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Effects of a Mindfulness-Based Stress Reduction (MBSR) Course on Neurocognitive Markers of Ageing and Dementia in Typically Ageing Older Adults

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Effects of a Mindfulness-Based Stress Reduction (MBSR) Course on Neurocognitive Markers of Ageing and Dementia in Typically Ageing Older Adults

Shelby DeMeulenaere School of Psychology Bangor University December 2018

Thesis submitted to the School of Psychology, Bangor University in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Declaration and Consent

Yr wyf drwy hyn yn datgan mai canlyniad fy ymchwil fy hun yw'r thesis hwn, ac eithrio lle nodir yn wahanol. Caiff ffynonellau eraill eu cydnabod gan droednodiadau yn rhoi cyfeiriadau eglur. Nid yw sylwedd y gwaith hwn wedi cael ei dderbyn o'r blaen ar gyfer unrhyw radd, ac nid yw'n cael ei gyflwyno ar yr un pryd mewn ymgeisiaeth am unrhyw radd oni bai ei fod, fel y cytunwyd gan y Brifysgol, am gymwysterau deuol cymeradwy.

I hereby declare that this thesis is the results of my own investigations, except where otherwise stated. All other sources are acknowledged by bibliographic references. This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree unless, as agreed by the University, for approved dual awards.

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Summary

According to the United Nations World Population Prospects 2017, one of the fastest growing populations globally are older adults, aged 60 and above (United Nations Department of Economic and Social Affairs- Population Division, 2017). Indeed, it is predicted that the number of older adults will increase from an estimation of 962 million in 2017 to 2.1 billion in 2050. Given this predicted trend in population ageing, there is a critical need for investigations on interventions that may promote healthy ageing.

In this context, a growing body of studies have suggested that mindfulness-based interventions (MBIs) could be effective in improving well-being (Greiger et al., 2016) and reducing neurocognitive declines in ageing (Gard, Hölzel, & Lazar, 2014; Malinowski, Moore, Mead & Gruber, 2014) and age-related diseases, such as AD (Larouche, Hudon, & Goulet, 2014; Wells et al., 2013). However, empirical investigations of MBIs with older adults are limited, and few studies have explored the psychological mechanisms by which MBIs may impact markers of ageing and AD. As such, this PhD study aimed to provide insights into the psychological and neurocognitive effects of an MBI with older adults and possible underlying psychological mechanisms.

The first chapter of this thesis described the cognitive and brain changes that occur across an ageing spectrum. In addition, theories of ageing and interventions that may promote successful ageing were discussed. MBIs were considered as potential interventions in aging, and research on mindfulness with older adults was reviewed. Chapters 2 and 3 detailed the methodology used in this PhD study, including Electroencephalography (EEG)/Event-related potentials (ERPs) and Proton Magnetic Resonance Spectroscopy (¹H-MRS). Chapter 4 provided a critical, theoretical review on the potential of MBIs in preventing or delaying the offset of AD. In particular, the review highlighted the roles of stress in AD pathology, and considered the psychological and psychophysiological mechanisms that MBIs may impact the stress process. Chapters 5 and 6 presented a feasibility-pilot investigation utilising ¹H-MRS and an ERP study using a pseudo-randomised wait-list controlled design, that examined the effects of an eight-week standardised Mindfulness-Based Stress Reduction (MBSR) course with typically ageing older adults. Findings from these investigations indicated limited effects of an MBSR course on physiological measures associated with ageing and AD, including neurometabolites (N-Acetyl Aspartate, myo-Inositol, Creatine, gamma-Aminobutryric acid, and Glutamate) and Event-Related Potential Components (N400 and P600). However, improvements in self-report levels of stress, neuroticism, depression, and well-being were documented for the training group following the MBSR course. Chapter 7 considered the findings and implications of this PhD study in relation to the limitations. It also proposes recommendations for future research in this area.

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Chapter One

Introduction

Introduction

A wealth of empirical evidence has indicated that healthy ageing is accompanied by a range of changes in the brain (Raz et al., 2004; Raz et al., 2005; Reyngoudt et al., 2012) and cognitive function abilities (Kerchner et al., 2012; Park et al., 2002). In this context, neuroimaging studies have helped to provide insight into the specific age-related neural changes in brain volume, chemistry, and connectivity that occur in healthy ageing. In particular, longitudinal magnetic resonance imaging (MRI) studies with healthy adults have documented age-related reductions in the grey matter and white matter volume of the brain (Raz et al., 2004; Raz et al., 2005; Resnick et al., 2003). Neural regions that showcased declines in grey matter volume included the hippocampus (Raz et al., 2004; Raz et al., 2005), anterior cingulate cortex (ACC; Resnick et al., 2003), orbital frontal lobe (OFL; Resnick et al., 2003), and inferior frontal lobe (IFL; Resnick et al., 2003). White matter volume reductions were noted in the prefrontal areas (Raz et al., 2005) and more globally across the brain (Resnick et al., 2003). Buckner (2004) suggested that white matter integrity of frontal lobe areas may show declines specific to ageing. Interestingly, Head et al. (2004) found that the anterior corpus callosum was impacted more by age-related reductions in white matter integrity, than the posterior corpus callosum, measured through mean diffusivity and anisotropy. Other crosssectional research with healthy young adults and older adults has also indicated significant declines in global grey matter (Ge et al., 2003) and white matter volume (Guttman et al., 1989).

Functional magnetic resonance imaging (fMRI) studies have also reported declines in connectivity of the Default-Mode Network (DMN) in ageing (Hafkemeijer, van der Grond, & Rombouts, 2012). The DMN is a brain network that shows enhanced activity when at rest (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001), and is associated with mind-wandering (Fox et al., 2015). Regions of the DMN network, including the Posterior Cingulate Cortex (PCC), Middle Temporal Gyrus, Superior Frontal Gyrus, and Superior Parietal Region, show decreased connectivity in normal ageing (Damoiseaux et al., 2007). Interestingly, Vida-Piñeiro et al. (2014) found that decreased connectivity in the DMN (particularly between the Medial Prefrontal Cortex and Precuneus) was associated with decreased gray integrity in posterior brain regions, such as the precuneus and Superior Parietal Lobe in healthy older adults.

Magnetic resonance spectroscopy (MRS) studies have reported age-related modifications in neurometabolite concentrations. For example, Reyngoudt et al. (2012) documented an age-related increase in myo-Inositol (mI) and Creatine (Cr), neurometabolites thought to be associated with glial proliferation (Reyngoudt et al., 2012; Rosen & Lenkinski, 2007), in the PCC of healthy adults, aged 18 to 76 years. A meta-analysis of four studies similarly reported increases in Cr concentrations in parietal regions in ageing (Haga, Khor, Farral, & Wardaw, 2009). Moreover, Haga et al. (2009) documented a trend towards age-related decline in N-Acetyl-Aspartate (NAA), a neurometabolite linked to cell neuronal viability (Soares & Law, 2009) or neural health (Stagg & Rotham, 2014) in frontal lobe regions.

Studies on Event-Related Potentials (ERPs), a measure of brain-wave responses that are time-locked to a stimulus (Luck, 2005), have also effectively indicated synaptic changes that may contribute to cognitive decline in ageing (Friedman, 2011). Indeed, ERP studies have shown age-related increases in the latency of the P300 component, an ERP marker associated with attention processes (Polich, 1996), and the N2b component (Schiff et al., 2008), which is involved in conscious attention processes (Patel & Azzam, 2005). Together, these findings may indicate declines in attention processes in ageing. In addition to the aforementioned ERP components, the N400 component, a component associated with semantic processing (Kutas & Federmeier, 2011), may be sensitive to ageing processes (Friedman, 2011). Kutas and Iragui (1998) reported age-related reductions in the amplitude and increases in the latency of the N400 effect, which is measured by subtracting ERP responses to congruous items from ERPs to incongruous items, in a semantic categorization task with adults, aged 20 to 80 years. Given that semantic processes remain intact in ageing (Hedden & Gabrieli, 2004; Park et al., 2002) it could be argued that the N400 effect is modulated due to declines in working memory in ageing (Friedman, 2011).

From a cognitive perspective, declines in working memory (Park et al., 2002), processing speed (Kerchner et al., 2012), inhibition (Persad, Abeles, Zacks, & Denburg, 2002, and encoding in healthy ageing have been reported (Glisky, 2007; Hedden & Gabrieli, 2004; Park & Reuter-Lorenz, 2009). Working memory is conceptualised as a system with limited capacity that is involved in the maintenance of information while a cognitive task is completed (Baddeley & Hitch, 1974; Baddeley, 1992; Baddeley, 2010; Buckner, 2004; Glisky, 2007). Specifically, Baddeley and Hitch (1974) suggest that working memory is composed of three components including the central executive, phonological loop, and visuospatial sketchpad. The central executive acts as an attentional control system (Baddeley, 1996; Collette & Van der Linden, 2002), and is thought to be responsible for the coordination of the phonological loop and visuospatial sketchpad (Baddeley, 1996). Moreover, it is involved in retrieval strategy selection (Baddeley, 1996; Collette & Van der Linden, 2002) and manipulation of information in long-term memory (Baddeley, 1996). The phonological loop and visuospatial sketchpad serve as storage systems (Baddeley, 2003). While the phonological loop is responsible for the processing of verbal information, the visuospatial sketchpad is employed in the maintenance of visuospatial information (Baddeley, 2002; Collette & Van der Linden, 2002).

In relation to ageing, a large study of 345 adults, aged 20 to 92 years, indicated agerelated decreases in working memory abilities in letter rotation task and a line-span task that involved visuospatial decisions, such as remembering the display position of a line segment (Park et al., 2002). Longer processing speeds in ageing may underlie these changes in working memory (Glisky, 2007; Salthouse, 1992; Salthouse, 1996). Declines in processing speed, which is the speed of information processing (Salthouse, 1996; Hedden & Gabrieli, 2004), have been reported to correlate with age in a large study of 131 adults, aged 55 to 87 years (Kerchner et al., 2012).

In addition to slower processing speeds, impairments in inhibitory processes may also lead to changes in working memory in ageing (Glisky et al., 2007; Hasher & Zacks, 1988). Inhibition is a broad construct that refers to the intentional or unintentional suppression of cognitive, affective, and motor processes (MacLeod, 2007; Dillon & Pizzagalli, 2007). In relation to working memory, decrements in cognitive inhibition may allow for the processing of goal-irrelevant stimuli in the context of the working memory, and thus lead to a reduction in working memory resources used to process goal-relevant stimuli (Glisky et al., 2007; Hasher & Zachs, 1998). While declines in inhibitory processes, measured through behavioural and neuropsychological assessments (Persad et al., 2002; Collette, Germaine, Hogge, & Van der Linden), have been reported in the ageing literature, limited studies have examined the role of inhibition in working memory declines. Only one behavioural study, to my knowledge, has provided support for the role of cognitive inhibition in working memory in ageing (Salthouse & Meinz, 1995). However, this study also indicated that processing speed contributes to decrements in working memory. Therefore, changes in processing speed in ageing should be considered when examining the link between inhibitory processes and working memory (Salthouse & Meinz, 1995).

In addition to decrements in inhibitory processes in ageing, researchers have proposed that memory encoding may show declines in healthy older adults (Glisky, 2007; Hedden & Gabrieli, 2004; Park & Reuter-Lorenz, 2009). Encoding is a stage of the memory system that involves processing information from stimuli in the context of meaning (Craik & Rose, 2011). In ageing, declines in episodic memory, a memory system involved in remembering past experiences (Tulving, 1993; Tulving, 2002) are thought to be caused by decreases in encoding

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abilities (Dennis, Daselaar, & Cabeza, 2007); although, few behavioural studies have examined encoding in ageing.

In age-related diseases, such as Alzheimer's Disease (AD), declines in cognitive functions and reductions in brain tissue content are also present; however, these declines are differentiated from healthy ageing due to their severity (Fox, Cousens, Scahill, Harvey, & Rossor, 2000; Toepper, 2017). Indeed, increases in severity of changes over normal ageing is a hallmark of dementia. For example, a longitudinal study involving MRI revealed an accelerated rate of decreases in global grey matter for patients with AD in comparison to healthy ageing older adults (Thompson et al., 2003). Similarly, Du et al. (2001) found increased volume loss in the hippocampus and entorhinal cortex in patients with MCI, a prodromal phase to dementia (Gauthier et al., 2006), and AD in comparison to healthy older adults. Increased rates of atrophy in regions including the frontal lobe, parietal lobe, anterior cingulate cortex (ACC), and PCC in AD as compared to MCI have been reported in a longitudinal MRI investigation (McDonald et al., 2009). White matter volume reductions have also been identified in temporal lobe areas including the parahippocampal gyrus in studies of AD (Li, Pan, Huang, & Shang, 2012). Changes in white matter structure may help to dissociate AD from healthy ageing (Buckner, 2004). In persons with AD, aged 59 to 79 years, decreases in fractional anisotropy (FA), a measure of white matter microstructure (Alexander, Lee, Lazar, & Field, 2007) have been reported in the left anterior temporal lobe in comparison to healthy older adults, aged 60 to 81 (Damoiseaux et al., 2009).

From a functional perspective, AD is also characterised with decreases in the DMN connectivity (Greicius, Srivastava, Reiss, & Menon, 2004; Hafkemeijer et al., 2012). However, connectivity in AD can be distinguished from ageing through examining particular brain regions of the DMN. For example, Greicius et al. (2004). found decreased connectivity between the PCC and hippocampus for participants with mild AD in comparison to healthy

older adults. Additional research on mild AD has also documented decreased connectivity between the PCC and brain regions including the left Hippocampus, right Dorsal-Lateral Prefrontal Cortex, and right thalamus (Zhang et al., 2009). Considering these findings, researchers have suggested that declines in connectivity of the PCC and hippocampus may be potential biomarkers of AD (Mevel, Chételat, Eustache, & Desgranges, 2011). Interestingly, research has found an association between accumulation of β -amyloid in regions, such as the PCC, and functional connectivity of the DMN (Palmqvist et al., 2017). In AD, the buildup of β -amyloid plaques in the brain may be defining characteristic, in addition to neurofibrillary tangles (Jack et al., 2013).

In addition to structural and functional changes in AD, studies have indicated reductions in NAA/Cr concentration levels and increases in mI/Cr concentration levels in the PCC for persons with AD in comparison to healthy older adults (Kantarci et al., 2000). ERP studies have also highlighted changes in ERP markers, including the N400 and P600, in MCI and AD. For example, Olichney et al. (2006) found differences in the effects of repetition on the N400 and P600 to a semantic categorisation task in participants with mild AD in comparison to typically ageing older adults. In particular, Olichney et al. (2006) documented a more positive P600 amplitude to new-related items as opposed to repeated-related items for typically ageing older adults. Moreover, a more negative N400 amplitude was reported for new-unrelated items in relation to repeated-unrelated items for typically ageing older adults. For participants with mild AD, no significant effects of repetition were reported for the N400 and P600.

AD is also marked by declines in cognitive functions including episodic memory (Dubois et al., 2010), semantic memory (Hodges & Patterson, 1995), and executive function (Bäckman, Jones, Berger, Laukka, & Small, 2005). Hodges and Patterson (1995) reported significant impairments of episodic memory, as measured by neuropsychological assessments

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including the Logical Memory test, for persons with minimal to moderate AD in comparison to healthy older adults. In addition, deficits in semantic memory, a declarative memory system involved in conceptual knowledge of the world (Binder & Desai, 2011; Squire & Zola, 1998) were noted on assessments including the category fluency test for persons with AD.

In both ageing (Glisky, 2007) and AD (Toepper, 2017), there is individual variability in the degree of neurocognitive decline, and variability in how the decline impacts each individual. Theories on cognitive functions in ageing, including the Scaffolding Theory (Park & Reuter-Lorenz, 2009) may help to explain this variability in healthy ageing and AD. The Scaffolding Theory of Ageing and Cognition (STAC; Park & Reuter-Lorenz, 2009) suggested that the ageing brain may recruit alternative neural pathways, in the presence of differential neural declines in order to maintain cognitive function skills. Interestingly, a positron emission tomography (PET) study documented bilateral activation of prefrontal cortex areas for older adults, aged 61 to 72 years, to a working memory task in comparison to young adults, aged 19 to 30 years, who displayed activation in only the left prefrontal cortex areas (Reuter-Lorenz, Marshuetz, Jonides, & Smith, 2001). These results may indicate that older adults recruit additional neural pathways to compensate for cognitive challenges experienced during a working memory task, thus providing support for STAC (Park & Reuter-Lorenz, 2009). In a revised model of the STAC, Reuter-Lorenz and Park (2014) further described that lifestyle factors, such as cognitive training, may preserve neural structures impacted in ageing, and possibly lead to enhanced ability to establish compensatory pathways in the presence of neural decline. Conversely, researchers describe that factors, such as stress, may lead to enhanced neural declines in ageing, and a decreased ability to compensate for these neural changes.

Similar to STAC, the theory of cognitive reserve could account for variability in in ageing and AD (Stern, 2002). Cognitive reserve can be defined as the ability to cope with brain changes in ageing and AD by recruiting compensatory neural pathways and employing

cognitive strategies (Stern, 2002). Stern (2012) proposed that cognitive reserve may decrease the susceptibility of neurocognitive changes in healthy ageing and AD. Moreover, cognitive reserve may lead to fewer clinical signs of AD despite neural changes. Cognitive reserve is thought to be enhanced through high levels of education, increased intelligence, employment, and cognitively-stimulating activities (Stern, 2003; Whalley, Deary, Appleton, & Starr, 2004).

Together, STAC and the theory of cognitive reserve highlight the promising potential of non-pharmalogical interventions to offset or successfully cope with neurocognitive changes in healthy ageing and AD (Reuter-Lorenz-Park, 2014; Stern, 2012). In the context of healthy ageing, several intervention approaches have been identified (Lustig, Shah, Seidler, & Reuter-Lorenz, 2009) such as strategy training, cardiovascular activity, and multi-modal activity. These intervention approaches may also be salient to AD. Strategy training is a type of intervention that is designed to identify an area of decline, and incorporate specific training techniques that may ameliorate this decline (Lustig et al., 2009). Memory is a common focus for strategy training in research on ageing (Lustig et al., 2009: Rebok, Carlson, & Langbaum, 2007), and studies have indicated the effectiveness of memory strategy training in older adults (Ball, Berch, & Helmers, 2002). For example, in an RCT on cognitive interventions, improvements in memory were noted following a memory training course for older adults, aged 65 to 94 years (Ball et al., 2002). Cardiovascular activity may also lead to improvements in neurocognitive declines in ageing (Colcombe & Kramer, 2003; Colcombe et al., 2003), and reduce the risk of developing AD (Laurin, Verreault, & Lindsay, 2001). Multi-modal interventions integrate psychosocial, physical, and cognitive training (Lustig et al., 2009). By incorporating multiple techniques, multi-modal interventions may lead to improvements in cognition and psychosocial factors, such as well-being (Lustig et al., 2009).

A potential promising multi-modal training, in the context of ageing and AD, are mindfulness-based interventions (MBIs). MBIs may be considered a multi-modal intervention

because they involve psychoeducational training; for example, Mindfulness-Based Stress Reduction (MBSR) training includes a session on the physiological stress response, and how participants may use mindfulness to regulate stress responses (Bishop, 2002; Kabat-Zinn, 1990). Moreover, through encouraging participants to bring attention to the present moment, mindfulness practice may involve some elements of cognitive training. Mindfulness courses may also involve elements of physical training, with interventions such as MBSR, incorporating mindful walking and yoga.

The term mindfulness has been derived from Buddhist philosophies where it is described as "sati" in Pali, the recorded language of Buddhist teachings (Siegel, Germer, & OLendzki, 2009). Sati was characterised as a form of "awareness, attention and remembering" (Siegel et al., 2009, p. 18). In a western secular context, mindfulness is often described as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment" (Kabat-Zinn, 2003; p. 145). While this a commonly cited definition of mindfulness, there is still debate on the conceptualisation of mindfulness in research (Dorjee, 2010).

Bishop et al. (2004) proposed a two-component model of mindfulness training that involved the self-regulation of attention and orientation to experience. In particular, researchers suggested that mindfulness training requires sustained attention to a physical anchor, such as the breath, and the ability to switch attention from distractors back to the breath. It was argued that this may prevent the processing of ruminative thoughts, feelings, and sensations by encouraging focus to the present moment (Bishop et al., 2004). The attitude or orientation towards the present moment experience is also essential to mindfulness practice. Bishop et al. (2004) indicated that mindfulness training should be conducted with an open and accepting attitude towards oneself when the mind wanders from the breath, and to the emotions and sensations that arise in the practice. Elaborating further on the components of mindfulness practice, Shapiro, Carlson, Astin, and Freedman (2006) introduced a three-component model of mindfulness that involved intention, attention, and attitude. It was suggested that together these components form the basis of mindfulness practice. Intention was described as the reason or purpose for completing mindfulness practice. Similar to the Bishop et al. (2004) model, attention to the present moment and non-judgemental attitude to one's experience are essential elements of mindfulness practice. Other models including the Liverpool Mindfulness Model (Malinowski, 2013) and Buddhist Psychological Model (BPM) of Mindfulness (Grabovac, Lau, & Willet, 2011) have been developed in order to elucidate elements of mindfulness practice.

Mindfulness was first introduced by John Kabat-Zinn as a secularised training programme, known as MBSR for medical patients suffering with chronic pain (MBSR; Kabat-Zinn, 1990; Kabat-Zinn, 2003). MBSR was designed as an eight-week group-based programme that aimed to increase mindful attention, and reduce stress (Grossman, Niemann, Schmidt, & Walach, 2004; Kabat-Zinn, 1990). Over the course, attendants are required to meet for 2.5 hours each week, and engage in mindfulness practices, such as a body scan or yoga (Kabat-Zinn, 1990; Grossman et al., 2004). Alongside the weekly group-based session, participants are asked to practice mindfulness at home for 45 minutes each day. Throughout each practice, participants are encouraged to focus their attention on the present moment, and practice an open, kind attitude to their experiences (Kabat-Zinn, 1990; Baer, 2003).

While MBSR was first utilised in a medical setting, it has been effectively employed across a variety of settings for clinical and non-clinical populations (Chiesa & Serretti, 2009; Grossman et al., 2003; Kabat-Zinn, 2003). In addition to MBSR, Mindfulness-Based Cognitive Therapy (MBCT) is a commonly used secularised intervention of mindfulness (Segal, Williams, & Teasdale, 2002). Derived from the MBSR, MBCT is an eight-week group-based intervention that integrates cognitive training with mindfulness practices (Baer, 2003; Segal et al., 2002). MBCT was developed to reduce depression relapse by encouraging individuals to view negative thoughts and sensations as transient events. Research on MBCT has indicated the effectiveness of this intervention for depression relapse (Piet & Hougaard, 2011; Kuyken, Warren, & Taylor, 2016).

