for this study, and the research focus on state mindfulness and attention, potential subjects will be screened for low mood and anxiety symptoms, and those scoring above a cut-off (see below) will not be invited to complete the experimental session.

4.2.3 Sample Size and Rationale

We aim to analyse all 80 participant's data. Participant will be allocated randomly to one of four groups (N=20/group): breath counting + modafinil; arithmetic task + modafinil; breath counting + placebo; or arithmetic task + placebo, with n=10 females/group.

The sample size was calculated using GPower software, assuming medium sized effects (f=0.2855) in a repeated measures, within-between ANOVA with 95% power, and alpha level of a=0.05 (Thomas et al., 2021). This calculation indicated that 52 participants were required in a four-group design. This is based on the State Mindfulness Scale, which will be measured three times during the lab session. The effect size was taken from the results of a RM-ANOVA on SMS scores from our previous study (chapter three; Thomas et al., 2021), which yielded a d value of 0.571, and translates to an effect size of f=0.2855. A test-retest correlation of 0.47 was used as per the findings of the authors of the scale (Tanay & Bernstein, 2013). We decided to use a total sample size of 80 (20/group), to ensure adequate power, given uncertainty about effect sizes yielded from other outcomes.

We will stop data collection after 80 participants have been tested, with the exception that there are participants who withdraw their data or do not complete the session, in which case we will attempt to test new participants to replace whole participant data cases that are lost.

4.2.4 Screening Measures

4.2.4.1 Patient Health Questionnaire-2 (PHQ-2). The PHQ-2 is a brief self-report questionnaire which enquires about the frequency of anhedonia and depressed mood, using two questions, over the past two weeks. Participants are asked to choose a response which best corresponds to how often they have been bothered by the following problems, from 0 = "not at all" to 3 = "nearly every day". The total scores is obtained by summing the scores from the two questions, with the cut-off for inclusion in this study as a total of 3 (the identified optimal cut-off when using the scale to screen for depression (Kroenke, Spitzer, & Williams, 2003)).

4.2.4.2 Generalised Anxiety Disorder 2-itemGAD-II. The GAD-2 is a brief initial screening tool used for generalised anxiety disorder, using two questions. Participants are requested to choose, over the last two weeks, how often they have been bothered by feelings of anxiety, and uncontrollable worrying (two key components of anxiety disorders), on a scale of 0 = "not at all" to 3 = "nearly every day". The total scores is made from the sum of the two question scores, with a score of 3 used as a cut-off for identifying cases whereby further diagnosis is warranted (Spitzer, Kroenke, Williams, & Löwe, 2006).

4.2.5 Manipulated Variables

We manipulate both the type of behavioural strategy (breath counting task or arithmetic task) and drug (modafinil or placebo) in a 2 x 2 design, which results in four groups: (i) breath counting + modafinil; (ii) arithmetic task + modafinil; (iii) breath counting + placebo; and (iv) arithmetic task + placebo. These manipulations allow for the examination of a) whether a breath-counting task has significant effects on state mindfulness, attention, autonomic activity and mind-wandering compared to a control (arithmetic) task; b) if modafinil has significantly different effects on state mindfulness and these outcomes relative

to placebo; and c) whether the combined effect of breath counting and modafinil will have additive/synergistic effects on these outcomes.

4.2.5.1 Breath-counting Task. This task was adapted from the task validated by Levinson et al. (2014) as a behavioural measure of mindfulness, as well as an effective training method to improve self-reported mindfulness and decreased mind-wandering compared to controls. Participants are instructed to be aware of the breath, and count breaths from 1 to 9 to aid in maintaining this attention, over the course of a 15-minute period. Participants press a response button once for each breath from 1-8, and twice for breath 9. A clicker is connected to the Biopac unit to record a) the total number of clicks, and b) the number of double clicks made by the participants during the BCT.

4.2.5.2 Arithmetic Task: This task was created by the team as an active behavioural control task, and designed to be similarly engaging as the breath counting but engage distinct cognitive processes to those implicated in the mindfulness task. Participants view a screen that shows recurrent simple single-digit additions, and are instructed to complete these additions in their head, whilst pressing the clicker once per addition from addition 1-4, and twice on the 5^{th} of each set. Although a behavioural response was required upon completion of each calculation, unlike the breath-counting task, there was no behavioural index of accuracy (sums were completed mentally). The sums used were tested for average speed of completion, and made to match the average resting breath speed of approximately four seconds (Flenady, Dwyer, & Applegarth, 2017). Participants in the arithmetic task were also instructed to double click at the end of a 'set' of sums, which was every five sums – tested to approximately match counting difficulty to maintaining counts up to nine breaths in the mindfulness condition. The arithmetic task will be matched in timing to the BCT, also lasting 15 minutes.

The eventual task design was based on pragmatic as well as scientific considerations. As noted previously (also in chapter two), there are inherent risks in closely matching behavioural controls to active conditions in that the control procedure may inadvertently activate the process of interest (mindfulness). Here, we aimed to balance matching task demands, response type, complexity and duration of instructions and task duration with the requirement that the two tasks should engage distinct psychological (e.g. arousal and attention) processes, as far as possible. It is accepted however, that in the absence of objective measures of some of the ostensibly matched characteristics, it is possible that sub-optimal matching was achieved. Moreover, given the behavioural measure of mindfulness used here (button presses) is only relevant to the mindfulness (breath counting) condition, it is not possible to eliminate the possibility that the arithmetic task also engages mindfulness-related processes to some extent.

4.2.5.3 Capsule content: In the active drug groups, capsules will contain a 200mg tablet of modafinil (Glenmark Pharmaceuticals Europe Limited, UK). The dose was chosen according to the demonstration of enhanced cognitive performance in previous studies, compared to lower doses (Turner et al., 2003). The modafinil tablets were over-encapsulated into opaque gelatin capsules with additional skimmed milk powder (Marvel, Premier Foods). The placebo capsules were identical, but filled only with skimmed milk powder. All capsules will be taken orally.

4.2.6 Measured Variables

4.2.6.1 State Mindfulness. The primary outcome measure will be responses on the State Mindfulness Scale (SMS, Tanay & Bernstein, 2013). It measures mindfulness using a conceptual model which is aligned with traditional Buddhist scholarship as well as theoretical definitions of mindfulness, with reference to attentional processes (Anālayo,

2013; Bishop et al., 2004). The SMS queries elements of mindfulness along two subscales, mindfulness of body and of mind (see examples below). Participants rate each item based on their experience in the 10-minutes prior, using a five-point scale from 1 = "not at all" to 5 – "very well" (see Table 4.1 for an example of scale items). State mindfulness will be measured three times during the lab session: pre-drug, pre-strategy, and post-strategy; as well as once at follow-up.

Table 4.1

Example items from the SCS (Tanay & Bernstein, 2013)

Item
Mind subscale
I was aware of different emotions that arose in me
Body subscale
I noticed physical sensations come and go

4.2.6.2 Sustained Attention. The psychomotor vigilance task (PVT) is a reaction-timed task which provides a measure of sustained attention. It has demonstrated sensitivity to both mindfulness training and the consumption of modafinil (Dinges & Weaver, 2003; Kaul, Passafiume, Sargent, & O 'hara, 2010). The PVT has been optimised for use via a PC, without necessity for task-specific hardware (see Khitrov et al., 2014). As per suggestions from Khitrov and colleagues (2014), a high-performance gaming mouse was used to record responses. During this task, participants are instructed to watch the screen with their hand on the mouse, and click the mouse as soon as they see a visual stimulus (a millisecond timer showing reaction time) appearing on the screen. This will be measured once during the lab session (post-strategy), directly after the mind-wandering task has been completed.

4.2.6.3 Respiration Rate. A respiration belt attached to a Biopac MP35 unit will be used to measure a) the average length of each participant's breath cycles at baseline, and b) how many breath cycles are completed during the BCT (for accuracy calculations). For those assigned to the BCT, this will be another key outcome.

4.2.6.4 Mind-wandering. The tendency to shift attention to non-task related thoughts (termed mind-wandering) will be assessed using an adapted version of the task described by Mrazek et al. (2012), which captures both self-caught and probe-caught instances of mind-wandering. During this task, participants will be instructed to practice the strategy they had just learned, and press the mouse button if their mind wandered from the strategy. Fifteen probes (constituting a bell tone) would be presented at pseudo-random intervals of 40-80 seconds (with an average of 60s) over the course of the 16-minute task. This would be completed once, during the post-strategy (T3) phase.

4.2.6.5 Positive and Negative Affect Scales. The international short form positive and negative affect scales (I-PANAS-SF, Thompson, 2007) will be assessed at baseline (T1), post-drug (T2) and post-strategy (T3). It has a total of 10 items, and has been accepted as psychometrically suitable in comparison to the 20-item version.

4.2.6.6 Trait Mindfulness. The five facet mindfulness questionnaire (FFMQ, Baer et al., 2006) will be used to measure trait mindfulness at baseline. Here will we use the 15-item version, which has been demonstrated to hold the same convergent validity as the 39-item version (Gu et al., 2016).

4.2.6.7 Depression, Anxiety and Stress. The depression, anxiety and stress scales (DASS, Lovibond & Lovibond, 1995) will be used to measure negative affect experienced in the week prior at baseline.

4.2.6.8 Subjective Drug Effects. The drug effects questionnaire (DEQ, Morean et al., 2013) will be used to evaluate subjective effects of the drug during the lab session, before the behavioural tasks are completed.

4.2.6.9 Credibility and Expectancy of Behavioural Tasks. The credibility and expectancy questionnaire (Devilly & Borkovec, 2000) will be completed after the instructions to the BCT/arithmetic tasks are read to measure to what extent participants believe the tasks will be helpful in improving their concentration.

4.2.6.10 Task Compliance. A compliance check will be completed after the BCT/arithmetic task, whereby participants indicate on a Likert scale (0 to 7) to which extent they followed the task that they completed.

4.2.6.11 Behavioural and Drug Condition Guess. At the end of the study, both the participant then researcher complete a guess as to which condition(s) they expected the participant had been assigned to.

4.2.6.12 Physiological Measures. Heart rate and blood pressure will be recorded at baseline, after drug administration (+rest), and after the BCT/arithmetic task. Heart rate variability will be measured throughout the lab session using a Firstbeat Bodyguard 2 device.

Table 4.2

Table detailing study measures/tasks and their timings

	STUDY PERIOD				
TIMEPOINT	Enrolment	Experimental session			Follow-up
		Pre-drug	Post-drug	Post-strategy	
PHQ-2	□				
GAD-2	□				
SMS		□	□	□	□
PANAS		□	□	□	□
Heart Rate Variability		□	□	□	
Blood Pressure		□	□	□	
DASS-21		□			□
FFMQ		□			□
Drug administration		(□)			
DEQ-5			□	□	
Breath counting/arithmetic task			(□)		
Compliance Check				□	
Mind-wandering task				□	
Psychomotor vigilance task				□	
Estimation of daily practice					□

Note. Brackets here indicate that the event will occur at the end of the battery of measures in the indicated time point, bridging into the next time point. Bold font indicates key processes during the study.

4.2.7 Design

This would be a 2 x 2 factorial, double-placebo controlled randomised experimental study with a mixed design, exploring both between- and within-subjects variables. No

counterbalancing is required. Neither the participants, research personnel, nor researchers who conduct the analyses will be aware of the behavioural or drug treatment group to which participants have been assigned.

4.2.7.1 Randomisation. We will be randomising at two levels: for drug type and behavioural task. The assignment of participant numbers across the four groups will be balanced across gender and number of participants (at 40 and 80). The random numbers used will be created using a randomisation function from http://random.org.

Drug randomisation: The capsules will be over-encapsulated by researchers that are not involved in any experimental procedures, and before each testing session, will be put into labelled envelopes according to participant number, so that testing remains double-blind.

To ensure blinding of the researcher to the task type (BCT/arithmetic), a second researcher will be present only to set up that task and ensure the participant's comprehension of the instructions. This second researcher will not interact with the participant or the researcher conducting the experiment.

4.2.8 Ethical Considerations

This study received ethical approval from the University College London Research Ethics Committee, under Project 12267/001, and all procedures will be conducted in accordance with the principles of the Declaration of Helsinki.

4.2.8.1 Informed Consent. All participants will be given informed consent, with the receipt of information about the study at the first available opportunity (on registering interest in the study), and opportunities to re-read information and ask any questions before commencement of experimental procedures on the day of participation.

4.2.9 Statistical Analysis

4.2.9.1 Statistical Models. H 1, 2, and 3 – To investigate main effects of drug and strategy, as well as their interactive effects on state mindfulness, a repeated measures analysis of variance (ANOVA) will be conducted, with drug group (placebo/ modafinil) and strategy (breath counting/ arithmetic) as between-subjects factors, and time (T1 – T3) as the within-subjects factor (3 x 2 x 2 ANOVA).

PVT (reaction times) and mind-wandering instances will be analysed using a 2 x 2 univariate ANOVA, with drug group and strategy as between-subjects factors. If the mind-wandering data is over-dispersed, this data will be analysed using a negative binomial regression.

H4 – A univariate ANOVA will be used to explore differences in time spent practicing the BCT/arithmetic task (in minutes) in the 7 days following the lab session, using drug group (placebo, modafinil) as the between-subjects factor.

4.2.9.2 Transformations. We do not intend to transform our data, unless it shows clear departures from normality, and only if transformations improve the distribution of the scores.

4.2.9.3 Follow-up Analyses. Significant main effects or interactions will be followed up by Bonferroni-corrected pairwise comparisons.

4.2.9.4 Inference Criteria. For analyses of primary outcomes, we will adopt an alpha threshold of .05. P-values below this threshold will be considered statistically significant.

4.2.9.5 Data Exclusion. Outlying data points (i.e. scores with studentised residuals ≥ 3) will be winsorized in accordance with recommendations of Tabachnick and Fidell (2001), namely replaced by $x_{(highest\ non\text{-}outlier)} + 1$.

4.2.9.6 Exploratory Analyses. We will explore whether baseline values in trait mindfulness predict the magnitude of change in state mindfulness throughout the lab session,

using a simple mediation model with strategy/drug group as the predictor (X), trait mindfulness score as the mediator (M), and change in state mindfulness as the outcome (Y) variable.

I. We will explore whether the time spent practicing the task(s) in the week following is associated to the change in state mindfulness from T2 to T3, using a bivariate correlation between time spent practicing and change in state mindfulness (T3-T2). If this reveals a significant correlation, we will run a mediation analysis to estimate whether time spent practicing mediates the effect of strategy and drug on change in state mindfulness (T3-T1).

4.3 COVID-19 Interruption

Recruitment of participants commenced at the beginning of March 2020. At this point, we had seven potential participants screened and interested in taking part, and collected data from four participants, before needing to suspend data collection due to the first pandemic lockdown (mid-March 2020). We aimed to re-start data collection as soon as possible, but due to repeated COVID waves and restrictions on in-person research, data collection could not be completed during the timeframe of this PhD.

Chapter 5

Contemplating Psychedelics: A Thematic Analysis of User Accounts Exploring Synergistic Effects of Psychedelics and Meditative Practices

5.1 Introduction

5.1.1 Historical Psychedelic use and Recent Related Theory

Psychedelic compounds have been used by humans from various cultures and traditions for thousands of years. Naturally occurring hallucinogenic substances such as psilocybin, mescaline (derived from the peyote and San Pedro cacti) and N,N-Dimethyltryptamine (DMT, a molecule found in various plants, which are combined with monoamine oxidase inhibitors to make Ayahuasca) have played an important role in traditional, ceremonial, and therapeutic applications in certain cultures. Since the discovery of naturally occurring psychedelics, synthetic counterparts were synthesized, such as lysergic acid diethyladmide (LSD) in the 50's, which were used as adjuncts to psychotherapy in the 60/70's, before criminalisation fuelled by political incentives (Cohen, et al., 1967, Irwin and Egozcue, 1967). Together, these naturally occurring and synthetic compounds with primarily serotonergic functions form the group of 'classic psychedelics'. Despite the scheduling of most psychedelics across continents, the therapeutic and perspective-altering potential of classic psychedelics has led to extensive recreational use across the globe, as well as tourism economies associated with ceremonial use, of some substances where they are legally administered growing rapidly over the years (Kjellgren, Eriksson, & Norlander, 2009). Though limited data has been collected on trends of recreational use, there is some evidence of the normalisation of recreational drug use in the UK (Mesham et al., 1994), and extensive recreational use of psychedelics in Europe (McCambridge, Winstock, Hunt, & Mitcheson, 2006).

A resurgence in research around the psychedelic state is evolving our understanding of consciousness (e.g.: Carhart-Harris et al., 2014), as well as the effects of the psychedelic state, both acutely and longer-term. Commonly reported subjective effects of classic psychedelic include alterations in perception, mood, and various domains of cognition (Dos Santos & Hallak, 2020). Mystical experiences are a collection of experiences involving changes in relation to the self and the world that make up a key element of subjective effects acutely arising from psychedelic consumption. Reports of mystical experiences include the increased interconnectedness, connection with a sacred entity, sense of truth, and transcendence of usual state of mind, or concept of the self (Stace, 1960). Such alterations of conscious experience have been associated with enhancements in creativity, divergent thinking, and enhanced wellbeing (Topp et al., 1999; Jones et al., 2009; (Kuypers et al., 2016) Gandy, 2019; Sampedro et al., 2017; Griffiths et al., 2006). It is noteworthy that despite having different pharmacokinetic action to classic psychedelic substances, 3,4-Methylene-dioxymethamphetamine (MDMA) and ketamine both produce psychedelic-like effects, show high rates of recreational consumption, and demonstrate potential for therapeutic use (Kamboj et al., 2018; Mithoefer et al., 2018), they were not included in the current investigation. Interestingly, in a recent unpublished cross-sectional internet survey including 1298 psychedelic users, 67% responded that they had a meditation practice, indicating that meditation practice is highly prevalent among people who use psychedelics (Azmoodeh, 2020).

5.1.2 Background and Current Understanding of Meditative Practices

Much like psychedelic substances, meditative practices have been a core aspect of traditional spiritual practices in cultures across the world, particularly prominent in India, China, Japan and Tibet. The term meditation essentially denotes ‘practices that aim to

monitor and regulate attention, perception, emotion and homeostasis' (Fox & Cahn; Tang et al., 2015). Some scholars include spiritual practices such as traditional ceremonial or ritualistic dancing, or yogic postural (asana) practice under the umbrella of meditation practices (West, 1987). Indeed, the variety of meditative practices spans Buddhist, yogic, Hindu and shamanic traditions, to name a few. The majority of contemplative research has focused on techniques stemming from Buddhist traditions, with a particular emphasis on mindfulness meditation.

Focused attention and open monitoring styles are commonly referenced subtypes of meditation in mindfulness literature. Focused attention practices involve sustaining attention to a particular object, such as the breath-focused meditations and mantra recitation. Open awareness practices involve maintaining a particular awareness to the content of the mind, such as thoughts and feelings that arise. These techniques have been incorporated into interventions such as mindfulness-based stress reduction (MBSR, Kabat-Zinn et al., 1992) and acceptance and commitment therapy (S. C. Hayes, Strosahl, & Wilson, 2011). Meditation techniques with relationship and values as central themes focus on (building) compassionate and loving thoughts towards the self and others, and have resulted in therapeutic programs such as cognitive-based compassion training. Object- and subject-oriented insight practices attempt to change the way the mind naturally approaches phenomena using training, which have been incorporated into therapeutic techniques such mindfulness-based cognitive therapy (MBCT). See Table 5.1 for examples of different types of meditation practices and programs that apply them. Though the distinction between different styles of meditation is not central to this investigation, to demonstrate the variety of commonly practiced forms of meditation, examples are displayed below.

Table 5.1

Examples of meditation practices and related clinical interventions (C. Dahl et al., 2015)

Attentional Family	**Constructive Family**	**Deconstructive Family**
Focused attention	Relationship Orientation	Object-oriented Insight
E.g.: Breath Counting	E.g.: Loving-kindness	E.g.: Vipassana
Open Monitoring	Values Orientation	Subject-oriented Insight
E.g.: Mindfulness-based Stress Reduction	E.g.: The Four Thoughts	E.g.: Cognitive Behaviour Therapy

Note. Though this typology groups common forms of meditation practice and meditation-based interventions into the above categories, note that practices may contain elements of all three families, and the above categorisation is based on the primary mechanisms of each practice.

Thus, 'meditation' does not refer to a single practice, approach, or state of mind. Rather, meditative practices can be considered a varied array of practices that utilise many different cognitive capacities (C. J. Dahl, Lutz, & Davidson, 2015; Lutz et al., 2008). Relatedly, different practices will instigate a range of neurophysiological changes, be modulated by many variables (such as experience level), and have a wide range of effects (Tang et al., 2015).

5.1.3 The Benefits of Meditative Practices

Though subjective effects of meditation vary according to the particular practice, beneficial effects span across cognitive and affective processing, including enhancements in positive affect, attention, memory, sensory processing, and immunology (Gill et al., 2020; Jiménez et al., 2020; Sedlmeier et al., 2012). In particular, mindfulness based intervention programs, which generally span 8-12 weeks have been shown to help with indications of chronic and stress-related pain, depression, anxiety, panic disorders, eating disorders and

relapse from depression (see Baer, 2003; Khoury et al., 2013). In experimental contexts, brief mindfulness-based interventions (spanning between one to four sessions) have also proven useful for anxiety, depression, emotion regulation, stress management, and cognitive functions such as attention, memory (Howarth et al., 2019).