In relation to healthy ageing and AD, initial findings are mixed, but do indicate that MBIs may potentially impact neurocognitive declines associated with ageing and AD (Berk, Van Boxtel, & van Os, 2017; Gard, Hölzel, & Lazar, 2014). In particular, studies have documented improvements in tests of executive function (Moynihan et al., 2013) and verbal memory (Lenze et al., 2014) following an MBI. Despite the promising nature of these findings, Berk et al. (2017) highlighted that these studies should be interpreted with caution due to limitations including lack of control/active control groups and baseline differences. Other studies have also indicated no effects of MBSR in comparison to an active control group on cognitive function for healthy older adults (Mallya & Fiocco, 2015). At a neural level, studies on subjective cognitive decline (Smart, Segalowitz, Mulligan, Koudys, & Gawryluk, 2016) and MCI (Wells et al., 2013) have reported increases in overall brain volume (Smart et al., 2016) and increases in the connectivity of the Default Mode Network (DMN; Wells et al., 2013). From a psychological perspective, improvements in depression (Splevins, Smith, & Simpson, 2009), stress (Splevins et al., 2009; Oken et al., 2017), and quality of life (Oken et al., 2017) have also been documented following an MBCT (Splevins et al., 2009) and MBSR course (Oken et al., 2017) for older adults. Altogether these findings highlight the need for future multi-method investigations involving neuroimaging techniques with self-report assessments to examine how MBIs may impact well-being and markers associated with ageing and AD.

The current thesis aimed to explore how mindfulness training may affect neurocognitive markers of ageing and AD. In Chapter 2 and 3, the methodology employed in this PhD Study, including electroencephalography/Event-Related Potentials (EEG/ERP) and proton magnetic resonance spectroscopy (¹H-MRS), is outlined. Chapter 4 incorporates a critical, theoretical review on the pathways by which MBIs may impact neurocognitive decline, and includes recommendations for future investigations. Chapter 5 and 6 detail the pseudo-randomised longitudinal investigations of an MBSR programme for typically ageing older adults using self-report measures, ¹H-MRS, and EEG/ERP methodologies. Finally, Chapter 7 discusses the overall pattern of the research findings in the context of previous research and limitations of both experimental studies. In addition, suggestions for future studies on mindfulness and ageing are proposed.

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Chapter 2

Proton Magnetic Resonance Spectroscopy (¹H-MRS)

Introduction

Proton Magnetic Resonance Spectroscopy (¹H-MRS) is a non-invasive imaging technique that is utilised in the measurement of neurometabolite concentration (Rae, 2014; Soares & Law, 2009; Stagg & Rotham, 2014). It was first discussed as a brain imaging modality in 1983 by Behar and Colleagues in a published study on lactate concentrations in rats experiencing hypoxia (Behar et al., 1983; Stagg & Rotham, 2014). However, it was not until 1985 that the first paper on the use of ¹H-MRS on the human brain was published (Bottomley, Edelstein, Foster, & Adams, 1985; Stagg & Rotham, 2014).

¹H-MRS data collection relies on similar physics to magnetic resonance imaging (MRI) to acquire information on neurometabolites (Duncan, 1996; Stagg & Rotham, 2014). Different to MRI techniques, ¹H-MRS measures the resonance frequency of metabolites, which is displayed in a spectrum. In particular, ¹H-MRS is dependent upon protons that spin upon their axis, thus creating a magnetic field around themselves (McQuarrie, 1988). The orientation of each proton spins is random. However, when placed in an external magnetic field, the spin of a proton will align to or against the magnetic field. Protons that align to the magnetic field are in a low energy state in comparison to protons that align against the magnetic field (McQuarrie, 1988; Stagg & Rotham, 2014).

In an external magnetic field, protons precess at the Lamour Frequency (McQuarrie, 1988; Stagg & Rotham, 2014), which is dependent on the strength of the external magnetic field and the gyromagnetic ratio of the nucleus (Stagg & Rotham, 2014). When a resonance frequency (RF) pulse is applied at the Lamour frequency, protons absorb energy and change from high or low energy states (McQuarrie, 1988; Stagg & Rotham, 2014; Tognarelli et al., 2015). After the RF pulse is terminated, protons return to equilibrium and generate energy in the form of an RF pulse. In particular, precessing protons induce an oscillating current in the RF receiver that decays with time (Rhodes, 2017; Stagg & Rotham, 2014; Tognarelli et al.,

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2015). The electrical signal generated from this process is known as the Free Induction Decay (FID) signal. When Fourrier transformed into the frequency domain (Rhodes, 2017), the FID signal shows the frequency by which protons precess on different molecules. This is displayed in a spectrograph with the x-axis representing the frequency that each neurometabolite resonates in parts per million (ppm), and the y-axis representing the signal amplitude of each neurometabolite (Soares & Law, 2009).

Each proton may resonate at different frequencies due to differences in the magnetic field exposure (Stagg & Rotham, 2014). Protons can experience the magnetic field applied differently due to the electrical environment of the proton (McQuarrie, 1988; Stagg & Rotham, 2014). In particular, each proton is surrounded by different number of electrons, which also produce a local magnetic field (Tognarelli et al., 2015). Electrons can shield the proton from the external magnetic field (Stagg & Rotham, 2014). This causes a change in the resonance frequency of the proton that is known as a chemical shift.

In addition to chemical shifts, the resonance frequency of the proton is impacted by scalar coupling. Scalar coupling is present between protons that are chemically bound via the surrounding electrons (Rule & Hitchens, 2006). It occurs when the spin of a nearby proton interacts with the chemically bound electrons that surround another proton (Rhodes, 2017; Rule & Hitchens, 2006). This leads to polarisation of the electrons, which modifies the exposure of the magnetic field on the proton. Consequently, the signal acquired from the proton may exhibit a splitting pattern. Together, chemical shifts and scalar coupling can be used to identify neurometabolites by providing information on the chemical structure of the neurometabolite (Rhodes, 2017).

While there are multiple proton nuclei (³¹P, ²³NA, ¹⁹F, ¹³C) that spin, most MRS studies focus on hydrogen (¹H; Duncan, 1996; Stagg & Rotham, 2014). ¹H is present in high concentrations, and is sensitive to magnetic resonance due to its high gyromagnetic ratio

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(Duncan, 1996; Stagg & Rotham, 2014). ¹H-MRS allows for the measurement of neurometabolites with ¹H nuclei including Creatine, Glutamate, gamma-Aminobutryric acid, myo-Inositol, and N-Acetyl-Aspartate (Rae, 2014; Soares & Law, 2009; Stagg & Rotham, 2014).

Neurometabolites

Creatine (Cr), which is derived from creatine and phosphocreatine (Rae, 2014), is associated with neurometabolic energy processes (Rhodes, 2017). It resonates at 3.02 ppm (Rhodes, 2017). A reduced concentration of Cr is thought to indicate cell death due to disease, injury, or hypoxia.

Glutamate (Glu) is an excitatory neurotransmitter of the Central Nervous System (CNS; Stagg & Rotham, 2014) that is associated with metabolic activity (Rae, 2014). It resonates between 2.20 to 2.40 ppm (Rhodes, 2017). Decreased levels of Glu have been reported for persons with Alzheimer's Disease (AD; Fayed, Modrego, Rojas-Salinas, & Aguilar, 2011) and major depression disorder (MDD; Hasler et al., 2007).

gamma-Aminobutryric acid (GABA) is an inhibitory neurotransmitter within the brain that acts as a neurotransmitter and a metabolite (Stagg & Rotham, 2014). It is synthesised from glutamate (Rae, 2014), and resonates between 2.00 to 2.50 ppm (Soares & Law, 2009). GABA is involved in a multitude of physiological processes, such as learning, memory, and sleep (Möhler, 2006; Rae, 2014). Reduced levels of GABA have been reported in MDD (Hassler et al., 2007), ageing (Gao et al., 2013), and Mild Cognitive Impairment (MCI; Riese et al., 2017)

myo-Inositol (mI), found in the brain, is derived from dietary sources, de novo synthesis, and receptor stimulation (Rae, 2014; Stagg & Rotham, 2014). It resonates at 3.56 ppm (Soares & Law, 2009). mI is involved in the maintenance of cell volume and the second messenger system of the cell (Rae, 2014). While it is commonly thought to be a marker of glial proliferation (Soares & Law, 2009), researchers caution that changes in mI may not be specific

to gliosis (Öz et al., 2010; Stagg & Rotham, 2014). Increased levels of mI have been documented for AD (Zhu et al., 2006), MCI (Kantarci et al., 2000), and Hungtington's Disease (Sturrock et al., 2010).

N-Acetyl-Aspartate (NAA), exhibits a main peak at 2.02 ppm (Soares & Law, 2009), and N-Acetyl-Aspartate-glutamate (NAAG) does so at 2.06 ppm (Florian, Preece, Bhakoo, Williams, & Noble, 1995). Both NAA and NAAG overlap in standard MRS acquisitions, and therefore they are often reported together as total NAA (tNAA; Gao & Barker, 2014). NAA is considered to be a possible marker of neuron density (Soares & Law, 2009) and neural integrity (Rhodes, 2017). Decreased levels of NAA have been reported in AD (Kantarci et al., 2000), Post-Traumatic Stress Disorder (PTSD; Schuff et al., 2008), and Multiple Sclerosis (Filippi et al., 2003).

The next sections will consider the use of ¹H-MRS in ageing and mindfulness research. Moreover, it will describe acquisition and post-processing procedures for ¹H-MRS data collection. The specific parameters utilised for this study will also be discussed.

¹H-MRS, Ageing, and Age-Related Diseases

In relation to ageing, ¹H-MRS investigations may provide insights into metabolic changes in typical ageing and age-related diseases. Importantly, researchers suggest that ¹H-MRS may help to differentiate declines that occur in typical ageing and age-related diseases (Parnetti et al., 1997). For example, Parnetti et al. (1997) documented a significant difference in NAA/mI levels in grey matter of frontal and temporal lobe regions for patients with AD in comparison to healthy ageing older adults. Moreover, Kantarci et al. (2000) reported declines in NAA/Cr levels and increases in mI/Cr levels in the Posterior Cingulate Cortex (PCC) for patients with probable AD in comparison to typically ageing older adults. ¹H-MRS may also be utilised to track the progression of AD (Kantarci et al., 2007). In a longitudinal investigation,

Kantarci et al. (2007) found a correlation between annual percentage changes of NAA/Cr levels in the PCC and annual changes on the Dementia Rating Scale for persons with MCI and AD.

While research is limited, studies have found an association between neurometabolite changes and volumetric changes in ageing (Schuff et al., 1999) and AD (Ding et al., 2008; Dixon, Bradley, Budge, Styles, & Smith, 2002). In particular, Schuff et al. (1999) found an association between age and decreases in NAA/Cho levels in the hippocampus in healthy participants, aged 36 to 85 years. The decreases in NAA/Cho levels in the left hippocampus were also correlated with volume reduction in the left hippocampus. Dixon et al. (2002) similarly documented reduced levels of NAA in the left hippocampus tissue, corrected for atrophy, in those with AD in comparison to healthy older adults. Moreover, the levels of NAA in the left hippocampus tissue, corrected for atrophy, were correlated with left hippocampal volume. Neurometabolite changes in AD have also been associated with declines in white matter integrity measures, including Fractional Anisotropy (FA) and mean diffusivity (MD), in a Diffusion Tensor Imaging (DTI) study (Ding et al., 2008). Specifically, Ding et al. (2008) reported a link between increases in mean diffusivity of the right cingulum bundle and decreases in NAA/Cr of the PCC for participants with moderate to severe AD.

¹H-MRS and Mindfulness

Dissimilar to age-related research, no studies have employed ¹H-MRS to examine the effects of mindfulness-interventions, such as Mindfulness-Based Stress Reduction, on neurometabolites. However, a yoga intervention study reported increases in GABA/Cr levels in the whole brain for yoga practitioners who completed 60 minutes of yoga in comparison to an active control group who completed a 60 minute of reading (Streeter et al., 2007). Given that research has documented decreases in GABA concentration levels in the Occipital Lobe of persons with Major Depression Disorder (Sancora et al., 2004), the findings could indicate that yoga practice may be an effective non-pharmacological treatment for MDD.

From a neural perspective, the global increases in levels of GABA could indicate increased inhibition (Stagg & Rotham, 2014), which may be associated with decreased neural activity. Indeed, previous research has found that individuals with higher levels of GABA in the Anterior Cingulate Cortex (ACC) was correlated with negative Blood-Oxygenated Level Dependent (BOLD) responses in the ACC to an emotional processing task (Northoff et al., 2007). However, this inference should be taken with caution given that only global GABA levels were measured in the study conducted by Streeter et al. (2007), as opposed to measurement in a single voxel. As such, it is not possible to state where in the brain GABA levels may show increases due to yoga practice. Moreover, the study did not measure BOLD responses in conjunction with the ¹H-MRS measures, which could help to ascertain how the increases in global GABA are associated with neural activity.

In addition, a cross-sectional study found increased mI in the PCC for meditators in comparison to control participants (Fayed et al., 2013). Additionally, decreased Glu and NAA in the left thalamus were also reported for meditators. While the increased levels of mI in the PCC could indicate glial proliferation in the PCC (Soares & Law, 2009), Fayed et al. (2013) argued that the increased concentration of mI may be associated with interleukin IL-2 receptor. IL-2 is a cytokine involved in immune regulation, and is thought to target microglia (Schneider et al., 2012). Given that mI is located in glial cells (Haris, Cai, Sing, Hariharan, & Reddy, 2011), Fayed et al. (2013) suggested that the increased mI in the PCC may be linked to increases in the IL-2 receptor. Given that Glu is mainly found on neurons (Stagg & Rotham, 2014), the researchers of this study suggested that the decreased Glu could indicate reductions in neural function of the left thalamus. The decreased NAA for meditators could indicate declines in neural density (Soares & Law, 2009), which may be associated with decreased tissue volume or neural dysfunction (Fayed et al. 2013), in the left thalamus. However, future research is necessary to elucidate the neural mechanisms that underlie increased mI in PCC

and decreased Glu and NAA in the left thalamus for meditators. Overall, these studies (Fayed et al., 2013; Streeter et al., 2007) provided tentative evidence that mindfulness practice may modulate neurometabolite levels.

¹H-MRS Data Acquisition

¹H-MRS data is acquired using an MRI scanner and specialised software. Data can be acquired from a single voxel, using STimulated Acquistion Echo Mode (STEAM; Frahm, Merboldt, & Hänicke, 1987) Point RESolved Spectroscopy (PRESS; Bottomley, 1987), or MEscher GArwood Point RESolved Spectroscopy (MEGA-PRESS; Mescher, Kirsch, Garwood, & Gruetter,1998). Alternatively, data can be acquired from multiple voxels using chemical shift imaging (CSI; Brown, Kincaid, & Ugurbil, 1989).

While single voxel techniques apply three RF slice-selecting pulses and gradients, CSI also uses a phase encoding gradient to measure data across multiple voxels in the brain (Drost, Riddle, & Clarke, 2002; Mandal, 2012). Single voxel techniques may be considered advantageous to CSI because they have a shorter acquisition time and specific spatial localisation (Hsu et al., 1999; Mandal, 2012). In this PhD study, single voxel techniques, including PRESS and MEGA-PRESS, were employed. Therefore, the next section will detail the methods utilised with this acquisition technique.

Single Voxel Techniques

STEAM applies three 90° slice-selecting RF pulses with orthogonal magnetic field gradients (Drost et al., 2002; Stagg & Rotham, 2014). The single voxel of interest is localized at the intersection of the three slices. In comparison to other data acquisition techniques, STEAM has advantages including that it can be collected with a short echo time (TE) and that it allows for more precise volume selection (van der Graaf, 2010).

PRESS involves a similar technique to STEAM; however, it differs in the RF pulses applied. In particular, PRESS uses one 90° RF pulse to excite proton nuclei, and then two 180°

RF pulses for refocus (Stagg & Rotham, 2014; van der Graaf, 2010). PRESS is advantageous due to the two-fold increase in signal to noise ratio (SNR) in comparison to STEAM (van der Graaf, 2010). However, PRESS is limited with how short the TE can be.

MEGA-PRESS is a spectral editing technique that is utilized to measure GABA. GABA can be difficult to measure because it overlaps with other neurometabolites, such as Cr, Glu, and NAA (Edden & Barker, 2007; Mescher et al., 1998; Mullins et al., 2014). MEGA-PRESS, a variant of PRESS that utilises frequency specific editing pulses, allows for a more precise measurement of GABA by editing out signal from other neurometabolites (Edden & Barker, 2007; Mullins et al., 2014). It is collected as two acquisition sequences ("ON and "OFF") (Edden & Barker, 2007; Mescher et al., 1998; Mullins et al., 2014). In the "ON" sequence, an inversion RF pulse is applied to excite GABA that resonate at 1.90 ppm. This pulse refocuses the evolution of scalar coupling of GABA at 3.02 ppm. In the "OFF" sequence, an inversion RF pulse is applied at a different frequency, thus leading to no changes in the evolution of scalar coupling (Edden & Barker, 2007; Mescher et al., 1998; Mullins et al., 2014). Offline, the "ON" sequence is subtracted from the "OFF" sequence. As a result, the edited spectrum displays signals from neurometabolites that are impacted by the RF pulse applied at 1.9 ppm.

Voxel Localisation and Regions of Interest

Before conducting ¹H-MRS data acquisition, an anatomical T₁-weighted image is collected (van der Graaf, 2010). This image is utilised to help locate the voxel of interest (VOI) that data is acquired from. In this PhD study, a T₁-weighted image (slice thickness = 0.7 mm; TR/TE = 18/(3.5,5.1,6.7,8.5,10.1) ms, TE = 6.8 ms; FOV = $224 \times 224 \times 175$ mm; flip angle = 8°) in the sagittal plane was acquired to identify the VOI in the PCC and Anterior Cingulate Cortex (ACC). Using the T₁-weighted image, the VOI was located using the Corpus Callosum as a reference. This method of voxel localization has been previously employed in the NeuroSKILLS project (Rusiak, Kehoe, Bokde, & Mullins, 2014) at Bangor University.

For this study, the PCC and ACC were selected as regions of interest. Both regions are impacted by ageing (Good et al., 2001) Reyngoudt et al., 2012) and age-related diseases (Choo et al., 2010; Karas et al., 2004). Moreover, the PCC has been effectively investigated as a ROI in older adults for an ¹H-MRS study in the NeuroSKILLS project (Rusiak et al., 2014) and in relation to meditative practice (Fayed et al., 2013). Additionally, the ACC has been effectively examined previously in a dispositional mindfulness study in the Bangor Brain Imaging Lab (Brickley, Morgan, Dorjee, & Mullins, 2015).

The PCC is located in the medial inferior parietal lobe within the posteromedial cortex (Leech & Sharp, 2014). The PCC is involved in cognitive processes including autobiographical memory retrieval (Maddock, Garrett, & Buonocore, 2001) and attention regulation (Leech, Kamourieh, Beckmann, & Sharp, 2011). In typical ageing, the PCC may showcase little structural changes, such as grey matter volume reduction (Smith, Chebrolu, Wekstein, Schmitt, & Markesberry, 2007). However, the PCC may show reduced Blood Oxygen Level Dependent (BOLD) activity, as part of the Default Mode Network (DMN) in ageing (Damoiseaux, 2007). At a metabolic level, research has indicated an increase in Cr and mI in the PCC in ageing (Reyngoudt et al., 2012). The PCC also shows declines in grey matter volume in AD (Choo et al., 2010) and reduced BOLD activity (Greicus, Srivastava, Reiss, & Menon, 2004). Moreover, increases in mI/Cr and decreases in NAA/Cr, have been documented in AD. (Kantarci et al., 2000).

The ACC is located in the medial frontal lobe near the corpus callosum (Carter, Botvinik, & Cohen, 1999). It is thought to be involved in conflict monitoring (van Veen, Cohen, Botvinick, Stenger, & Carter, 2001) and emotion processing (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). Research has documented decreases in grey matter volume in the ACC in ageing (Good et al., 2001) and AD (Karas et al., 2004). While the ACC is less studied as a region of interest in ¹H-MRS studies of ageing, few studies have documented neurometabolite changes in ageing and AD. In particular, Chiu et al. (2014) reported increases in NAA, Cho, and Cr in the ACC were positively associated with ageing. In AD, decreases in NAA/Cr and increase in mI/Cr in the ACC were linked with behavioural and psychological symptoms of dementia (Shinno et al., 2007).

Voxel Size

In ¹H-MRS studies, SNR increases as the voxel size increases (Mandal, 2012). As such, larger voxel sizes, such as $2 \times 2 \times 2 \text{ cm}^3$, have been used in research on ageing and AD (Kantarci et al., 2009). Moreover, studies on transcendental meditation have also employed a $2 \times 2 \times 2$ cm³ voxel (Fayed et al., 2013). In this PhD study, a voxel size of 2.5 x 2.5 x 2.5 cm³ was used. This voxel size has effectively been utilised in previous research studies, as part of the NeuroSkills Project project (Rusiak et al., 2014), at Bangor Brain Imaging Lab.

Shimming

In addition to voxel size, SNR is impacted by B_0 magnetic field inhomogeneity (Drost, 2012). Moreover, B_0 inhomogeneity can lead to narrow spectra linewidths thus causing difficulty in neurometabolite identification and quantification (Drost, 2012; Juchem & de Graaf, 2017; Stagg & Rotham, 2014). To improve homogeneity, B_0 shimming is performed using an automatic process that involves an external shimming coil. Using the vendor-supplied higher-order shimming algorithm, shimming was conducted on a 3.0 x 3.0 x 3.0 cm³ voxel that included the voxel of interest.

CHESS Water Suppression

Water is present in large concentrations in the human brain (Drost, 2012; Stagg & Rotham, 2014). Indeed, it is estimated that the human brain is composed of approximately 70.00% to 80.00% of water (Ernst, Kries, & Ross, 1993; Stagg & Rotham, 2014). In ¹H-MRS investigations, water is considered a confound because it resonates at 4.65 ppm and its large peak covers other neurometabolites' peaks. Therefore, water is suppressed to accurately

measure neurometabolites. To complete water suppression, multiple techniques can be employed such as frequency selective saturation or spectral editing (Stagg & Rotham, 2014). A commonly applied water suppression technique is CHEmical Shift Selective pulses (CHESS; Drost, 2012; Haase, Frahm, Hänicke, & Matthaei, 1985), which relies on the different chemical shifts produced by water and neurometabolites (Stagg & Rotham, 2014). With CHESS, water is specifically excited by applying a frequency-selective RF pulse, with a a 90° flip angle (Stagg & Rotham, 2014; Haase et al., 1985). Following this, a dephasing gradient is utilised before completing PRESS, MEGA-PRESS, or STEAM. The process of CHESS causes zero magnetisation of water, thus suppressing the signal of water during acquisition. In relation to ageing and AD, previous research has employed CHESS as a water suppression technique (Gao et al., 2013; Kantarci et al., 2000). As such, the current PhD study used CHESS as a method to control for water signal.

TR/TE

In addition to water signal, other factors, such as echo time (TE) and repetition time (TR) may impact the quality of MRS data (Stagg & Rotham, 2014). Echo time (TE) is the time from an applied RF pulse until the signal peaks (Rajan, 1998). It is suggested that the duration of TE affects the ability to distinguish and identify neurometabolites' peaks (Blüml, 2013). In particular, a longer TE (TE > 135 ms) allows for a better measurement of Cho, Cr, and NAA, but reduces the ability to identify peaks, such as Glu or GABA. A longer TE is also considered advantageous because it is less impacted by eddy currents. Eddy currents are caused by gradient pulses, and result in the creation of magnetic fields in addition to the B₀ field (Drost et al., 2002). Eddy currents can lead to phase shifts and low SNR, thus impacting the quality of spectra. A short TE (TE < 35 ms); however, allows for the quantification of more metabolites (Blüml, 2013). Moreover, it leads to improved SNR in comparison to a longer TE.

Repetition time (TR) is the time between each applied RF pulses (Bitar et al., 2006; Westbrook & Talbot, 2019). Repetition time can impact SNR if its duration is too large in comparison to the relaxation times of each neurometabolite (Blüml, 2013). However, it is typically recommended to have a longer repetition time that is 1.00 to 1.50 times longer than the T1-relaxation times of each neurometabolite.

For ¹H-MRS studies, van der Graaf (2010) suggested that researchers use a long TR and short TE to reduce signal loss. For the measurement of GABA, a TR of 2000 ms (Harris, Puts, Barker, & Edden, 2016; Mullins et al., 2014) and TE of 68 ms (Rotham, Petroff, Behar, & Mattson, 1993; Mullins et al., 2014) are commonly used. Research on AD (Kantarci et al., 2000) and meditation (Fayed et al., 2013) has also used a TR of 2000 ms. In this current PhD study, a TR of 2000 ms and TE of 68 ms was utilised.

Offline Data Processing

After data acquisition, spectra can be processed in a variety of software packages including LC Model (Provencher, 1993), jMRUI (Naressi et al., 2001; Stefan et al., 2009), and TARQUIN (Wilson, Reynolds, Kauppinen, Arvanitis, & Peet, 2011). In this PhD study, TARQUIN 4.3.10 (Wilson et al., 2011) was used. TARQUIN is considered an acceptable program for fitting spectra. It uses simulated basis sets to automatically fit spectral data according to the acquisition parameters of a study (Mullins et al., 2014; Wilson et al., 2011). Wilson et al. (2011) suggested that it is equally effective in comparison to other programmes, such as LC Model (Wilson et al., 2011).

Using TARQUIN, an automatic zero-phase correction is applied to data, which enhances the visualisation of MR spectra (Osorio-Garcia et al., 2012; Wilson et al., 2011). In addition, Eddy Current Correction (Klose, 1990) can be completed to control for low SNR and line shape distortions due to eddy currents (Kreis, 1997; Osorio-Garcia et al., 2012; Wilson et al., 2011. Next, the signal from water is removed using Hankel Singular Value Decomposition (HSVD; Barkhuijsen, De Beer, & Ormondt, 1987) with a cut-off of 45 Hz.

In TARQUIN, pre-processing parameters, such as the start point and end point of the data set, can modified according to the investigation. In this PhD study, the start point for PRESS and MEGA-PRESS data was set to 10. This process helps to remove baseline data that is distorted with broad signals (Wilson et al., 2011). For PRESS, the last 1024 points are also removed.

Following this, water concentration is defined for an unsuppressed water image that is collected prior to PRESS and MEGA-PRESS acquisition procedures. Pure water concentration is 55.5 moles(mo)/1 (Brooks et al., 2001; Keevil et al., 1998), thus water concentration was set at 55.55 mo/1 for this PhD study. In addition, in TARQUIN, water is attenuated as if pure water with no relaxation effects. This process is used to scale signal amplitude for neurometabolites to the unsuppressed water image, and control for differences in T_2 relaxation (Wilson & Reynolds, 2015).

The reference signal for the data set can also be manipulated in TARQUIN. The reference signal typically includes peaks that are visible in the data acquired, and is used to align data to reference points (Wilson et al., 2011). In this study, the reference signal was 1H NAA Cr Cho Lip, which is the default in TARQUIN.

Following data processing, it is recommended that partial volume correction is completed to control for differences in neurometabolite levels across grey matter, white matter, and cerebrospinal fluid (Quadrelli, Mountford, & Ramadan, 2016). Partial volume correction may also be especially pertinent when water is utilised as an internal reference. Water is typically used as an internal reference to allow for an absolute quantification of neurometabolites instead of ratios, such as mI/Cr. (Kreis, 1997; Kreis, 2004; Jansen, Backes, Nicolay, & Kooi, 2006) Given that the concentration of water can also vary across tissue types (Ernst et al., 1993), it is essential to control for these differences (Quadrelli et al., 2016). In this PhD study, absolute quantification methods were used, and thus partial volume correction of tissue types was completed using a Matlab Code (Gasparavoic et al., 2006) designed by Dr. Nia Goulden and Dr. Paul Mullins at Bangor University. The relative GM, WM and CSF portions of the regions of interest can then be used to correct the concentration estimates for tissue specific water content and relaxation (Gasparovic et al., 2006).

In addition to partial volume correction, researchers suggest that spectral data is examined in terms of quality (Kreis, 2004; Stagg & Rotham, 2014). In this context, factors, including Cramér-Rao Lower Bound (CRLB) and SNR, can be used for the quality assessment of data. CRLB is a measurement of the least possible variance of the estimated fit of spectra data (Cavassila, Heugen, Ormondt, & Graveron-Demilly, 2001; Stagg & Rotham, 2014). It indicates the error of the estimated neurometabolite concentration (Helms, 2008; Mandal, 2012). It is recommended that estimated neurometabolite levels have a CRLB below 50 % (Kreis, 2004). If the CRLB is above 50%, researchers should consider removing the data from analyses. More recently, researchers suggested that the CRLB of an estimated concentration of a neurometabolite should be below 20% to be included in data (Stagg & Rotham, 2014). In addition to CRLB measurements, SNR can be interpreted to determine the quality of spectra data (Kreis, 2004). In Tarquin, SNR is calculated by dividing the ratio of the maximum signal height in the spectrum minus the baseline signal by twice of the root mean square of the residual signal between 0.50-4.00 ppm (Wilson & Reynolds, 2015). The residual signal is composed of noise and errors in the smoothness of the baseline (Wilson et al., 2011). While researchers have proposed that SNR values should be above 4 (Jansen et al., 2006), it is good practice to define strict SNR cut-off values for quality assurance (Stagg & Rotham, 2014). This PhD study excluded spectra data from data analysis if the CRLB level was above 25% and/or if SNR was below 20.

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Chapter 3

Electroencephalography (EEG) and Event-Related Potentials (ERP)

Introduction

Electroencephalography (EEG) is a non-invasive neuroscientific method that is used to measure and record electrical potentials from the brain (Briton et al., 2016; Light et al., 2010). It was first introduced in a published paper by Hans Berger in 1929 (Davidson, Jackson, Larson, 2000; Luck, 2014). In this paper, Berger documented that electrical brain activity could be recorded at the scalp by using saline-covered electrodes at frontal and occipital sites (Berger, 1929, Davidson et al., 2000; Luck, 2014; Vaque, 2008).

This electrical activity is produced by pyramidal cortical neurons perpendicular to the cortex (Britton et al., 2006; Luck, 2014). It was once theorised that the electrical activity at the scalp was generated from a summation of action potentials (Davidson et al., 2000), an increase in voltage in the cell body that travels down the axon to the axon terminal (Luck, 2014). However, signals from action potentials can be difficult to acquire at the scalp because of the timing of action potentials, which is approximately a millisecond (ms; Luck, 2014; Briton et al., 2016). As such, it is considered that the electrical activity is derived from the summation of inhibitory and excitatory postsynaptic potentials that occur at the same time across several pyramidal neurons (Briton et al., 2016; Davidson et al., 2000; Luck, 2014).

Postsynaptic potentials are changes in voltage caused when neurotransmitters bind to membrane receptors of the postsynaptic cell, which results in ion channels opening and closing (Luck, 2014). Different to action potentials, postsynaptic potentials are easier to record from the scalp because they can last for over 100 ms and they occur in the dendrites and cell bodies. Postsynaptic potentials can be either excitatory or inhibitory. Excitatory postsynaptic potentials (ESPS) are evoked when an excitatory neurotransmitter is released from the apical dendrite of the pyramidal cortical cell. As a result, positively-charged ions, such as sodium (Na⁺) and potassium (K⁺; Purves, Augistine, Fitzpatrick et al., 2001), move from the extracellular matrix to the inside of the neuron membrane (Dickter & Kieffaber, 2014; Luck, 2014; Marcuse, Fields,

& Yoo, 2016). Moreover, negative charged ions, such as chloride (CI⁻; Purves, Augistine, Fitzpatrick et al., 2001 move from inside the neuron membrane (Dickter & Kieffaber, 2014; Luck, 2014; Marcuse, Fields, & Yoo, 2016) to the extracellular matrix. This leads to a negative charge in the extracellular matrix and a positive charge in the neuron membrane. An inhibitory postsynaptic potential (ISPS); however, is caused when an inhibitory neurotransmitter is released (Dickter & Kieffaber, 2014; Luck, 2014; Marcuse, Fields, & Yoo, 2016). This leads to negatively-charged ions moving from the extracellular matrix into the neuron membrane. In addition, positively-charged ions flow outside of the neuron membrane to the extracellular matrix. This results in a positive charge in the extracellular matrix and a negative charge in the neuron membrane.

When the negative and positive charges are separated by the cell body, a dipole is created (Dicketer & Kieffaber, 2014; Luck, 2014). When dipoles from each neuron are aligned parallel to the surface of the skull, and each neuron receives the same input (excitatory or inhibitory), the summation of voltages created from the dipole can be recorded as electric potentials at the scalp (Luck, 2014). The summation of dipoles can be difficult to calculate, though, because of the many folds of the cortex. As such, the equivalent current dipole (ECD), which is the average of the orientation of each dipole is used.

Given that the brain is a conductor of electricity, the voltage created from postsynaptic potentials across multiple neurons is rapid (Luck, 2014), and can be detected within ms (Light et al., 2010; Otten & Rugg, 2005). This allows for the excellent temporal resolution, which is a particular advantage of EEG methodology in comparison to functional magnetic resonance imaging (fMRI) where the hemodynamic responses may peak around four to six seconds after the onset of a stimulus (Bandettini et al., 1992; Buxton, Uludag, Duncan, & Liu, 2004; Mayer et al., 2014). However, unlike fMRI, which can detect activity within a three to four-millimetre voxel (Glover, 2012), EEG recordings have poor spatial resolution. Because electricity travels
across the entire conductor, the head for EEG recordings, it is difficult to specifically determine the origination of the electrical potential (Luck, 2014). Moreover, high-resistance areas, such as the skull, can lead to further spread and attenuation of the electrical potential.

From EEG recordings, Event-Related Potentials (ERPs) can be obtained. ERPs are scalp-recorded voltage changes in EEG recordings that are averaged and time locked to an event or stimulus (Kappenman & Luck, 2011; Luck, 2014; Light et al., 2010). The ERP waveform, seen at the scalp, is characterised by varying positive and negative peaks that occur across time. While ERPs are caused by specific neural regions (Luck, 2014), it is difficult to identify each region due to the nature of EEG acquisition described above. Polarity, latency, and scalp distribution help to distinguish ERP components. In cognitive neuroscience, the amplitude and latency of ERP components may provide insights into cognitive, affective, and sensory processing (Duncan et al., 2009; Kappenman & Luck, 2011; Sokhadze et al., 2017).

Studies of ERP components may be particularly useful to understanding changes in cognitive processes, such as memory and executive function, that occur in ageing and Alzheimer's Disease (AD; Olichney, Yang, Taylor, & Kutas, 2011). For example, studies have indicated longer latency for the N2b (Alain, McDonald, Ostroff, & Schneider, 2004) and P3b components (Fjell, Walhovd, Fischl, & Reinvag, 2007), which researchers have suggested provides evidence for slower processing in ageing (Luck & Kappenman, 2011). In addition, less negative N400 amplitude and delayed N400 latency has been reported for older adults in a sentence reading task with distractors (Phillips & Lesperance, 2003). Researchers theorised that these modulations in the N400 component may reflect declines in inhibitory processes (Phillips & Lesperance, 2003). In MCI and AD, studies have indicated an absence of repetition suppression effects on the N400 and P600 amplitudes, which may indicate impairments in memory processes (Olichney et al., 2006; Olichney et al., 2008).

In the context of mindfulness research, ERP components have been utilised to investigate the impact of mindfulness practice on attention (Moore, Gruber, Derose, & Malinowski, 2012), inhibition (Sanger & Dorjee, 2016), and affective processing (Eddy et al., 2015) in adolescents (Sanger & Dorjee, 2016) and young adults (Eddy et al., 2015; Moore et al., 2012). In an ageing population, mindfulness-based practice has been shown to impact ERP components associated with attention processes, such as the P300 (Smart, Segalowitz, Mulligan, Koudys, & Gawryluk, 2016) and the N200 (Malinowski, Moore, Mead, & Gruber, 2017). In particular, Malinowski et al. (2017) documented a more negative N200 amplitude to all stimuli on an emotional Stroop-task following an eight-week mindfulness-based intervention for healthy older adults, aged 55 to 75 years. In addition, a reduction in reaction time was reported following the mindfulness training for the training group in comparison to a brain training group. Researchers suggested that these findings may indicate improvements in attention processes required for the task. Similarly, Smart et al. (2016) reported an increase in the P300 amplitude to a Go/NoGo task for older adults with subjective cognitive decline following a mindfulness-based intervention in comparison to a psychoeducation program on ageing. Complimenting Malinowski et al. (2017) study, this finding could also indicate that mindfulness training may lead to improvements in attention processes (Smart et al., 2016). In the next section, ERP components of interest for the current study will be discussed.

ERP Components of Interest: the N400 and the P600

The N400

The ERP component, N400, is a negative-going component that typically peaks in amplitude around 400 ms after the presentation of a stimulus (Kutas & Federmeir, 2011). It was first discovered by researchers when an oddball paradigm was modified to include an incongruent completion of a sentence (Kutas & Federmeir, 2011; Kutas & Hillyard, 1980). The N400 amplitude is modulated by semantic expectations, with more negative N400 amplitudes

occurring when a semantically unrelated item is displayed (Kutas & Federmeir, 2011; Luck, 2014). While the N400 is often associated with language processing, the N400 can be evoked to other stimuli, such as pictures (Ganis, Kutas, & Sereno, 1996; Kutas & Federmeir, 2011). As such, it is argued that the N400 may be modulated by meaningful stimuli (Kutas & Federmeir, 2011; Luck, 2014). In addition, the N400 amplitude is impacted by word frequency (Duncan et al., 2009; Van Petten & Kutas, 1990), repetition (Besson, Kutas, & Van Petten, 1992; Duncan et al., 2009), and concreteness (Duncan et al., 2009; Holocomb, Kounios, Anderso, & West, 1999). Unlike the N400 amplitude, the latency of the N400 is considered to be relatively stable across manipulations (Kutas & Federmeir, 2011).

The N400 is typically maximal at central and parietal electrode sites on the scalp to words, but shows a different scalp distribution to other stimuli types including pictures and faces (Kutas & Federmeir, 2011). The scalp distribution of the N400 is also biased to the right hemisphere where the amplitude of the N400 can be slightly more negative-going (Kutas & Federmeir, 2011; Luck, 2014). The time window for the N400 peak amplitude is between 350 to 550 ms (Duncan et al., 2009). However, the time range may vary depending on the task and participant sample. Potential neural substrates for the N400 include the left temporal lobe (Van Petten & Luka, 2006), anterior fusiform gyrus (McCarthy, Nobre, Bentin, & Spencer, 1995), and the parahippocampal gyri (McCarthy et al., 1995).

Theories of the N400 suggest that the component may reflect context integration (Brown & Hagoort, 1993; Kutas & Federmeir, 2000), access to semantic memory (Kutas & Federmeir, 2000), and recognition memory (Friedman & Johnson, 2000). Context integration refers to the process by which words are integrated semantically into a context of a sentence (Brown & Hagoort, 1993; Kutas & Federmeir, 2000). In terms of the N400, context integration implies that words that are related to context-based information, stored in working memory systems, are easier to integrate into a sentence, and can be reflected by a less negative-going

N400 amplitude. In addition to context integration, Kutas and Federmeir (2000) argued that the access to semantic-based information in the long-term memory systems may impact the amplitude of the N400. Hagoort (2007) proposed that the N400 is associated with semantic unification, which is the integration of a word into the preceding context (Luck, 2014).

Alternatively, Friedman and Johnson (2000) suggested that the N400 may index recognition memory in tasks that involve repetition. Recognition memory involves judging whether a stimulus has been experienced at an earlier time-point (Rugg & Curran, 2007; Squire, Wixted, & Clark, 2007). Models of recognition memory suggest that recognition memory is composed of two memory systems including familiarity and recollection (Yonelinas, 1994; Yonelinas, 2003). The recollection system involves recalling contextual information from stimuli previous presented, and the familiarity system entails assessing the familiarity of a presented stimuli (Voss & Federmeier, 2011; Yonelinas, 2003). In a recognition memory task, the N400 may index the familiarity memory system (Curran & Hancock, 2007). In particular, the N400 amplitude may be modulated by familiar items with a less negative amplitude to repeated items that are recognised (Curran, 2000; Kutas & Federmeier, 2011).

The P600

The P600 is a positive going component that typically peaks in amplitude around 600 ms after stimulus presentation (Osterhout & Holocomb, 1992). The P600 was first described by Osterhout & Holocomb (1992) in a published study on syntactic anomalies. The P600 amplitude is modulated by syntactic structure, with a more positive P600 amplitude appearing to syntactic (Hagoort, Brown, & Groothusen, 1993) and semantic violations (Van Herten, Kolk, & Chwilla, 2005). The P600 amplitude is also modulated by repetition in word recognition tasks (Olichney et al., 2008). Similar to the N400, the P600 can be elicited to non-linguistic stimuli, such as music (Patel, Gibson, Ratner, Besson, & Holocomb, 1998) and mathematical operations (Martín-Loeches, Casado, Gonzalo, De Heras, & Fernández-Frias,

2006). The latency of the P600 component is thought to be impacted by the difficulty of the reprocessing of syntax errors (Friederici, 1995; Gouvea, Phillips, Kazanina, & Poeppel, 2010)

Like the N400, the P600 is observed at central parietal electrode sites (Sassenhagen, Schlesewsky, Bornkessel-Schlesewsky, 2014). The typical time window for the P600 is from 500 ms to 800 ms. Research has suggested that the neural generators of the P600 are the bilateral temporal lobe (Service, Helenius, Maury, & Salmelin, 2007) and the hippocampus (Fernández et al., 1995).

Several P600 theories have been proposed to understand the underlying cognitive processes of this component (Kaan, Harris, Gibson, & Holocomb, 2000). A prominent theory developed by Friederici (1995) is that the P600 reflects the process of repairing a violation of syntax (Frieerici, 2011; Kan et al., 2000). Other researchers suggested that it is associated with the difficulty of reprocessing a syntactic violation (Kan et al., 2000; Osterhout, Holocomb, & Swinney, 1994). Alternatively, Coulson, King and Kutas (1998) suggested that the P600 is linked with the P3b, and thus may represent context updating and attention processes (Sassenhagen et al., 2014). In memory recognition and repetitive semantic categorisation tasks, the P600, which is sometimes referred to as the Late Positive Component (LPC; Olichney et al., 2013), may reflect the encoding (Olichney, Yang, Taylor, & Kutas, 2011; Jackson & Snyder, 2008) and retrieval of memories (Olichney et al., 2011; Van Petten, Kutas, Kluender, Mitchiner, & McIsaac, 1991). The next section will discuss the ERP paradigm, a repetitive semantic categorisation paradigm, used in the current PhD study. It will detail how the task is used to measure ERP components, the N400 and the P600, and what these two components may index. It will also consider how these components are potentially modulated by AD, ageing, and MBIs.

An ERP Task for the N400 and P600

In age-related literature, word repetition paradigms have been employed to investigate the N400 and P600 ERP components (Olichney et al., 2006; Olichney et al., 2011; Olichney et al., 2013). Both components are modulated by repetition, with amplitudes attenuating to old words as opposed to new words (Van Petten et al., 1991). Repetition paradigms may index implicit memory processes (Rug & Coles, 1995). As such, they may provide unique insight into memory changes in ageing and AD.

Repetitive Semantic Categorisation Task

In this PhD study, a repetitive semantic categorisation task, modified from previous research on normal ageing (Olichney et al., 2013), MCI (Olichney et al., 2008; Olichney et al., 2013), and AD (Olichney et al., 2006; Olichney et al., 2013), was employed to understand the potential preventive effects of a Mindfulness-Based Stress Reduction (MBSR) course on cognitive decline. In particular, the task was chosen to provide insights into how mindfulness practice could modulate ERP components associated with memory processes, such as semantic and episodic memory, that decline in ageing (Burke, White, & Diaz, 1987; McDaniel, Einstein, & Jacoby, 2008) and AD (Dubois et al., 2010).

In the repetitive semantic categorisation task used for the PhD study, participants were presented with a recorded categorical statement via computer speakers, such as "A baking appliance". This was different to the aforementioned studies (Olichney et al. 2006; Olichney et al., 2008; Olichney et al., 2013) where the researchers verbally presented the categorical statements to the participants. By presenting it via computer speakers, the timing presentation and inflection by which the category was spoken could be carefully controlled for across participants. Following this, a word that was either congruent or incongruent was displayed on the computer screen. Participants were asked to determine whether the word was congruent or incongruent with the semantic category previously presented by pressing the "z" key if the

word was congruent to the category and the "m" key if the word was incongruent. In Appendix F, an example of a trial presented to participants in this task is included.

The task was composed of three blocks which were counterbalanced across participants. In each block, 80 (40 congruent and 40 incongruent) target items were presented. Congruent target items were used to measure episodic memory processes, as indexed by the P600 ERP component (Olichney et al., 2000; Olichney et al., 2013). Incongruent target items were utilised to measure semantic memory processes, as indexed by the N400 ERP component (Kutas & Federmeir, 2011; Olichney et al., 2013). Both incongruent and congruent targets items were presented in a random order, and were repeated across all the blocks, were presented in a random order. More specifically, the 80 (40 congruent and 40 incongruent) target items were first presented to participants in Block 1 of the task. In Block 2 and Block 3, target items were repeated to participants. This repetition element may index participants' semantic memory to processing repeated incongruent target items and episodic memory to processing repeated congruent targets items. Specifically, Olichney et al. (2000) suggested that repetition may improve a participant's recall of a target item, and thus improve their accuracy and response time in processing a semantic category and word. In relation to the N400, repetition of an incongruous target item may lead to an attenuation (less negative) of the N400 amplitude, which may reflect enhancements in semantic processing due to the previous presentation of the item. For the P600, repetition of a congruous target may produce less positive P600 amplitude, which could indicate improvements in retrieval or encoding of the item due to previous presentation (Olichney et al., 2011).

In addition to the target items, 80 (40 congruent and 40 incongruent) filler items were also displayed in a random order. Filler items were similar to target items; they included a categorical statement and a response. However, filler items were used to help ensure that participants did not become aware of the repetition of target items. In total 480 trials were in the task; however, only 240 trials (target trials) were analysed.