As per the review of single-session experimental literature that forms chapter two, preliminary evidence indicates single session laboratory sessions may be useful for temporarily enhancing some emotion regulation capacities, alongside attentional performance and cognitive bias. There is also evidence that a single session of mindfulness meditation can be useful for reducing habitual behaviours (e.g. risky drinking (Kamboj et al., 2017). Learned skills and mechanisms proposed to underlie therapeutic benefits of meditation include: attention regulation, body awareness, emotion regulation, alterations in perspective on the self, pro-sociality, acceptance, decentering and non-attachment (Baer, 2003; Hölzel et al., 2011; Vago & Silbersweig, 2012).

In mindfulness literature, the concept of 'decentering' is suggested as an important component of change following meditation practice (Bernstein et al., 2015; Vago & Silbersweig, 2012). Decentering, is defined as the capacity to practice awareness of thoughts, feelings and sensations as passing occurrences (Fresco et al., 2007). This is a particularly useful element of mindful awareness (also known as reperceiving in earlier models, E.g.: Shapiro et al., 2006), since it allows practitioners to observe content of the mind without getting 'caught up' or 'lost' in difficult thoughts, keeping distance from unhelpful thoughts rather than ruminating excessively (Fresco et al., 2007; Vago & Silbersweig, 2012). Psychological distancing is suggested as a protective factor against cognitive vulnerability. This stands because, alongside rumination, fusion of the self and negative thoughts are

critical in exacerbating negative emotion, enhancing, or maintaining anxiety, thus these tendencies predict vulnerability to psychopathology (Smith & Alloy, 2009).

Though distinct concepts, enhancing one's capacity for decentering from thoughts and emotions, and appreciate that they are transient in nature lends itself to the practice of non-attachment (Vago & Silbersweig, 2012). Non-attachment can be understood as a realisation of the impermanence of mental phenomena (Sahdra, Shaver, & Brown, 2010), which is accompanied by a release from grasping onto a particular sense of self, specific desires, objects or goals. Indeed, it is understood in Buddhist literature that attachments are sources of suffering, and thus, if one can learn to cultivate a stance of non-attachment, suffering will decrease. Data from meditation retreat participants indicates that non-attachment may facilitate improvements observed after meditation practice, on outcomes such as: acting with awareness, self-directedness, non-reactivity, negative affect, and satisfaction with life (Montero-Marin et al., 2016).

Following from the concepts of decentering and non-attachment, changes in self-perspective are not uncommon consequences of repeated meditation practice, with alterations in perception of 'the self' are proposed as a key mechanism underlying the benefits of mindfulness meditation (Tang et al., 2015). Though acute subjective experiences are not generally the key focus of meditation research, mystical-like experiences have been reported in experienced meditators, with accounts of ego loss, or awareness of a self that is outside of the ego (Reavley & Pallant, 2009; Russ & Elliott, 2017). Reductions in egoic thoughts have been associated with higher ability to cope with stressors and superior maturity (Emavardhana & Tori, 1997), while higher levels of selflessness, cooperativeness, and self-transcendence have been associated with meditation experience (Haimerl & Valentine, 2001).

5.1.4 Potential Benefits of the Psychedelic State

The aforementioned 'psychedelic renaissance' refers to a growth in evidence base to support potential clinical applications of psychedelics for the treatment of mental health disorders (Wheeler & Dyer, 2020). The psychedelic state appears to produce desirable effects across perceptive, emotional, self-referential and cognitive domains, which may have beneficial implications in various mental health applications. For example, psilocybin has shown promise in reducing symptoms of depression (Carhart-Harris et al., 2016), anxiety (Roland R Griffiths et al., 2016; Mithoefer et al., 2018; Moreno, Wiegand, Taitano, & Delgado, 2006) and substance dependence (Pisano et al., 2017, Bogenschultz et al., 2015, Johnson et al., 2015).

The mechanics of how these changes occur is currently under investigation, however there is evidence that changes in functional connectivity in the brain are important in these alterations, and that resulting reductions in long-term patterns of thinking and behaving allow for changes in perspectives (Carhart-Harris et al., 2014; Swanson, 2018). Certain elements of the psychedelic experience have been highlighted in recent research as associated with these beneficial effects. For example, psychedelic-induced mystical experiences may predict desirable shifts in attitudes and behaviours (Griffiths et al., 2006, 2011), instigate personality changes such as increases in openness (Erritzoe et al., 2019; MacLean, Johnson, & Griffiths, 2011) and produce improvements in depressive symptomology (Roseman et al., 2018); and reductions in anxiety (Ross et al., 2016).

Ego dissolution is another key element of acute psychedelic experiences, which involves a disintegration of the sense of self, or loss of boundaries between the self and other/world (Nour et al., 2016). Experiences of ego dissolution have been found to predict sustained improvements in wellbeing (Nour 2016), and lasting increases in trait mindfulness

(Uthag et al., 2018). Psychedelic-associated ego dissolution may reduce anxiety and depression related to chronic life-threatening diseases (Sandler, 2015), alongside reductions in narcissistic tendency (Halpern, 2003). Similar to the meditation literature, these changes in self-concept (involving a less ego-centric stance) resulting from states of 'expanded consciousness' appear to be an important aspect of psycho-social changes observed after psychedelic consumption (Majić, Schmidt, & Gallinat, 2015).

5.1.5 The overlap (or synergy) Between Psychedelics and Meditative Practices

In response to the preliminary research outlined above regarding meditative and psychedelic experiences both having the potential to cause mystical-type experiences, changes to the perception of the self and alterations in stance towards (or reactivity to) content of the mind, observations and hypotheses regarding their potential synergy, or overlap have been discussed in recent literature. For example, Payne and colleagues (2021) propose a set of distinct synergies that describe how psychedelic and mindfulness-based interventions may combine beneficially. See Table 5.2 for a summary of the proposed synergies, which, it should be noted, at this stage are based primarily on scientific opinion rather than empirical findings.

Table 5.2

Synergies between mindfulness and psychedelic interventions (Payne et al., 2021)

	Name	Direction	Description
1	*Mindful state recognition*	P → M	Psychedelic use may help participants to identify the mindful state
2	*Motivation for mindfulness practice*	P → M	Acute psychedelic-induced effects that resemble meditative states may encourage sustained mindfulness practice
3	*Depth of mindfulness*	P → M	Psychedelics may increase the depth of the meditative experience by way of encouraging non-avoidance, mindful attention and curiosity
4	*Mindful compassion*	P → M	Psychedelics may increase the compassionate aspect of self-referential thought, encouraging a more compassionate practice
5	*Psychedelic non-avoidance*	M → P	Mindfulness may reduce negative reactions and avoidance during a psychedelic trip
6	*Sustained psychedelic proximity and generalisation*	M → P	Mindfulness may assist in maintaining the beneficial effects of the acute psychedelic experience, by way of eliciting non-ordinary states of consciousness that resemble the psychedelic state, and integrating insights into everyday life

Note. The direction (→) indicates a proposed causal association. P = Psychedelic, M = Mindfulness.

In relation to treating depression in particular, mindfulness and psilocybin have been proposed as potentially compatible combination treatments, based on the review of psychological and biological effects of both intervention approaches (Heuschkel & Kuypers, 2020). Focusing on the psychological factors as examples, strategy-based mood enhancement provided by mindfulness may be complementary to content-based mood enhancements demonstrated from psilocybin consumption. For example, reductions in emotional reactivity and enhancement of acceptance through mindfulness strategies may help deter negative thought patterns from prevailing after the subjective effects of the psychedelic afterglow

subside. In respect to executive functioning, mindfulness meditation can enhance cognitive control capacities, whereas psilocybin can encourage disinhibition acutely, and cognitive flexibility in the long-term. Additionally, this review suggests that both modalities hold the potential to enhance interpersonal social skills, a strong predictor for wellbeing (Heuschkel & Kuypers, 2020).

Finally, Millière and colleagues (2018) review available evidence regarding similarities and differences between meditative practices and psychedelic-induced states from the perspective of phenomenology and neurophysiology, with a particular focus on changes to self-related experience. Here it is proposed that meditation and psychedelics may affect similar aspects of self-consciousness in diverse ways. The attainment of 'mystical' or 'peak' experiences (involving a loss of self-consciousness, and therefore loss of boundaries between the self and world) appear to be key in producing beneficial effects of psychedelic-assisted therapy, with the magnitude of mystical-type experience predicting improvements in general well-being, among other psychological outcomes (Pahnke et al., 1971; Carhart-Harris et al., 2018).

Aside from anecdotal evidence of similarities and potential synergies between the two altered states, there is growing evidence that psychedelics can increase psychological indices associated with long-term mindfulness practice, such as trait mindfulness (Madsen et al, 2020; Sampedro et al, 2017; Franquesa et al, 2018). Specifically, ayahuasca consumption in a retreat setting across four sessions induced significant increases in non-reacting, and non-judging facets of the FFMQ (Soler et al., 2016), which was akin to improvements demonstrated after an 8-week MBSR program, importantly, without any particular practice or intention to enhance present-moment awareness or mindfulness. Additionally, there is preliminary evidence that psychedelic consumption can increase decentering (Soler et al,

2016, 2018; Uthaug et al, 2018; Murphy-Beiner & Soar, 2020), a key cognitive capacity trained by meditative practices.

Collectively, there are similarities between effects of psychedelics and meditative practices, as well as the potential mechanisms that relate to enhancements in wellbeing associated with each approach. It may be that similar states of altered consciousness are reached though both practices, since both seem to perpetuate a loss of self-world boundaries; as well as detached stance towards internal event. Though there are also clear differences between the two states, their neurophysiological underpinnings, and the methods with which they take effect (Carhart-Harris et al., 2014; Heuschkel & Kuypers, 2020; Millière, Carhart-Harris, Roseman, Trautwein, & Berkovich-Ohana, 2018). Studies combining the two techniques are necessary to elucidate the potential overlap or synergy between the two states.

5.1.6 Psychedelics and Meditation in Combination

To date, experimental studies combining psychedelics and meditative practices are very few. Of most relevance is a double-blind placebo-controlled study completed by Smigielski and colleagues (2019), whereby experienced meditation practitioners were given high doses of psilocybin on the fourth day of a five-day retreat. Functional connectivity analyses on imaging data demonstrated an association between subjectively felt ego dissolution and decoupling of medial prefrontal and posterior cingulate cortices (which are thought to mediate the sense of self). The degree of connectivity and ego dissolution predicted enhancements in psychosocial outcomes at 4-month follow-up. Psilocybin appeared to facilitate the neurodynamic changes in self-referential networks expected from meditation practice. This study provides the first empirical evidence that psilocybin may enhance the effects of meditation, on neurobiological, social and psychological levels, underlining the link between altered self-experience and following alterations in behaviour.

This study also provides preliminary evidence of a potential bi-directional beneficial relationship between the two states, since meditation practice may have protected or buffered against psychedelic-induced anxiety - a common side-effect at the dosage administered - which was not reported by retreat attendees (Smigielski et al., 2019).

Though to the author's knowledge there are no other experimental studies combining psychedelics and meditation to date, there is evidence that 'spiritual support' (which involved meditation practice) enhances some beneficial effects of psilocybin (Griffiths et al., 2018). In this study, predictors of sustained beneficial effects were psilocybin-induced mystical experiences, and rates of meditation or other spiritual practice, with common persisting effects including enhanced ratings on a range of prosocial and wellbeing indices. Promisingly, meditation practices are being integrated into psychedelic-assisted therapy trials (Carhart-Harris et al., 2016), and related qualitative reports indicate that 'acceptance' and 'connection' are key therapeutic change processes involved in psychedelic-assisted therapy (Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017). Though it remains unclear how psychedelics and meditative practices may interact, it is increasingly apparent that the two states of consciousness may be combined with potentially beneficial effects. One method of further examining the interaction between psychedelics and meditative practices is to explore user accounts of those who engage with both – particularly those who may engage in some formal meditative practice after having taken a psychedelic.

5.1.7 Present Study Aims and Objectives

This thematic analysis aims, for the first time, to explore the effects of combined psychedelics and meditative practices in a sample of psychedelic users. Qualitative approaches such as thematic analysis can be useful to inform future research and theory (Braun & Clarke, 2006), which may be particularly useful in this novel field of combined

psychedelic and meditation application. Thus, we hope to use text responses from users to inspire future directions in psychedelic and contemplative research, potentially to highlight key mechanisms, benefits, or aspects to be avoided.

5.2 Methods

This study was granted approval from the UCL Ethics Committee, with Project ID: 15153/001. The data used in this investigation derives from a parent cross-sectional internet survey, and as such, only methods and materials relevant to the present analysis is described here.

5.2.1 Study Design

This data derives from a cross-sectional web-based study, which involved responses from 1324 participants. From this larger pool of participants, 258 participants met the criteria for inclusion in this investigation (see below).

5.2.2 Participants

Participants responded to advertisements on social media platforms, the UK Psychedelic Society, and the Multidisciplinary Association for Psychedelic Studies (MAPS), a non-profit organisation based in the United States.

Participants were required to be at least 18 years old, having had at least one psychedelic experience in their life, having taken a psychedelic shortly before completing a meditative practice (i.e. having combined psychedelics and meditation), and have provided a prose response to the free-text question relating to this experience.

Psychedelic drugs included: psilocybin (including magic mushrooms and truffles); Lysergic acid (LSD) and analogues; ayahuasca and yage; N, N-dimethyltryptamine (DMT) and changa; peyoté and San Pedro, and salvia divinorum. While 3,4-methylenedioxymethamphetamine (MDMA) and ketamine have psychedelic-like effects,

since they are neurochemically distinct from the above classic psychedelics, they were not included in this study.

5.2.3 Procedure

The survey was hosted by Qualtrics. Participants first confirmed they met the above minimum age requirement and that they had previously consumed a psychedelic drug. Those who met these criteria proceeded to read an information sheet and provide informed consent. Demographic questions included age, gender, ethnicity, religious inclination and education. Participants were asked about their previous experience with psychedelics and meditation, as well as current patterns of meditation practice.

Participants indicated which drug they had used before meditating (limited to a single option), and were asked to comment on their experience of using psychedelics before meditating. Participants were provided with a broad definition of meditation, specifically:

"Meditation can mean different things to different people. Here we mean a practice in which you deliberately set time aside to use techniques to rest the mind and body by suspending the tendency to analyse or judge your experience. Many techniques can be used in meditation: focusing on an object, sound, experience or on the breath; using a mantra or chanting; special breathing practices (pranayama). It can involve sitting or lying still, or deliberate movement; it can be practiced alone or in groups, with or without an instructor. Some examples of types of meditation are: Vipassana, Zen meditation, Anapana Sati, mindfulness, transcendental meditation, yoga/yogic breathing, Qigong. There are many other types."

5.2.4 Quantitative Analysis

Data including demographics and information regarding previous use of psychedelics and meditative practices were analysed using SPSS (version 25, IBM). Descriptive

frequencies, percentages, means (M), and standard deviations (SD) are provided on demographics, psychedelics used and prevalence of themes.

5.2.5 Thematic Analysis

To analyse prose responses to the open question regarding combining psychedelics and meditation, thematic analysis was deemed to be an appropriate approach (Braun & Clarke, 2006). An inductive coding approach was used to create semantic themes, making the analytical approach data-driven, with the aim of primarily describing patterns in the data before any interpretation. The steps involved are summarised below, adapting the suggested process from Braun and Clarke (2006) to our approach of double coding and matching the coded data sets, to improve the reliability of the analysis. As per good qualitative research practice guidelines (Stiles, 1999), two researchers independently coded the data to ensure that the chosen semantic approach was maintained (i.e. that only codes which directly originated from the data were kept), and maintain that the analysis was as impartial as possible.

Table 5.3

Table summarising the step-by-step processes involved in the present thematic analysis

Phase	**Process**
1. Familiarisation with the data	Data were studied, and initial ideas noted by the first and second author
2. Generation of initial codes	Interesting elements of the data were manually coded in a systematic way across the data set by both authors
3. Matching of codebooks	The two codebooks were refined to one ‘master’ codebook
4 Checking codebook against data	Finalised codes were checked against the raw data to ensure that they were representative of the data
5. Searching for themes	Codes were formed into initial themes and subthemes
6. Reviewing themes	Verifying that themes work in relation to coded extracts (through mutual agreement), and creating a thematic map

Phase	Process
7. Defining and naming themes	Ongoing process to refine the specifics of each theme and the wider story the data tells, producing clear definitions and names for each theme
8. Production of report	Compelling extracts of data were selected to be used as examples, and analysed a final time, relating back to the research question and literature, then written up.

Note. Adapted from Braun & Clarke (2006)

It is worth noting that due to the open ended nature of responses invited through the use of an open text box with limited guidance on the required response, it is assumed that the request to "comment" on their experiences was varyingly interpreted by participants, thus producing a rich and diverse set of responses. In line with the inductive approach chosen to analyse the data, we attempted to limit researchers' preconceptions or theoretical motives, to keep the analysis as data-driven as possible. Thus no responses were disregarded in the analysis process; rather themes were created that should give a broad understanding of the variety of responses collected, both in terms of the style and content.

Due to the nature of the question asked, an assumption was made that participants were referring to the experience of consuming psychedelics *before* engaging in a meditative practice rather than the other way around (and that subjective experiences refer to the combination of the two), unless participants explicitly stated that, for example, meditation occurred *before* taking the drug.

5.3 Results

5.3.1 Sample Characteristics

5.3.1.1 Demographics. Participants (N = 256) in this study were between 18 to 72 years of age (M = 31.8, SD = 10.8), with a majority of non-religious (64.8%), and male (65.6%) responders. Most participants were educated to Bachelors level (62%), and

predominantly white (77%). The majority of American (47%) and British (17%) participants reflects the recruitment channels used, considering MAPS are a US-based organisation with a large reach, and base of the Psychedelic Society and authors involved in the study being in the UK. See Table 5.4 for a full outline of the sample demographics.

Table 5.4

Sample demographics

		Frequency	%
Gender	Male	168	65.9
	Female	70	27.1
	Other	18	7.0
Ethnicity	White	198	77.1
	Mixed Heritage	35	14.0
	Asian	9	3.5
	Black	2	0.8
	Hispanic/Latin American	4	1.6
	Other	7	2.7
Religion	No Religion	166	65.1
	Christian	11	4.3
	Buddhist	16	6.2
	Hindu	4	1.6
	Jewish	4	1.6
	Muslim	2	.8
	Spiritual	14	5.4
	Other	39	15.1
Education Level	GCSE/Equivalent	10	3.9
	A-Level/Equivalent	87	33.7
	Bachelor's Degree	117	45.3
	Master's Degree	33	13.2
	Doctoral Degree	9	3.9

5.3.1.2 History of Psychedelic Use and Meditative Practices.

Participant reports indicated an average of 11.2 years since their first psychedelic experience at the time of completing the study (SD = 10.7), with six months on average since last use (M = 0.5, SD = 2.7). Participants indicated that their meditation practice began nine years prior to completing the study (M = 9.03, SD = 10.05), with an average of 16 practices per month (M

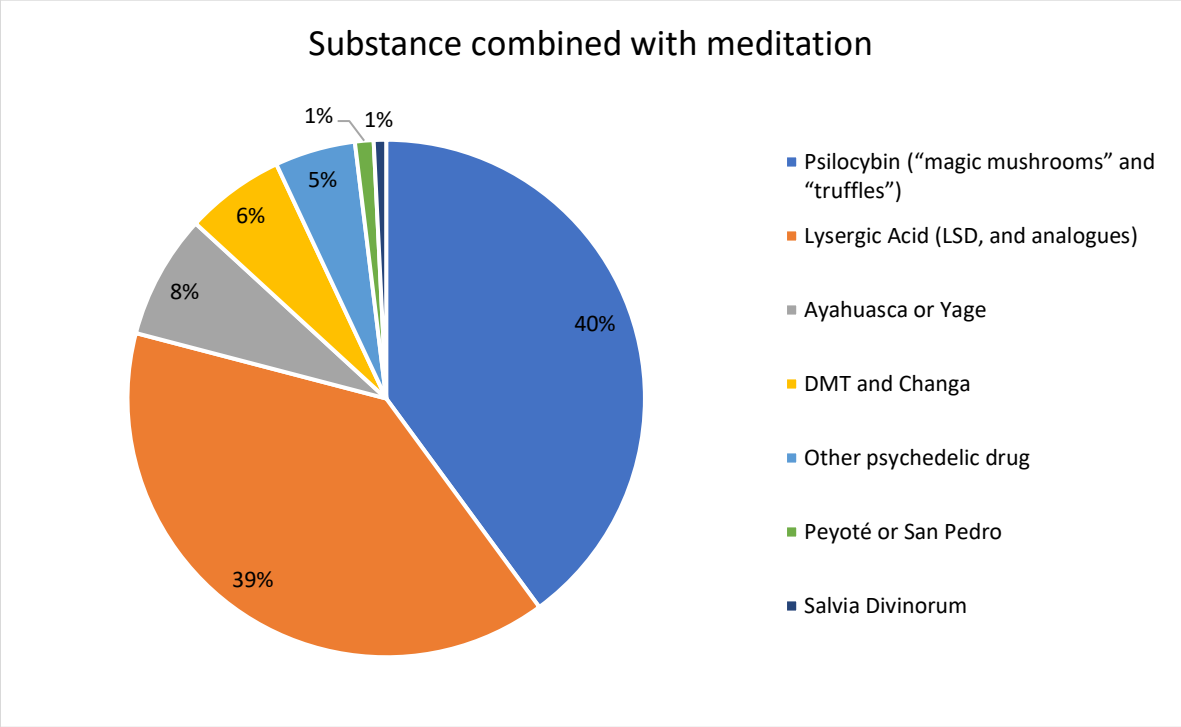
= 15.89, *SD* = 9.46), involving typically 32 minutes per day (*M* = 32.35, *SD* = 32.19). Participants reported having their most significant psychedelic experience approximately four years before participating in the survey (*SD* = 6.74), with a strong majority (89.1%) starting to engage in meditative practices after their first engagement with psychedelics, and 34.4% beginning to meditate after the most significant psychedelic experience. Psilocybin and LSD were the compounds most commonly combined with meditative practices (see Table 5.1 for a summary of substance choices).