The number of syllables in categorical statements was similar across incongruent and congruent target trials. Categorical statements for target trials were obtained from Van Overschelde et al. (2004), Battig & Montague (1969), and McEvoy & Nelson, (1982). Moreover, word length, imageability, word frequency, and concreteness were matched across congruent and incongruent target trials using MRC (Coltheart, 1981) and Celex (Baayen, Piepenbrock, & Gulikers, 1995) databases. See Appendix A for a list of target semantic categories and words. Given that participants completed the task at two time points (pre and post), the task version was also counterbalanced across time points for participants to help reduce possible practice effects.

The next sections will review how AD and ageing may modulate ERP components, including the N400 and P600, that are associated with semantic and episodic memory processes. Specifically, it will discuss how these components, measured to a repetitive semantic categorisation task, may change in AD and ageing. Finally, it will consider the impact of an MBI on these ERP components and memory processes in typically ageing older adults.

AD

In relation to AD, research has reported declines in semantic (Rogers, Ivanoui, Patterson, & Hodges, 2006) and episodic memory (Carlesimo et al., 2010), as measured by neuropsychological assessments. ERP studies, using a repetitive semantic categorisation task, provide further support for declines in these memory processes (Olichney et al., 2006; Olichney et al., 2008). For example, a series of studies (Olichney et al., 2006; Olichney et al., 2008; Olichney et al., 2013) using the repetitive semantic categorisation paradigm, noted a reduced effect of repetition (old versus new) for the amplitude of the P600 and N400 ERP components in participants with cognitive impairment, including AD (Olichney et al., 2006) and MCI (Olichney et al., 2008) in comparison to typically ageing older adults. In particular, Olichney et al. (2006) reported no significant effect of repetition (old versus new) on the N400 and P600 amplitude for participants with mild AD. Similarly, Olichney et al. (2008) documented no significant effect of repetition on the N400 and P600 amplitude for participants with MCI who converted to AD within 3 years. This absence of a repetition effect for the N400 amplitude may indicate impairments in semantic memory processes in AD and MCI (Kutas & Federmeir, 2011; Olichney et al., 2013). Moreover, the lack of a repetition effect for the P600 amplitude could reflect declines in episodic memory processes in AD and MCI (Olichney et al., 2000; Olichney et al., 2013). Interestingly, Olichney et al. (2013) reported a smaller repetition effect (e.g. less positive P600 amplitude to repeated congruous items versus new) on the P600 amplitude in cognitively normal older adults who subsequently developed MCI or AD within 9 years in comparison to typically ageing older adults. This could suggest that a word repetition paradigm may be particularly useful to examining early neurocognitive changes that may precede the diagnosis of AD.

Ageing

Unlike AD, research has suggested that semantic memory processes remain relatively stable in healthy ageing (Balota, Dolan, & Ducheck, 2000). However, in paradigms that tax attention resources, older adults may display decrements in semantic memory (Balota et al., 2000, Burke et al., 1987). In contrast to semantic memory, declines in episodic memory are well-documented in healthy ageing (McDaniel et al., 2008). Specifically, typically ageing older adults may exhibit impairments in episodic memory processes including encoding and retrieval (Friedman, Nessler, & Johnson, 2007).

While no ERP research has utilised the repetitive semantic categorisation task to specifically examine semantic and episodic memory processes in ageing, studies have employed repetition tasks to investigate the N400 and P600 (LPC) components in healthy older

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adults. For example, Swick and Knight (1997) examined the effect of repetition on the LPC between healthy young adults, aged 18 to 32 years, and healthy older adults, aged 57 to 83 years, using a continuous recognition task. In this task, participants were presented with new words, repeated words, new non-words, and repeated non-words. Moreover, they were instructed to press one button for new items and another button for old items. Healthy young adults displayed a more positive LPC amplitude to repeated items in comparison to healthy older adults. Joyce et al. (1998) also reported a reduction in the repetition effect for LPC amplitude on a modified lexical decision task. In this task, participants were presented with words and pseudo-words. In addition, they were instructed to indicate whether the item presented was a word, pseudo word, new, or repeated. A more positive LPC amplitude was found to repeated items for young adults, aged 18 to 26, in comparison to older adults, aged 60 to 79. In both studies, the more positive LPC amplitude may reflect the recollection of a repeated item in young adults (Swick & Knight, 1997; Joyce et al., 1998). In older adults, the decreased repetition effect on the LPC could indicate declines in explicit memory processes, involved in recollection. Interestingly, contrasting findings have been reported to a lexical decision task (Swick & Knight, 1997). Specifically, Swick and Knight (1997) reported a more positive LPC amplitude to repeated items in healthy older adults in comparison to young adults. The researchers of this study suggested that the enhanced repetition effect for the LPC to the lexical decision task may indicate increased processing of repeated items for older adults.

Converse to these findings, a study on AD reported a less positive P600 amplitude to repeated congruous items in comparison to new items on a repetitive semantic categorisation task for older adults (Mean Age = 77.10) (Olichney et al., 2006). This discrepancy in the modulation of the P600 amplitude across studies may be due to the difference in tasks used in each study (Olichney et al., 2006; Joyce, 1998; Swick & Knight, 1997). It should also be cautioned that the repetitive semantic categorisation task may measure different memory

processes in comparison to the aforementioned repetition tasks (Joyce, 1998; Swick & Knight, 1997). Indeed, Olichney et al. (2006) suggested that the P600 repetition effect to the repetitive semantic categorisation task may measure episodic memory processes, such as encoding. Therefore, the finding of a repetition effect on the P600 amplitude could indicate enhanced episodic memory processes, including encoding, in older adults in comparison to persons with AD. However, it is unknown how repetition-related modulations on the P600 amplitude may differ between older adults and young adults. Given that older adults may display impairments in episodic memory (McDaniel et al., 2008), it could be hypothesised that the repetition effect on the P600 amplitude to the repetitive semantic categorisation task may be reduced in older adults in comparison to healthy young adults.

Dissimilar to the P600/LPC component, the N400 amplitude to repeated items may not display changes in ageing. For example, Hamberger and Friedman (1992) reported a less negative N400 amplitude to repeated items in comparison to new items on a word classification task. No significant differences were noted for the N400 repetition effect between young adults (Mean Age = 29.94), middle-aged adults (Mean Age = 48.86), and older adults (Mean Age = 70.11). Rugg, Mark, Gilchrist, and Roberts (1997) also documented no differences of the repetition effect, between older adults (aged 62-74) and young adults (aged 19-29), for the N400 amplitude to a repetitive word task. In line with these findings, Olichney et al. (2006) reported a less negative N400 amplitude to repeated incongruous items on repetitive semantic categorisation task for older adults. Olichney et al. (2006) suggested that the repetition effect on the N400 amplitude may index semantic memory processes. Importantly, it should be noted that Olichney et al. (2006) did not examine differences in the N400 repetition effect between healthy young adults and older adults. Altogether, the findings could indicate that semantic processes are unimpaired in ageing. Thus, it could be hypothesised that the repetition effect on

the N400 amplitude to a repetitive semantic categorisation task would be similar for healthy, young adults and older adults.

MBIs

No study has examined the impact of an MBI on semantic and episodic memory, as indexed by the N400 and P600 components. However, one study on trait mindfulness indicated that these components, measured to a semantic affective word task, could be potentially modulated by mindfulness practice (Dorjee, Lally, & Thierry, 2015). Specifically, Dorjee et al. (2015) reported a more negative N400 amplitude and less positive P600 amplitude to emotional words for healthy young adults (aged 18-28 years) with high trait mindfulness. These findings could suggest that trait mindfulness may impact semantic and elaborative processing involved in emotion regulation (Dorjee et al., 2015). While this study (Dorjee et al., 2015) provided insights into the potential impact of an MBI on semantic processing, it is still unknown how an MBI may affect semantic memory in older adults.

As reviewed previously, older adults may display limited declines in semantic memory (Balota et al., 2000). However, impairments in semantic memory may be detected in older adults when using a cognitively demanding task (Balota et al., 2000). Given that the repetitive semantic categorisation task, used in this PhD study, involves repetition and semantic judgements, it could be postulated that the task may demand increased attention and working memory resources. As such, this task may detect subtle changes in semantic memory that occur in typical ageing. Previous research on MBIs have reported improvements in attention control and working memory in adults, aged 21 to 57 years (Chambers, Yee Lo, & Allen, 2007). Therefore, mindfulness practice may enhance semantic memory through the improvement of attention and working memory abilities in typically ageing older adults. In relation to the N400, this may be reflected in enhanced repetition suppression effects of the N400 amplitude following an MBI.

In the context of episodic memory, Brown, Goodman, Ryan, and Anãlayo (2016) found improvements in episodic memory, as assessed by a recognition memory and reading-based recall task, following a brief mindfulness training. Therefore, it could be posited that an MBSR course would lead to enhancements of episodic memory processes in typically ageing older adults. The potential improvement in episodic memory may be reflected in an enhanced repetition suppression effects of the P600 amplitude following an MBI. In the next sections, a description of online acquisition methods and offline data processing is provided.

EEG Online Acquisition

To record EEG data, electrodes are placed on the head using a conductive gel that allows for an electrical connection between each electrode and the scalp (Luck, 2014). The EEG signal recorded from the scalp electrodes is less than 100 microvolts, therefore, the signal is amplified by 1,000-100,000 microvolts. Then, an analog-to digital converter is used to convert the signal into digital form for the computer.

In EEG recordings, there are three types of electrodes including active, ground, and reference. (Luck, 2014). EEG data acquired at the scalp reflects the voltage between the active electrodes and the ground electrode. The ground electrode serves as a reference to all voltages, and is connected to the ground circuit of the EEG amplifier (Luck, 2014). Because the amplifier produces electrical noise, the EEG signal acquired between the ground and active electrodes may be contaminated. To mitigate this issue, a differential amplifier is used to remove noise from the ground electrode. This is completed by subtracting the potential recorded at the ground electrode from the potential of the active electrodes and reference electrode (Luck, 2014).

In this PhD project, participants were fitted with a 32 Ag/AgCI EasyCap[™] electrode cap (Brain Products) using a saline-based gel. Caps with Ag/AGCI electrodes are frequently

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used in research studies, and includes electrodes that are covered in silver and silver chloride (Luck, 2014). Electrodes were placed according to the 10-20 International System on the EasyCapTM, which is a common system utilised for EEG recordings (Luck, 2014). See Appendix B for the electrode montage used in this study. Two electrodes were also placed above and below each participants' right eye to record ocular movement throughout the task. The ground electrode for this study was FPz, which has been effectively used in multiple experiments in the Laboratory for Developmental Neuroscience of Well-Being (http://dorjeelab.net). In addition, ERP research on dispositional mindfulness has also utilised FPz as a ground electrode (Dorjee et al., 2015). During EEG acquisition, the reference electrode (Luck, 2014) was the right mastoid. The mastoid is a bony protrusion located behind the ear. It has minimal electrical activity, which is key to the reference site (Luck, 2014). Similar to the ground electrode, the mastoid has been successfully used as a reference site in the Laboratory for Developmental Neuroscience of Well-Being as the reference of Well-Being, and previous studies have used the mastoid as the reference (Dorjee et al., 2015; Eddy et al., 2015; Kappenman, Farrens, Luck, & Proudfit, 2014).

During data acquisition, the EEG signal was acquired at a collection rate of 1 kHz using the SynAmp amplifiers. In addition, it was bandpassed filtered at 0.01-200 Hz. By filtering the data online, it is possible to remove voltage changes caused by noise (Luck, 2014). Bandpass filters suppress high frequencies, caused by electrical noise, and low frequencies, caused by voltage drifts. This broad filter is considered acceptable for filtering online (Luck, 2005; Luck, 2012), and has been used in studies from the Laboratory for Developmental Neuroscience of Well-Being.

To maximise the signal to noise ratio during EEG acquisition, participant completed the experimental task in a copper-shielded (faraday cage) lab space. A faraday cage is used to control for environmental electrical noise that may contaminate EEG signal (Sullivan, Diess, Jun, & Cauwenberghs, 2008). In addition, the impedance of the electrodes was kept below 7 kiloOhms during recording. Impedance can be conceptualised as the quality of electrical connection between the scalp and the electrodes (Luck, 2014). High impedance, caused by dead skin cells, sweat, and sebum on the scalp, can lead to increased levels of noise in the data.

EEG Offline Procedures

Following data acquisition, the recorded EEG signal is inspected and cleaned for artifacts, which is the noise created from non-neural sources (Luck, 2014). Several types of artifacts can be seen in EEG data including muscular movement, electrical noise, voltage drifts, eye-blinks, and skin potentials. Artifacts are considered detrimental to EEG data because they can lead to low signal to noise ratios (Luck, 2014). Moreover, artifacts may affect conclusions derived from the data. In particular, artifacts, that occur in a systematic manner, may skew the averaged waveform for a particular condition if they are not removed. To mitigate the problems associated with artifacts, researchers can utilise an artifact rejection or artifact correction procedure (Luck, 2014). While artifact rejection involves removing contaminated trials, artifact correction calculates the effect of an artifact and removes this from the data.

Following data cleaning, the EEG signal is filtered. Filtering helps to remove further noise in the data, such as voltage shifts and muscular movement (Luck, 2014). Next, the EEG recording is epoched to time-lock the signal to the stimulus. This creates segments of the EEG data that include the time before and after the onset of the stimulus. Baseline correction is then performed, which controls for voltage drifts and offsets that are elicted by skin potentials, sweating, and electrical noise (Luck, 2014). Specifically, it calculates and removes the voltage changes, caused by drifts and offsets that occur before the stimulus onset, from the epoched data. After baseline correction, the EEG data is averaged, which involves averaging the epoched EEG data across all trials for each condition (Luck, 2014). The process of averaging leads to ERP data. By averaging across trials for each condition, the signal to noise ratio is

increased (Luck, 2014). Finally, the mean amplitude, peak amplitude and peak latency are calculated for each conditions and participant. To calculate the amplitude and latency for an ERP component, a time window is first defined. The peak amplitude is then determined by finding the most positive or negative point of the ERP waveform in this time window. The time at which this peak point occurs is the peak latency (Luck, 2014). Mean amplitude; however, is calculated by averaging the voltage at each time point of the ERP waveform in the window.

For visual inspection of the data, a grand averaged waveform can also be created. The grand averaged waveform depicts the average ERP waveform for each condition and electrode across all participants in a group (Luck, 2014). The grand averaged waveform can be used, in conjunction with recommendations from previous research, to determine the time window for the ERP component (Handy, 2005).

For this PhD project, EEG data was processed offline using the NeuroScan Edit Programme. First, the data was manually inspected for artifacts including movements and voltage drifts. All trials with artifacts, excluding eye-blinks, were manually rejected from the data. Artifact rejection procedures are commonly used in ERP research, and are considered an acceptable method to manage artifacts (Luck, 2014). Eye blinks were corrected by using an algorithm from NeuroScan Edit that identifies typical eye blinks for each participant. The electrical activity created by each eye blink is then subtracted from the EEG signal.

Next, EEG data was filtered using a 0.1 Hz high pass filter and zero-shift low pass filter of 30 hz, 48 db/oct slope filter. Following filtering, the data was re-referenced to the averaged mastoids (right and left) as the reference. The average mastoid is considered appropriate for electrode caps with a smaller number of electrodes (Dien, 1998; Luck, 2014) Moreover, it is commonly used in research studies (Dorjee et al., 2015; Federmeier, Wlotko, Ochoa-Dewald, & Kutas, 2007; Luck et al., 2014).

Next, data was epoched with 100 ms before the stimulus (target word) and 1000 ms after the stimulus (target word). This filter and epoch time window has been applied across multiple experiments in the Developmental Neuroscience and Well-Being Laboratory. Moreover, previous research on the N400 and P600 has employed a similar filter and time window for epoching (Dorjee et al., 2015). Baseline correction was applied utilising signal 100 ms prior to the stimulus onset.

The data was then averaged using correct trials only. Previous research has suggested that analyses on the N400 should exclude incorrect trials (Duncan et al., 2009). Therefore, this recommendation was applied to both the P600 and the N400 analyses. Finally, grand averaged waveforms, the average waveform across participants for each electrode and trial condition (Luck, 2014), was calculated.

Based on previous research (Duncan et al., 2009; Kutas & Federmeier, 2001; Sassenhagen et al., 2014 and visual inspection of the grand averaged waveform, the time window of the N400 was identified as 350 ms to 500 ms. In addition, the P600 time window was identified as 540 ms to 710 ms. Central parietal electrode sites were chosen for data analysis for the N400 and P600 based on previous research (Kutas & Federmeir, 2011; Sassenhagen et al., 2014). Visual inspection of the grand averaged waveforms was then used to confirm the effect of the N400 and P600. To reduce researcher bias, Luck and Gaspelin (2017) recommend defining the time window and electrode sites of interest based on previous research alone. However, the researchers stated that due to variations across experiments, is not always possible to determine these parameters in this manner. Therefore, the current study employed both methods to identify the time window and electrodes of interests for the components.

For data analysis of the N400 and P600, the mean amplitude was utilised. The mean amplitude is considered a superior measurement to the peak amplitude for multiple reasons

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(Luck, 2014; Luck & Gaspelin, 2017). One reason, discussed by Luck (2014), is that the mean amplitude may be more representative of an ERP component. Because the peak amplitude is defined by a single point, it may not reflect the time course of an ERP component. Moreover, the peak amplitude is more biased by high-frequency noise (Clayson, Baldwin, & Larson, 2013; Luck et al., 2014; Luck & Gaspelin, 2017) than the mean amplitude. In the Laboratory for Developmental Neuroscience of Well-Being, the mean amplitude is used across experiments. In addition, in research on mindfulness, the mean amplitude has been utilised (Dorjee, 2015).

For the N400 amplitude analyses, an average of mean amplitudes at electrode sites (Pz, CPz, CP1, CP2, Cz) within the selected time window (350-500 ms) was used. For the P600 amplitude analyses, an average of mean amplitudes at electrode sites (Cz, C1, C2, CP1, CP2, CPZ) within the selected time-window (540-710) ms was used. Luck and Gaspelin (2017) suggested that ERP analyses are often confounded by family-wise errors because they involve large ANOVAs with multiple factors. In this study, no hypotheses were formed in terms of the electrodes of interest. Therefore, it was deemed acceptable to average across the electrodes to reduce family-wise errors. CPz was used for the latency analyses of both the N400 and P600.

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Chapter 4

The Potential of Mindfulness-Based Approaches in the Prevention of Dementia: A

Neurocognitive Review

Abstract

With a predicted increase in incidence of dementia, there is increasing interest in interventions that may prevent or offset its progression. Recent studies suggest that mindfulness-based approaches (MBAs) have preventive potential in dementia. However, very few studies examined neurocognitive mechanisms that may mediate such preventive effects. To stimulate research in this area, this article proposes a neurocognitive model of mechanisms through which mindfulness may be effective in dementia prevention. Specifically, in the context of dementia context, we outline how mindfulness impacts on the stress process at cognitive, neural and hormonal levels. We propose that mindfulness may impact the stress process at several levels leading to neuroplasticity and hormonal changes, which in turn could offset dementia onset and progression. Building on the proposed model, we provide methodological recommendations for future multi-method integrative research on mindfulness in dementia prevention using event-related brain potentials, imaging methods, and genetic markers.

Introduction

In 2015, the global estimation of people with dementia was 46.8 million (Prince et al., 2015). Despite predictions that the number of dementia diagnoses may increase to 131.5 million by 2050 (Prince et al., 2015), a recent study conducted by Wu et al. (2015) has suggested that the prevalence of dementia across Western Europe might be stabilizing or even decreasing. Researchers of this study suggested that this may be a repercussion of programs that target access to health care and education. This highlights the importance of prevention programs in reduction of the dementia risk. Understanding of pathology and risk factors of dementia is instrumental to findings effective pathways of intervention (Chen, Lin, & Chen, 2009; Prince, Albanese, Guerchet, & Prina, 2014).

Dementia is characterised by impairments in memory, behaviour, and daily functioning (Grabowski & Damasio, 2004; Prince & Jackson, 2009; Sheehan, Karim, & Burns, 2009). There are many different underlying causes of dementia including: Alzheimer's disease, Vascular Dementia, and Lewy's Body Dementia (Ford, 2014; Sheehan et al., 2009). Each cause has a distinct neuropathology and behavioral characteristic (Grabowski & Damasio, 2004; Prince & Jackson, 2009). In this review, we will focus predominately on Alzheimer's disease.

Alzheimer's Disease

Alzheimer's disease (AD) is a leading cause of dementia (Sheehan, Karim, & Burns, 2009) accounting for approximately 60%-80% of dementia cases globally (Alzheimer's Association, 2014; Kumar, Singh, & Evakali, 2015). Amyloid plaques and neurofibrillary tangles are essential biomarkers of AD (Jack et al., 2013; Perl, 2010; Sheehan et al., 2009). These may lead to the subsequent neurological pathologies associated with dementia (Braak & Braak, 1991; Jack et al., 2013) such as atrophy of grey matter of the medial temporal lobe (Jack et al., 1997), atrophy of the frontal lobe (Möller et al., 2013), reduced white matter integrity of fiber bundles (Agosta et al., 2011; Villain et al., 2008) and decreased connectivity in the default

mode network (DMN; Greicius, Krasnow, Reiss, & Menon, 2004). The neural shifts may be linked with short-term memory loss, inability to orient to time or place, and impairments in language (Jahn, 2013; Sheehan et al., 2009).

While AD is commonly associated with increased age (Wimo & Prince, 2010; Lindsay et al., 2002), many factors influence the development of this syndrome including presence of the APOE ɛ4 allele (Corder et al., 1993; Kim, Basak, & Holtzman, 2009; Reinvang, Espeseth, & Westlye, 2013), low levels of education (Ott et al., 1995), drug use (Juan et al., 2004), hypertension (Kivipelto et al., 2001; Nagai, Hoside, & Kario, 2010), and obesity (Gustafason, Rothenberg, Blennow, Steen, & Skoog, 2003; Kivipelto et al., 2005). Alongside these, high levels of perceived stress (Johansson et al., 2013; Peavy et al., 2012) are a salient risk factor. Yet very few studies have investigated how reduction in stress may lower dementia risk. Indeed, non-pharmacological methods that target stress in the context of dementia prevention and treatment remain understudied (Innes & Selfe, 2014; Walach & Loef, 2012).

Mindfulness-based approaches (MBAs) have been shown to reduce stress in a range of clinical and non-clinical adult populations (Carlson, Speka, Faris, & Patel, 2007; Dobkin, 2008; Shapiro, Astin, Bishop, & Cordova, 2005; Young & Baime, 2010), and initial research suggests that MBAs might reduce dementia risk (Larouche, Hudon, & Goulet, 2014; Marciniak et al., 2014; Innes & Selfe, 2014). The current paper aims to examine how MBAs may delay the onset or modify the progression of dementia by modulating the stress response process. In particular, we will consider the psychological, cognitive, physiological, and neurological mechanisms of mindfulness that may impact the stress processes linked with dementia.

Mindfulness-Based Approaches

Mindfulness originated in Buddhist meditation practices (Grossman & Nan, 2011; Hanh, 1998), and in the Western secular context it is conceptualised as an awareness developed through attending to thoughts and sensations in the present moment with an accepting, nonjudgmental, kind, and open attitude (Baer, 2003; Bishop et al., 2004; Kabat-Zinn, 2003; Shapiro, Carlson, Astin, & Freedman, 2006). However, there is no consensus on the definition of mindfulness across Buddhist and secular conceptions (Dorjee, 2010). The most common secular approaches fostering mindfulness are: Mindfulness-Based Stress Reduction (MBSR; Kabat-Zinn, 1990) and Mindfulness-Based Cognitive Therapy (MBCT; Segal, Williams, & Teasdale, 2002). Both MBSR and MBCT (often referred to as MBAs) are eight-week courses developing mindfulness in weekly group sessions and through daily home practice (Kabat-Zinn, 1990; Kabat-Zinn, 2003; Segal et al., 2002). Although both approaches overlap, MBSR promotes adaptive methods to manage stress in both clinical and non-clinical populations (Baer, 2003; Kabat-Zinn, 1990). MBCT; however, has been developed as a treatment of recurrent depression (Teasdale et al., 2000).

While conclusive evidence on the effects of MBAs in dementia prevention is virtually absent, extensive research, mostly with young and middle age adult populations, has documented beneficial effects of mindfulness and mediation practice on cognitive functions relevant to dementia and age-related declines (Berk, van Boxtel, & van Os, 2017; Gard, Hölzel, & Lazar, 2014). For example, Jha, Stanley, Kiyonaga, Wong, and Gelfand (2010) found improvements in working memory capacity, as measured by an Ospan Test, following an eightweek adapted MBSR course for 29 high-stress military personnel (Mean Age = 30.00) that engaged frequently in mindfulness practice. In addition, Brown, Goodman, Ryan, and Anãlayo (2016) reported enhanced performance on a recognition memory task, as measured by a Remember-Know Task, for 44 young adults (aged 18-27) who listened to two 9-minute audio-recordings of mindfulness training in comparison to an active control group (N = 49) who listened two 9-minute audio recordings that covered how to integrate important elements of your life into future plans and human perception. Initial research with older adults also suggested improvements in cognitive function skills, such as executive function and memory

(Lenze et al., 2014; Moynihan et al., 2013). In a large randomised clinical trial (N = 201), older adults aged 65 and above, displayed improvements in executive function, as indexed by the trail making test A and B ratio, following a MBSR intervention in comparison to a wait-list control group (Moynihan et al., 2013). Lenze et al. (2014) similarly documented improvements in verbal memory tasks, such as a paragraph recall test, following an MBSR course for 32 older adults (aged 65 and above) who experienced anxiety and self-reported cognitive impairment. Closer to the argument of dementia prevention, Innes, Selfe, Brown, and Rose (2012) documented self-reported improvements in retrospective memory in Mild Cognitive Impairment (MCI)/AD patients (Mean Age = 75.00, N = 6), and their caregivers (Mean Age = 71.50, N = 6) after completing 22 minutes of daily yoga meditation practices over eight weeks. MCI is a clinical syndrome denoted by cognitive decline that is atypical for one's education or age (Gauthier et al., 2006; Petersen et al., 1999). It is considered a prodromal phase for dementia, with some research suggesting approximately 50% of MCI patients will receive a dementia diagnosis within five years (Gauthier et al., 2006).

Neuroimaging findings in healthy and cognitively impaired populations further support the potential of MBAs in dementia prevention and treatment (Allen et al., 2012; Hölzel et al., 2011; Lazar et al., 2005; Prakash, De Leon, Klatt, Malarkey, & Patterson, 2013; Taylor et al., 2013; Wells, Yeh, et al., 2013). In 16 healthy adults aged 25-55 years, Hölzel et al. (2011) reported increases in grey matter density in the left hippocampus, a region of the temporal lobe that atrophies in AD (Jack et al., 1997), following MBSR course. Additional cross-sectional research by Lazar et al. (2005) documented increased cortical thickness in Brodmann's areas 9, the Dorsolateral Prefrontal Cortex (DLPFC; Macdonald, Cohen, Stranger, & Carter, 2000) and 10, the Rostral Prefrontal Cortex (RPFC; Gilbert et al., 2006) for insight meditators (Mean Age = 38.20, N = 20) in comparison to healthy control participants (Mean Age = 36.80, N =15) with no meditation experience. Considering research indicates atrophy of the prefrontal cortex in AD (Burgmans et al., 2008) and that this effect was most prominent for older participants age 40-50 years (Lazar et al., 2005), there is an indication here that meditation may offset atrophy of the prefrontal cortex that can occur in AD (even though other factors such as lifestyle may have been contributing factors in this study). Research has also shown a link between high dispositional, also referred to as trait, mindfulness and increased connectivity of DMN areas (posterior cingulate cortex and precuneus) during a resting-state fMRI scan in 25 older adults aged 60-75 years (Prakash et al., 2013). The DMN is a network of brain regions including: the hippocampus, posterior cingulate, areas of the prefrontal cortex, inferior parietal lobule, and temporal cortex (Buckner, Andrews-Hanna, & Schacter, 2008), which shows reduced connectivity in AD (Greicus, Srivastava, Reiss, & Menon, 2004; Hafkemeijer, van der Grond, & Rombouts, 2012). Wells, Yeh et al. (2013) also reported an increased in connectivity of the DMN (specifically between the Posterior Cingulate Cortex to the Bilateral Medial Prefrontal Cortex and the Posterior Cingulate Cortex (PCC) to the Left Hippocampus), and a trend towards less hippocampal atrophy in older adults (Mean Age = 73.00) diagnosed with MCI following an MBSR course.

The findings of increased connectivity in the DMN are particularly interesting, given that research has found decreased activity in the DMN regions, such as the PCC and precuneus, for experienced meditators (Brewer et al., 2011). Researchers of this study suggested that through inhibiting mind-wandering, mindfulness may lead to decreases in DMN activity. This may be relevant to the progression of AD; the amyloid precursor protein, that serves as the building block of β -amyloid plaques (Zheng & Koo, 2006), is processed in more active brain regions (Buckner et al., 2009; Simic, Babic, Boroovecki, & Hof, 2014). In relation to the DMN, it is thought that the neurons of the DMN may be particularly vulnerable to β -amyloid deposits because they are highly active (Buckner et al., 2005; Simic et al., 2014). Interestingly, a study using positron emission tomography amyloid imaging, has found increased levels of β -amyloid
deposits in regions of the DMN (Buckner et al., 2009). Thus, it could be hypothesised that mindfulness practice, through decreasing default mode-network activity associated with mind-wandering, may reduce or inhibit β -amyloid deposits in regions, such as the PCC (Choo et al., 2010), that are impacted in AD.

Together, these findings suggest that mindfulness may impact relevant markers of dementia progression. Since all the above evidence was indirect, conclusive evidence and the pathways by which mindfulness and meditation may prevent dementia remains elusive. Researchers propose that the stress-reducing effects of mindfulness practice (e.g., reduction in cortisol levels) might be a key factor to its possible effectiveness in dementia prevention (Larouche et al., 2014; Innes & Selfe, 2014; Wells , Yeh et al, 2013). Yet, few studies have explored the effect of mindfulness-based approaches on stress responses in older adults from a preventive perspective, and none in the context of dementia.

Stress as a Risk Factor of Dementia

Converging findings have illustrated the important role of stress in dementia onset (Johansson et al., 2010; Johansson et al., 2013; Peavy et al., 2012; Wang, Wahlberg, Karp, Winblad, & Fratiglioni, 2012; Wilson, Arnold, Schneider, Li, & Bennett, 2007). For example, high-levels of work-related stress (Sindi et al., 2016; Wang et al., 2012) and stress-related pathologies, such as post-traumatic stress disorder (PTSD; Yaffe et al., 2010), have been linked with increased dementia risk. Other research has suggested that the amount of stressors experienced in midlife may influence the development of dementia, with an experience of stressors associated with a heightened risk (Hazard Ratio = 1.17) for AD (Johansson et al., 2013). Despite these findings, other research conducted by Wilson et al. (2007) found no link between chronic distress (measured through self-report questionnaires on neuroticism, anxiety, and depression) and biomarkers of dementia including amyloid plaques and neurofibrillary tangles in 219 older adults (Mean Age= 85.40). However, Wilson et al. (2007) did document

an association between stress and dementia experienced in late life. The authors suggested that stress may impact dementia onset by modifying neural structures associated with memory and stress-regulation.

It is important to consider that it is not simply the experience of stress that seems to link with dementia risk, but the reactivity to the stressor. For example, Crowe, Andel, Pederson, and Gatz (2007) reported that high self-reported emotional reactivity to stress heightened the risk of developing dementia in 2049 older adults (Mean Age = 79.10). To investigate the mechanisms underlying the association between stress and dementia, it is essential to look closer at the neurobiology of the stress response.

Stress and Stress Processes

Stress is operationalised as the process by which an event or threat (stressor) disturbs the homeostasis or well-being of an individual (Chrousos, 2009; Sapolksy, 2015; Ulrich-Lai & Herman, 2009). When a stressor occurs, complex processes involving neurocognitive and hormonal mechanisms is initiated in order to restore equilibrium (Valentino & Bockstaele, 2015). While stress is commonly associated with negative effects, this is the case for extreme stress levels and chronic stress, whereas stress can be evolutionary beneficial in low to moderate doses (Aschbacher et al., 2013; Nesse, Bhatanagar, & Young, 2010; Sapolksy, 2015; Yerkes & Dodson, 1908). Specifically, moderate amounts of stress may enhance potentiation in the hippocampus (Diamond, Bennett, Fleshner, & Rose, 1992; Sapolsky, 2015). In this review, we will outline the general stress response, and focus on the deleterious effects of chronic perceived stress.

The stress response is elicited through two avenues depending on the type of stressor, biogenic or psychosocial (Girdano, Duseky, & Everly, 2009; Everly & Lating, 2013). Biogenic stressors are stimuli (e.g., exposure to chemicals or high temperature), which automatically induce neurophysiological stress processes in the absence of cognitive appraisal. From a neural

perspective, biogenic stressors may recruit the sensory cortices, thalamus, brainstem, and amygdalae to react to threatening stimuli (Debiec & LeDoux, 2009; Herman, 2012; Reser, 2016). Psychosocial stressors indirectly evoke the stress response when a stimulus is cognitively appraised as demanding (Cohen, Evans, Stokols, & Krantz, 1986; Everly & Lating, 2013; Girdano et al., 2009). Psychosocial stressors may recruit brain regions involved in appraisal including the rostral dorsal anterior cingulate (dACC), dorsomedial prefrontal cortex (dmPFC), and amygdalae (Etkin, Egner, & Kalisch, 2011; Kalisch & Gerlicher, 2014). Although demanding stimuli are typically perceived as threatening or harmful, pleasant stimuli can also be deemed as taxing and evoke the stress response (Selye, 1973).

In the chain of neurophysiological responses to both types of stressors (Everly & Lating, 2013), first the autonomic nervous system (ANS) responds via the sympathetic adrenomedullary axis (SAM; Ulrich-Lai & Herman, 2009), which begins with the activation of the sympathetic preganglionic neurons (Tsigos & Chrousos, 2002) located in the brain stem and spinal cord (Horn and Swanson, 2013). Upon activation, the preganglionic neurons send signals to the paravertebral ganglia (Ulrich-Lai & Herman, 2009), which then projects to organs such as the blood vessels and sweat glands (Horn & Swanson, 2013). Preganglionic neurons also send signals to the chromaffin cells located in the adrenal medulla (Horn & Swanson, 2013; Ulrich-Lai & Herman, 2009) via pre- and paravertebral ganglia. As a result, the medulla releases epinephrine and norepinephrine (Gunnar & Quevedo, 2007; Horn & Swanson, 2013; Smeets, 2010; Tsigos & Chrousos, 2002; Wolf, 2003) which bind to receptors located throughout organs, such as the heart (Gunnar & Quevedo, 2007). In conjunction with the sympathetic response, the locus coeruleus, a modulator of sympathetic responses (Samuels & Szabadi, 2008), releases norepinephrine in the brain (Tsigos & Chrousos, 2002; Valentino & Van Bockstaele, 2008). Altogether, these chemicals lead to an increase in attention and arousal (Gunnar & Quevedo, 2007; Tsigos & Chrousous, 2002).

In addition to the SAM axis, the Hypothalamic-Pituitary-Adrenal (HPA) axis is activated to respond to stressors (Oken, Chamine, & Wakeleand, 2015). When biogenic stressors occur, sensory cortices activate the stress response through communication to catecholaminergic brain stem neurons (Herman, 2012; Kvetnansky, Sabban, & Palkovits, 2009). The brain stem region, nucleus of the solitary tract, then transmits stress-related sensory information to the paraventricular neurons of the hypothalamus via catecholamine neurotransmitters (Cunningham, Bohn, & Sawchenko, 1990; Smith & Vale, 2006; Ulrich-Lai & Herman, 2009). Psychosocial stressors; however, may rely on frontal and limbic structures, such as the hippocampus, medial prefrontal cortex, and amygdalae to appraise the threat (Herman et al., 2003; Herman, 2012; Ulrich-Lai & Herman, 2009). The frontal and limbic structures activate the HPA-axis indirectly through projections to the brainstem and hypothalamus (Arnsten et al., 2009; Herman et al., 2003; Swanson & Petrovich, 1998).

Once the HPA-axis is activated a series of neurophysiological reactions commences beginning with the paraventricular neurons (PVN) of the hypothalamus secreting a corticotrophin-releasing hormone (CRH; Herman, Ostrander, Mueller, & Figueiredo, 2005; Smeets, 2010; Xiong & Zhang, 2013). Upon the release of CRH, adrenocorticoptropin (ACTH) is discharged from the pituitary gland (Smeets, 2010; Xiong & Zhang, 2013), which then prompts the adrenal cortex to secrete glucocorticoid hormones into the bloodstream (Smeets, 2010; Xiong & Zhang, 2013). Glucocorticoid hormones (cortisol in humans; Anacker et al., 2013), aid in preparing energy resources for stress responses (de Kloet, Joëls, & Holsboer, 2005; Xiong & Zhang, 2013), and also play a vital role in the regulation of the HPA-axis response (de Kloet et al., 2005Herman et al., 2005). In particular, glucocorticoids may play a role in the activation of the stress response by binding to type 1 mineral (MR) corticoid receptors (Xiong & Zhang, 2013), and also act in a negative feedback manner by binding type II glucocorticoid (GR) receptors (Xiong & Zhang, 2013) to terminate the release of ACTH

(Herman et al., 2005; Xiong & Zhang, 2013). MR receptors, which are located predominately in the hippocampus, and some regions of the amygdalae, locus coeruleus, and paraventricular neurons (Joëls & Baram, 2009) are saturated by cortisol during low to moderate stress levels (Sapolsky, 2015). MR receptors may be involved in the initiation of the stress process and stress appraisals (de Kloet et al., 2005; Xiong & Zhang, 2013). When high levels of stress occur, cortisol binds to GR receptors (Sapolsky, 2015). As glucocorticoid levels increase and MR receptors become overloaded, the GR receptors inhibit HPA-axis activity via the hypothalamus (Phillips et al., 2006) and the pituitary gland (Smith & Vale, 2006). GR receptors responsible for down-regulating the HPA axis are located throughout the brain in regions such as the hippocampus (Frodl & O'Keane, 2013; Joëls & Baram, 2009), prefrontal cortex (Herman & Cullinan, 1997; Wolf, 2003), and the amygdalae (Smith & Vale, 2006).

Frontal Limbic Regulation of the HPA Axis

While the hippocampus and prefrontal cortex receptors are potentially involved in the attenuation of the HPA-axis stress response (Herman et al., 2003; Herman et al., 2005; Herman & Cullinan,1997; Smith and Vale, 2006), the amygdalae receptors may heighten the stress response (Smith & Vale, 2006). When exposed to glucocorticoid hormones, central amygdalae neurons show an enhanced expression of corticotropin-releasing hormones (CRH) mRNA (Makina, Gold, & Schulkin, 1994). In addition, the amygdalae may display improvements in synaptic plasticity due to stress exposure (Sapolksy, 2015) as suggested by initial research with rats (Vyas et al., 2002).

Unlike the amygdalae, the glucocorticoid overexposure to the hippocampus and prefrontal cortex experience has damaging effects (Campbell & MacQueen, 2004; Frodl & O'Keane, 2013; Kremen et al., 2010; Sapolsky et al., 1986). According to Sapolsky (2015), an overabundance of glucocorticoid hormones may cause neurodegeneration in the hippocampus. Consequently, the negative feedback loop of the HPA-axis, which is responsible for inhibiting

glucocorticoid release, may be interrupted and thus lead to further increased glucocorticoid exposure in the hippocampus (Sapolsky et al., 1986). In addition, glucocorticoids may decrease brain derived neurotrophic factor (BDNF), a protein (Laske et al., 2007) that is critical for neurogenesis (Mattson, Maudsley, & Martin, 2004), spine growth of dendrites (Bennett & Lagopoulos, 2014) and the development of neural connections (Frodl & O'Keane, 2013). Both ageing (Ziegenhorn et al., 2007) and AD (Laske et al., 2007) may be associated with declines in BDNF. In relation to stress, reductions in BDNF during stress-induced cortisol responses can decrease neurogenesis in the hippocampus (Campbell & MacQueen, 2004; Smith, Makino, Kvetnansky, & Post, 1995). Similar to the hippocampus, the prefrontal cortex may show detrimental stress-related plasticity changes (McEwen & Morrison, 2013) due to a decrease in BDNF levels (Arnsten et al., 2009; Issa et al., 2010).

In view of the deleterious effect of glucocorticoid hormones on neural regions associated (hippocampus and prefrontal cortex) with dementia, it can be suggested that stress affects the manifestation of this syndrome through the production of glucocorticoid hormones. Supporting this theory, previous studies have indicated that higher cortisol, a glucocorticoid hormone, may be linked with cognitive decline and atrophy of grey and white matter within the brain (Cox et al., 2015; Csernansky et al., 2006; Lupien et al., 1998; Peavy et al., 2012; Swaab et al., 1994). For example, a longitudinal investigation of 51 older adults (aged 60-87 years) found a 14% smaller hippocampal volume for persons who experienced high levels of cortisol exposure in comparison to participants who displayed moderate levels of cortisol exposure (Lupien et al., 2005). Additionally, a study of 172 Alzheimer's patients (aged 47-89) found that increased basal (a standarised cortisol measurement; Nicholson, 2007) cortisol levels were significantly associated with smaller hippocampal volume as indexed by an increasing temporal horn width (Huang et al., 2009). This link between dementia and stress

highlights the need for research on prevention programs that place an emphasis on stress reduction.

Mindfulness-Based Approaches and Stress Reduction

Mindfulness-based approaches seem particularly relevant here given that they target cultivation of adaptive stress management skills (Carlson et al., 2007; Epel, Daubenmier, Moskowitz, Folkman, & Blackburn, 2009; Larouche et al., 2014; Wells, Ker et al., 2010). Indeed, following both MBSR (Carlson et al., 2007; Dobkin, 2008; Shapiro et al., 2005; Young & Baime, 2010) and MBCT (Splevins, Smith, & Simpson, 2009), significant reductions in stress levels as assessed by self-report questionnaires have been documented for adults (Carlson et al., 2007; Shapiro et al., 2005) and older adults (Splevins et al., 2009; Young & Baime, 2010). These findings should be taken with caution though due to smaller sample sizes and lack of control group in some studies. Other longitudinal research investigating the effects of a MBSR course in comparison to a Progressive Muscle Relaxation (N = 40) has documented no changes in self-report perceived stress following a MBSR course (N = 57) for older adults aged 60 and above (Mallya & Fiocco, 2015). Interestingly, the participants in this study were healthy adults, and it could be that mindfulness is most useful to highly distressed individuals.

Mindfulness-based techniques have also been shown to impact on cortisol levels (O'Leary, O'Neill, & Dockray, 2015). Following MBSR program, decreases in morning AUC (area under the curve) net cortisol and Ln (log-transformed) daily cortisol levels have been documented (Carlson et al., 2007). AUC cortisol refers to a statistical measurement in which a trapezoidal formula is used to measure overall cortisol levels across different collection time points (Pruessner, Kirschbaum, Meinlschmid, & Hellhamer, 2003; Saxbe, 2008). Therefore, mindfulness training may not only reduce perceived levels of stress, but could also effectively and positively impact the neurophysiological and hormonal mechanisms of the stress response.

We will now investigate the neurocognitive mechanisms of stress reduction through mindfulness and their specific implications for future research on dementia prevention.

Neurocognitive Mechanisms of Mindfulness in the Context of Stress Processing: Implications for Ageing and Dementia

In this section, we will focus on the impact of mindfulness training on the cognitive and associated neurophysiological stress process including stress appraisal, attention regulation, attitude towards stress experience, stress reactivity and coping resources and corresponding stress-related neurophysiological mechanisms affecting the sympathetic response, amygdala activation, and stress-inhibitory brain regions. Each mechanism will be explained in relation to stress, dementia, and ageing, and then discussed in relation to possible modulations by mindfulness. We will also identify areas for future investigations for each of the mechanisms in the context of evaluating the potential impact of mindfulness on cognitive and neurophysiological markers of dementia. See Appendix C for a diagram on the proposed role of mindfulness on the cognitive and associated neurophysiological stress process.

Cognitive Appraisal of Stress and Mindfulness

A key initial cognitive component of the stress response is the cognitive appraisal of a stimulus as harmful (Gaab, Roheleder, Nater, & Ehlert, 2005; Oken et al., 2015). According to Folkman, Lazarus, Dunkel-Schetter, Delongis and Gruen (1986) and Lazarus (2001), the appraisal process can be divided into a primary and secondary appraisal. The primary appraisal begins with an examination of an internal/external stimuli in relation to an individual's well-being, ideals, and goals. For example, a potential threat is first identified and then evaluated in terms of possible impact on quality of life. Appraised stimuli can be categorised into three domains: irrelevant to well-being, positive, or stressful (Peacock & Wong, 1990). If stimuli are deemed stressful, the secondary appraisal process commences. This process involves the assessment of resources needed to cope with the perceived stressor (Folkman, 1984; Folkman

et al., 1986; Peacock & Wong, 1990). Stressors can be classified as harm/loss, threat, or challenge (Folkman, 1984; Lazarus, 1981; Lazarus, 2001; Monroe & Kelley, 1997; Peacock & Wong, 1990). Harm/loss describes adversity that has previously been experienced. However, a threat or challenge considers future events. A threat is anticipated damage to one's well-being (Folkman, 1984, Lazarus, 2001; Monroe & Kelley, 1997). Similar to a threat, a challenge involves anticipated damage. However, a challenge describes the perceived ability to manage or cope with damage. If the stimulus is deemed as a stressor and taxing on coping resources, the stress process is then evoked (Folkman et al., 1984). As new environmental information on the threat is interpreted and coping resources are utilised, primary and secondary appraisals are updated (Folkman, 1984; Skinner & Beers, 2016).