5.3.1.3 Summary of Psychedelic Compound Used in Combination with Meditation.

Figure 5.1 illustrates which psychedelic substances were chosen to combine with a contemplative practice. Note, participant could choose only one drug to select as their drug of choice to combine with meditation.

Figure 5.1

Pie chart illustrating psychedelic substances consumed prior to meditation



Note. ‘Other psychedelic dugs’ included mescaline and 4-AcO-DMT

5.3.2 Thematic Analysis of Responses

Five main themes emerged from the analysis, with associated subthemes categorising components of each wider theme (see Table 5.5). Since participant responses frequently covered more than one sub-theme within one subordinate theme, it is important to appreciate that the themes are not assumed to exist in isolation to one another. Rather, themes and subthemes are presented as interrelated components of the combined psychedelic and meditative experience. A thematic map representing the theme and subtheme breakdown is presented in Figure 5.2.

Table 5.5

Overview of themes and subthemes

Theme	Total number of mentions (sub-theme breakdown)
A. Compatibility: Alignment between the two states	39
I. Intuitive meditation	(9)
B. Enhancement: A synergistic relationship	103
I. Enhanced meditation experience	(65)
i. Enhanced depth/quality of meditation	(23)
ii. Enhanced meditation ability	(24)
iii. Shortcut to the meditative state	(10)
C. Subjective Effects	121
I. Acceptance	(5)
II. Connection	(20)
III. Instilling a peaceful/ calm set	(17)
IV. Transformation	(20)
V. Negative Effects	(25)
i. Difficulty meditating	(15)
ii. Overwhelm	(5)
D. Meditation as a Tool	46
I. Meditation as preparation	(30)
II. Meditation as a navigational tool	(12)
E. Contextual Considerations	62
I. Reflections on personal processes	(36)
II. Advice for implementation	(13)

Note. The above counts represent the number of times each (sub-)theme was generated from the data. Sub-theme totals are presented in brackets.

A. Compatibility: Alignment Between the Two States

The theme of "compatibility" relates to an association that the psychedelic and meditative experience are a good combination. Some participants focused primarily on the similarity of the two states, with a note on psychedelics creating a stronger subjective experience, for example:

"They make the same effect although less intense with yoga/meditation."

Explicit mentions of compatibility, and suggestions to meditate on psychedelics peppered the data set:

"They work well together."

Some suggestions compatibility often also alluded to the utility of meditation during a psychedelic experience (see Theme D).

A.I. Intuitive Meditation

Some participants noted a spontaneous or intuitive cause for meditation after having taken psychedelics, whereby they may often 'end up' meditating without prior plans to do so. This intuitive element was true not only for experienced meditators, but those with no prior experience also appeared to access a meditative state of mind with a notable aspect of ease:

"After a 7 gram psilocybin mushroom trip. I meditated for 2 hours straight. Had never meditated before that day."

B. Enhancement: A Synergistic Relationship

Linking closely to the theme of compatibility, many participants spoke to the idea that meditative practices may enrich, enhance, or heighten aspects of the psychedelic experience:

"[Meditating on psychedelics] enhanced the experience tenfold"

Participants also reported that combining psychedelics with meditative practices enhanced the spiritual quality to their experience.

"... I feel that meditating greatly increased the experience in a spiritual way. This was my most profound experience"

B.I. Enhanced Meditation

Some participants drew attention to the idea of psychedelics being an augmentation tool for meditative practices, for example:

"If used appropriately, psychedelics greatly enhance my meditation practice."

With some accounts specifying that the experienced enhancement is dose-dependent:

"Up to a certain dosage, it heightens the meditation"

B.I.i. Enhanced Ability to Meditate

Participants made particular emphasis on the improved ability to engage with meditative practices whilst under the influence of psychedelics, describing an enhanced ability to control and tend to the content of the mind, practice awareness of their mental state and patterns of thinking, think more flexibly than usual, and hold a decentred mind state.

"Found it helped step back and observe passing thoughts"

Some extracts pointed to an unusually strong 'peak' experience, which was paired with an indication of higher quality and duration of focus during the meditative practice:

"Using psychedelics before meditating helps you get to an extreme high in your meditation, and it allows your mind to focus more on the meditation and for a longer period of time."

B.I.ii. Enhanced Depth/Quality of Meditative Experience

Closely linked to the above suggestions of enhanced meditation ability, some participants also detailed an increased depth and/or quality of the experience, or less difficulty attaining a deep meditative state and maintaining it. Specifically, some extracts alluded to a symbiotic relationship between psychedelics and meditative practices whereby

the combination allowed for a more beneficial result by way of getting deeper into the experience.

“I find I am able to go a lot "deeper" and gain more useful insight by combining psychedelics and meditation, as each enhances the other”

Others referred to the depth, strength, and subjective feeling of the meditative experience being augmented. Alternatively, some extracts linked the enhanced depth of meditation with a limit in concentration capacity related to the psychedelic state.

“it makes the experience of meditation feel much more profound, although I wasn't able to meditate for as long as I would sober”

B. I. iii. Psychedelics as a Shortcut to Meditative State

Accounts often alluded to the psychedelic drug assisting participants in achieving a quality of mind associated with meditation, with some indicating specific processes or insights that were specifically helpful:

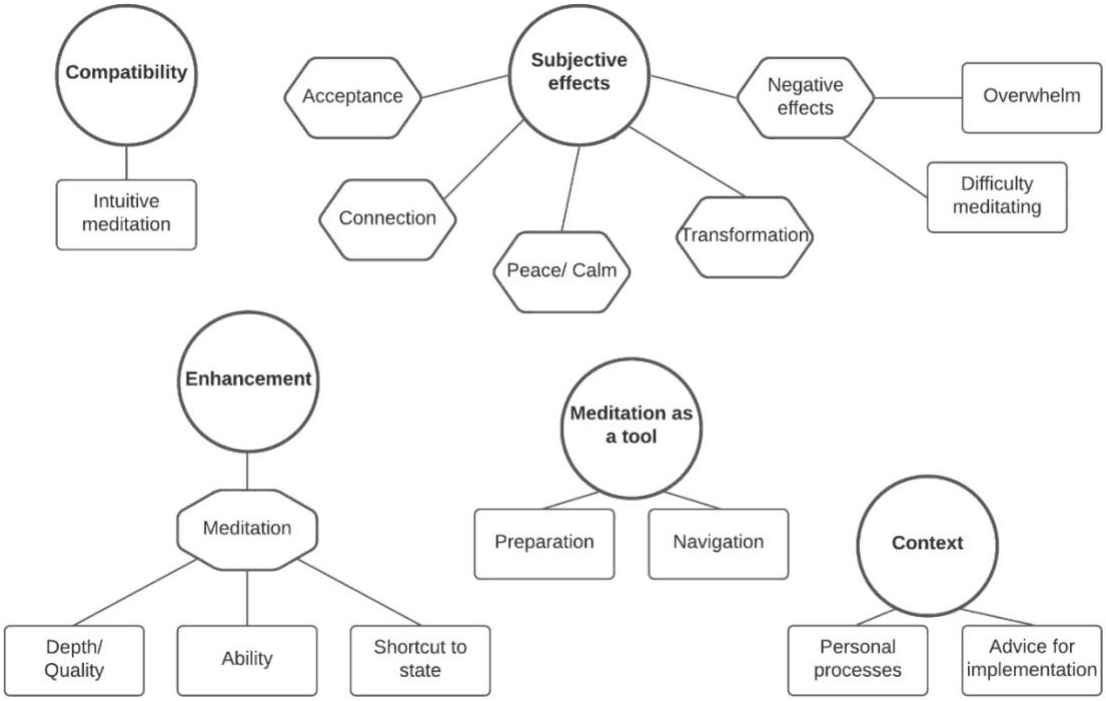
"The psychedelic felt as if it was a catalyst or helping hand, so to speak, to realize I am not my thoughts”

Participants alluded to ‘arriving’ at a place, or achieving some *quality* of mind more quickly than would be expected due to the combination of the drug and meditative practice.

“Psychedelics essentially give you a shortcut to the place an experienced practitioner would reach through meditating.”

Figure. 5.2

Thematic map diagram showing themes and subthemes



C. Subjective Effects of Combined Use

Though closely interlinked with enhancements of experience, other "subjective effects" were considered separately to the mentions of enhancement, detailing more regarding felt effects of the combined psychedelic and contemplative experience. These were regarded as positive by the large majority, including accounts of processes that could fall into categories such as 'acceptance' and 'transformation'. These themes appear closely linked to those proposed by Watts and Luoma (2020) in their model of psychedelic psychotherapy.

C. I. Acceptance

Participants commonly noted experiencing elements of acceptance, often co-occurring with mentions of reduced judgement towards the self. This is reminiscent of descriptions of mindfulness (Bishop et al., 2004). Some extracts suggested that acceptance

was directly related to calm composure, and connection to the self, possibly explaining some of the facilitation in engaging with meditation (as per section B.I.).

"My experience is that psychedelics help me to enter a meditative state more readily and with less judgement of self."

Closely linked to the subtheme of 'Transformation', there was also commonly an emphasis on acceptance allowing for, or surrendering to challenging content of the mind.

"I had to deal with me, my past, my future and myself, my ego. I couldn't run away because there was nothing to distract me."

C. II. Connection

Participants shared feeling grounded, connected to themselves, their bodies as well as their environment. This sense of connection was often linked to an ineffable, indescribable, or enlightening nature of experience.

"Felt more aware of the connection between my body/mind as well as the connection between Me and The World. Grounded, aware, more in tune with spirituality"

Mentions of connection to the self and others were also related to the process of transformation (as explored in C.IV.).

"…Take both and you grow as a person. You learn about the light in your heart and mind and that of others. You make a difference with the world and create happiness to all…"

C. III. Instilling a Peaceful/ Calm Set

Participants noted having "very peaceful" and "calm" experience, comprising a sense of absolute "relaxation".

"I found my mind was in a state of effortless stillness, serenity..."

Mentions of relaxation and serenity were also linked to successful preparation for the experience through mediation *prior* to psychedelic use/effects (which is elaborated in section D.I.i).

"It helped me start off the trip in a positive and relaxed way..."

Subjective experiences of peacefulness were linked to connection to the present experience (as per C. II.)

"Getting into a state of calmness and inner peace, losing sense of self and being emerged into the senses."

Accounts of tranquillity linked to extracts of 'Enhancement', denoting experiences of meditation depth, and associated harmony previously unknown (as explored in B.I.ii).

"Many levels deeper in meditation into a whole new headspace of peace never experienced before."

Some extracts linked acceptance and peacefulness to the transformation of their perception and/or experience.

"My best trips have been from taking mushrooms/acid and just sitting and breathing for hours. It's resulted in an overall calmness and sureness of myself and who I am. Helped to dissolve my fears and insecurities."

C. IV. Transformation

In contrast to the previous three sub-themes, which detailed various acute effects of the combination, this subtheme refers to extracts which revealed enduring positive consequences of having combined psychedelics and meditation, characterised by changes such as freedom from previous states of mind or being, revelations, and/ or a sense of deeper understanding.

"It is one of the most liberating experiences of my life"

Alterations in perception were also linked to a greater ability for compassion for others.

"It was a wondrous experience to say the least, that left me with a profound feeling of altruism that lasted for far longer than the trip itself."

C. V. Negative Effects

Those who noted effects that hinted at the combination of psychedelics and meditative practices being unhelpful predominantly referred to an overwhelming intensity of experience, or a difficulty maintaining concentration towards meditation. Few accounts implied that the process of focus required for meditation did not seem natural in the psychedelic state, or that the effects were not reliable per se.

"I found it uncomfortable to try and control my trip through meditation"

C. V. i. Becoming Overwhelmed

Distinct from the subtheme of "Peace/ Calm", a small number of participants felt that the combination of psychedelics and meditative practices was too intense, despite simultaneously reporting subjectively positive effects, highlighting the nuanced nature of potential benefits of the combination:

"There can be a profound sense of connection and peace which is always there when meditating but is almost overwhelming when tripping as well."

Some participants revealed a fear deriving from a potential loss of control over their thoughts or experience.

"Scary how thoughts can be irrational. Decided to stop meditation because of the rabbit hole I created."

Others linked their sense of overwhelm with the undeniable acceptance that the experience brought them, detailing that being present with their experience was difficult.

"I find meditating actually make it more likely to have a challenging [experience] because it forces me to be [with] my thoughts and emotions."

C. V. ii. Difficulty Meditating

In contrast with the theme of Enhancement (B. I.), some participants reported a decreased capacity to engage with, or maintain a meditative state. This difficulty was linked to dosage – with suggestions that it may be a dose-dependent relationship:

"I think you need to get the dose right or it isn't possible to meditate!"

Some participants reported that the difficulty was navigable, either with time or surrendering to the process, which allowed for an enhanced experience if successful in doing so.

"Harder to concentrate, but if you can let go, a magical experience."

D. Meditative Practices as Tools

As noted in the methods, participants were asked about their experience of meditation after consuming a psychedelic, and thus responses were assumed to be referring to their combined effects, unless specified otherwise. Overall, this theme summarises extracts which spoke to the utility of meditative practices in the process of the psychedelic experience. Some participants did specify that they meditated before having taken the psychedelic, which were captured within the first sub-theme.

D. I. Meditative Practices as Preparation

Despite the framing of the question (referring to meditating after psychedelic use), a considerable number of participants referenced the utility of meditation as a good preparatory tool for the psychedelic experience. Extracts within this subtheme refer to meditation helping both before and during the onset of the psychedelic effects, relating to creating an ideal state of mind to enter the experience, and buffer against early anxious thoughts.

"Great way to let the anxiousness that is often associated to the wait period of psychedelic onset. It's also a great way to sort of stretch the mind prior to a psychedelic experience."

The utility of meditation in preparation for the psychedelic experience was related to senses of connection, calm effects, and enhanced sensory or creative experiences (as per themes B and C), with participants alluding to meditation specifically as a catalyst for the positive, or buffer for potential negative experiences.

"I believe in meditating not just after but also BEFORE taking psychedelics. It's extremely important to root oneself beforehand. I've had the most powerful results when I do shavasana (corpse pose) and breath awareness before any kind of entheogenic journey."

Participants revealed that meditation was important for intention-setting prior to the experience, which was at times also linked to acceptance and the processing of emotions.

"It helps to be conscious with the experience form the start en helps to set intention en check in do deal with/surrender to emotions as fear"

Some extracts commended the potential for meditation completed prior to the onset of drug effects to change the nature of the psychedelic trip in a profound and positive way, with particular references to mystical qualities of the experience:

"I decided to meditate immediately following ingestion of the mushrooms in order to focus my intention of the experience. I had finished meditating before I began feeling the effects of the mushrooms, however I feel that meditating greatly increased the experience in a spiritual way. This was my most profound experience in which I gain much insight into the nature of things, and was more than a recreational trip."

D. II. Meditative Practices as Navigational Tools

This subtheme delineates accounts of meditation being used to manage the psychedelic experience – often alluding to buffering against unnerving or negative effects such as anxiety, or to maintain a sense of tranquillity (as per C. III).

"Being in meditation helps navigate potential difficult thoughts/experiences that might come up during the trip."

Participants revealed that meditation was particularly useful to facilitate alterations in self-perception or self-awareness, often referring to experiences of ego dissolution (Nour, Evans, Nutt, & Carhart-Harris, 2016):

"Meditation made ego deaths easier and smoother to accept"

Others noted that their meditative practice enables acceptance, and "surrender" to the experience (as per C.I), with an appreciation that effects might be overwhelming without the meditative element.

"I credit my ongoing meditation practice as well as the meditation session I had immediately prior to taking 5-MEO-DMT with my ability to let go and surrender into what I imagine would otherwise have been a negative experience due to its overwhelming nature."

In contrast to the above, and relating to the subtheme of Connection (C. II), one participant found that the sense of grounding arising from engaging in meditative practices allowed them to avoid becoming overwhelmed (C. V. ii), by way of gaining a sense of control over the trip:

"I remember feeling less consumed or overwhelmed by the experience, more stable and like the visuals were more decided by my mind than my surrounding environment"

E. Contextual Elements

The final theme explores extracts which refer to details of the environment, or 'setting' that the combination of psychedelics and meditative practices were (or should be) used in. This theme includes subthemes, which outline participant's reflections on their personal processes, and extracts which relate to advice for use of psychedelics and meditation together. Some extracts simply noted the historical context for their experience:

"I played ambient music, closed my eyes and practiced deep breathing"

E. I. Reflections on Personal Processes

Participants specified how and when they combined psychedelics and meditative practices, some indicating a more ritualistic, intentional or habitual approach to the process.

"Meditation and prayer before each experience."

Some highlighted meditative practices as essential components to the psychedelic experience, alongside other key contextual elements of the experience.

"Mediation, breathing, music and nature are the most important parts of the experience"

E. II. Advice for Implementation

The final subtheme collated extracts which provided considerations and recommendations on how to (or not to) combine psychedelics and meditation, with common mentions of 'set' and 'setting' (i.e.: one's mental state and physical surrounding):

"Allowance and receptivity are key. Go with the flow and not fight it."

Participants often made suggestions around dosage – frequently encouraging modest doses, or at least, intentionality around the choice of dosage:

"Low doses are the best option."

Lastly, considerations were made regarding having a level of familiarity or prior experience with meditation and psychedelics before exploring their combined effects.

"I think you need to be proficient and experienced at both, or with someone who is who can guide you"

5.4 Discussion

To the author's knowledge, this is the first exploration of psychedelic drug user's naturalistic experiences of engaging in meditative practices under the effects of (and in some cases, prior to) psychedelic substances. Participant's responses broadly described the compatibility of the two states, an enhancement of the meditative experience, subjective effects of combining them, the use of meditation as a tool for the psychedelic experience, and contextual considerations relating to combining psychedelics and meditation. Below, a few prominent themes will be discussed, namely: the subjective effects of the combination, the effects of having consumed a psychedelic on the meditative practice, and potential synergies that may underlie these interactions, attempting to relate these novel findings into existing theory and published literature.

5.4.1. The Felt Effects of Combining Psychedelics and Meditative Practices

An enhanced ability to accept the experience was a key recurring theme resulting from this analysis. This is in line with a key focus of mindfulness meditation – holding a non-judgmental stance towards content of the mind (Bishop et al., 2004). Accordingly, acceptance may predict the benefits resulting from mindfulness-based therapy (Baer, Smith, Hopkins et al., 2006), and spontaneous enhancements in acceptance have been demonstrated as a result of psychedelic consumption without any meditation element (Soler et al., 2018, 2016). Acceptance has also been highlighted as a key change-process in previous qualitative

work in those partaking in psilocybin-assisted therapy for treatment resistant depression (Watts et al., 2017), alongside connection.

Much like Watts and colleagues' (2017) qualitative report on accounts of psilocybin-assisted therapy, increased feelings of connection was a key theme in the current investigation. Participants in both studies reported greater connection to their senses, themselves, others, the world and a greater spiritual concept. Changes in self-concept reported by participants reflects the mechanism of change proposed in both meditation and psychedelic literature to date (Millière et al., 2018). In the present dataset, feelings of connection were associated with subjective feelings of tranquillity, as well as indications of transformation.

Experiences of peaceful and calm mental states are common both to meditative and psychedelic experiences (Anālayo, 2013; Stace, 1960). Participants in this study alluded to a synergistic relationship between the two effects, whereby explanations of tranquillity experienced were often recounted to be much greater than resulting from either experience alone. Ritualistic psychedelic use has been associated with increases in serenity and tranquillity, even in first-time consumers (Barbosa, Giglio, & Dalgalarrondo, 2005). Mentions of peaceful and calm experiences in this dataset often also coincided with notes of acceptance and connection, with indications of the combination of meditation and psychedelics used to maintain a sense of peacefulness, potentially thanks to an ability to practice acceptance and connect to themselves.