Frontal limbic brain regions, such as the hippocampi, amygdalae, and medial prefrontal cortex, are thought to underpin the appraisal process (Herman et al., 2012; Ulrich-Lai & Herman, 2009). Together these regions receive and integrate contextual information from brain areas associated with sensory, memory, and alerting processes (Ulrich-Lai & Herman, 2009) to determine the appropriate response to a threat. Although it is understood that these brain areas are involved in the appraisal process, there is limited research specifying contribution of each area to this process.

There is also a lack of research on stress appraisal process and in relation to dementia. However, studies with healthy adults have shown a link between appraisal and cortisol levels (Gaab et al., 2005; Harvey, Nathens, Bandiera, & Leblanc, 2010). For example, Gaab et al. (2005) found that an anticipatory cognitive appraisal, such as threat or challenge, was associated with increases in integrated salivary (AUG and AUCg) cortisol responses to a Social Stress Test in 81 healthy young male adults (aged 20-36). Similarly, Harvey et al. (2010) investigated stress appraisals in 13 medical professionals while completing a high stress and low-stress resuscitation practice. Findings revealed that when the practice was perceived as a threat, a positive relation between levels of mean salivary cortisol measured after the practice and cognitive appraisals was present.

While reductions in perceived stress after mindfulness training are well documented in adults (Carlson et al., 2007) and older adults (Young & Baime, 2010), studies have not examined the impact of mindfulness on stress appraisal as such. Yet, other mechanisms that closely impact on, or could even be considered part of, the stress appraisal have been investigated in relation to mindfulness. According to Epel et al. (2011), these mechanisms include the positive impact of mindfulness on promoting self-regulation of attention, a decentered less reactive awareness of experience, and development of adaptive coping resources needed to process threatening information. All of these are considered in what follows.

Modulations in attention systems.

Attention is a complex process involving the selective focus on stimuli salient to personal goals and disengagement from goal-unrelated stimuli (Ocshner & Gross, 2005). According to Posner and Petersen (1990), the attention process involves three distinct networks - orienting, alerting, and executive attention. The orienting network enables directing of attention towards salient sensory stimuli (Posner & Petersen, 1990; Petersen & Posner, 2012). Orienting recruits regions of the parietal and temporal lobe, including the temporoparietal junction and superior colliculus (Raz & Buhle, 2006). The alerting network, located in the thalamus and locus coeruleus (Raz, 2004), enhances arousal for the detection of relevant stimuli. The executive attention network, located in the anterior cingulate and the lateral ventral prefrontal cortex (Raz, 2004; Raz & Buhle, 2006), is involved in conflict monitoring of cognitive and emotional information (Raz, 2004).

Beyond Posner's model of attention, neuroimaging evidence has identified the salience network (SN; Seeley et al., 2007), central executive network (CEN; Menon & Uddin, 2010), and default mode network (DMN; Greicius, Krasnow, Reiss, & Menon, 2003). The SN, which

involves the orbitofrontal insula, dorsal anterior cingulate cortex, and ventrolateral prefrontal cortex, is responsible for detection of self-relevant cognitive, affective, and homeostatic stimuli (Goulden et al., 2014; Seeley et al., 2007). The CEN, located in the dorsolateral prefrontal cortex and posterior parietal cortex (Menon & Uddin, 2010), processes salient stimuli while maintaining goal sets (Miller & Cohen, 2001; Sridharan, Levitin, & Menon, 2008) and updating working memory (Müller & Knight, 2006; Sridharan et al., 2008). The DMN is a task-negative network (Raichle et al., 2001) that recruits regions including the medial prefrontal cortex, hippocampi, posterior cingulate cortex, and inferior parietal lobule (Buckner et al., 2008). Research has documented that this network is active when the brain is at rest and not engaged in a task (Greicius et al., 2003; Raichle et al., 2001). As such, the DMN is implicated in mind-wandering (Mason et al., 2007).

The attention networks may be central to correctly identifying threatening information and ignoring irrelevant stimuli underlying stress appraisal (Ellenbogenm Schwartzman, Stewart, & Walker, 2002). Specifically, the orienting network may play a role in engaging or disengaging attention to environmental threats (Petersen & Posner, 2012; Raz & Buhle, 2006). Pilgrim, Marin, and Lupien (2010) found that 25 healthy adults, aged 18 to 30, who were quick to orient attention towards stress-related stimuli, displayed higher cortisol responses to a socialstress test. Facilitating the orienting towards the threat, the alerting network may enhance arousal and attention towards environmental stressors (Aston-Jones & Cohen, 2005; Raz & Buhle, 2006). This network could be particularly influential in activating the HPA-axis response since the locus coeruleus of the alerting network has projection pathways to the amygdala (Sara, 2009; Ulrich-Lai & Herman, 2009). The executive attention network may contribute to detection and resolving of conflicts (Berger & Posner, 2000) in the stress appraisal process. It may also override habitual responses (Wang, Liu, & Fan, 2012) to environmental stressors. Similar to the alerting network, the neural underpinning of executive attention (the anterior cingulate cortex-ACC) is implicated in HPA axis activity (Wang et al., 2005; MacLullich et al., 2006) through ACC connections with the amygdala (Beckmann, Johansen-Berg, & Rushworth, 2009). Hence, the executive attention network may regulate amygdala activity towards fear-related stimuli (Das et al., 2005; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003) and emotional conflicts (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). The salience network may impact the stress appraisal process (Hermans, Henckens, Joëls, & Fernández, 2014) through attention to salient stimuli, such as threats, and ignore irrelevant stimuli (Seeley et al., 2007). Interestingly, Seeley et al. (2007) documented connections from the salience network to the amygdalae and hypothalamus- regions implicated in HPA-axis activation (Herman et al., 2003). In contrast, the central-executive network activity may be dampened in the stress process (Arnsten, 2000; Hermans et al., 2014) to allow for a quick response to threat-related stimuli. This could be because the central-executive network involves more complex (hence slower) processes including retrieval of information about goals and other relevant information from the memory (Sridharan et al., 2008). Therefore, it could be hypothesised that the central executive network is key to primary appraisal, where stimuli is evaluated in relation to goals.

Attention, ageing and the stress response.

There are conflicting results on age-related changes in attentional processes (Mahoney, Verghese, Goldin, Lipton, & Holtzer, 2010; West & Alain, 2000). Mahoney et al. (2010) documented a negative relation between chronological age and executive attention performance in the Attention Network Test (ANT, Fan et al., 2002) with a sample of 184 older adults, aged 70 and above. This effect was noted after controlling for reaction time, education level, and global disease status. Similarly, Zhou, Fan, Lee, Wang and Wang (2011) found a decline in executive attention performance on a revised ANT for older adults (aged 61-80) in comparison to young adults (aged 20-38) and middle-aged adults (aged 40-59). In addition, a

significant decline in alerting was documented for older adults in comparison to other agedgroups. Jennings, Dagenbach, Engle, and Funke (2007) and Williams et al. (2016) also reported slower alerting for older adults in comparison to young adults on the ANT after controlling for reaction time. However, no differences were noted for executive attention or orienting between age groups in their studies. This discrepancy in findings could be due to modifications of the task used.

The findings showing a decline in the alerting and executive networks could have implications for the stress appraisal process in older adults, even though no previous studies have investigated such effects. Specifically, the reduction in alerting processing could impact the speed of threat assessment and response, which could have adverse consequences in situations requiring quick threat detection. The diminished executive processing could impact on the ability to override the habitual responses and ensure alignment between stress appraisal, values, and goals.

In light of these findings, ERP and imaging studies may offer useful insight on the effects of ageing on attention processes. ERPs are time-locked averaged brain wave responses to stimuli, such as faces or sounds (Luck, 2005; Sur & Sinha, 2009). Juckel et al. (2012) examined the effects of age amongst 32 male participants, aged 20-55, using ERPs and fMRI simultaneously during an oddball paradigm. The ERP marker examined was the P300 - a positive occurring component that indexes attention resource allocation (Polich, 2007). The P300 amplitude was reduced, and latency increased for older participants in comparison to young participants. Kropotov, Ponomarev, Terschenko, Müller, and Jäncke (2016) similarly documented decreases in the P300 amplitude and increases in the P300 latency with age to go stimuli in a Go/NoGo Task in a sample of 454 adults, aged 18-89 years. Moreover, an increase in the P300 amplitude and decrease in the N200 amplitude to no-go stimuli was reported. The N200, a negative occurring ERP component linked with the executive attention network

(Rueda, Posner, & Rothbart, 2005) and anterior cingulate cortex activity (van Veen & Carter, 2002), may index conflict monitoring (Donkers & van Boxtel, 2004) and inhibition (Falkenstein, Hoormann, & Hohnsbein, 1999). Together these findings may indicate reductions in effective allocation of attention resources and declines in the inhibition of task-irrelevant stimuli. In terms of the stress response, these declines could have a consequences for employment and inhibition of attention resources involved in the threat detection and appraisal phases of the stress response process. At the neural level, an increase in the P300 amplitude has been theoretically linked to increases in the phasic activity of the locus coeruleus which releases norepinephrine (Nieuwenhuis, Aston-Jones, & Cohen, 2005) and this can stimulate hormonal changes in the HPA axis (Chrousos, 1997; Tsigos & Chrousos, 2002). Importantly, norepinephrine from the locus coeruleus (LC) also might have a protective role in the ageing brain and Alzheimer's disease (Heneka et al., 2010; Mather & Harley, 2016).

A decline in attention regulation was also documented in fMRI research. Specifically, the fMRI findings in the Juckel et al. (2012) study indicated that young participants, compared to older participants, displayed increased recruitment of attention areas including the anterior cingulate cortex, dorsolateral prefrontal cortex, and tempoparietal junction. Also using fMRI, Milham et al. (2002) reported differences across age in neural recruitment during a Stroop Task. To incongruent and congruent trials, younger adults (aged 21-27, N = 12) recruited bilateral dorsolateral prefrontal cortex, precuneus cortex, bilateral superior and inferior parietal lobes. However, older adults (aged 60-75, N = 10) recruited more superior temporal gyrus and anterior inferior prefrontal cortex. Given the role of the dorsolateral prefrontal cortex in the central executive network (Menon & Uddin, 2010) and the superior parietal lobe in the orienting network (Posner & Petersen, 1990), the aforementioned results may indicate declines in self-regulation of attention in older adults.

A similar pattern of deterioration in attention for reasons beyond natural developmental trajectory has been reported for those with MCI and AD (Levinoff, Saumier, & Chertkow, 2005; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2011; Saunders & Summers, 2011). Using a choice reaction task in which participants were asked to respond to numbers presented on a computer, Levinoff et al. (2005) found slower reaction times for 34 MCI (Mean Age = 74.10) and 30 AD participants (Mean Age = 73.90) in comparison to 52 normally ageing controls (Mean Age = 74.00) - indicating impairments in focused attention. In research with ERPs, Papaliagkas et al. (2011) have documented longitudinal changes over 23 months, such as increased P300 latency and less N200 negativity in response to targets in auditory oddball task in participants with 22 MCI (Mean Age = 67.40). The reduced N200 amplitude may reflect a decrease in attentional inhibition to irrelevant stimuli. A consequence of this dampened inhibition could be less effective attention allocation, as reflected by an increase in the P300 latency. Just like in healthy ageing, this decline in attention abilities could impact effective modulation of stress appraisal through attention networks in those with MCI and AD.

Mindfulness, ageing and attention processing.

Given that mindfulness-based approaches involve regulating attention with nonelaborative quality (Shapiro et al., 2006; Bishop et al., 2004; Tang et al., 2015), mindfulnessbased practices may promote self-regulation which impacts on the stress response. Selfregulation is operationalised as the process by which a person may control affective states, behavior, and cognition, and typically involves attention regulation and emotion regulation (Baumeister, Schmeichel, & Vohs, 2003; McCleland, et al., 2010). In relation to attention, Rueda et al. (2005) distinguished three attention processes essential to self-regulation; conscious detection, inhibition, and conflict resolution. However, other attentional processes, such as orienting and alerting, may also be involved in self-regulation of attention. Orientation of attention may contribute to conscious detection of salient stimuli (Rueda et al., 2005). Inhibition involves suppression of orienting attention towards unimportant stimuli and conflict resolution is the shifting of attention to salient stimuli in the presence of conflicting stimuli. Together, these processes may recruit the anterior cingulate and lateral prefrontal cortex (Asplund, Todd, Snyder, & Marois, 2010; Posner & Rothbart, 2009; Weissman, Giesbrecht, Song, Mangun, & Woldorff, 2003). Now we turn to specific research evidence examining the impact of MBAs on self-regulation.

Jha, Krompinger, and Baime (2007) found that following a MBSR course, 17 medical students (Mean Age = 24.00 years) displayed improvements in orienting attention on the ANT in comparison to a control group (Mean Age = 22.00, N = 17). In a randomised control using MBSR (N = 16), a non-mindfulness stress reduction course (N = 15), and control group (N = 16), young adults (aged 20-36 years) who completed MBSR training displayed improvements in selective attention as indexed by error rates on a d2 test of attention (Jensen, Vangkilde, Frokjaer, & Hasselbach, 2012). In addition, the MBSR group displayed decreases in cortisol levels in comparison to the inactive control group. However, the link between improvements in attention and reduced cortisol levels was not explored. Allen et al. (2012) documented a reduction in Stroop conflict response times to an affective Stroop Task for a mindfulness-based intervention group (aged 18-50, N = 30) in comparison to a group-reading intervention (N = 31). In addition, activity in the left Dorsolateral Prefrontal Cortex (DLFPC) was detected throughout the task in the mindfulness training group. Considering that the dorsolateral prefrontal cortex is connected with the central executive network (Menon & Uddin, 2010), results could possibly indicate improvements in attention processing of stimuli.

Research on short-term mindfulness interventions has reported discrepant findings. For example, Tang et al. (2007) found improvements in executive attention on the ANT for 80 meditation-naïve undergraduate students (Mean Age = 21.80) following a five-day training of integrative body-mind training (IBMT) in comparison to a control group who completed

relaxation training. IBMT is a five-day group-based course that integrates mindfulness, imagery, and relaxation techniques. Practices for the course are approximately 20 minutes daily, during which participants listen to a CD to engage in techniques such as body-posture adjustment. Interestingly, Tang et al. (2007) also reported that participants who engaged in 20 minutes of IBMT training after a stress-inducing mental arithmetic task displayed lower salivary cortisol in response to the task. This study did not investigate direct links between the enhancement in executive attention and cortisol responses. However, it is possible that the executive attention improvement was associated with modulations in the ACC (demonstrated in a study evaluating the same program with 86 Chinese undergraduate students (Mean Age = 21.45) (Tang et al., 2009). This modulation may be linked to changes in stress appraisal process, which in turn could impact on the HPA-axis regulation and result in reduced cortisol levels.

Josefsson, Lindwall, and Broberg (2014) examined the impact of a shortened mindfulness-based intervention on executive attention amongst working-age adults. The mindfulness-based intervention incorporated elements of MBSR and MBCT, but only met twice a week for 45 minutes across four weeks. Participants were randomised into a mindfulness-meditation group (Mean Age = 48.90, n = 46), relaxation training group (Mean Age = 50.40, N = 40), or control group (Mean Age = 45.10, N = 40). Following the intervention, the mindfulness group displayed no improvements in executive attention, as measured by the Stroop Task, in comparison to the relaxation and control group. More recently, Watier and Dubois (2016) investigated the effects of a brief mindfulness practice on executive attention in 78 undergraduate students, aged 17-46. Students were allocated to a 10-minute attention exercise, mindfulness exercise, or mental arithmetic exercise. Findings revealed no difference in executive attention, measured by an emotional Stroop Task, across exercise conditions. Clearly, these findings are less encouraging with regard to the potential effects of mindfulness

on attention and the stress response than those by Tang et al. (2007) and Tang et al. (2009). This could be due to differences in tasks, design, and intervention type.

Event-related potential (ERP) studies have also examined modulations in the attention processes after mindfulness training with implications for stress appraisal (Slagter et al., 2007; Moore, Gruber, Derose, & Malinowski, 2012; Quaglia, Goodman, & Brown, 2015). Following a three-month Vipassana meditation retreat, Slagter et al. (2007) found less positive amplitudes of the P3b component during an attention-blink paradigm in 17 healthy practitioners (aged 22-64 years) in comparison 23 control group participants (aged 20-62 years). The P3b is a positive peak that is a sub-component of the P300 wave occurring around 200-500 ms (Polich, 2007). It is sensitive to attention-related updating of memory set (Polich, 2003; Polich, 2007; Polich & Criado, 2006). The reduced P3b amplitude could imply that meditation enhances efficient distribution of attention resources to goal-related stimuli. In terms of stress appraisal, the P3b has been theoretically linked to activation of the locus coereulus-norepinephrine system (Nieuwenhuis et al., 2005; Nieuwenhuis, De Geus, Aston-Jones, 2011; Polich & Criado, 2006). This could indicate that mindfulness may enable adaptive modulation of the locus coeruleus and reduction in stress-related attention capture, consequently, allowing for more efficient allocation of attention resources to salient stimuli.

Further ERP research has highlighted a link between self-report trait mindfulness and early attention processing, as indexed by the N200 component, for 53 healthy young adults (Mean Age = 19.09; Quaglia et al., 2015). During this study, healthy young adults were instructed to respond emotional faces in a go-no-go facial discrimination task. Findings suggested that trait mindfulness predicted a more negative N200 amplitude to both go and nogo stimuli. Other longitudinal research has also reported a similar modulation of the N200 for congruent and incongruent trials in a Stroop Task in young adults (Mean Age = 36.10, N = 12) who completed shortened (10 min.) mindful-breathing meditation for 16 weeks in comparison to a control group (Mean Age = 34.70, N = 16; Moore et al., 2012). The aforementioned N200 modulation may indicate that mindfulness enhances the ability to inhibit reactions towards irrelevant information, even though it is surprising that the N200 modulation was observed to both congruent and incongruent trials. In a longitudinal study with 19 adolescents, a selective modulation of the N200 for task-irrelevant stimuli to an oddball task following a school-based mindfulness course in comparison to a wait-list control group (N = 21) has been reported (Sanger & Dorjee, 2016). The ability to inhibit response when appropriate is relevant to the stress appraisal process, when attention resources may be allocated habitually towards perceived threats (Bishop, 2008; Koster et al., 2004).

Research on mindfulness and attention in older adults is sparse; however, few studies have reported promising findings. A qualitative study with 27 community-dwelling older adults (Mean Age = 74.30) reported improvements in attention following an MBSR course (Morone, Lynch, Greco, Tindle & Weiner, 2008). Specifically, participants expressed having a clearer and focused attention after the mindfulness course. The qualitative nature of the study limits conclusive inferences, but provides initial tentative evidence warranting further investigation. Sperduti, Makowski, and Piolino (2016) investigated differences on a modified ANT in 19 young adults (Mean Age = 27.16) naïve to meditation, 16 older adults naïve to meditation (Mean Age = 67.12), and 16 older adults (Mean Age = 67.69) with approximately 11-44 years of meditation experience. After correcting for age-related decline in reaction time, older adults with meditation experience displayed enhanced executive attention scores in comparison to older adults naïve to meditation. In addition, older adults with meditation experience to younger adults naïve to meditation. Thus, researchers suggest that meditation may reduce age-related declines in attention, even though such inference should be taking with caution due to the cross-sectional nature of the study.

Using ERPs to investigate the impact of mindfulness practices in comparison to a braintraining exercises on cognitive and emotional processes, Malinowski, Moore, Mead, and Gruber (2015) reported an increase in negativity of the frontal-central N200 amplitude during an emotional-counting Stroop task with 18 older adults, aged 55-75 years, following 8 weeks of shortened (10 min.) daily mindfulness practices in comparison to a brain training group (*N* = 18). Although the N200 amplitude was increased across all conditions of the Stroop Task, Variable Resolution Electromagnetic Tomography (VARETA) indicated that increases in the N200 amplitude for the mindfulness training group may be related with modifications in attention areas, such as the right superior parietal lobule and right angular gyrus. In addition, Smart, Segalowitz, Mulligan, Koudys, and Gawryluk (2016) reported an increase in the P300 amplitude to a Go/NoGo task for older adults with subjective cognitive decline, aged 65-85 years, following an eight-week mindfulness intervention. Together, the findings may suggest that mindfulness training improves attention processes. However, the question remains on whether mindfulness training could reduce attention deficits linked to dementia.

Given the lack of evidence, future research could explore how attention modulation due to mindfulness training impacts the stress-related cortisol response. Specifically, it may be interesting to examine if mindfulness practice decreases the P300 amplitude to threatening stimuli while also reducing cortisol levels in an ageing sample. A similar paradigm could be also employed with MCI patients with neuroimaging techniques (MRI and fMRI) examining if mindfulness may also promote increased grey matter in the hippocampus and increased connectivity of the DMN.

The quality of attention.

It is not only attention processing as such, but also a shift in attitude – the quality which we bring to paying attention – that contributes to the therapeutic effects of mindfulness (Bishop et al., 2004). The quality of mindful attention is often described as non-judgmental, open, and kind (Bishop et al., 2004). Development of these qualities of attention may promote a "decentered" perspective (Carmody, Baer, Lykins, & Olendzki, 2009; Shapiro et al., 2006) of cognitions and affective states (Fresco et al., 2007; Safron & Segal, 1990; Shapiro et al., 2006; Teasdale, 1999). Through decentering these can be perceived as fleeting mental phenomena rather than unchangeable facts. In relation to stress appraisal, decentering may enable flexible non-reactive processing of threatening information.

To examine the link between decentering and perceived stress, Carmody et al., (2009) completed an intervention study with 309 adults (aged 19-77) enrolled in MBSR courses who experienced stress-related problems, chronic pain, and anxiety. While self-report trait mindfulness and self-report decentering increased following the intervention, both of the constructs combined predicted less psychological stress (Carmody et al., 2009). It can be conjectured that mindfulness and decentering together cultivate flexible attention towards the stress appraisal process. As a result, individuals may be capable of adaptively responding to salient stress-related information which decreases stress.

Encouraging initial evidence of improvements in decentering in older adults comes from a mixed-methodology investigation of changes after MBSR training (Martins, 2014). This study revealed an inverse relation between change in self-report decentering and self-report perceived stress in 24 older adults, aged 65-73. Qualitative interviews, with a subset of the participants, provided further insight into how decentering may impact the stress process by influencing the cognitive appraisal. For example, one participant noted that they were able to "stop and observe," (Martins, 2014, p.155) thoughts with more "awareness and discernment," (Martins, 2014, p.155) which could offset the habit to emotionally reacting to threatening information. Importantly, the same study also found positive association between decentering and improvements in cognitive abilities including working memory and processing speed. Future longitudinal research could examine whether improvements in decentering mediate reductions in the P300 and cortisol levels to threatening information following MBAs in older adults and those with MCI. To more closely link this to the stress appraisal process, neurophenomelogical methods could be applied. Neurophenomenology includes a qualitative feedback indexing a participant's introspective experience throughout a task with neurocognitive assessments (Lutz &Thompson, 2003). In the context of research on decentering an ageing, neurophenomenology would provide insights into how participants may invoke a decentered attention to process and appraise threatening stimuli and how this relates to P300 and possible cortisol decreases.