The concept of transformation refers to experiences of insight and/or change in emotionality or mental state, often involving positive and persisting change after acute effects of the drug have passed. This is a common theme in psychedelic literature, whereby participants report enduring effects involving meaningfulness, spirituality, positivity, positive

behaviour changes, and social connection, with effects persisting for up to 14 months after consumption (Griffiths et al., 2006, 2008, 2011). Changes in perspectives, attitudes, and personality traits have been demonstrated following psychedelic consumption (Griffiths et al., 2018; MacLean et al., 2011). Changes in perception towards the self are also proposed as a key mechanism underlying the benefits of mindfulness meditation (Hölzel et al., 2011). There is also evidence that, in the context of a spiritual program involving a single administration of psilocybin, that rates of meditation practice was a positive predictor of enduring beneficial effects of the program (Griffiths et al., 2018), alluding to synergistic effects of meditation and psilocybin.

The collection of effects falling under the 'negative effects' subtheme summarised extracts that indicated some uncertainty around the factors affecting the usefulness of combining psychedelics and meditation, which generally described a sense of becoming overwhelmed or a difficulty concentrating on the meditative practice. Becoming overwhelmed by distress has been documented as the most common negative side effect of psychedelic consumption, often referred to as a 'bad trip' (Johnson, Richards, & Griffiths, 2008). This could be augmented by an enhanced awareness of one's thoughts and feelings, catalysed by engaging in meditation, as has been demonstrated in experimental mindfulness literature (Watford & Stafford, 2015). Participants also referred to a sense of becoming overwhelmed simultaneously to positive effects, illustrating that they can co-occur. Indeed, survey data indicates that, among a pool of participants who had experienced a 'bad trip', despite 39% of respondents classifying the experience as one of their top five most difficult lifetime experiences, 84% reported benefitting from the trip, and degree of difficulty during the experience predicted subsequent increases in well-being (Carbonaro et al., 2016).

5.4.2. The Effects of having Consumed Psychedelics on the Meditative State

An important theme in this dataset was the perceived enhancement of the meditative practice, within the context of having previously consumed a psychedelic. Participant accounts often related to improved ease in accessing the meditative state (psychedelics being referred to as *shortcuts* to the meditative state), enhanced ability to *maintain* the meditative state or practice, or an enhanced *depth* or *quality* of experience during the practice. The concept of psychedelics helping as a 'shortcut' to a meditative state is not exclusive to modern literature or conceptualisations. There are collections of evidence which suggest that Buddhist 'adepts' would use psychedelics such as the psilocybin mushroom to helping attain enlightenment (Hajicek-Dobberstein, 1995; Winkelman, 2019). Participant responses made reference to an enhanced ability to 'appreciate they are not their thoughts' – referring to meta-awareness – a proposed mechanism of mindfulness (Vago & Silbersweig, 2012).

An enhanced ability to *maintain* engagement in a meditative practice after having consumed a psychedelic may be partly due to temporary drug-induced enhancements in state mindfulness (for example Soler et al., 2016; Thomas et al., 2021). Though a strong case may not be made based on this current qualitative data alone, in chapter three of this thesis, there was evidence that those who were randomly assigned to the active drug (modafinil) engaged in significantly longer self-practices in the week following the experimental session, compared to those who received placebo. These results support the concept of 'mindful state recognition' (i.e., that a drug may be able to enhance one's ability to recognise the mindful state) and enhance the related motivation to practice (Payne et al., 2021), which may be pharmacologically assisted. Psychedelic experiences have been characterised by affective experiences of peace, harmony, and introversion (Griffiths, 2006), which may assist in both the engagement and maintenance of a mindful state.

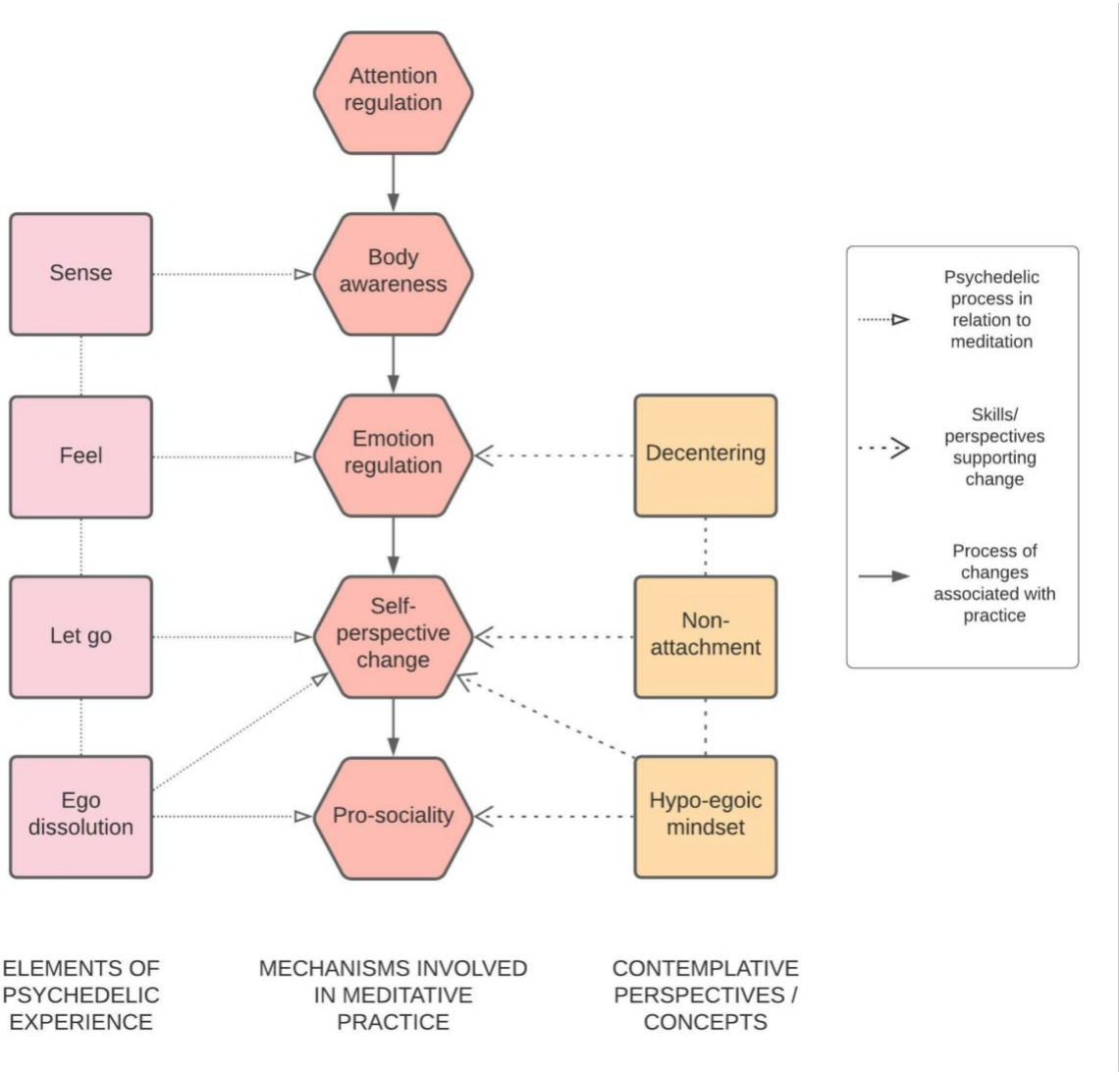
The psychedelic state appears to be conducive to kind and compassionate states (e.g. Kamboj et al., 2018) (alongside the more well-known joyful acute effects), which may help to maintain a non-judgmental stance towards thoughts and experiences. Responses in this study falling under the theme of compatibility speak to this, as does an empirical study exploring the combined effect of compassionate imagery and MDMA, which demonstrated support for a potential additive effect of the drug and contemplative practice (Kamboj et al., 2018). A psychedelic-associated reduction in self-judgmental processing may play a part in this enhanced ability to hold a compassionate state of awareness (Soler et al., 2018, 2016).

It is possible that less judgmental, more compassionate states of mind may support, or be linked to the enhanced ability for confronting content of the mind (or 'non-avoidance') reported after consumption of psychedelics (e.g. Bouso et al., 2012; Watts et al., 2017). Non-avoidance may support both the maintenance of the mindful state (in so that one is less likely to withdraw from the experience), as well as help in 'deepening' or enhancing the quality of the experience (such that participants are more likely to face and accept challenging experiences rather than turn away or avoid them, Guss, Krause, & Sloshower, 2020). Indeed, an enhanced 'depth of mindfulness' has been proposed as a useful consequence of combining psychedelics and meditation (Payne et al., 2021), and a recent placebo-controlled study provided some initial evidence that psilocybin appears to increase meditation depth (Smigielski et al., 2019). It is also plausible that the psychedelic state widens the 'range' of acceptable emotionality, such as anxiety, as has been demonstrated in MDMA trials for PTSD; such that psychedelic users can move 'through' difficult experiences, accept and surrender to them, allowing for entering into deeper altered states (Mithoefer et al., 2018). Our data, along with other qualitative psychedelic reports allude to greater insights and 'profound' experiences being attained after reaching some particular depth or quality of

(meditative) experience. For example, the Accept Connect Embody (ACE) model places meaningful results after ‘diving down’ and ‘accepting’ the emotional content (Watts & Luoma, 2020). See Figure 5.3 for a schematic regarding how the psychedelic state may change or enhance the meditative experience. Inspiration was taken from theorisations of mechanisms of mindfulness (e.g. Hölzel et al., 2011), related contemplative skills (e.g. Vago & Silbersweig, 2012), and the ACE model of psychedelic psychotherapy (Watts & Luoma, 2020).

Figure 5.3

A diagram to schematise how the psychedelic state may affect elements of the meditative experience or process



Note. Considering the acute nature of most commonly reported psychedelic effects, and the longer-term benefits associated with meditation practice, this diagram serves to simply draw parallels between potential catalysts of change, demonstrating how they may relate to one another, rather than delineate specific temporal or causal claims.

5.4.3. Processes or Mechanisms that may Underlie the Proposed Synergy Between Meditation and Psychedelics

Though there are effects associated with the psychedelic state that seem particularly well suited to the meditation, there are also mechanisms and concepts that are most well situated within mindfulness literature (or appear to be common between the psychedelic and mindful state), which may contribute to these synergies. For example, during the psychedelic experience, participants commonly noted that meditation was useful to 'help navigate' the trip. One skill commonly associated with meditation practice that may be useful for the managing of challenging content of the mind is decentering. Enhanced ability to distance from the content of one's mind may help move past challenging aspects of the psychedelic trip. Indeed an ability to decentre from unhelpful or troubling thoughts and witness them pass rather than identify heavily with them may be in part responsible for the 'buffering' effects that participant in this study alluded to, whereby meditation may have assisted in avoiding becoming overwhelmed by intense psychedelic effects. Decentering has been found to correlate negatively with depressive rumination (Fresco et al., 2007), thus may be particularly helpful to encourage acceptance and surrender during the psychedelic experience (Watts & Luoma, 2020).

Related to decentering is the Buddhist principle of non-attachment. Non-attachment may be understood as a 'loosening of attachments to outcomes and a solid sense of self' (K. W. Brown & Ryan, 2003; Mcintosh, 1997). Much like ruminative thoughts, attachment-based thoughts revolve around desire for a goal that is unattained, and are is a negative predictor for mental health and well-being (Mcintosh, 1997). Attachment-based thoughts may arise as fixations on desires for unattained objects or goals, the tendency to control or attempt to maintain what is present, or removal of aversions that are experienced in the

present moment. Conversely, those who do not have attachment to objects or outcomes to feel they need to be happy are better able to cope with stress than those that do (McIntosh, Harlow & Martin, 1995). Practicing non-attachment may be considered a relatively advanced meditative skill which includes releasing the need for things to be different from how they are, rather accepting, or having a willingness to be present with what is. It may be that even early stages of this 'loosening' are beneficial for the psychedelic journey, such that one can more easily surrender to their experience, which can be of an unpredictable nature. Attachment is also seen in regards to a self-concept, whereby people generally build, cling to, and defend an image of who they are. This form of attachment is seen as a core source of suffering, since other attachments are related to the self-concept (Sahdra et al., 2010). Weakening of a rigid sense of self, may assist in the manifestation of less egoic thoughts, and more pro-social thoughts and behaviours (Majić et al., 2015).

Relatedly, participants described the meditative practice as assisting them in 'surrendering to' the experience of ego-dissolution. Likely closely related to the skills of decentering, acceptance, and connection that have been covered – some participants relayed that mediation made experiences of ego death or loss of sense of self easier to accept. Ego dissolution has been demonstrated as a predictor of desirable outcomes of psychedelic consumption (Nour et al., 2016), which may be supported by experience with altered states and the 'loss of self' that is not uncommon during meditation in experienced practitioners. An enhanced ability to re-orient attention may also be useful in this context. Primary experimental evidence of this 'buffering' effect comes from Smigielski and colleagues' 2019 study whereby virtually no indications of anxiety or loss of cognitive control were reported after administration of high doses of psilocybin in experienced meditators, demonstrating that

a mindful state of awareness, as well as contemplative setting may be conducive to beneficial psychedelic experiences.

5.4.4. Implications

These findings provide a novel and rich account of users' experiences regarding engaging in meditative practices after having taken psychedelics. Specifically, participants spoke to the compatibility of the two approaches to access altered states of consciousness, the ability for psychedelics to enhance meditative practices, and meditation as a useful tool before and during the psychedelic journey. This is useful to inspire quantitative research exploring the modulation of meditative states (as per chapter three). Considering it does appear to be possible to enhance state mindfulness pharmacologically (e.g. Thomas et al., 2021), and that psychedelic states may provide a good context for meditation, this implies that experimentally manipulated combinations of psychedelic compounds and specific meditation practices may be worthy of exploring. Indeed, psilocybin has demonstrated potential to help reduce symptomology of obsessive compulsive disorder (Moreno et al., 2006) – a disorder which is associated with spontaneous mind-wandering (Seli, Risko, Purdon, & Smilek, 2017), and a single ketamine infusion can improve treatment outcomes following a mindfulness-based program for participants with cocaine dependence (Dakwar et al., 2019).

5.4.5. Strengths and Limitations

Strengths of this investigation include the large sample size, and a detailed qualitative analysis, which yielded new insights into the naturalistic combination of meditation with psychedelics. However, the recruitment technique and methodology used limit the extent to which findings may be generalised. Since the sample were self-selecting to discuss a psychedelic experience, it was potentially more likely to attract those who had positive

experiences to account. On the other hand, no mention of meditation was made in the recruitment material, with the attempt to avoid a source of expectation bias. In terms of the present sample of participants, we did recruit a reasonably varied sample in terms of education level and ethnicity, however the participants were predominantly based in Britain or America. Future research may seek to capture a more diverse sample by using sampling strategies that target psychedelic users from a larger number of countries.

5.4.6 Future Research

The novel findings reported here may be used to inform hypothesis-driven empirical studies that further explore the relationship between psychedelic and meditation-related experiences and effects. For example, it may be informative to query what drive the transformative elements of the psychedelic trip. The anecdotes presented here suggest that acceptance, connection, tranquillity may be contributing factors in terms of psychological stance, or 'set'. This might be investigated by integrating elements of different types of meditation (e.g., acceptance-based or loving-kindness) into the preparation of controlled studies to explore which protocol was most likely to elicit transformative effects. Conversely, it may be interesting to run studies using experience sampling to attempt to uncover which elements of the psychedelic experience instigate a spontaneous drive to meditate. This could be beneficial to see how specific psychoactive substances can support meditation, and potentially how certain aspects of the altered state might be created using non-pharmacological approaches. Similar to the first suggestion, it may be useful to gain quantitative data to ascertain which components of the meditation helped with the navigation of the psychedelic trip. This might help inform the application of psychedelics within therapeutic contexts, in regards to the ideal preparation and management of participant experiences during the trip. From the perspective of risk management, gaining more insight

into skills that may equip psychedelic users to help navigate their trip may also become particularly useful, especially if the scheduling of psychedelic substances changes in the future – it may be useful to have data to inspire suggestions regarding efficient and safe ways to manage difficult experiences. Finally (and much in line with chapter three), researchers may wish to explore which psychedelics are the most useful to enhance subject's ability to meditate and the depth/quality of the meditation. Smigielski and colleagues (2019) provide an example of how this may be tested in a retreat context with psilocybin, and research is emerging which suggests that other classic psychedelics such as ayahuasca may be a desirable drug target for pharmacologically-assisted meditation (e.g. Uthaug et al., 2021).

Chapter 6

Mindful of the Ceremony: An Exploration of the Association Between Ayahuasca Use in a Naturalistic Setting, and Changes in Mindfulness and Psychological Health

Key Points

- We aimed to explore how changes in mindfulness capacities relate to changes in anxiety, depression and psychological wellbeing in participants who took part in an ayahuasca retreat in a naturalistic setting.
- Self-report measures were used to assess mindfulness, anxiety, depression, and psychological wellbeing at the beginning of the retreat, at the end of the retreat, and at follow-up six months later. Following linear multilevel models that explored the associations noted above, longitudinal mediation models were used to explore whether post-retreat mindfulness mediated the relationship between ayahuasca consumption (number of ceremonies) and anxiety or depression scores at follow-up. These data were collected as part of a larger study.
- Increases in mindfulness predicted improvements in anxiety, depression, and subjective wellbeing, but did not mediate the effects of ayahuasca ceremonies on anxiety or depression, when controlling for earlier measurements of mindfulness and anxiety or depression.

6.1 Introduction

6.1.1 Ayahuasca: the Vine of the Soul

Ayahuasca is an Amazonian brew that has been used ritualistically for spiritual and healing purposes by indigenous communities for at least 150 years (Spruce, 1873), with suggestions that use likely predates this (Halpern, Sherwood, Passie, Blackwell, & Ruttenber, 2008; Luna, 2011). The brew is made by combining *Banisteropsis caapi* and *Psychotira*

viridis or *Diplopterys cabrerana*, which contain monoamine oxidase inhibitors, and N,N-dimethyltryptamine (DMT) respectively (McKenna et al.,1984). DMT is a serotonergic psychedelic which has agonistic effects at the 5-HT_{2A} receptor (among other 5-HT receptors, see (S. Ruffell, Netzband, Bird, Young, & Juruena, 2020), and knock-on glutamatergic and neuronal excitatory effects (Carbonaro et al., 2015; Klodzinska et al., 2002). Though subjective effects vary across participants and dose, ayahuasca consumption commonly induces an introspective state, accompanied by visual imagery, and intense emotions, and the yielding of new perspectives on problems (Riba et al., 2001, 2003). This may explain why interest in ayahuasca has dramatically grown over the years, with use in some Brazilian churches, and increasing numbers of tourists who seek a spiritual/healing experience, enhanced self-awareness or personal development (Kjellgren et al., 2009). Importantly, improvements in mood, quality of life, and general well-being have been found as a result of ayahuasca use (Santos et al., 2007), as well as significant improvements in pathologic symptomology (de Osório et al., 2015; Hamill, Hallak, Dursun, & Baker, 2018).

6.1.2 Psychological Effects of Ayahuasca

A considerable body of research supports the concept that use of ayahuasca in appropriate settings (such as churches or retreat centres) can improve mental health and wellbeing indices. Reviews exploring the psychological effects of ayahuasca broadly come to the same conclusion: consumption appears to increase positive mood, introspection, whilst having anti-depressant and anxiolytic, and anti-addictive potential (Domínguez-Clavé et al., 2016; Dos Santos, Balthazar, Bouso, & Hallak, 2016; dos Santos, Osório, Crippa, & Hallak, 2016; Hamill et al., 2018). Improvements in anxiety and depressive symptomology have been demonstrated in both traditional and clinical contexts, with rapid onset of effects, and maintaining at 21 day follow-up (de Osório et al., 2015; Santos, Landeira-Fernandez,

Strassman, Motta, & Cruz, 2007). For example, Osorio and colleagues administered one dose of ayahuasca to subjects currently experiencing a depressive episode, and found that alongside reductions in anxiety, participants demonstrated reductions in depression scores of as much as 82%, which were sustained until follow-up three weeks later (de Osório et al., 2015). Subsequently, a first randomised placebo-controlled trial has been completed which administered ayahuasca to participants with treatment-resistant depression, revealing significant antidepressant effects in comparison to placebo (Palhano-Fontes et al., 2019). Ayahuasca users also score higher on purpose in life and psychological well-being alongside lower ratings of psychopathology (Bouso et al., 2012). The literature demonstrating beneficial effects of ayahuasca on mental health is fast growing, though the vast majority of studies are either cross-sectional, or have modest sample sizes, with investigations of short- or long-term effects on mental health rarely tested in more than 20 participants.

Recently, our collaborators published an account of the general patterns of effects of ceremonial ayahuasca use on mental health, self-compassion and psychological health in 63 participants (Ruffell et al., 2021). Ayahuasca retreat participants completed pre- and post-retreat questionnaires, alongside a six-month follow-up. When comparing pre-retreat to post-retreat scores, they found significant improvements in depression, anxiety, psychological health, and self-compassion scores, which maintained at 6-month follow-up. Each subscale of the self-compassion scale showed significant and sustained increases across the three time points. Ruffell et al. (2021) also explored the nature of autobiographical memories of participants, linking improvements in mental health symptomology to changes in memory valence (in particular, reductions in a tendency to recall negative autobiographical information). Enhancements in psychological health indices following ayahuasca consumption do also appear to be accompanied by higher ratings of social and emotional

functioning (Barbosa, Cazorla, Giglio, & Strassman, 2009), potentially revealing clues as to which processes may support the aforementioned improvements in mental health and wellbeing.

6.1.3 Ayahuasca Meets Contemplative Science

The therapeutic effects of ayahuasca have been linked to heightened mindfulness capacities. Soler and colleagues (2016) found that one ayahuasca session in a non-religious setting significantly improved mindfulness capacities, particularly on the non-judging and non-reactivity subscales of the Five Facet Mindfulness Questionnaire (FFMQ), as well as enhancing decentering abilities as measured by the Experiences Questionnaire. Subsequently, the effects of four weekly ayahuasca sessions were directly compared to an 8-week mindfulness stress reduction course, whereby participants in the ayahuasca groups demonstrated comparable increases on the non-judging subscale of the FFMQ, despite having no specific intentions around improving mindfulness capabilities (Soler et al., 2018).

A recent study additionally found that, alongside improvements in non-judging and non-reactivity, attentional and emotional acceptance elements of mindfulness were enhanced after a single administration of ayahuasca (Murphy-Beiner & Soar, 2020). Enhancements demonstrated in the 'observing' element of mindfulness may help us understand how ayahuasca acutely benefits mindful awareness. It may be that acute enhancements in present-moment awareness facilitated by ayahuasca assist participants to 'recognise' the mindful state, and access it more easily in the future, similar to the synergy that has been suggested in relation to psilocybin-enhanced mindfulness (Payne et al., 2021). Introspective states are also common to the ayahuasca experience (Domínguez-Clavé et al., 2016), and psychedelic states are known to enhance one's sensory experience, thus the acute drug experience, and residual

effects in the afterglow period may facilitate awareness of one's thoughts and feelings – which constitute key elements of mindful awareness.

Higher ratings of self-acceptance have also been demonstrated in ayahuasca users in comparison to catholic retreat participants, alongside superior mood, and healthier habits such as reduced alcohol consumption (Harris & Gurel, 2012). Similarly, a thematic analysis exploring experiences of participants completing ceremonial ayahuasca ceremonies to heal eating disorders highlighted the internalisation of more self-love and self-acceptance as key to their therapeutic process (Renelli et al., 2020). These attitudes relate to the concept of self-compassion. More specifically, Neff (2003) describes self-compassion as 'being touched by and open to one's own suffering, not avoiding or disconnecting from it, generating the desire to alleviate one's suffering and to heal oneself with kindness', as well as the capacity to offer non-judgmental understanding to pain, difficulties and failures, such that one's experience is situated as part of the larger 'human experience' (Neff, 2003). It is commonly measured using the self-compassion scale, which has six subscales, involving three contrasting pairs: *self-judgement*, is placed in opposition to *self-kindness*; *common-humanity*, in contrast to *isolation*; and *mindfulness*, which relates to having a balanced approach to negative experiences, including awareness without becoming *over-involved* (Neff et al., 2007; Neff, 2003). Of particular relevance to psychedelic-induced improvements in mental health, is the emphasis on being kind to oneself in the face of difficulty, which may serve as a good framework for understanding mindful attention in the context of potentially challenging psychedelic experiences. Mindfulness in this context is proposed to be a balanced state of awareness, which sits between over-identification with, and dissociation from experience, such that one can perceive clearly and accept the content of the mind.

Psychedelic use in general has been linked to enhanced 'openness' to experience (Erritzoe et al., 2019; MacLean et al., 2011) – a quality that may be particularly helpful for engendering a state of non-judgmental, mindful awareness. This may be facilitated by the 'disinhibition' commonly reported during psychedelic use (Heuschkel & Kuypers, 2020). Reductions in DMN activity have been associated with both the psychedelic state and that of mindfulness meditation (Barrett & Griffiths, 2018; Fox et al., 2016), which appears to mediate the loss of one's concrete sense of self; with extent of 'ego-loss' and related changes in functional connectivity appearing to predict psychological benefits from the therapeutic approaches (Barrett & Griffiths, 2018; Smigielski et al., 2019). Furthermore, Sampedro and colleagues (2017) found that enhancements in self-kindness and reductions in both judgmental processing and inner reactivity linked to increased DMN-TPN connectivity. The 'afterglow' effect (and related changes in functional brain dynamics) demonstrated following ayahuasca consumption (involving elevations in mindfulness capacities), was sustained for two months after consumption of ayahuasca in a controlled setting (Sampedro et al., 2017). The study by Ruffell et al (2021) discussed above provided some preliminary evidence that enhancements in mindfulness, which may be related to ayahuasca consumption, were sustained for six months after retreat participation (S. G. D. Ruffell et al., 2021). The association between mindfulness and other psychological outcomes following ayahuasca, however, is yet to be explored.

6.1.4 Mindfulness Capacities and Psychedelic-induced Enhancements in Psychological Wellbeing

There is a growing number of studies that suggest that enhancements in mindfulness and improvements in mental health indices demonstrated after the consumption of psychedelics may be linked. For example, mindfulness ratings have been closely associated

with the anti-depressive effects of ayahuasca (Mian, Altman, & Earleywine, 2020). It is worth noting that these data involved cross-sectional retrospective reports, thus, like much of the research on naturalistic use of ayahuasca (which tends to be of a cross-sectional nature e.g. Barbosa et al., 2009; Barbosa et al., 2016; Bouso et al., 2012; Kavenska & Simonova, 2015; Murphy-Biener & Soar, 2020; Osorio et al., 2015; Uthaug et al., 2018), it cannot be assumed that the effects reported are due to the drug *per se*. Mindfulness ratings do negatively predict depression in healthy samples (K. W. Brown & Ryan, 2003), thus longitudinal designs are necessary to decipher whether *changes* in mindfulness predict *changes* in mental health indices.

Qualitative reports of psychedelic-assisted therapy do support the concept that mindfulness-related abilities such as acceptance may be key in supporting the therapeutic process (Bogenschutz et al., 2018; Watts et al., 2017). Alongside the early neuropsychological investigations noted above, which demonstrated that neural changes associated with ayahuasca consumption predicted increases in the non-judging facet of the FFMQ months later (Sampedro et al., 2017), there appears to be a pattern in the literature linking mindfulness capacities to psychedelic-associated changes in mental health and wellbeing indices. Non-judgemental awareness appears to be a relatively stable attribute of mindful awareness, changing less following mindfulness training than other facets (Montero-Marin et al., 2016), and both non-judging and non-reactivity components inversely predict anxiety (Soysa & Wilcomb, 2013), hence, ayahuasca consumption may facilitate changes in mindfulness, and such changes may predict improvements in psychopathology resulting from naturalistic ayahuasca use. Quantitative studies are required to elucidate how these mechanisms may relate to each other.

Another mental phenomenon deemed as key in underlying the beneficial effects of mindfulness on wellbeing and emotional experience is decentering. It refers to the ability to 'step out of' one's experiential perspective, and observe thoughts and feelings in a detached manner (Fresco et al., 2007). Accordingly, decentering engenders a distance from the internal experience and a reduction in reactivity to thoughts, and as such, enhancement in this ability may lead to less emotional responses to experiences (Bernstein et al., 2015; Shapiro, Carlson, Astin, & Freedman, 2006). Ayahuasca consumption appears to improve decentering capacities (Murphy-Beiner & Soar, 2020; Soler et al., 2018). In preliminary accounts of patient experiences of psilocybin-assisted therapy, increases in, and mentions of mindfulness-related ability (in particular, acceptance and connection) appear to be a salient component of change experienced by patients (Bogenschutz et al., 2018; Watts et al., 2017). The literature regarding decentering supports the notion that psychedelics enhance mindfulness-like capabilities (Soler et al., 2016), and that these have a knock on effect on anxiety and depression.

To summarise, contemplative abilities are being increasingly linked to the psychological health benefits demonstrated after psychedelic consumption. In particular, there is some evidence that mindfulness capacities may support improvements in disorder symptomology arising after ayahuasca consumption, and the benefits of cognitive capacities related to mindfulness (such as less judgmental processing) have been linked to improvements in mental health symptomology and subjective well-being (e.g. Soysa & Wilcomb, 2015). However, to date, these links have been made tentatively, predominantly using uncontrolled and/or single measurement designs.

6.1.5 Evidence to Date of the Relationship between Mindfulness Ability and Psychedelic-induced Changes in Psychological Health and Wellbeing

In addition to being potential outcomes of psychedelic treatment, self-compassion and mindfulness-related capabilities have been proposed as key 'change processes' in psychedelic-assisted therapy for depression. Specifically, during the preparation phase, patients are encouraged to accept a variety of emotional experiences (both desired and ordinarily 'aversive') as opposed to avoidance and disconnection (Watts et al., 2017). Qualitative analyses of participant experiences revealed 'acceptance' and 'connection' as two of such key processes.

Self-report data from psychedelic users indicates that increases in psychological flexibility mediate the relationship between the acute effects of psychedelics and related decreases in depression and anxiety (Davis et al., 2020). This construct involves multiple components, or processes, although willingness to make emotional contact with the present moment is a particularly important theme (S. C. Hayes et al., 2011). Similarly, self-compassion (and self-rumination) may partially mediate the effects of psychedelic experiences on changes in depression, anxiety and stress in psychedelic users (Fauvel, Strika-Bruneau, & Piolino, 2021). Though the aforementioned cross-sectional studies inspire hypotheses regarding potential mechanisms underlying psychedelic-associated change, they rely on reports of affect and experience at two different time-points (namely, before and after an important psychedelic experience), which were collected in retrospect of both time-frames, potentially years later than the experience in question. Further studies with data collected at multiple time points will be useful to help elucidate the mechanisms of psychedelic-associated improvements in psychological health.

Taken together, ayahuasca may be a useful pharmacological strategy to enhance contemplative abilities, and it is important to understand the psychological mechanisms that might underpin these changes, both to maximise potential benefit from the drug, and make appropriate pairings between pharmacological and psychological modalities in the future. In this chapter, I extend previous findings by exploring the relationship between ayahuasca use (in a ceremonial context), mindfulness and psychological health. Specifically, if mindfulness-related capacities predict or mediate the effects of psychedelics on mental health outcomes, this would present a significant opportunity to enhance treatment efficiency in protocols implementing psychedelic-assisted therapies.

6.1.6 Aims and Research Questions

We aim to investigate whether change in mindfulness capacities predict improvements in mental health and wellbeing indices after ayahuasca consumption, and whether mindfulness capacities mediate the relationship between ayahuasca and related changes in anxiety and depression symptomology.

Research questions:

1. Do enhancements in mindfulness predict improvements in anxiety, depression, and psychological well-being?
2. Do changes in mindfulness mediate the effect of number of ceremonies on anxiety or depression, whilst correcting for earlier measurements of mindfulness and anxiety/depression?

Considering the observational nature of the data, I took a longitudinal analysis approach, to allow for causal associations to be tested as well as possible, given the constraints of the design. Number of ceremonies was used as a primary predictor because

(alongside retreat length) it was the only ‘treatment-related’ variable that varied across participants and was chosen as the best proxy for ‘dose’.

6.2 Methods

6.2.1 Setting and Participants

This investigation used data that was collected as part of a collaboration with researchers from Kings College London, at The Ayahuasca Foundation - an ayahuasca retreat centre and research facility, located in Iquitos, Peru. Direct involvement in data collection was precluded by time and funding constraints. The participants were self-selected participants of the Foundation’s retreat. They were then approached by the researchers to invite them to participate. Participants were provided with information prior to arriving at the retreat centre, as well as before commencing the retreat, with opportunities to ask any questions, informed consent obtained, and right to withdrawal explained. Seven retreat attendees in total (one in each group) decided not to participate in the research. All data collection procedures complied with the declaration of Helsinki, and ethical approval was obtained from Exeter University institutional ethics committee (#CLESPsy000893 v2.0). See Ruffell et al., (2021) for the aforementioned published report detailing general mental health, memory valence and epigenetic outcomes.

The Ayahuasca Foundation pre-defined criteria for participation in ayahuasca retreats, which were assessed by means of a pre-selection screening questionnaires completed by prospective retreat attendees prior to acceptance on the retreat. Specifically, prospective participants with a history or diagnosis of psychosis, schizophrenia, bipolar or any personality disorder were not invited to attend the retreats. In addition, information on use of psychotropic medication was obtained. Given the special caution required in psychedelic treatments all those with a history of serious mental illness could not be accepted onto the

retreat. Those undergoing treatment using psychotropic medications were requested to taper off use, with the support of a medical professional prior to attendance. A medical doctor was present for the duration of the retreat processes to provide assistance in case of medical emergency.

6.2.2 Design

A naturalistic observational design was implemented, with measurements taken at three time points:

T1 - Baseline (the day before arrival to the retreat centre)

T2 – Post-retreat (the day following the last ceremony)

T3 – Follow-up (6 months after the last ceremony)

6.2.3 Measures

A variety of single time point measures were taken as part of the larger study. For the current investigation, the following time invariant variables were:

- Demographics (gender, ethnicity, employment status, mental health diagnosis, substance use problems, previous engagement with psychological treatment, and psychotropic medication use)
- Number of ceremonies completed per participant

In addition, the following outcome measures were assessed at all three time points (apart from MEQ, which was collected at T2 only).

6.2.4 Mindfulness Measurement

Mindfulness was measured using the self-compassion scale (SCS), a 26-item scale exploring six components of self-referential attitudes, including self-kindness, common humanity, mindfulness, self-judgement, isolation and overidentification (Neff, 2003). The

mindfulness facet is measured by four items that reflect one's capacity to be connected to the present moment.

There is evidence that the SCS may be better suited to measuring individual facets of self-compassion than one overarching construct (Williams, Dalgleish, Karl, & Kuyken, 2014). In the current study, only the mindfulness facet was examined. Participants are instructed to choose on a scale of 1 (almost never) to 5 (almost always), how they typically act towards themselves in difficult times. For example, "When I'm feeling down I try to approach my feelings with curiosity and openness". The mindfulness subscale is made up of four items, thus there was a possible total of 20 (high scores indicate higher mindfulness).

6.2.5 State-Trait Anxiety Inventory (STAI)

The STAI is a measure of symptoms of anxiety, with high internal consistency and test-retest reliability (Spielberger, 1983). It consists of 20 items each indexing state *or* trait anxiety, whereby higher scores indicate higher anxiety symptomology. In this study, only trait anxiety scores were analysed. Participants were asked to choose, on a scale of 1 (almost never) to 4 (almost always) how much each statement represented how they generally felt. Examples of trait items included: "I feel nervous and restless" and "I am calm, cool, and collected". A sum of the 20 items is taken, summing to a possible maximum score of 80.

6.2.6 Beck Depression Inventory – Second Edition (BDI-II)

The BDI is a self-report measure of depressive attitudes and symptoms comprising 21 items, which demonstrates high internal consistency (Beck & Steer, 1988). Items are scores from 0 (I do not (feel)/ I am not….) to 4 (I feel/ I am…), for example one item scores from 0 = I do not feel sad > 3 = I am so sad and unhappy that I can't stand it; and another ranges from 0 = I am not particularly discouraged about the future > 3 = I feel the future is hopeless and things cannot improve. Participants were asked to pick one statement in each question

group that best described how they had been feeling in the past two weeks. The maximum possible score is 63, with scores of 0-13 considered in the minimal range, scores of 14-19 indicating mild depression, scores of 20-28 suggestive of moderate depression and 29+ indicative of severe depression symptomology.

6.2.7 Clinical Outcomes in Routine Evaluation – Outcome Measure (CORE-OM)

The CORE-OM is a clinical tool for screening and monitoring psychological wellbeing, which is commonly used before the start and after completion of a course of therapy (Evans et al., 2000). It includes four domains, of which here we examine only the 'subjective well-being' domain. Participants were asked to rate on a scale of 0 (not at all) to 4 (most or all of the time) how often they have felt in such way in the past week. This subscale assesses a range of elements of psychological well-being, such as "I have felt optimistic about my future" and "I have felt overwhelmed by my problems". The maximum possible score for the subjective well-being subscale is 16. Low scores on the wellbeing subscale are indicative of more 'healthy', or 'less distressed' presentations.

6.3 Procedure

Eligible participants received instructions to commence a 'washout' period for the two weeks prior to arrival at the retreat, which involved avoiding any recreational or medical drugs, supplements, or herbal remedies. The Ayahuasca Foundation also recommended avoiding red meats, high fat content foods, as well as foods high in salt and sugar.
Retreat lengths were varied between eight days to one month, with ayahuasca ceremonies offered approximately every 2-3 days. Participants embarking on the shortest retreat had the opportunity to partake in up to four ceremonies, those who stayed for two weeks had six ceremonies, during the three-week retreat there were nine ceremonies, and during the one-month retreat there was a total of 11 ceremonies held. Despite the set number of ceremonies

offered depending on the length of the retreats, participation in each ceremony was optional, thus the number of ceremonies varied across participants. See descriptives for values associated with retreat length and number of ceremonies.

Ceremonies were completed using traditional Shipibo methods (see Gonzalez et al., 2021 for a summary of traditional methods), led by the local shaman, commencing in the evening and lasting for approximately five hours. The ceremony space consisted of a circular wooden building, with mattresses laid around the perimeter for each participant. Attendees were instructed not to interact with each other, though four to five facilitators were present for each ceremony to assist and provide support to the participants throughout the experience. Participants were advised to set their intentions for the experience at the beginning of the ceremony, before consuming (approximately 150ml of) the brew. As per the local tradition, ceremonies were held in darkness, and accompanied throughout by 'medicine songs', sung by the shaman and facilitators.

Pre- and post-retreat testing was completed on location with a researcher, and the follow-up was completed remotely via an online survey.

6.4 Data Analyses

The data were analysed in two parts. First, to run multilevel models on the data whilst taking into account all three time points of each variable, the data was transformed into long format, using subject ID as the case group identifying variable, and time (T1-3) as the index variable. Subsequently, longitudinal mediation models were analysed using wide-format data (such that scores from specific time points were chosen as particular variables. Multilevel models and mediation analyses were performed on SPSS 24 (IMB Corporation), using the PROCESS macro V3.4 for mediation analyses (Hayes, 2012). Missing data were excluded

case-wise from mixed model and panel mediation analyses. Continuous data are presented as means (standard deviations, SDs).

Multilevel models were used to explore whether enhancements in mindfulness predicted change in the outcome variables (anxiety, depression, and wellbeing). This multilevel approach was chosen since there was significant variation in the intercepts (baseline means) and slopes for the relevant scores, and since such models can account more effectively for missing data without compromising statistical power (Field, 2017). Time values were re-coded so that baseline measurements were included as the comparison category for effects of time, hence Time values of 3 indicated pre-retreat scores, values of 2 indicated post-retreat scores, and values of 1 indicated follow-up scores. Number of ceremonies was a covariate in the multi-level models, and a predictor in the majority of mediation analyses, considering it was the most closely related to 'dosage' of ayahuasca, whereas participants could have had a longer retreat with less ceremonies. There were no other covariates included in the simple multilevel models.

Three multilevel models were used to explore the predictive relationship between mindfulness and the three mental health/wellbeing outcomes (namely: anxiety, depression, and wellbeing), which were analysed in a separate model, controlling for number of ceremonies completed. As such, the psychological health variable (anxiety, depression, or wellbeing) was included as the dependent variable, with time as a fixed factor, and both number of ceremonies and mindfulness as covariates (to explore predictive effects). The subject ID variable was entered as random effect to allow the participant specific intercepts to randomly vary at level 2. A diagonal covariance matrix was used since it improved the fit of the second model without reducing fit of any other models, and improved model convergence (Bates, Kliegl, Vasishth, & Baayen, 2015). As per suggestions from Field

(2017), models were tested with different covariance structures, to ascertain that there was no other structure that fit the models significantly better. Parameter values were obtained using maximum likelihood estimation. A confidence interval of 95% was assumed. Number of ceremonies completed were included as a covariate in the multilevel models. See Table 6.1 for a summary of analyses completed.

Table 6.1

A summary of analyses completed, indicating the role of the main variables for each research question

Model	Predictor/ IV	Mediator	Outcome/ DV	Research question
1	Mindfulness	-	Anxiety	1
2	Mindfulness	-	Depression	1
3	Mindfulness	-	Well-being	1
4	Ceremonies	Mindfulness (T2)	Anxiety (T3)	2
5	Ceremonies	Mindfulness (T2)	Depression (T3)	2

Note. Considering the data was treated in longitudinal format for the analyses of models 1-3, the predictor references *change* in mindfulness, and outcomes refer to *changes* in anxiety, depression, and well-being.

Mediation models were chosen to explore the relationship between ayahuasca consumption (indexed by number of ceremonies completed) and psychological health outcomes because they allow for the elucidation of mechanisms that may subserve the relationship between the independent and dependent variables (in this case, mindfulness was

proposed as the mediating variable). In these analyses, antecedent variables are akin to the independent variable, and consequent variables are akin to dependent variables.

For the mediation analyses, the repeated measures nature of the data was taken into account by performing longitudinal panel mediation models using the three waves of measurement (see Fig. 6.1 for path diagram). This involved modelling later measurements of the outcome variables (anxiety and depression), using earlier measurements as covariates. Specifically, the outcomes of interest (anxiety or depression) were modelled at time 3 from the mediator (mindfulness) at time 2 and the predictor (number of ceremonies) at time 1, while using earlier measurements of mindfulness (T1) and anxiety/depression (T1 + 2) as covariates.