Mindfulness and stress reactivity.

Stress reactivity can be defined as the disposition by which an individual automatically responds to demanding experiences on a cognitive, affective, physiological, and behavioral level (Schlotz et al., 2011; Skinner & Beers, 2016). Reactivity to stressful experiences is influenced by the appraisal process and previous life experiences. Higher stress reactivity is linked with the proneness to identify situations as threatening, and thus plays a part in the appraisal process and neurophysiological responses that commence once a stressor is identified (Schlotz et al., 2011).

Developmental theories on ageing, such as the socioemotional selectivity theory, potentially indicate reduced reactivity as healthy ageing progresses (Carstensen et al., 1999; Carstensen et al., 2006). In particular, the socioemotional selectivity theory suggests that in the process of ageing one becomes more aware of the finite time in life. With this feeling most relevant to older adults, a priority is placed on obtaining emotional satisfaction and enhancing quality of life. Consequently, it could be theorised that older adults may prioritize effective emotion regulation towards stressful stimuli and thus decrease stress reactivity.

In addition to enhanced emotion regulation, older adults may display attention biases towards positive information (Mather & Carstensen, 2005). For example, Mather and Carstensen (2003) documented reduced response times during a dot-probe task when the dot appeared near a positive face for 52 older adults, aged 62-94 years. Moreover, older adults displayed increased response times to dot probes present near a negative face in comparison to a neutral face. In comparison to 52 young adults, aged 18-35 years, older adults showed a significant attention bias toward neutral faces in comparison to negative faces and a marginally significant bias towards positive faces as compared to neutral faces. While it can be argued that attentional biases towards positive information may disrupt the threat detection process, Mather and Knight (2006) reported faster detection time for threat stimuli in comparison to non-threat stimuli for 35 older adults (aged 65-82 years) and 33 young adults (aged 18-28 years) during a visual search task of faces. Considering this evidence, Mather and Carstensen (2005) suggested that older adults display limited changes in automatic processes, such as threat detection. However, attention biases toward positive information may influence stress reactivity on a cognitive and affective level. In particular, it may lead to the conscious re-direction of attention away from stimuli that is not perceived as positive, such as negative, non-threatening stimuli. For example, Rösler et al. (2005) examined the orienting of attention and sustained attention to negative, neutral, and positive images using an eye-tracking test for young adults (Mean Age = 26.50) and older adults (Mean Age = 64.40). Although both young and older adults displayed a similar orienting of attention, indexed by a saccade, to negative images in comparison to neutral images, young adults showed increased sustained attention, indicated by dwell time, for negative images presented next to a neutral image. These findings could indicate that older adults may attend towards negative stimuli, but re-direct their attention when the stimuli are not interpreted as a threat

(Mather & Carstensen 2005). Thus, the attention bias towards positive information may inhibit the proneness to process negative information as a threat in older adults.

A bias towards positive information may also promote adaptive emotion regulation used to cope with stressors (Taylor, Bomyea, Amir, 2011), thus leading to declines in stress reactivity. For example, research with undergraduate students (Mean Age = 19.17) has reported a correlation between decreases in self-reports of anxiety before a social stress test and increases in attention biases for positive information following an attention training paradigm (Taylor et al., 2011). Researchers of this study concluded that training attention towards positive information may predict a more adaptive response to potential stress.

Interestingly, previous work has documented reduced emotional reactivity to stressors in older adults (Birditt, Fingerman, & Almeida, 2005; Neupert, Almedia, & Charles, 2007). Kisley, Woods, and Burrows (2007) reported a link between ageing and reductions in the Late Positive Potential (LPP) amplitude when 51 adults, aged 18-81, viewed negative images. The LPP, a positive occurring ERP component that occurs around 400-500 ms after stimulus onset, is an indexer of attention processing to emotional stimuli (Dennis & Hajcak, 2009; Schupp et al., 2000), and is associated with amygdalae activation (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012). As such, it may be a potential marker sensitive to reductions in stress reactivity, with less positive LPP representing decreased attention allocation to threat-related stimuli. Additionally, Mather et al. (2004) found reduced amygdala activity while viewing negative images amongst 17 older adults (aged 70-90) in comparison to 17 young adults (aged 18-29). The authors suggest that this finding may be indicative of diminished arousal to unpleasant stimuli in older adults.

However, other research has documented conflicting results on reactivity across ageing (Mroczek & Almeida, 2004; Stawski, Sliwinski, Almeida, & Smyth, 2008). For instance, a similar modulation of the LPP amongst 20 older adults (aged 60-77) and 19 young adults (aged

18-26) has been documented when participants were instructed to view images and decrease/increase affect to images (Langeslag & Van Strien, 2010) from the International Affective Pictures System (Lang, Bradley, & Cuthbert, 1999). This discrepancy in findings may be explained by the task instruction to regulate emotions to the images as opposed to passively viewing images. In addition, a large (N= 1,012) questionnaire study with adults, aged 25 to 74, indicated a stronger association between daily life stress and negative affect in older adults as compared to younger adults (Mroczek & Almeida, 2004). Researchers suggest that this may be due to an increase in reactivity after repeated exposure to a stimuli in life.

Given these contradictory findings, it is important to consider that reduced reactivity and the priority to effectively regulate emotions may not be consistent across all older adults. For example, Charles and Carstensen (2010) suggest that personality traits, such as neuroticism, may predict differences in levels of emotional reactivity to stressors in older adults. Mroczek and Almeida (2004), using questionnaires with a sample of 1,012 adults, reported persons with high trait neuroticism displayed a stronger link between daily stress and negative affect in persons in comparison to those with low trait neuroticism. Moreover, an experience of a chronic illness (Piazza, Charles, & Almeida, 2007), and loneliness (Hacket, Hamer, Endrighi, Brydon, & Steptoe, 2012) may lead to differences in affective and stress reactivity (Charles & Carstensen, 2010). In a questionnaire study with 983 adults, aged 25 to 74 years, Piazza et al. (2007) found that ageing was linked with reduced affective reactivity in participants who experienced three or less chronic illness. However, older adults who reported four or more chronic illnesses had similar stress reactivity scores to young and middle-aged adults. Hacket et al. (2012) revealed a positive relation between self-report loneliness and stress ratings at baseline and during recovery from behavioral stress tests in 524 healthy adults, aged 53-76 years. Conversely, no association between stress ratings immediately following the task

and loneliness were seen. As such, there is no clear consensus on how reactivity may change across the life-span.

While the debate about lower reactivity to stress in the ageing population remains unresolved, a recent study has shown increased self-report emotional reactivity to stresssors in 15 MCI participants (Mean Age = 75.33) in comparison to 25 healthy older adult controls (Mean Age = 73.56; Rickenbach, Condeelis, & Haley, 2015). This study provides tentative evidence that stress reactivity may be heightened as cognitive impairment occurs which leads to the question of whether mindfulness could be effective in this context.

Converging evidence has documented decreases in emotional reactivity to stressors and stress reactivity following MBSR and MBCT courses for persons who experienced remitted depression (Britton, Shahar, Szepsenwol, & Jacobs, 2012) and anxiety (Hoge et al., 2013). Moreover, studies have found links between higher dispositional mindfulness and decreased stress reactivity as indexed by less activation in the amygdalae (Way, Creswell, Eisenberger, & Lieberman, 2010). In this study, Way et al. (2010) examined amygdalae activation while viewing negative emotional faces in 27 healthy undergraduate students, and reported an inverse relation between right amygdala responses to negative stimuli and self-report dispositional mindfulness. However, Way et al. (2010) suggest these findings may be due to differences in resting state activity of the amygdalae. From a structural standpoint, researchers have documented a reduction in grey matter density of the right amygdala for 26 healthy adults (aged 25-55) following an MBSR course (Hölzel et al., 2009), which correlated with less perceived stress as measured by a questionnaire.

Interestingly, a qualitative investigation as part of a randomised controlled trial on MBSR for 9 older adults (Mean Age = 73.00) with MCI reported a reduction in stress-reactivity (Wells, Kerr, et al., 2013). In addition to a reduction in stress-reactivity, Wells, Yeh et al. (2013) documented an increase in functional connectivity of the DMN. However, the findings

need to be interpreted with caution given the small sample size in this study. Nevertheless, the results provide initial evidence that, interventions with a focus on decreasing reactivity, such as mindfulness training, could be particularly useful in MCI. From a broader perspective, it also raises the question of whether training in mindfulness before the onset of MCI or progression onto dementia could mitigate some of the reactivity symptoms and stress-related brain changes later on.

One avenue of addressing such questions in future research would be through long-term longitudinal mindfulness intervention studies examining modulation of the amygdalae activation during a threat-induction task, as a possible neural marker of reactivity (Liu et al., 2012), across healthy ageing and MCI progression. To further enhance ecological validity of such research, an experience sampling method investigating how mindfulness practice influences participants' reactions to everyday stress in their lives could be collected and the data related to findings from neurocognitive measures.

Mindfulness and coping resources.

A traditional model of the stress appraisal process (Lazarus, 1966) identifies coping resources as a mediator of stress reactions. Coping resources are physical, social, psychological elements that can be utilised to cope with stressors (Lazarus & Folkman, 1984). Examples of coping resources include: physical well-being, social support, self-esteem, and monetary resources. In particular, when coping resources are deemed as insufficient to process threatening information, this can initiate the neurophysiological stress process (Lazarus, 1966; Olff, 1999). Contrary, if coping resources are available and appropriately implemented in relation to a person's goals and the environment, the stress process may be terminated (Cohen, Evans, Stokols & Krantz, 1986; Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen, 1986; Lazarus, 1966). Coping can be defined as the behavioural or cognitive actions employed to modulate affective responses to internal and external stimuli perceived as demanding, and to modify disturbances in the person-environment relation that leads to stress (Folkman et al., 1986; Lazarus, 1993; Lazarus & Folkman, 1984). This definition considers the individual's disposition to coping, personal goals, and the environment in which the stimuli are appraised as a threat (Folkman et al., 1986; Folkman & Moskowitz, 2004; Skinner & Beers, 2016). Coping strategies can be classified as adaptive or maladaptive (Lazarus, 1993; Taylor & Stanton, 2007). Adaptive coping is characterised by the effective modulation of stress in the context of the person-environment relation (Lazarus, 1993; Zeidner & Saklofske, 1996). Adaptive coping may result in a reduction of harm and stress (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Moritz et al., 2016). Other factors including personality (Carver & Connor-Smith, 2010) and social support (DeLongis & Holtzman, 2005) may influence coping behaviours. Similar to the appraisal process, as environmental information is updated in relation to the threatening stimuli, appropriate coping resources may change (Skinner & Beers, 2016).

Looking specifically at older adult literature, there is discrepant evidence on how coping strategies change across the age-spectrum (Yancura & Aldwin, 2008). While a 20-year longitudinal questionnaire study with 719 older adults (Mean Age = 61.00) has reported a decreased utilisation of both adaptive and maladaptive coping strategies in ageing (Brennan, Holland, Schutte, & Moos, 2012), other cross-sectional questionnaire research has revealed no differences in coping across 35 middle-aged (aged 45-64) and 63 older adults (aged 65-89; Hamarat et al., 2002). Nevertheless, there is consensus that coping does play an important role in the well-being of older adults (Moos et al., 2006; O'Donnell, Badrick, Kumari, & Steptoe, 2008). For example, Moos et al. (2006) found that usage of avoidant-focused strategies was linked with more depressive feelings and alcohol use in 297 older adults, aged 55-65 years. Providing convergent validity to these findings and a link with physiology of stress, O'Donnell et al. (2008) reported that the utilization of self-report social-support and problem-engagement

coping strategies amongst 542 older adults Mean Age = 60.90) was related to lower AUC cortisol calculated using cortisol levels at 4 time points throughout the day. Considering this evidence and the association between increases in cortisol levels and dementia, it could be implied that more adaptive coping may be linked to less dementia risk — a hypothesis that requires further investigation.

In cognitive impairment and dementia, it can be hypothesised that coping behaviors change with the decline of neural functions that underlie emotion, cognitive, and appraisal processes. However, there is a real lack of research on dementia and coping to provide evidence for this hypothesis. A cross-sectional questionnaire study comparing coping strategies in 30 healthy older adults (aged 62-90 years) and 30 older adults diagnosed with AD (aged 67-89) documented no significant differences in coping styles across groups (de Souza-Talarico, Chaves, Nitrini, & Caramelli, 2008). Nevertheless, AD participants with higher mini mental status examination (MMSE) scores significantly reported using more problem-focused coping strategies; strategies intended to modify the source of stress (Carver & Connor-Smith, 2010). In general; however, AD participants tended to utilize emotion-focused coping strategies; strategies focused on regulating emotions in response to a threat (Carver et al., 2010). Researchers of this study suggest that problem-focused coping strategies may be employed when persons can access semantic memories to find the most appropriate way of modifying the source of the stress. The implications of this study are, however, limited due to the small sample, and also due to the subjective nature of questionnaires.

In regards to mindfulness, several studies have documented an increased utilization of adaptive coping strategies following MBSR (Dobkin, 2008; Walach et al., 2007; Witek-Janusek et al., 2008). For example, Witek-Janusek et al. (2008) documented higher usage of adaptive strategies, such as optimistic coping and social-support coping, and decreases in cortisol levels following MBSR for 38 women (aged 35-75 years) diagnosed with breast-

cancer. However, no changes in self-report mindfulness were noted following the MBSR course. Dobkin (2008) noted a trend towards more adaptive coping strategies in 13 women (aged 37-70 years) treated for breast-cancer and a significant reduction in perceived stress levels following the MBSR intervention was found.

A qualitative study on pain in 27 older adults (Mean Age = 74.30) showed that through an intervention similar to MBSR, several participants recognised their personal pattern of maladaptive coping strategies, such as repressing pain (Morone, Lynch, Greco, Tindle, & Weiner, 2008). Participants noted a shift towards more effective coping with pain following the mindfulness course. Accordingly, mindfulness practice could attenuate the stress appraisal process by promoting more adaptive coping and thus impact subsequent neurophysiological reactions that may affect dementia pathology.

However, there is a need for more direct research investigating how potential improvements in adaptive coping following a mindfulness course may lead to decreased cortisol levels and improved cognitive function in older adults and MCI participants. Specifically, to understand how modifications in adaptive coping strategies may mediate potential effects of mindfulness on dementia progression, neuroimaging evidence examining possible increases of grey matter density in the hippocampus could utilised in conjunction with a daily cortisol collection. It could be predicted that mindfulness may increase adaptive coping, which results in lower cortisol levels and thus have a protective effect on grey matter density of the hippocampus or increased connectivity of the DMN.

Another avenue for investigation is to utilise neurophenomenological feedback in conjunction with a fMRI task in which participants would be instructed to view and modify emotional reactions to threatening images. During each block, participants would be instructed to utilise their preferential coping strategies. After each block, participants would be prompted to identify the coping strategy utilised and describe their experience while viewing the images. In addition, participants could subjectively rate the effectiveness of the coping strategy employed. This task could be completed before and after a mindfulness intervention with MCI participants. Such research may elucidate how mindfulness enhances adaptive coping responses and modulates the neural stress appraisal process, such as amygdalae activity to threats.

Shift from Top-Down to Bottom-Up Amygdalae Regulation through Mindfulness

The Hypothalamic-Pituitary-Adrenal (HPA) axis is indirectly activated by the amygdalae (Smith & Vale, 2006), which leads to the release of cortisol used recruiting energy resources needed to cope with a stressful occurrence (Xiong & Zhang, 2013). Mindfulness may counteract cortisol release (Brand, Holsboer-Trachsler, Naranjo, & Schmidt, 2012) by attenuating amygdalae activation through two avenues (top-down or bottom-up) (Chiesa, Serretti, & Jakobsen, 2013; Hölzel et al., 2011; Prakash et al., 2014). For example, mindfulness practice may attenuate the amygdalae activation in top-down manner through cognitive reappraisal strategies (Chiesa et al., 2013). Initially, this process may require an increased demand on attentional resources and working memory. This is reflected in increased prefrontal cortex activity coupled with decreases in amygdalae activation (Chiesa et al., 2013; Modinos, Ormel, & Aleman, 2010). In this way, mindfulness may promote recruitment of the prefrontal cortex—a brain region with bidirectional connections to the limbic system, thus enabling modulation of the threat response (Arnsten, 2009; Marek, Strobel, Bredy, & Sah, 2013; Price, 2005).

Creswell, Way, Eisenberger, and Lieberman (2007) reported an association between high self-report dispositional mindfulness and enhanced activation of prefrontal cortex regions, such a bilateral ventrolateral prefrontal cortex, ventromedial prefrontal cortex, right dorsolateral prefrontal cortex, while 27 healthy undergraduates affectively labelled emotional faces. In addition, deactivation of the bilateral amygdalae was seen in the high dispositional

mindfulness group. Interestingly, recruitment of prefrontal regions was negatively correlated with amygdalae activity in these participants. Similarly, Modinos et al. (2010) documented a link between high self-report dispositional mindfulness and increased activation of the dorsomedial prefrontal cortex when 18 healthy participants (Mean Age = 21.10) reappraised negative images. Activity in the right dorsal medial prefrontal cortex was also negatively linked with the left amygdala activity when viewing negative images. A study by Taylor et al. (2011) found a comparable pattern of activation in 10 beginner meditators, aged 22-54 years, where a deactivation in the left amygdala was seen during mindful processing of negative and positive images. In addition, beginner meditators, when asked to process images in a mindful way, displayed increased activation of the right and left medial frontal gyrus (MFG), right inferior parietal lobule (IFPL), and the right posterior cingulate cortex (PCC). This study differs; however, from Modinos et al. (2010) and Creswell et al. (2007) because no links between frontal activity and the down-regulation of the amygdala were examined.

Mindfulness practice may also encourage a more effortless modulation of the stress response through the utilization of bottom-up regulation processes that focuses on modifying the emotional response as it arises (Chiesa et al., 2013). Bottom-up regulation is marked by decreased amygdalae and prefrontal activation (Chiesa et al., 2013; Gard et al., 2012; Hölzel et al., 2011; Zeidan et al., 2011; Grant, Courtemanche, & Rainville, 2011; Taylor et al., 2011), in addition to more recruitment of sensory processing (insular cortices) and executive attention areas (anterior cingulate). Indeed, cross-sectional studies investigating pain processing in healthy meditation practitioners and controls have revealed reduced activation in the prefrontal cortex areas (lateral prefrontal cortex; Gard et al., 2012) and amygdalae (Grant et al., 2011). However, they also reported increased recruitment of right posterior insula and anterior cingulate (rostral anterior cingulate cortex and right dorsal anterior cingulate cortex) while anticipating pain (Gard et al., 2012) and experiencing pain (Grant et al., 2011). These findings

could indicate that more experienced meditators require less cognitive effort, possibly associated with accepting awareness of pain sensations, to regulate stress responses (Hölzel et al., 2011).

From the perspective of ageing, healthy older adults have intact emotion regulation abilities despite declines in cognitive control (Mather & Carstensen, 2005; Prakash, De Leon, Patterson, Schirda, & Janssen, 2014). In fact, compared with younger adults, older adults may be more effective in regulating emotions to negative stimuli (Gross et al., 1997), even though some studies reported declines in emotion regulation abilities that depend on executive function (Consedine & Mauss, 2014; Opitz, Rauch, Terry, & Urry, 2012). As mentioned in our discussion about stress reactivity, possible increases in emotion regulation with age may be due to an enhanced motivation to allocate cognitive resources to process emotional stimuli (Carstensen et al., 2006). Therefore, in healthy ageing there might be additional demand on cognitive resources during emotion regulation to counteract the loss in cognitive control (Kryla-Lighthall & Mather, 2009).

Neuroimaging investigations on emotion processing in 19 older adults (aged 62-64 years) have documented prefrontal down-regulation of the amygdala while viewing emotional images (Urry et al., 2006), with some research indicating enhanced prefrontal regulation amongst 19 older adults (aged 64-81 years) in comparison to 20 young adults (aged 18-35 years; Leclerc & Kensinger, 2011). Interestingly, top-down inhibition of the amygdalae (Urry et al., 2006) documented in older adults was correlated with decreases in daily cortisol levels. Therefore, interventions, such as mindfulness-based practices, that encourage top-down modulation of amygdalae may be effective in decreasing the stress hormone linked with dementia development. Long-term meditation practice could have similar or possibly enhanced preventative effects resulting from bottom-up modulation of the amygdalae.

Importantly, amygdalae regulation amongst older adults may vary according to cognitive abilities. Specifically, those with MCI (Whitwell et al., 2008, Yao, Hu, Liang, Zhao, & Jackson, 2012) and AD (Möller et al., 2013) can display atrophy in the frontal lobes associated with cognitive impairment, which could diminish effective top-down regulation of the amygdalae to threatening information. Supporting this hypothesis, Wright, Dickerson, Eeczko, Negeira, and Williams (2007) found increased bilateral amygdalae responses to negative and neutral faces in participants with 12 mild-AD (Mean Age = 71.80) in comparison to 12 healthy older adults (Mean Age = 71.30). The authors suggested that this could be due to atrophy in prefrontal regions. Mindfulness could be used to promote or enhance bottom-up modulation of the amygdala (instead of top-down modulation) in older adults with a declining capacity to recruit prefrontal regions.

From the neuropsychological perspective, the potential of mindfulness in engaging both top-down and bottom-up regulation pathways raises interesting questions about the most appropriate intervention for cognitive decline observed in MCI and dementia. Although medication may be a common treatment for dementia (Singh & O'Brien, 2009), therapeutic approaches including cognitive rehabilitation and cognitive training are used to enhance cognitive function (Clare & Woods, 2003). Whilst cognitive training and cognitive rehabilitation focus on ameliorating impaired cognitive domains (Clare & Woods, 2003; Sohlberg & Mateer, 2001), cognitive rehabilitation also aims to build compensatory pathways used to cope with a decline in cognitive function (Clare & Woods, 2003; Clare, 2010; Sohlberg & Mateer, 2001). Mindfulness could be effective due to dual pathways of action – acting both to restore top-down regulation and to create compensatory bottom-up pathways. Further research on the efficacy of therapeutic approaches could lead to development of programs that specifically target bottom-up or top-down regulation based on the neuropsychological profile of the clients with MCI or dementia.

Future cross-sectional and longitudinal investigations examining differences in amygdalae modulation across ageing and meditation experience will provide the essential evidence needed to elucidate our understanding of the interactions between cognitive decline in ageing and mindfulness. Neuropsychological assessments that specifically index frontal lobe function (Glisky, Polster, & Routhieaux, 1995) could be used in combination with cortisol measures and fMRI of amygdalae activity and structure to explore neural pathways by which mindfulness may reduce HPA axis activity in older adults and those with MCI. It may be that mindfulness practice differentially alters regulation of the amygdalae in ageing depending on cognitive abilities and amount of meditation practice.