6.5 Sample size

Sample size was determined by pragmatic considerations, namely by the number of consenting participants per retreat, and the number of retreats that could be assessed during the funding period.

6.6 Results

6.6.1 Descriptive Statistics

Sixty-three participants between the ages of 19 to 63 (M = 37, SD = 9.7) completed the study. See Table 6.2 for a summary of sample demographics. Twenty-six (41.3%) participants reported having previously used ayahuasca, ranging between 1-80 times (M = 5.9, SD = 13.2).

Table 6.2

Sociodemographic characteristics of participants

Baseline characteristic		
	n	%
Gender		
Female	25	39.7
Male	35	55.6
Undisclosed	3	4.7
Ethnicity		
Asian	2	3.2
Black	1	1.6
Hispanic	3	4.8
White	50	79.4
Other	6	9.5
Not disclosed	1	1.6
Employment status		
Student	6	9.5
Part-time employed	6	9.5
Unemployed	8	12.7
Freelance	17	27
Full-time employed	26	41.3
Mental health diagnosis		
Attention deficit hyperactivity disorder	5	4.8
Post-traumatic stress disorder	5	4.8
Depression	9	14.3
Bipolar	2	3.2
Learning disability	1	1.6
Co-morbid: Depression/ PTSD/ ADHD/ Anxiety	8	12.7
Substance use problem (current/historic)	27	42.9
Previous engagement with psychological treatment	33	52.4
Psychotropic medication use (current/historic)	18	28.6

6.6.2 Retreat Characteristics: Length and Number of Ceremonies

Participants completed between 2 and 11 ceremonies (*M:* 7.22, *SD:* 3.94), with retreat lengths spanning between 8 to 28 days (*M:* 18.06, *SD:* 8.05).

6.7 Linear Multi-Level Models

6.7.1 Model 1: Mindfulness as a Predictor of Change in Anxiety

Modelling SCS mindfulness and STAI scores over time (T1-T3) showed that mindfulness significantly predicted anxiety ratings, b = -9.17, $F(1, 170.1) = 111.7$, $p < .001$, with STAI scores decreasing as mindfulness increased. On average, a single unit of increase in SCS mindfulness was accompanied by a decrease on the STAI of 9.17, $t(170.1) = -10.57$, $p < .001$, 95% *CI* [-10.89, -7.46]. Number of ceremonies did not predict STAI scores, $p < .05$.

6.7.2 Model 2: Mindfulness as a Predictor of Change in Depression

SCS mindfulness also significantly predicted change in depression symptomology, $b = 4.84$, $F(1, 116.03) = 66.56$, $p < .001$, whereby one unit of increase in SCS mindfulness was associated with a decrease of 4.84 in BDI scores, $t(116.03) = -8.15$, $p < .001$, 95% *CI* [-6.02, -3.67]. Number of ceremonies did not predict BDI scores, $p < .05$.

6.7.3 Model 3: Mindfulness as a Predictor of Change in Well-being

Similarly, changes in CORE-OM wellbeing were predicted by SCS mindfulness ratings, $b = -2.45$, $F(1, 138.31) = 83.18$, $p < .001$, such that a single unit of increase in SCS mindfulness was accompanied by a decrease in CORE-OM well-being of 2.45, $t(138.31) = -9.12$, $p < .001$, 95% *CI* [-2.98, -1.92], which indicates an increase in subjective well-being from baseline to follow-up. Number of ceremonies did not predict CORE-OM well-being scores, $p < .05$.

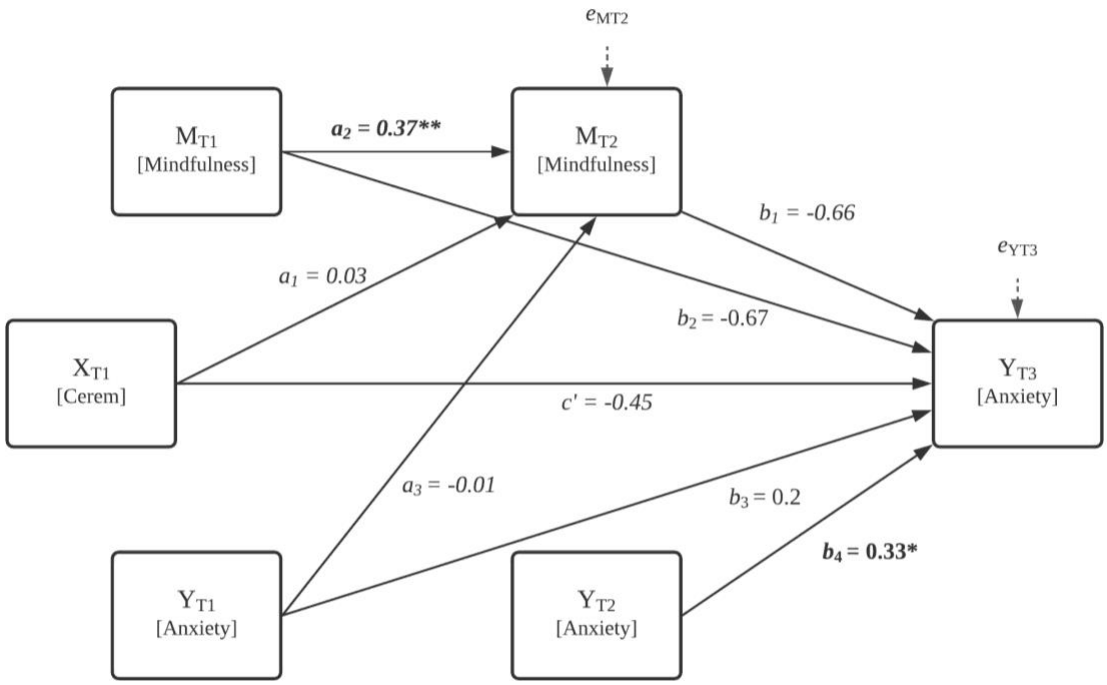
6.8 Longitudinal Panel Mediation Analyses

6.8.1 Model 4: Mindfulness as Mediator of the Effects of Number of Ceremonies on Anxiety

This analysis revealed that number of ceremonies did not predict SCS mindfulness post-retreat (a_1 pathway), though T1 SCS mindfulness significantly and positively predicted T2 SCS mindfulness (a_2 pathway). Baseline STAI was not related to post-retreat mindfulness (a_3 pathway). Number of ceremonies did not predict anxiety at follow-up (as indicated by the *c'* pathway), hence there was no evidence of a direct effect of number of ceremonies on anxiety. Earlier ratings of anxiety predicted later measurements (b_4 pathway), though no other pathways were significant (including the effect of mindfulness at T2, as per b_1 pathway), thus there was no evidence for mindfulness ratings mediating the effects of retreat length on anxiety ratings. This model accounted for 71% of variance in anxiety at T3, $F(5,47) = 9.7$, $p < .0001$. Since zero falls between the lower and upper bound of the bootstrapped confidence interval, the indirect effect (-.023) is assumed to be non-significant 95% *CI* [-.25, .19]. All panel mediation model coefficients and related values are provided in Table 6.3.

Figure 6.1

Path diagram of longitudinal panel mediation model (model 5) with three waves of measurement of anxiety



Note. In this model, number of ceremonies was included as the predictor, mindfulness post-retreat as the mediator, and follow-up depression scores as the outcome, with earlier measurements of mindfulness (T1) and depression (T1 + T2) as covariates. Cerem = number of ceremonies; bold - $p = .05$; ***** - $p < .05$; ****** - $p < .01$.

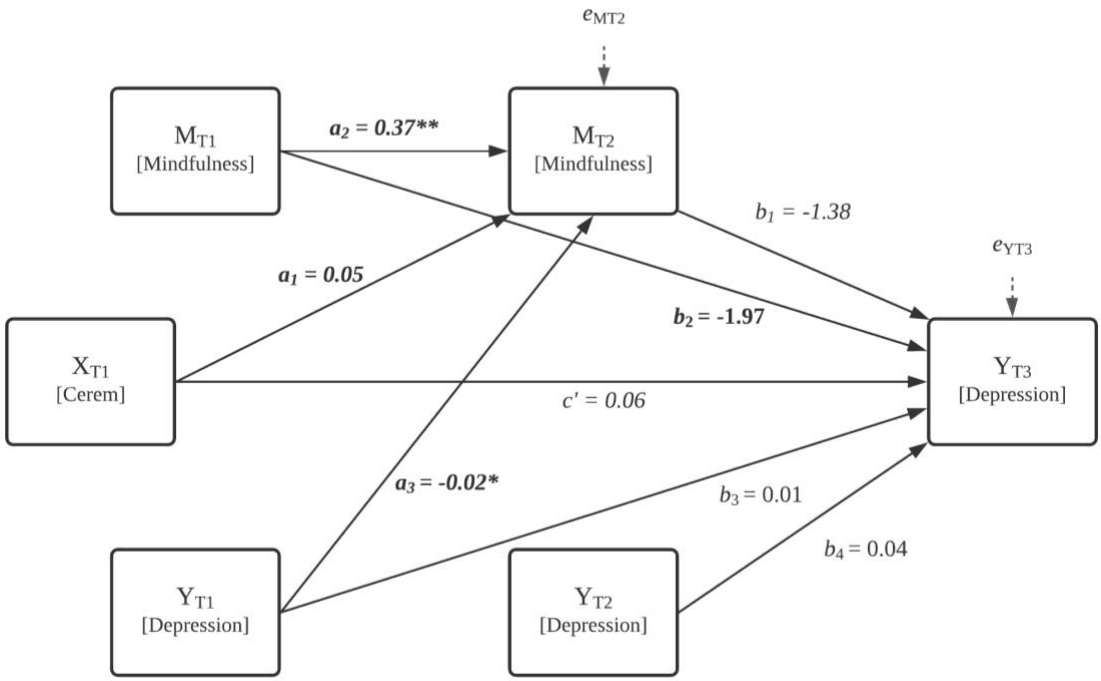
6.8.2 Model 5: Mindfulness as Mediator of the Effects of Ceremonies on Depression

As depicted in Figure 6.2, number of ceremonies demonstrated a marginally significant predictive relationship with T2 mindfulness (a_1 pathway values), with baseline (T1) measurements of mindfulness and BDI depression significantly predicting SCS mindfulness at T2 (a_2 and a_3 pathways). No direct effect of ceremonies on follow-up depression scores was found (*c'* pathway). Post-retreat mindfulness did not predict depression (b_1 pathway), but baseline mindfulness scores did marginally predict depression at

follow-up (b_2 pathway). Depression at T1 and T2 (b_3 and b_4 pathways) did not predict depression at T3. This model accounted for 28% of variance in depression at T3, $F(5,49) = 3.7$, $p < .01$. The indirect effect of number of ceremonies on depression at T3 via mindfulness at T2 (-.076) was not significant: 95% *CI* [-.27, .09].

Figure 6.2

Path diagram of longitudinal panel mediation model (model 5) with three waves of measurement of depression



Note. In this model, number of ceremonies was included as the predictor, mindfulness post-retreat as the mediator, and follow-up depression scores as the outcome, with earlier measurements of mindfulness (T1) and depression (T1 + T2) as covariates. Cerem = number of ceremonies; bold - $p = .05$; ***** - $p < .05$; ****** - $p < .01$.

Table 6.3

Model coefficients for the longitudinal panel mediation analysis

Model 4						Consequent		
		M (Mindfulness T2)				*Y* (Anxiety T3)		
Antecedent		Coeff.	*SE*	*p*		Coeff.	*SE*	*p*
X_{T1} (Cerem)	a_1	0.03	0.03	.217	c'	-0.45	0.33	.185
M_{T2} (Mind)		_	_	_	b_1	-0.66	1.78	.711
M_{T1} (Mind)	a_2	0.37	0.14	.009*	b_2	-0.67	1.76	.704
Y_{T1} (Anx)	a_3	-0.01	0.01	.113	b_3	0.2	0.12	.108
Y_{T2} (Anx)		_	_	_	b_4	0.33	0.12	.013*
Model 5						Consequent		
		M (Mindfulness T2)				*Y* (Depression T3)		
Antecedent		Coeff.	*SE*	*p*		Coeff.	*SE*	*p*
X_{T1} (Cerem)	a_1	0.05	0.03	**.054**	c'	.056	0.22	.801
M_{T2} (Mind)		_	_	_	b_1	-1.377	1.1	.215
M_{T1} (Mind)	a_2	0.37	0.12	.003**	b_2	-1.971	0.99	**.052**
Y_{T1} (Dep)	a_3	-0.02	0.01	.013*	b_3	.009	0.08	.911
Y_{T2} (Dep)		_	_	_	b_4	.041	0.1	.686

Note. Bold – $p = .05$; * - $p < .05$; ** - $p < .01$

6.9 Discussion

In this naturalistic study, we examined the relationship between ayahuasca consumption, mindfulness, anxiety, depression, and subjective well-being. Linear multilevel model analyses revealed that, whilst controlling for number of ceremonies, mindfulness significantly predicted improvements in anxiety, depression, and psychological well-being. Although it is not possible to definitively attribute these effects to the ayahuasca ceremony *per se*, the observed effects are consistent with previous observations from controlled studies (see further discussion below). To explore the role of mindfulness on these effects, mediation analyses were conducted on the longitudinal data to examine how *changes in* mindfulness may have mediated changes in anxiety and depression. Changes in mindfulness in particular have been proposed as an important mechanistic contributor to the beneficial effects of psychedelics, particularly ayahuasca (Sampedro et al., 2017; Soler et al., 2016). However, in the longitudinal mediation models, when accounting for earlier measurements of the mediator and outcome variables, there was no evidence for mindfulness mediating the effect of ayahuasca ceremonies on the mental health outcomes investigated. Rather, the mediation models revealed the predictive role of baseline levels of mindfulness on post-retreat mindfulness, and post-retreat anxiety and depression on follow-up measurements of these outcome variables. Taken together, ceremonial ayahuasca consumption in a naturalistic setting appears to be beneficial for indices of mindfulness ability and anxiety and depression. Furthermore, changes in mindfulness predicted improvements in anxiety, depression, and well-being, though due to the lack of evidence for mediation, it is unclear to which extent these changes were likely to be caused by ayahuasca or other factors.

6.9.1 Changes in Mindfulness may Predict Improvements in Psychological Health/ Wellbeing

Our first set of analyses indicated that enhancements in mindfulness (likely related to the psychedelic retreat) predicted improvements in anxiety, depression, and wellbeing, controlling for the number of ceremonies completed. To the author's knowledge, these findings are the first account of the relationship between mindfulness, anxiety, depression, and well-being outcomes over time in the context of traditional ayahuasca ceremonies. These results support mindfulness literature demonstrating that, for example, reductions in judgmental processing predicted decreases in anxiety (Soysa & Wilcomb, 2015). There is also evidence suggesting that changes in mindfulness following ayahuasca consumption were associated with the alleviation of depressive symptomology (Mian et al., 2020). Enhancements in decentering (paired with a non-judgmental attitude) may support the reduction in cognitive processes known to be common in psychopathologies such as rumination and worry (Nolen-Hoeksema, 1991, 2000). This, in turn, is likely to engender lower levels of cognitive and emotional reactivity, which are significant predictors of MBI outcomes (Gu et al., 2015). In terms of process, the distance gained from not being over-identified or reactive may allow for more opportunity to notice pathological thoughts, and redirect attention to connect with the present moment, rather than engage in habitual thought patterns triggered by emotions (Baer, 2003; Shapiro et al., 2006). Our finding of increases in mindfulness predicting decreases in depressive symptomology support the idea that the ability to remain distanced from thoughts and feelings may be an important psychological mechanism underpinning ayahuasca-induced enhancements in psychological health. As Shapiro and colleagues suggest, it follows that once one can perceive mental phenomena as

impermanent and appreciate that they will pass, there becomes more potential for tolerance of unpleasant thoughts and emotions (2006).

Alongside mindfulness, cognitive flexibility has been proposed as a psychological mechanism which may be in part responsible for the therapeutic effects of ayahuasca (Murphy-Beiner & Soar, 2020). There also appears to be a greater ability to think in novel creative ways – an ability which may enhance the creation of new cognitive and emotional strategies, and support psychological flexibility (Kuypers et al., 2016). Cognitive or psychological flexibility has been also proposed as a mechanism underlying the benefits of mindfulness-based interventions (Gu et al., 2015). Emotional, cognitive and behavioural flexibility are also theorised as key 'mechanisms' of mindfulness, which may assist meditators to avoid becoming over-identified with their thoughts and feelings, perceiving with more clarity, and becoming likely to respond in less automatic or reactive ways (Shapiro et al., 2006). It may also be a useful capacity to encourage other mindfulness-related skills. As briefly summarised in the introduction, there is evidence of enhanced functional connectivity between the DMN and TPN, which accompanied enhancements in mindfulness capacities following ayahuasca consumption (Sampedro et al., 2017). Within the context of these results, this suggests that changes in mindfulness (and the related psychological health benefits) may have a basis within neurobiological changes in the brain. Indeed, maladaptive rumination in depression has been linked to dominance of DMN activity over TPN activity (Hamilton et al., 2011), hinting at an example of such neural changes.

Psychedelic experiences do not always have a 'positive' acute effect - some of these effects are acutely challenging and anxiety-provoking. The results presented here might suggest that mindfulness-based strategies could be employed during acute psychedelic-induced dysphoric states to help transform acutely difficult experiences into more beneficial

effects on psychological wellbeing, that could potentially be sustained over a 6-month period (e.g. Van Dam, Sheppard, Forsyth, & Earleywine, 2011). In fact, recent manuals for psilocybin-assisted psychotherapy have chosen Acceptance and Commitment Therapy (ACT) as the psychotherapeutic approach (Guss et al., 2020), and teach mindful diaphragmatic breathing as part of anxiety management training (Mithoefer, 2017). Acceptance is an element of mindful awareness which has become central to modern psychotherapeutic approaches (Baer, 2003; S. C. Hayes, 1994). It is defined as "experiencing events fully and without defence, as they are" (Hayes, 1994, p. 30) . Hayes suggests that practicing acceptance provides an opportunity to avoid creating maladaptive habits and behaviours to avoid unpleasant symptoms, which could be tolerated safely with the understanding that they will pass (Hayes, 1994). Having a higher capacity for acceptance may in turn increase tolerance to anxiety or other pathological symptoms, whilst encouraging psychological flexibility (Villagrá Lanza & Menéndez, 2013). Indeed, findings indicate that acceptance negatively predicts psychopathology (Hayes et al., 1994). Acceptance appears to be a core component of exposure – a strategy for enhanced emotion regulation during mindfulness – whereby practitioners learn to allow themselves to be fully affected by their experience, and embrace acceptance towards sensory and affective responses rather than responding to them (Hölzel et al., 2011; Shapiro et al., 2006). Thus, it may not be surprising that here, mindfulness was a significant predictor of psychological health and wellbeing, and our suggestion would be that future research continues to include measures of mindfulness to further explore the relationship between psychedelic-induced changes in contemplative ability, and related changes in mental health symptomology.

6.9.2 Relationship Between Current and Previous Findings on Psychedelics, Mindfulness and Psychological Health

Unlike the findings of Davis and colleagues (2020) and Fauvel and colleagues (2020), we did not find changes in mindfulness to mediate the relationship between psychedelic consumption and related improvements in mental health indices. This could be explained on a theoretical basis, which calls into question the findings of the aforementioned cross-sectional data. To begin with, cross-sectional survey studies have been used previously to query a *change* in mindfulness or self-compassion, as well as changes in mental health indices. Such surveys, which are collected at one time point, but query both contemplative and psychological health aspects of participant's mind state. This is problematic for multiple reasons, the first being that in this design, participants refer to their state of mind both before and after their most salient psychedelic experience, which creates great opportunity for overestimation of the beneficial effects. This is particularly true considering 87% of participants rated as 'advocates for the therapeutic use of psychedelics', and data being collected in response to experiences that could have up to six years prior to the date of survey completion (Fauvel et al., 2021). Hence, though valuable for generating theories and hypotheses, the cross-sectional design calls is not set up to confidently make causal claims made regarding psychedelic-associated changes in mental health and wellbeing.

Furthermore, from the standpoint of statistical approach, mediators (mindfulness, self-compassion and psychological flexibility) and mental health outcomes (depression, anxiety, and stress) have been computed as change scores, which refer to concepts that change over the same period of time, and are therefore very plausibly interlinked (e.g. psychological flexibility and depression, before and after an important psychedelic experience). To appropriately infer some causality in a longitudinal design, it is optimal to

control for earlier measurements of the variables of interest, as suggested by Hayes (2018), and implemented here. One issue that this raises however, is the need for a generous sample, since the inclusion of more parameters (i.e. earlier measurements of mediator and outcome variables) can underpower an otherwise robust model such as our longitudinal mediation models.

Despite evidence of some additive effects of mindfulness and pharmacological compounds (Kamboj et al., 2017; Smigielski et al., 2019). The current results did not support the notion that improvements in mindfulness are an *intermediate* beneficial outcome of psychedelic use which has a consequent effect on anxiety/depression. One question raised by this research is whether baseline mindfulness may be a better predictor of post-retreat psychological health than involvement in psychedelic ceremonies. Our models did not test the link between baseline mindfulness and post-retreat psychological health (a cross-lagged/ path analysis would be necessary to explore this relationship), however, considering change in mindfulness was a significant predictor of change in anxiety and depression, and number of ceremonies completed was not, this would be an interesting relationship to examine – possibly to indicate how much future therapeutic set-ups may wish to focus on the preparation element of the psychedelic experience. Indeed, survey data indicate that rather than dose, frequency of use or intensity of experience, certain baseline trait variables may be the strongest predictors of psychedelic-associated changes in well-being (Haijen et al., 2018), reminding us of the importance of non-drug elements of the psychedelic experience. It would require a more ambitious study of the retreat process (i.e. more measurements of each contemplative/ psychological well-being variable) and a different analytic approach (namely cross-lagged/path analysis – to investigate the relationship between each variable at each

time point) to examine the effects of baseline mindfulness on psychological well-being indices over the course of a retreat.

6.9.3 Quantifying the Psychedelic Experience: Quantity or Quality?

The lack of predictive effect of number of ceremonies (as a covariate) on change in anxiety, depression or subjective-wellbeing provokes the question regarding the best way to quantify psychedelic consumption. Despite dose-dependent effects of ayahuasca demonstrated on subjective *psychedelic* effects (Riba et al., 2001), transformative components of the ayahuasca experience are found to occur in an unpredictable manner (Wolff, Ruffell, Netzband, & Passie, 2019). Though, considering previous analyses (e.g. Ruffell et al., 2021) were not based on the potential *mediating* role of ayahuasca-induced changes in mindfulness, we sought to explore whether number of ceremonies may be predictive of this. However, in line with previous results demonstrating 'sporadic' improvements in wellbeing associated with psychedelics (Haijen et al., 2018), the quantity of ceremonies was not predictive of changes in mindfulness. Looking forward to future research, it may be more informative to measure the *quality* rather than *quantity* of the psychedelic experience (such as mystical qualities, or insights gained), may represent a useful proxy of the 'intensity' of the experience (e.g.: Davis, Barrett & Griffiths, 2020). This said, to further qualify any clinical applications of psychedelics such as ayahuasca, regardless of the measurement of psychedelic experience, the field will still rely on randomised controlled trials, that will be outside of the traditional context of the compounds.

6.9.4 Future Research Recommendations

Our results are consistent with a large body of previous research showing an association between changes in mindfulness capacity, and enhancements in psychological health in the context of an ayahuasca retreat. Specifically, to add to the findings of concurrent

increases in self-compassion and improvements in mental health indices by Ruffell and colleagues (2021), here I found that mindfulness may predict improvements in anxious, depressive, and subjective well-being symptomology. Since these findings relate to naturalistic ayahuasca use, our research raises the question as to whether changes in mindfulness following ayahuasca use would more reliably be observed in a more controlled laboratory or clinical context. Thus, the first recommendation for future research would be to perform the study in a controlled context to ascertain whether changes in mindfulness and mental health symptomology are observed following ayahuasca use and determine the extent to which any observed effects are due to set and setting (especially the other, non-pharmacological aspects of the ceremony). Palhano-Fontes and colleagues' recent study (2019) provides a basis for investigating the effects of ayahuasca in a randomised, placebo-controlled setting, which could effectively parse the contribution of a placebo effect. It does appear to be an important question at this time in history – while psychedelic drugs are gaining increasing attention as potential therapeutic tools - as to how much of the therapeutic potential may be due to social and contextual factors of traditional psychedelic consumption, that may not be, or rather should be better preserved when extrapolating to more clinical contexts. Particularly true with ayahuasca, non-pharmacological aspects of the ceremony and the surrounding community are important components of ayahuasca-related healing. Recent evidence suggests that feelings of 'perceived togetherness and shared humanity' during psychedelic ceremonies are important predictors of mental health outcomes (Kettner et al., 2021), however, these aspects might be more difficult to preserve in highly controlled laboratory experiments, and the reductionistic perspective of clinical and laboratory trials must be recognised, since only the pharmacological aspect will be well examined. Relatedly, naturalistic studies in traditional settings have the potential to show us how to work with

ayahuasca, and provide an opportunity to work towards decolonializing science (Reiter, 2020).

Another recommendation would be to explore the more complex dynamics using a cross-lagged or path regression approach, so as to explore the relationship between variables at a larger number of time points. For example, here we examined the effects of baseline mindfulness on follow-up anxiety and depression, but it was not possible to explore the effects of baseline mindfulness on anxiety or depression immediately post-retreat (T2). Though improvements in anxiety and depression appear to sustain to follow-up (Ruffell et al. 2021), just as baseline depression significantly predicted post-retreat mindfulness, baseline mindfulness may be an important predictor of post-retreat depression, an effect which may be diluted over the months between the end of the retreat and the follow-up measurement. It may also be easier to draw causal inferences between baseline mindfulness and depression immediately post-retreat, compared to depression scores at follow-up. Future psychedelic studies may also benefit from taking a pre-arrival baseline measurement of outcomes as some recent studies have (e.g. Kettner et al., 2021), to control for the effect of arriving in a retreat location, which may be associated with expectation effects. It would be desirable to further examine the effects of set and setting within the context of naturalistic ayahuasca consumption. Attempts of this nature have been made in recent literature (e.g. Uthaug et al., 2021), however results should be interpreted with caution considering the relatively low doses of active ayahuasca administered in the experimental group, and lack of successful masking to condition in the majority of participants. Successfully blinding participants to their condition presents a particular challenge to psychedelic trials, considering the acute subjective effects associated with these compounds (see Aday et al., 2021) for further discussion on this). Another approach, if more controlled approaches were not feasible (for

example due to resource constraints) would be to use a multiple baseline design within a naturalistic context, such that different groups of participants would arrive at the retreat location at the same time, but start their psychedelic ceremonies at delayed intervals. This would help elucidate whether the ayahuasca was responsible for changes in mindfulness and psychological health, or whether the setting (i.e. being present at the retreat location) is partly responsible for the improvements witnessed.

6.9.5 Implications

Considering the context within which these findings sit – a small but fast growing pool of findings related to the effects of ayahuasca – this pattern of results indicates that ayahuasca consumption may be useful to enhance mindfulness and psychological health, though we could not clarify a particular role of mindfulness in the enhancements of anxiety and depression. Specifically, the association between enhancements in mindfulness and improvements in anxiety, depression and well-being require further investigation to be able to determine if enhanced mindfulness capacities are intermediary to improvements in anxiety and depression symptomology. Results from our mediation analyses did highlight that levels of mindfulness at baseline were predictive of follow-up depression scores, which may be useful to explore in future research such that elements of mindfulness training could be incorporated into preparatory phases of psychedelic retreats.

Conversely, ayahuasca may also be a potential pharmacological tool for enhancements in mindfulness. Particularly during the afterglow phase, which is characterised by "increased openness to therapeutic intervention" (Domínguez-Clavé et al., 2016). Thus, resulting acute or short-term psychological effects triggered by ayahuasca may be helpful for consequent behavioural therapeutic approaches. As explored in the previous chapter, some people combine contemplative practices and psychedelics to produce synergy. Existing

literature and the first experiment reported in this thesis (see chapter three) suggest that specific drugs can be a useful adjunct to contemplative practice (Smigielski et al., 2019). This study may point towards a new potential drug target for this combined therapeutic approach, though this suggestion remains purely hypothetical at this time. Novel psychedelic studies such as that carried out by Smigielski and colleagues (2019) provide inspiration for how studies could be carried out that incorporate a psychedelic compound into a traditional mindfulness retreat context.

6.9.6 Limitations

Some key limitations should be noted that are associated with the naturalistic design implemented in this study. There was a lack of placebo with which to compare the effects of the ayahuasca, there was no control over dosing, and both participants and researchers were aware of the drug and associated potential subjective effects, which may have caused expectation effects, and together, increase risk of bias and hinder causal inference. Another limitation to note is that meditation experience, and regularity of practice was not recorded in this study. Frequency of engagement in meditation practice affects one's ability to be mindful in daily life, and unsurprisingly therefore, is a key predictor of wellbeing (Schoormans & Nyklíček, 2011; Soler et al., 2014). Additionally, factors such as age, gender, mental health diagnoses and possible undiagnosed conditions were not taken into account in these analyses. Indeed, there is evidence that different trends in therapeutic change occur between genders (Kettner et al., 2021), and it may also be the case that those who have a mental health diagnosis, or experience of psychological therapy show different trends in their change in wellbeing after psychedelic consumption.

By nature of the self-selected sample, it may be that participants attending ayahuasca retreats are particularly committed or motivated to pursue novel therapeutic approaches for

well-being, and/or particularly open to exploring altered states of consciousness. This recruitment approach particularly lends itself to expectation effects for these reasons. Additionally, there was a significant proportion of the sample included that classified as having a current mental health disorder at baseline, which it may be useful to analyse in separate subsets in future investigations (as per Ruffell et al., 2021). Finally, it is worth noting that relying on self-rated reports of behaviour and experience involves a potential limitation of accuracy. This may be particularly relevant to contemplative abilities such as self-compassion and mindfulness – as noted by Neff (2003), many people not aware of their emotional experiences day to day, or their lack of self-compassion if it is not something they are practiced at. Thus, it will be important to run multi-methods designs in the future, for example, to have behavioural or physiological approaches that supplement commonly used self-report scales.

6.9.7 Conclusion

This research provides preliminary evidence that within a naturalistic setting, ayahuasca consumption may produce beneficial effects on mindfulness, and psychological health (including anxiety, depression, and subjective well-being). Additionally, improvements in mindfulness may predict improvements in psychological health and well-being. Mindfulness did not mediate the effects of ayahuasca on anxiety or depression, therefore future research should continue to explore potential intermediary processes, ideally within a design that can be better controlled. This research builds on the already promising and fast-growing literature on the possible therapeutic potential of psychedelic drugs, and that more research is necessary to explore the dynamics between contemplative ability and mental health outcomes of psychedelic consumption.

Chapter 7

General Discussion

7.1 Summary of Findings

This collection of work used a variety of methodologies to answer the following core research questions:

- Is a single session of mindfulness adequate to create change across affective, behavioural, cognitive, and physiological outcomes?
- Is it possible to enhance elements of mindfulness practice using modafinil?
- What are the effects of combining psychedelics and meditation, as reported by psychedelic users?
- How might mindfulness change, and subsequently affect, other outcomes of ceremonial ayahuasca consumption?

See Table 7.1 for a summary of methodologies used and key findings from each chapter.

Table 7.1

Key findings from each chapter

	Methodology applied	**Key findings**
CH 2	Systematic review	Mindfulness inductions appear capable of enhancing state mindfulness, alongside indices of emotion regulation, affect, cognitive bias and attention performance. A large variety of methods are currently used in MM inductions. There is generally weak methodological rigor in MM inductions.
CH 3	Experimental trial	Modafinil can enhance state mindfulness.

	Methodology applied	Key findings
		Modafinil bolsters the effects of behavioural strategies on state mindfulness.
		Modafinil increases future self-practice of behavioural strategies.
CH 4	Protocol for experimental trial	*Findings not applicable, however the methodological research associated with this chapter revealed that
		breath-counting may be a useful approach to train *and* measure mindfulness.
CH 5	Thematic analysis	Users find psychedelics and meditation to be compatible, creating predominantly positive subjective effects.
		Psychedelics appear to enhance the depth and quality of meditation, and one's ability to 'access' and maintain it.
		Meditation is useful to prepare for and navigate the psychedelic experience.
CH 6	Naturalistic investigation	Ceremonial ayahuasca use increases mindfulness and subjective well-being, whilst reducing anxiety and depressive symptomology.
		Changes in trait mindfulness may predict the magnitude of improvements in anxiety, depression and subjective well-being, however mindfulness does not appear to mediate the effects of number of ceremonies on change in anxiety or depression

Though presented second, the empirical trial detailed in Chapter three was the first piece of research conducted as part of this thesis. This randomised controlled experimental trial investigated the effects of modafinil as an adjunct to a single-session mindfulness practice. At the time, there were no published empirical lab-based studies investigating the effect of combining a drug and contemplative practice. I found that modafinil could temporarily enhance state mindfulness, and bolster the effects of mindfulness and relaxation strategies on state mindfulness. Confirming previous research (Turner et al., 2003), modafinil

also enhanced sustained attention, and increased strategy self-practice time in the days following the lab session, regardless of a similar number of self-practice attempts between drugs groups. These findings indicate a potential faciliatory role of modafinil in early-stage practice or mindfulness and related techniques (such as relaxation). One set of results in my first empirical study that did not follow predictions was the lack of differential enhancement of state mindfulness after the mindfulness strategy relative to the control (relaxation strategy). This was potentially due to the active and control instructions being too closely-matched, thus producing similar interacting effects with modafinil. In contrast however, heart rate variability (HRV) measurements were significantly higher in the mindfulness group after the strategy, indicating parasympathetic activation which would be expected after successful manipulation of mindfulness. The methodological challenge highlighted by inconsistent effects of the behavioural strategies inspired the systematic review of single-session mindfulness literature that makes up the second chapter.

Chapter two systematically reviewed published single-session experimental studies implementing a mindfulness strategy focusing on the effect on state mindfulness, while also exploring indices of affect, behaviour and cognition. The evidence collected indicated that mindfulness inductions are capable of enhancing state mindfulness (at least somewhat), as well as creating improvements in the other neuropsychological domains investigated. A problematic element of reviewed studies was the large variation in methods used. For example, one mindfulness induction may last 15 minutes, with a focus on present-moment awareness, and awareness of the breath and body, which is compared with an active control of mind-wandering (e.g. Eddy et al., 2015). To relate the results of this study with a five-minute mindful eating task, which involves either mindfully eating two raisins (mindfulness condition) or eating two raisins with no further instructions, over the course of the same time

duration (control condition), may be problematic, considering it is impossible to ascertain which elements of mindfulness are being engendered using such different strategies. I also found a great variety of control tasks, implying there is no 'gold-standard' when it comes to choosing a control task, though active control tasks should be a minimum expectation of methodological rigor. Some studies used two control conditions, which probed different non-specific elements of the mindfulness task (e.g.: Lueke & Gibson, 2016). This is a desirable approach because it allows for the distinction between non-specific effects of mindfulness inductions, such as relaxation or maintenance of attention, as well as controlling for the mere fact of engaging in a task.

This heterogeneity is a well-known characteristic of mindfulness (intervention) research (Van Dam et al., 2018), though it was surprising to discover the similar design flaws populating the majority of single-session studies reviewed, considering the potential to more greatly control conditions. Ambiguity of strategy description was another challenge of this review of the literature and related interpretations, such that different elements of mindfulness are likely to engender differential effects (Tang et al., 2015), thus makes direct comparisons difficult. I also found that the studies included mostly lacked sufficient levels of methodological rigor. Specifically, it was very rare for studies to report that the outcome assessor was blind to the behavioural condition, analyses rarely pre-registered, or credibility of the strategy, and expectancy of the participant measured. Overall, I demonstrated that there remains potential to conduct and publish well-controlled, rigorous single-session mindfulness studies, and that results from preliminary research warrant more robust studies in support of these findings.

Following on from the methodological focus of chapter two, my second planned empirical chapter (CH4) proposed the implementation of a novel 'objective' approach to

train and measure mindfulness (Levinson et al., 2014), to potentially overcome some common methodological challenges, particularly in relation to an objective measure of mindfulness. Specifically, since it is possible to both train and measure breath-counting simultaneously (the latter relying on the use of a respiration monitor), it would be possible to measure the accuracy of participant's breath-counting, a validated measure of mindfulness 'performance' (Wong et al., 2018). The accuracy of breath counting can be used as a measure of mindfulness, to support the self-report elements of the data. Following the replication of Levinson and colleague's study in a large Asian sample (see Wong, Massar, Michael, & Lim, 2018), I expected the breath-counting task to produce significantly differential behavioural, cognitive, and physiological responses in comparison to the arithmetic task with which it was compared (as an active control strategy). An arithmetic task was chosen since single-session mindfulness studies have implemented them before, demonstrating sound discriminant validity in comparison to an attention task (Watier & Dubois, 2016). An arithmetic task can also be manipulated easily to match some elements of the breath counting task (such as duration and response style), whilst engaging participants to a modest degree (likely without arousing any stress or anxiety). Although the study could not be completed, the methodological and theoretical learnings from the planning of this study should benefit future related research by providing a common methodological approach that can be easily replicated.

In chapter five, I explored psychedelic user accounts of combining psychedelics and meditation by way of thematic analysis. This made it possible to build a rich data-driven picture of users (in Western cultures) experience of combining psychedelics and meditative practices. Results indicated that participants found psychedelics and meditative practices to be compatible, with suggestions of mutual enhancement. The analysis revealed that

psychedelics appear to improve access to the meditative state (often explained as an enhanced 'ability to meditate'), and increase the depth and quality of the meditative experience. Equally, meditative practices were highlighted as useful navigational tools, for the preparation and acute phases of the psychedelic trip.

In my final empirical chapter, the predictive effects of ayahuasca-associated increases in mindfulness on indices of psychological health and well-being were explored. Longitudinal mediation models were used to explore mindfulness as a potential mediator for changes in anxiety and depression symptomology demonstrated after participation in ayahuasca retreats. Results indicated a predictive association between changes in mindfulness and changes in anxiety, depression, and well-being, accounting for earlier measurements of each variable, and controlling for number of ceremonies completed. There was no evidence of a mediation effect of mindfulness in the relationship between number of ceremonies and changes in anxiety or depression, when controlling for earlier measurements of mindfulness and anxiety/depression. In contrast, the mediation analyses revealed predictive associations between baseline measurements and follow-up depressions cores, and baseline depression scores predicted post-retreat mindfulness scores. These unpredicted associations demonstrate the importance of extra-pharmacological aspects of psychedelic-associated changes in psychological health and well-being.

7.2 Findings in the Context of Literature and Theoretical Implications

The systematic review of single-session mindfulness studies (chapter two) helps to inform the 'dose' of mindfulness that is necessary to create beneficial change. This review of the literature adds an up to date summary of how mindfulness strategies can be useful when implemented in a very short time frame, and which methods tend to be implemented. Considering the novelty of this research question, I hope it provides some valuable

suggestions for future experimental research which are important to enable well-designed future studies on the pharmacology of meditative states.

My double-blind randomised controlled experiment (CH3) provides a basis for future combined contemplative and pharmacological experimental research. The combination of rigorous design, and novelty of interdisciplinary approaches will hopefully inspire future research to come. The key take-away is that (single-session) mindfulness can be pharmacologically assisted, and this combination may be helpful with regard to state mindfulness, attention, and affective outcomes. Although this research (as far as I understand) was the first of its kind to combine these specific approaches in a laboratory context, mindfulness strategies have been combined with a number of different therapeutic methods with promising results. For example, mindfulness strategies may pair well with non-pharmacological approaches for neurocognitive enhancement and to help remedy mental health disorders, such as brain stimulation and neuro-feedback (Crivelli, Fronda, & Balconi, 2019; Monnart et al., 2019). Recent experimental work also supports the conceptual logic behind pharmacologically-assisted meditation for first-time meditators. There is evidence that one's enjoyment of an initial mindfulness session can be experimentally augmented using tools to help improve affective state or experience (such as a positivity micro-intervention), and that specific qualities of the initial experience, such as enjoyment, predict continued practice (Van Cappellen et al., 2020).

Since the conception of this body of work, one empirical study has been published demonstrating the capacity for a pharmacological agent (in this case, the psychedelic psilocybin) to enhance the depth and quality of the meditative experience in experienced meditators (Smigielski et al., 2018). Psilocybin has also been administered to participants of a meditation retreat that involved different levels of contemplative and spiritual support,

whereby both higher doses of psilocybin and more frequent meditation practice were associated with greater enhancements to life meaning, life purpose, gratitude, interpersonal closeness, and forgiveness, among others (Roland R Griffiths et al., 2018). The findings from our first empirical study (CH3) support the case for pharmacologically-assisted contemplative practice, as did user accounts of combined psychedelic and meditative activities explored in chapter five. This may be due to drug-induced enhancements in non-avoidance, and/or enhancements in self-transcendence (as per Smigielski et al., 2018). Increases in mindfulness after psychedelic consumption are increasingly reported, with controlled trials reliably producing elevations in trait mindfulness that sustain to follow-up in months following the experimental session (Soler et al., 2018, 2016; Uthaug et al., 2021). This may be due to neurobiological changes that are common to both mindfulness and psychedelic consumption, such as reduced Default Mode Network (DMN) activation, alongside greater functional connectivity between the DMN and networks activated by attention demanding tasks (such as the ACC and dorsolateral PFC) (Barrett & Griffiths, 2018; Fox et al., 2016). Accordingly, Sampedro and colleagues (2017) found increases in connectivity between the ACC-medial temporal lobe after ayahuasca consumption, which correlated with increases in self-compassion (a commonly measured outcome in many studies of mindfulness), and predicted sustained increases in non-judging two months later. Additionally, the extent of ego dissolution, and associated brain connectivity (decoupling of the medial prefrontal and posterior cingulate cortices) predicted positive changes in psycho-social functioning in participants taking part in a psilocybin-augmented meditation retreat, four months later (Smigielski et al., 2019). Thus, in addition to attention-augmenting drug like modafinil, psychedelics may be useful adjuncts to contemplative practice, and these

benefits may stem from affective, attentional, cognitive and/or neurobiological changes associated with these approaches.

In summary, in chapter two, I found that single-session mindfulness inductions can improve adaptive affect, behaviour and cognition. In chapter three I showed that specific elements of mindfulness can also be enhanced by modafinil in a single-session experimental study. It appears that meditation and psychedelics may have synergistic effects, with psychedelic consumption becoming associated with increases in mindfulness, and mindfulness potentially enhancing subjectively experienced elements of the trip, while enabling the experience to be navigated safely. Though naturalistic and qualitative study findings (as per chapter five and six) should be supplemented with randomised controlled experimental data, they imply that cross-disciplinary research is valuable, and in particular, combinations of contemplative and pharmacological approaches to reduce suffering, increase personal connection, and enhance wellbeing warrant further exploration. It appears that the fields of contemplative and psychedelic research may be ripe for the design of rigorous empirical research that combine the two approaches to altering states of consciousness. Recent reviews appear concordant with this view (Eleftheriou & Thomas, 2021; Heuschkel & Kuypers, 2020; Payne et al., 2021).

7.3 Methodological Considerations

7.3.1 Challenges Associated with Mindfulness Research

7.3.1.1 First Person Perspective and Self-report. Self-report relies on an understanding of one's own conscious experience (Varela & Shear, 1999). Those who do not have training in awareness of the content of their mind will therefore be responding in a less reliable and valid way, since this awareness is likely clouded by distraction (Varela & Shear, 1999). This means that using the same measurement tools for novice and advanced

practitioners may threaten the validity of self-report measures. One solution is to measure behaviour using different perspectives, such as second or third person perspectives (Davidson & Kaszniak, 2015). In this collection of work, second and third perspectives were not used, however I can appreciate that this may be a useful approach, for example, to have community-rated estimations of health and well-being (as per Griffiths et al., 2018). One approach I did use to account for the limitations of self-report data was to combine self-rated questionnaires with behavioural and physiological measurements. For example, the use of heart-rate variability measurement alongside self-report measurements of mindfulness (see chapter three), and the use of a respiration measurement to verify breath counts (see chapter four).

7.3.2 Study Design/ Double Blinding

The systematic review in the second chapter of this thesis demonstrated that even in recent, single-session laboratory studies, double-blind procedures remain rare. It is understood to be challenging, or even impossible to successfully blind participants to their strategy condition in mindfulness research (Davidson & Kaszniak, 2015). However, my experiment in the third chapter illustrates one example of how this may be possible. Specifically, if recruitment information includes no mention of meditation or mindfulness, but rather cognitive training, or a similar guise, it is possible for participants to remain uninformed about the nature of the experiment, thus minimising expectation effects. A double-blinded behavioural condition also best suits designs with well-matched active controls such that there is less of a chance of participants guessing their assigned condition.

7.3.3 Active Control

The inclusion of an active control group was a key methodological strength of the study in chapter three, which I found to be relatively uncommon in single-session

experimental research (see chapter two). Though this challenge is not unique to the development of a mindfulness studies, it is important to consider. Ideally, one would aim for as many as possible of the non-mindfulness specific elements of the practice to be controlled for (Davidson & Kaszniak, 2015). Though the majority of literature that was reviewed included inactive controls, or controlled few factors other than time engaged in the strategy, our study (chapter three) demonstrated that it is likely possible to over-match the control condition to the mindfulness strategy, such that both strategies beneficially affect key outcomes, and it is not possible to determine strategy effects. MacCoon and colleagues (2012) demonstrate an intervention-level example of this, whereby self-report measures of negative affectivity, distress and even medical symptoms may respond to non-specific features of a mindfulness intervention that is well matched with an active control program.

7.3.4 Challenges Associated with Psychedelic Research

The literature concerning psychedelic drugs is well-populated by cross-sectional survey and naturalistic data, likely due to logistical and pragmatic reasons (such as the financial and practical implications associated with their legal status). These designs are not well suited to making causal associations between drug and outcomes, due to questions around extraneous factors such as context and lifestyle, as well as dosage (a predictor of subjective effects of psychedelics (Swanson, 2018)). Indeed, healthier lifestyle habits may be associated with the consumption of psychedelics (see Teixeira et al., 2022), which may confound cross-sectional data. One approach to balance these uncontrolled factors would be to more holistically measure participants' lifestyles before and following psychedelic consumption, and include more time-points and relate these to primary outcomes of interest. Although this would make online surveys lengthier, it would substantially improve interpretability and allow causal associations to be examined from the data.

The question of dosage is an interesting one when it comes to naturalistic or observational designs. In the interest of not interfering with the process, dosages of psychedelics are often not recorded. Considering it may be valuable to understand how much of a substance participants consume, researchers may seek to quantify dosage based on visual estimation (for example, in a naturalistic ayahuasca study). Another approach to quantifying dose in naturalistic or observational studies, with a compound such as MDMA (as per Kamboj et al., 2018), would be to accurately weigh each participant's dose before they take it and retrospectively assess the composition of the drug to determine purity. Despite the potential for re-scheduling of compounds that are certified as safe and well-tolerated (and the potential knock-on effect this would have in terms of facilitating well-controlled laboratory-based research), naturalistic experiments will remain important to create more ecologically valid data, therefore finding ways to measure dosage would be beneficial.

Specific to the understanding of the interaction between meditation experience and psychedelics in cross-sectional and experimental data, it is worth considering that participants' level of experience with meditation may impact their response to psychedelic compounds. In future studies examining the relationship between meditation and psychedelic use, it would be helpful to collect detailed information regarding past and current meditation experience, ideally with details of which types of practice participants are regularly engaging in, and whether this is predominantly in a self-practice or retreat context – since the latter is generally more intensive (Davidson & Kaszniak, 2015). Furthermore, in experimental research, it may be valuable to measure both state and trait mediation abilities (e.g. mindfulness) in order to assess how these different elements change over time, and interact with the consumption of psychedelics.

7.3.5 A Note on the Present Methodologies

Though results from survey data and naturalistic studies must be interpreted with caution, this collection of work benefits from utilising a variety of methodical approaches to answer questions related to the potential for drugs to enhance mindfulness, and explore the opportunity for synergistic action. Indeed, the importance of using multiple methods of enquiry is increasingly understood, with suggestions for triangulation where resources permit (Munafò & Davey Smith, 2018). Though I did not use the triangulation approach per se, it stands that the multimethod approach certainly may be useful to account for the different limitations of each methodology. For example, though the use of a randomised controlled design allows for restriction of potentially confounding extraneous variables, the results lack validity. The reductionistic perspective of a well-controlled laboratory study can partially be accounted for with the use of rich qualitative data, while the lack of validity from the RCT may be partially remedied by exploring naturalistic data. Though causality cannot be inferred from qualitative data, nor with much strength through longitudinal observational data, the creation of well-controlled RCT designs demonstrates how the questions of interactions between psychedelics can potentially be explored in the future.

7.4 Limitations

7.4.1 Chapter Specific Limitations

Despite the array of benefits associated with the multiple methods used in this thesis, there are also some limitations in regards to this body of work which should be noted. Considering the main aim of the parent study from which chapter six was born was not specifically related to mindfulness, and the research team were interested in measuring both mindfulness and self-compassion, due to the large number of questionnaires due to be included in the questionnaire battery, the mindfulness specific questionnaire that would have

been my first choice to investigate (FFMQ) was removed during the design phase, and the Self Compassion Scale was maintained as a measure to explore both self-compassion and mindfulness. Design decisions also feature within the limitations of the thematic analysis (chapter five), in which the qualitative aspect was secondary and could have benefitted from more specific questions posed to participants for the qualitative element of the data. For example, future survey questionnaires might probe specifically what the felt effects of having taken a psychedelic were on one's meditation experience. That said, the methodological choice to provide participants with an opportunity to comment freely on experiences of meditation after psychedelic use in chapter five allowed participants to expand the range of relevant and important themes beyond what was initially intended. One important outcome from this chapter was the notion that meditation is an important *preparatory* activity, despite the wording of the question referring to use of meditation *after* psychedelic use. The fact that participants discussed preparatory meditation despite being primed to discuss the combined effects of meditation and psychedelics, suggests this is an especially important topic for future investigation.

7.4.2 Sampling Limitations

As per the norm in university-based studies, despite a variety of sampling methods used, the majority of participants in my studies were from a Western, Educated, Industrialised, Rich and Democratic (WEIRD) society (Henrich, Heine, & Norenzayan, 2010). Whereas general psychology experiments often tend to recruit females more frequently than males (if this is not predetermined to be counterbalanced), psychedelic research (including chapter five and six) draw on data from predominantly male participants. This bias dies reflect the gender bias in psychedelic studies however (e.g. Studerus, Gamma, Kometer, & Vollenweider, 2012). The generalisability of the data in this thesis may be

limited because of the sampling strategies used in the empirical chapters. However the importance of more representative sampling is understood, and future research should seek to collect data from more diverse samples. One method to do so, would be to collaborate more with non-WEIRD universities to build up more diverse subject pools, and help to create a more comprehensive understanding of human psychology and consciousness (Henrich et al., 2010).

Limitations caused by changes necessitated by COVID-19

One limitation of this research was the inability to replicate our experimental findings with modafinil (CH3). This was due to the prolonged disruption associated with the COVID-19 pandemic which occurred at a critical point in the PhD (see chapter four). The fact of not being able to complete this element of the thesis highlighted a limitation in terms of flexibility of experimental designs that are classically run using face-to-face testing. Future studies may want to explore methods of becoming more robust to this type of interruption, e.g. exploring whether pharma studies could be done safely with remote testing.

7.5 Future Directions

A first, and probably most obvious, recommendation would be to replicate my primary randomised controlled experiment using the methodological improvements discussed in the fourth chapter, to assess whether modafinil reliably increases state mindfulness, and whether the benefits of a modafinil-assisted first mindfulness session are maintained in the medium to long term. It may be of value to collect more frequent measurements of experience, before, during, and after the experimental session if resources allow, as per experience sampling, so that the role of non-specific effects might be separated from the effects of the drug and mindfulness session. If the mindfulness plus modafinil condition appears to positively affect acute subjective effects, and subsequent self-practice in

healthy participants, this may justify exploring whether an extra-brief protocol can enhance engagement in a mindfulness strategy in specific populations that may suffer from low trait mindfulness. An example would be Attention Deficit Hyperactivity Disorder (ADHD) – a disorder characterised by difficulties in attention, mind-wandering, and co-morbid emotion dysregulation (Seli et al., 2015; Smalley et al., 2005). A short-term program combining pharmacologically-assisted contemplation with self-practice may provide a life-changing offering to those who rely on daily medication to help regulate their attention or emotional experience, such that, with practice, they could learn to self-regulate. In such populations, this combined contemplative and nootropic approach may be best suited to a program that spans a week, with one drug-assisted session. This would allow for familiarisation with the mindfulness approach, an experimental session, and familiarisation with self-practice exercises to complete – potentially using a structure that combines the retreat based approach used by Smigielski and colleagues (2019), and (brief) mindfulness-based interventions (Zeidan et al., 2011).

Another interesting question to probe would be whether pharmacological enhancement of mindfulness is reserved for nootropics. Recent data would suggest otherwise, indicating that psychedelics may also be preferable candidates (E.g.: Smigielski et al., 2019; Griffiths et al., 2018), however future research would benefit from testing this question in a laboratory context. If other psychedelic, or psychedelic-like compounds were capable of acutely enhancing mindfulness ability, this may provide a unique treatment opportunity for certain disorders. For example, if MDMA-assisted compassion focused contemplative techniques proved viable, considering the known prosocial acute effects of MDMA (Preller & Vollenweider, 2019), it may catalyse the creation of trust and empathy, which could be particularly beneficial in conditions characterised by difficulties with trust,

such as narcissistic personality disorder. There is some evidence that MDMA may be useful for the treatment of narcissism (Majić et al., 2015), however this has not been tested within the context of pharmacologically-assisted contemplation. Relatedly, a combined program of psychedelic mindfulness may be particularly useful for relationship building. Mindfulness interventions alone have demonstrated potentially useful effects in couple's therapy (Barnes et al., 2007), and considering the effects of empathogenic drugs such as MDMA, one might hypothesise that a combination of an acutely empathy-inducing experience with a practice that can be maintained outside of an experimental session might produce particularly promising effects, particularly given findings with other drugs presented in this thesis.

Relatedly, if mindfulness can create beneficial interpersonal change within the context of close interpersonal relationships, may this also translate to broader societal toleration? Early evidence suggests that an eight-week mindfulness workshop can increase support for political compromise in a historically difficult context (e.g. Alkoby, Halperin, Tarrasch, & Levit-Binnun, 2017). Specifically, Israeli students who received mindfulness training following an anger-inducing protocol were more keen to support peace-making policies, and this increase in support was mediated by a reduction in negative emotions, alongside negative perceptions (the latter being specific to the mindfulness condition only). These results align with my findings of reductions in cognitive bias in chapter two, and demonstrate that there may be potential for pharmacologically-assisted mindfulness to combat some of the extreme polarisation that seen in recent years. Mindfulness alone may not be the answer, but might it be possible to 'trip up' negative emotions towards others such as hate, using psychedelic-assisted contemplation? Psychedelics in a ceremony context do appear to have the potential to increase peacebuilding (Roseman et al., 2021), which inspires

the potential for multidisciplinary research that may catalyse change on both a personal and societal level.

If pharmacologically-assisted meditation is indeed enhanced using psychedelic compounds, considering the extensive duration of effects of some psychedelics, it may be valuable to test which drug is most well-suited to the mindfulness session. Though psilocybin has probably received the most research attention to date, it is possible that faster-acting psychoactive drugs such as DMT or ketamine (at low doses) are more practical and more effective to administer alongside contemplative practice. Although the suggestion may seem drastic, the subjective effects of both compounds are associated with ego-dissolution and mystical experiences (Reavley & Pallant, 2009), two effects which may predict post-acute improvements in mindfulness and well-being (Sampedro et al., 2017; Strassman et al., 2018).

That extra-pharmacological factors appears to play an important role in psychedelic-associated changes in mental health and wellbeing indices (see chapter six; Haijen et al., 2018), it would be beneficial to understand what the right ‘dose’ of contemplation may be before a psychedelic(-assisted) session. Although some benefits of contemplative practices are understood to be related to long-term practice, and expected to be observed solely in advanced practitioners (Lutz et al., 2008), some of these experiences (for example, the release or loss of a stable sense of self) are experienced after psychedelic consumption regardless of meditation experience. However, it is unclear how much contemplative practice would be optimal before psychedelic dosing. Indeed, some elements of mindfulness practice have been implemented in psychedelic trials (Guss et al., 2020), though future experimental trials may seek to explore the effects of different quantities of mindfulness during such a program (as per Griffiths et al. (2018) with spiritual support). The key aim here would be to provide familiarisation to the participants, without allowing enough time for them to become

bored or disconnected with the program. An important further consideration is that of which style would be best suited to psychedelic-assisted contemplation. Ideally, the experience of the participants would feature heavily in this decision. However, assuming that this practice was implemented with the central aim of assisting mindfulness-naïve participants (who may be at a natural disadvantage) to engage in meditative practices, it is likely that some form of focused attention practice might be most appropriate (since this is the style which is typically taught to novice practitioner). Particularly interesting is the opportunity (as explored in chapter four) to train mindfulness capacities whilst measuring them, as in the Breath Counting Task (Levinson et al., 2014).

7.6 Personal Reflections

This collection of research was a fantastic opportunity to gain experience managing a trial-specific research team. Going through the processes of recruiting, training, and supervising students, whilst managing own work load was both interesting and fruitful in terms of expectation and time management. Relatedly, completing this doctorate as part of a demonstratorship posed quite some significant time-management pressure. This was a rewarding process, which made me understand how different types of tasks (depending on their nature and who they relate to) will affect my mind differently, and how difficult it can be to prioritise one's own research amongst competing time-sensitive demands.

In terms of the methods used in this thesis, I was surprised how much I enjoyed the qualitative research process. Having only ever used quantitative methods previously, qualitative research appeared intimidating yet vague, however (thanks to some great collaboration), it was an interesting and thought-provoking process, which made clear how reductionistic experimental methods can be, and how valuable the rich data is in understanding the human experience. Relatedly, the process of collaborating on multiple

projects made it possible to gain a more widespread conceptualisation of questions that I dreamed of answering at the beginning of this research process, and had deemed unachievable, due to logistical restraints. I can also appreciate how having teams working together from different backgrounds will contribute to creating better solutions (Van Knippenberg, van Ginkel, & Homan, 2013).

It also feels important to note the power of understanding and accepting one's circumstance. I started this doctorate with bag loads of enthusiasm, a little naivety, and a sleep disorder that, despite a diagnosis, I did not completely acknowledge. Minimising the associated difficulties made it very hard to get support and make realistic plans during the course of this process. The reality of the situation, I came to accept after three years of more or less constant struggle, was that the alternative solutions available did not work well enough, and I had to commit to taking medication daily to make this process feasible. As it appears, connection to what is present, and accepting one's experience are not solely relevant to psychedelic therapy! Relatedly, learning to ask for and receive help are important reflections of this process. It provided me with the humbling appreciation that nothing can be done alone. Largely due to this process and the challenges associated with it, community has changed from what felt like an idealistic dream to the fundamental reason for continuing to work and try to create a more compassionate and hopeful future. Probably the most overwhelming lesson from this research process was to practice what I preach. In the middle and final stages of this process, overwhelming anxiety was not uncommon, and the natural tendency to try to control or avoid the discomfort was hard to avoid. Ironically but joyfully, alongside the unrelenting support of the people around, I can thank my contemplative practices for pulling me through and making it to the end.

8. Supplementary Materials

8.1 Strategy Design

Given that (i) strategy instructions were written by the author and the primary investigator (SKK), (ii) the latter's clinical and academic training in mindfulness meditation (iii) the previously published positive findings on mindfulness by this team, steps were taken to limit the potential influence of 'allegiance effects'. Firstly feedback on the strategy instructions was obtained from four PhD-level research-clinical psychologists with extensive experience and training in general behavioural therapy interventions (including mindfulness). None of the raters were active mindfulness researchers or practitioners and none had a declared allegiance to mindfulness-based interventions. They were also blind to the study aims. Modifications were made in response to feedback and the final instructions were rated on a 1("not at all") to 7 ("completely") scale for two questions: "To what extent are the two different sets of instructions likely to engage distinct subjective states" and "To what extent are the two different sets of instructions likely to engage distinct physiological states". The modal scores were 4 ("moderately") for both items. A second precaution against allegiance effects was that voice-recordings of both strategy instructions were provided by the same clinician (Dr Kate Sherratt), who was blind to study aims and had no other involvement in the study. KS has experience of delivering *both* mindfulness and relaxation interventions, but no declared allegiance to interventions incorporating either strategy.

8.2 Example Instructions

Mindfulness (full instructions: 786 words; duration: 8.37 min; Flesch-Kincaid grade level: 8.1).

> "*One technique that can calm the mind involves focusing your attention on the breath. Here, you will listen to some instructions on really becoming aware of the*

breath and focusing on the various sensations that might arise as you breathe. Practicing this technique may instil a sense of ease and stillness of the mind, potentially improving your ability to concentrate and manage stress.

" Have your feet flat on the floor and your legs uncrossed. As you're sitting, adopt a posture that allows you to be fully aware and alert. Try to straighten your back and raise your chest a little, without making yourself tense or stiff. Now, focus your attention on the area in your body where you feel the breath sensation most strongly. When breathing through the nose, people often feel the breath most vividly in or around their nostrils. Other people feel it most in their upper body as their chest rises and falls. Take a minute now, to notice where you feel your breath most strongly. [10 sec pause]. Now that you've identified where you feel your breath most strongly, focus your attention on that part of your body. Try to remain focused on the part of your body where you feel the breath sensation most clearly and strongly for remainder of the exercise. Other than focusing your attention on your breath, you don't need to do anything special with how you breathe. Just notice how your breath feels to you. Notice the various physical sensation as you breathe. Try to focus on the subtleties of these sensations and notice if and how they change….Continue to focus on the sensations of your breathe

Relaxation (full instructions 796 words; duration: 9.46 min; Flesch-Kincaid grade level: 7.7)

"One technique that can calm the mind involves deep, regulated breathing. Here, you will listen to some instructions on effectively controlling the breath by rhythmic deep breathing, pacing your in and outbreaths so that they're roughly the same duration. Practicing this technique may instil a sense of ease and stillness of the mind, potentially improving your ability to concentrate and manage stress.

Have your feet flat on the floor and your legs uncrossed. As you're sitting, adopt a posture that allows you to be fully relaxed. Try to loosen any muscles in your body where there's any stiffness. Ensure your posture is as comfortable as possible, releasing any tension. Now, consider how your body behaves as you breathe. Is your breathing shallow or deep? Is it quick or slow? Does your chest rise and fall as you breathe in and out or does your abdomen move as you breathe? Consider how long your in breath is compared to your out breath. [10 sec pause]. Now that you've identified Most importantly, aim to make your in and outbreath roughly equal in duration. Breathe in deeply into your abdomen letting your stomach rise as you breathe in through the nose….and letting your stomach fall as you breathe out from your mouth. Try to get into a rhythm so that your outbreath is a similar duration to your in breath. To do this, count the number of seconds during your in breath and the number of seconds of your out-breath, and gradually make these as even as possible".

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