Mindfulness and the Autonomic Nervous System (ANS) Regulation

Following the appraisal of a stressor, the sympathetic branch of the ANS is activated and releases epinephrine and non-epinephrine (Smeets, 2010; Wolf, 2003) to increase heart rate, respiration, and glucose levels (Gunnar & Quevedo, 2007; Wolf, 2003). This leads to increased energy resources and blood flow to relevant areas of the body in preparation for defensive responses (Gunnar & Quevedo, 2010). Also a part of the ANS, the parasympathetic branch works in an inverse relation to the sympathetic system (Tsigos & Chrousos, 2002); when active, the parasympathetic system down-regulates the stress response of the sympathetic branch (Ulrich-Lai & Herman, 2009). Although the ANS is considered separate from the HPAaxis, the sympathetic branch may impact cortisol regulation through its role in stimulating the adrenal cortex (Ulrich-Lai & Engeland, 2005; Ulrich-Lai & Herman, 2009). Thus, interventions, such as mindfulness-based training, that may influence cortisol release not only through cognitive and associated brain pathways, but also via ANS modulations (Burg et al., 2012; Mankus, Aldao, Kerns, Mayville, & Mennin, 2013; Nijjar et al., 2014; Tang et al., 2009).

To index changes in the ANS, heart-rate variability (HRV), the variation of the heart beats interval (RR) is utilised (Acharya, Joseph, Kannathal, Lim, & Suri, 2006; Stauss, 2003).

Heart-rate variability is a non-invasive measurement that indexes sympathetic and parasympathetic activity on the heart's sinoatrial node - a region responsible for commencing the heart beat (Allen, Chambers, & Towers, 2007; Kleiger, Stein, & Bigger, 2005; Malik & Camm, 1990; Stauss, 2003). The sympathetic and parasympathetic systems impact RR at high (0.15-0.4 Hz) and low frequencies (0.04-0.15 Hz) (Acharya et al., 2006; Kleiger et al., 2005). High frequency HRV (HF-HRV) is specifically linked with parasympathetic activity (Acharya et al., 2006; Ditto, Eclache, & Goldman, 2006; Nijjar et al., 2014), whilst the low frequency HRV (LF-HRV) is associated with sympathetic function.

Heart-rate variability is also influenced by the respiratory-related activity of the vagus nerve on the sinoatrial node (Allen, Chambers, & Towers, 2007; Eckberg, 2003). This activity, which is also known as respiratory sinus arrhythmia (RSA), impacts RR in the respiratory frequency band (Allen et al., 2007; Berntson, Cacioppo, & Quigley,1993). RSA is thought to be mediated by the parasympathetic system (Stauss, 2007), and as such has been used as a marker of its activation.

Developmental research indicates that sympathetic and parasympathetic activity, as measured by heart rate variability, may decrease as ageing occurs (Antelmi, De Paula, Shinzato, Press, Mansur, & Grupi, 2004; Fukasaki, Kawakubo, & Yamamoto, 2000). Indeed, Antelmi et al. (2004) documented decreases in LF-HRV and HF-HRV in ageing amongst 653 healthy participants, aged 14-81 years. Specifically, significant reductions in HF-HRV were seen until the fourth decade of life with the pattern stabilizing afterwards and non-significant decreases in older adults. However, the LF-HRV significantly declined beginning in the third decade of life and continued to decline throughout the older adult population.

As cognitive decline occurs, parasympathetic activity may decline further (Toledo & Junqueira Jr., 2009; Kim et al., 2006). For example, Collins, Dillon, Fincuane, Lawlor, & Kenney (2012) noted a significant reduction in the HF-HRF for 97 MCI participants, aged 68-
77 years, in comparison to 36 healthy control participants, aged 68-75 years. Collins et al. (2012) suggests that declines in parasympathetic activity may be caused by hypo-activity in the cholinergic system. Other research completed with 22 Alzheimer's patients, aged 60-89 years, reported an association between decreasing parasympathetic activity and cognitive performance on the neuropsychological test, CAMCOG (Toledo & Junqueira Jr., 2009). Divergent to these findings, Allan et al. (2007) found no differences in LF-HRV and HF-HRV between 39 AD patients, ages 65 and above, and 38 healthy age-matched controls. Discrepancy in the findings may be partially due to difference in HRV acquisition. For example, Allan et al. (2007) collected ECG data across 5 minutes, while Collins et al. (2012) collected across 10 minutes.

Nevertheless, the findings highlight the importance of interventions that could increase parasympathetic activation such as mindfulness. Indeed, studies with healthy adults have indicated that HRV measures are sensitive to ANS changes resulting from mindfulness-based training. Following an MBSR intervention, Niijar et al. (2014) found a decrease in LF-HRV and increase in HF-HRV during a self-guided sitting meditation task compared to a controlled breathing task following a MBSR course for 18 adults (Mean Age = 52.70). Heightened HF-HRV during meditation practice has also been noted after a short 5-day training course in Integrative Mind-Body training with 46 healthy undergraduate students (Mean Age = 21.45; Tang et al., 2009). With regards to RSA, Ditto et al., (2006) documented increases in RSA while meditations in comparison to a wait-list control group (N = 12) and young adults (N = 10) who completed relaxation activities, such as listening to a book on tape or progressive muscular relaxation, or

Together, these findings indicate that mindfulness-based practices may generate an adaptive physiological response to stress by promoting parasympathetic activity. As a result, it

can be theorised that mindfulness training might offset cortisol discharge by the adrenal cortex through its impact on the autonomic nervous system. To investigate this hypothesis, longitudinal investigations assessing adaptive increases in parasympathetic activity (measured by HRV indexers) and reductions in cortisol levels resulting from mindfulness training in ageing populations showing cognitive decline would be valuable.

Mindfulness and Neuroplasticity Changes in Inhibitory Brain Regions

Upon release of glucocorticoid hormones, the HPA axis activity is modulated through glucocorticoid negative feedback (Herman et al., 2005; Xiong & Zhang, 2013). In particular, glucocorticoids bind to inhibitory receptors located throughout brain regions, such as the hippocampus (Frodl & O'Kean, 2013). Given its vital role in HPA axis regulation, the hippocampus is also susceptible to neurodegeneration due to glucocorticoid overexposure (Campbell & MacQueen, 2004; Frodl & O'Keane, 2013; Sapolsky et al., 1986). According to the glucocorticoid cascade hypothesis (Sapolsky et al., 1986), this neurodegeneration in the hippocampus may lead to a dampening of HPA axis inhibition and as a result cause more hippocampal atrophy. With this in mind, programs that reduce glucocorticoid overexposure and enhance hippocampal integrity will be most effective in mitigating the impact of stress on cognitive decline in ageing and dementia.

In older adults, imaging studies have linked decreasing overall brain volume with ageing (Resnick et al., 2003). However, Lupien et al. (2007) documented no difference in the variability of hippocampal volume in 41 young adults (aged 18-24), 38 adults (aged 25-40 years), 42 adults (41-59), 40 older adults (aged 60-75 years), and 16 older adults (aged 76-85). Lupien et al. (2007) argued that this sample may not be representative of a typically ageing population due to the screening process resulting in exclusion of participants that have a history of clinical complications, such as cardiovascular disease or stroke. This might explain the lack of variability between young and older adults. In AD, hippocampal atrophy is considered a

common characteristic (Kehoe, McNulty, Mullins, & Bokde, 2014; Pennanen et al., 2004). Most interesting, AD has been linked with HPA-axis dysregulation (Popp et al., 2009; Raadsheer et al., 1995), which may be closely linked to hippocampal changes. For example, Popp et al. (2009) documented increased levels of cortisol in the cerebrospinal fluid for 66 AD participants in comparison to 34 MCI patients and 33 healthy controls. No significant difference was noted between MCI patients and controls. However, other research has also reported no differences in daily salivary cortisol levels collected across six time points in 16 MCI participants (Mean Age = 70.90) and 28 healthy older adults (Mean Age = 68.60; Wolf, Convit, Thorn, & de Leon, 2002). Thus, results indicate that currently the evidence is contradictory with regards to the role of cortisol dysregulation as an early marker of AD.

Interestingly, initial research has documented increased grey matter concentration in the left hippocampus after MBSR training in healthy adults (Mean Age = 38.00, N = 16) whilst the control group (Mean Age = 39.00, N = 17) displayed no significant differences in grey matter concentration at pre and post-testing (Hölzel et al., 2011). In addition, increased grey matter concentration (Hölzel et al., 2008) and volume in the right hippocampus has been reported in adult meditators (Luders, Toga, Lepore, & Gasser, 2009) in comparison to adult non-meditators. Although these studies did not analyze how structural changes in the hippocampus alter HPA axis activity, it can be hypothesised that relevant changes in this region would both be impacted by and modify the neurophysiological stress reaction.

While there is no conclusive evidence that mindfulness may target hippocampal atrophy in AD and offset HPA-axis dysregulation, Wells, Yeh et al. (2013) reported a non-significant trend (p = 0.07) towards less hippocampal atrophy in 8 MCI participants (Mean Age = 73.00) following an MBSR intervention in comparison to 5 wait-list control group participants with MCI (Mean Age = 75.00). Throughout the study, wait-list control group participants received treatment as usual. Considering the findings, it is plausible that

mindfulness-based interventions could regulate stress responses and modify atrophy seen in AD. More specifically, in beginner meditators it may reduce grey matter deterioration of hippocampi whereas long-term meditation practice may offset the trajectory of hippocampi atrophy in atypical cognitive decline. To examine these hypotheses, future studies could evaluate how mindfulness-based programs alter structural integrity in the hippocampus in MCI and AD participants and how this may relate to cortisol levels. Comparing mindfulness-based programs to active treatments may add further validity and insight into the effectiveness of mindfulness in this context.

Directions for Future Research

The previous sections have outlined distinct neurocognitive pathways by which mindfulness practice could impact the stress process linked with dementia. First, we discussed the potential of mindfulness in targeting early cognitive processes of stress, such as cognitive appraisal. By modifying stress reactivity, attention, and coping resources allocated to threatening stimuli, mindfulness practice may promote a more adaptive appraisal of stressors and thus offset subsequent neurophysiological response. Initial research suggests that these mechanisms, altered by mindfulness practice, result in less perceived stress (Dobkin, 2008; Martins, 2014) and reduced HPA axis release of cortisol (Tang et al., 2007; Witek-Janusek et al. 2008).

Other avenues of stress-related changes that were considered include: parasympathetic responses, neural regulation of the amygdala, and modifications in brain inhibitory regions. By enhancing parasympathetic axis activity, mindfulness practice may down-regulate the sympathetic activation of the adrenal cortex (Ditto et al., 2006; Ulrich-Lai & Engeland, 2005), a region responsible for cortisol discharge (Smeets, 2010). With regards to amygdalae regulation, mindfulness training may encourage a top-down or bottom-up regulation of the amygdalae, a key region in stress response pathways detecting threat (Gard et al., 2012;

Modinos et al., 2010). Finally, we discussed the effects of neuroplasticity changes in the hippocampus, a brain region responsible for glucocorticoid negative feedback (Frodl & O'Kean, 2013), following mindfulness-based interventions (Hölzel et al., 2011; Wells, Yeh et al., 2013).

In total, we posit that mindfulness may mitigate the risk-enhancing effects of stress in dementia by affecting these interacting cognitive and neurophysiological pathways. However, few studies have examined how specifically mindfulness training impacts the stress processes in ageing and the progression of dementia. Investigations integrating neuroimaging research with genetic, cognitive, behavioral, and self-report assessments may render insights into the promising potential of mindfulness training in dementia prevention. Assessments that can track how mindfulness could influence both the predisposition to dementia or early changes noted in dementia onset may help conclusively determine whether mindfulness can be effective in reducing the incidence of dementia.

Multi-method neuroscientific research in this context could benefit from utilizing imaging techniques such as Event-Related Potentials (ERPs), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), in conjunction with genetic testing. For example, ERPs such as the N400 (Olichney et al., 2008) can detect early changes linked with a high likelihood of progressing onto dementia (Taylor & Olichney, 2007). The N400, a negative occurring component with a maximum peak around 400 ms, is considered an index of semantic processing or recognition memory (Kutas & Federmeier, 2000; Kutas & Fdedermeier, 2011). Interestingly, abnormalities of the N400 in 32 MCI participants (Mean Age = 74.80) were associated with an increased risk of developing AD within three years (Olichney et al., 2008).

More closely related to stress-related processes, DTI allows for the measurement of white matter structure (Mori &Tounier, 2014), which may be sensitive to glucocorticoid exposure changes (Cox et al., 2015; van der Werff et al., 2014). DTI could be used to track

white mater changes associated with ageing (Head et al., 2004), mild cognitive impairment (Medina et al., 2006), and dementia (Naggara et al., 2006). It is distinguished for its ability to detect early markers of AD (Stricker et al., 2013), which could be a superior predictor, as compared to volume reductions, to AD progression (Fellgiebel et al., 2006; Kehoe, McNulty, Mullins & Bokde, 2014; Nir et al., 2012). Research on mindfulness-based practices, has documented increases in Fractional Anisotropy (a measure of white matter microstructures; Alexander, Lee, Lazar, & Field, 2007) in the anterior corona radiata, corpus callosum, and superior corona radiata following an IBMT training in comparison to a relaxation training for 45 healthy undergraduate students (mean age = 20.58; Tang, Lu, Fan, Yang, & Posner, 2012). Based on this evidence it could be suggested that mindfulness may impact white matter integrity in regions typically affected by dementia.

Another promising neuroimaging technique is Proton Magnetic Resonance Spectroscopy (¹H-MRS), which allows for the non-invasive measurement of neurometabolite concentration in the brain, including choline (Cho), creatine (Cr), myo-Inositol (mI), Glutamate (Glu), gamma-Aminobutryric acid (GABA) and N-Acetyl Aspartate (NAA; Bertholdo, Warcharakorn, & Castillo, 2013; Kehoe et al., 2014). It can track changes in neurometabolites, particularly increased mI and reduced NAA, that may signal early neural changes caused by dementia (Kantarci et al., 2007). While we have limited understanding of the association between neurometabolic modifications in stress, research has documented reduced NAA levels in the bilateral hippocampus and ACC in persons with PTSD (Mean Age = 28.90) in comparison to healthy young adults (Mean Age = 27.70) (Ham et al., 2007). Given that NAA is a potential marker of neuron density (Soares & Law, 2009) and integrity (Rhodes, 2017), the findings could indicate potential neural loss in the hippocampus and ACC due to the negative effects of chronic levels of stress and cortisol (Campbell & MacQueen, 2004; Sapolsky , 2015). Indeed, research has found decreased gray matter volume in the ACC (Yamasue et al., 2003) and hippocampus (Villareal et al., 2002) for persons with PTSD in comparison to healthy controls. Other investigations using ¹H-MRS have also documented reduced NAA/Cho levels in the left and right hippocampus for individuals, aged 18 to 65, undergoing corticosteroid therapy (Brown et al., 2004). Interestingly, Brown et al. (2004) reported reduced volume of the right and left hippocampus for individuals undergoing corticosteroid therapy in comparison to a matched control group. However, no correlation was found between NAA/Cho levels and reduced volume of the hippocampus in this study.

In the context of dementia, reduced levels of NAA in the bilateral hippocampus (Foy et al., 2011) for persons with AD has found. In addition, a study has shown a link between reduced NAA concentration in the hippocampus and reduced hippocampal volume in AD (Dixon, Bradley, Budge, Styles, & Smith, 2002). Although no study has specifically investigated the impact of stress on NAA and the progression of dementia, it could be hypothesised that increased levels of stress may influence the neural changes seen in AD, such as hippocampal atrophy. Due to neural loss in the hippocampus in AD, NAA levels may also decline in this region.

Research examining the effects of stress on mI, a neural marker that is potentially associated with glial proliferation (Soares & Law, 2009), is limited. However, one study has documented no changes in levels of mI in the PCC and bilateral hippocampus following a 4-day exposure to cortisol in healthy young males (Mean Age = 24.50) (Scheel, Ströhle, & Bruhn, 2010). Converse to these findings, Seedat, Videen, Kennedy, and Stein (2005) reported increased mI/Cr levels in the ACC in woman diagnosed with PTSD. Therefore, it could be theorised that the impact of stress on mI may be dependent on the level of perceived stress, with chronic stress associated with increases in mI levels.

The finding of increased mI levels, in response to stress, could have potential implications for neuroinflammation (Rosen & Lekinski, 2007) given that glial proliferation

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may occur in neuroinflammation (Burda & Sofroniew, 2014; Rosen & Lekinski, 2007). Interestingly, research has indicated that an overexposure to cortisol may increase the proinflammatory activity of microglial (Pearson-Leary, Osborne, & McNay, 2016), which could lead to neuroinflammation in regions such as the hippocampus (Sorrels, Caso, Munhoz, & Sapolsky, 2009; Sorrells, Munhoz, Manley, Yen, & Sapolsky, 2014). As such, it could be hypothesized that neuroinflammation of the hippocampus is potentially associated with increases in mI levels. However, further research is necessary to provide support for this theory.

In relation to AD, Pirrainen et al. (2017) suggested that the pro-inflammatory activity of the microglial, caused by stress, may contribute to the build-up of β -amyloid. Interestingly, Kantarci et al. (2011) reported an association between higher levels of mI/Cr in the Posterior Cingulate gyri and ¹¹C-Pittsburgh compound (PiB), a compound used to label amyloid plaques (Klunk et al., 2004), in cognitive normal older adults (Mean Age = 79.10). Longitudinal research with MCI participants has also indicated that increased levels of baseline Cerebrospinal fluid (CSF) β -amyloid predicted a marginally significant increase in mI/Cr levels in the PCC/precuneus at a 2 year and 4-year follow-up (Voevodskaya et al., 2016). Although no studies, to my knowledge, have investigated the link between mI levels, neuroinflamation, and amyloid plaques in AD, research has shown increased levels of mI/Cr have been found for persons with MCI and AD in the hippocampus (Wang, Zhou, & Li, 2009) and the PCC (Kantarci et al., 2002).

Other neurometabolites, including GABA (Gueli & Taibi, 2013; Riese et al., 2015) and Glu (Fayed, Modrego, Rojas-Salinas, & Aguilar, 2011). GABA, an inhibitory neurotransmitter (Stagg & Rotham, 2014), may restrict the HPA axis response to stress via the PVN neurons (Herman et al., 2005). GABAergic projections from the amygdala may also suppress GABA-inhibiting neurons on the PVN, thus stimulating the release of CRH. Glu, an excitatory neurotransmitter (Stagg & Rotham, 2014), may activate HPA axis via the neurons of the

paraventricular nucleus (PVN; Herman & Cullinan, 1997; Tasker & Dudek, 1991). Glu may also play a role in inhibition of the HPA axis response (Herman et al., 2005). Specifically, glutamatergic projections of the medial prefrontal cortex and hippocampus, may activate GABA neurons on the PVN of the hypothalamus. This may lead to an inhibition of the stressrelated release of CRH.

In regards to ¹H-MRS investigations of GABA and Glu, findings indicate that both neurometabolites may be modulated by stress (Hassler, van der Veen, Grillon, Drevets, & Shen, 2010; Rosso, Crowley, Silveri, Rauch, & Jensen, 2017). For example, Hasler et al. (2017) reported decreased prefrontal GABA levels in response to the threat of shock in comparison to a control condition in healthy adults, aged 19 to 49 years. Interestingly, the decreased levels of GABA correlated with higher levels of self-reported anxiety. Researchers of this study suggested that the increases in GABA may be a result of the down-regulation of GABA-inhibiting neurons in response to acute stressor. In contrast to this study, other research on acute stress has indicated no changes in Glu or GABA levels in the prefrontal cortex in response to a social stress test (Houtepen et al., 2017).

In PTSD, decreased GABA (Meyerhoff, Mon, Metzler, & Neylan, 2014) and increased Glu (Meyerhoff et al., 2014; Rosso et al., 2017) in comparison to trauma-exposed control participants has been reported in the temporal cortex and the hippocampus. This imbalance of GABA and Glu levels could potentially modulate the HPA-axis response to stressors in PTSD (Pitman et al., 2012). The increased levels of Glu, due to stress, may also have potential implications for neurodegenerative diseases, such as AD (Hynd, Scott, & Dodd, 2004; Mattson, 2008). In particular, excessive levels of Glu may lead to neural death associated with AD (Hynd, Scott, & Dodd, 2004; Mattson, 2008; Ogura, Miyamoto, & Kudo, 1988). However, studies examining the effects of stress on Glutamate and AD progression are limited. In relation

to AD, research has indicated decreased concentrations of GABA in the temporal cortex (Gueli & Taibi, 2013) and Glu in the PCC (Fayed, Modrego, Rojas-Salinas, & Aguilar, 2011).

Considering the potential links between neurometabolites and stress, ¹H-MRS may be an effective imaging tool to elucidate how mindfulness may affect the development of dementia by targeting neurophysiological stress processes. To date, no studies have investigated the impact of MBAs on ageing or dementia using ¹H-MRS. Future studies should consider employing ¹H-MRS, MRI, and cortisol measures to examine the impact of an MBA on the aforementioned neurometabolites (Glu, GABA, NAA, and mI), hippocampal structure, and cortisol levels.

Research using ERPs, DTI, and MRS in the mindfulness intervention context could be particularly powerful if combined with, genetic testing for the APOE ϵ 4 marker. This marker is considered a strong genetic risk predictor for AD (Corder et al., 1993; Reinvang, Espeseth, & Westlye, 2013). A meta-analysis on APOE ϵ 4 found that 48.70% of those diagnosed with AD have one APOE ϵ 4 allele at minimum (Ward et al., 2012). While there is no consensus on the global prevalence of APOE ϵ 4 allele (Farrer et al., 1997; Singh, Singh, and Mastanna, 2006), it is suspected that the risk of AD increases to approximately 91.30% in homozygous ϵ 4 carriers (Corder et al., 1993). Those with APOE ϵ 4 may display more atrophy in regions affected by dementia (Crivello et al., 2010) and greater cognitive decline (Scheipers et al., 2012) – making it intriguing to track how mindfulness could modify dementia onset in those at higher risk.

Conclusion

In sum, research on mindfulness in the context of dementia prevention is still in its infancy. Although preliminary evidence on the benefits of mindfulness amongst healthy adults is promising, methodologically rigorous studies are required to elucidate how mindfulness impacts on the stress pathways in ageing and how this may potentially offset the development of dementia. This review has proposed a neurocognitive model highlighting the pathways by which mindfulness affects the stress process increasing dementia risk. We hope that this review will stimulate future integrative multi-method neuroscientific investigations in this area.

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Chapter 5

The Effects of a Mindfulness-Based Stress Reduction (MBSR) Course on Well-Being, Perceived Stress, and Neurometabolite Markers of Dementia and Ageing

Abstract

Mindfulness-based interventions (MBIs) have been proposed as potential interventions for promoting well-being and preventing neurocognitive decline in ageing and age-related diseases, such as Alzheimer's Disease (AD). However, limited studies have investigated the impact of an MBI course on neurometabolites in typically ageing older adults. This pseudorandomised pilot investigation (N = 23) aimed to examine the effects of a Mindfulness-Based Stress (MBSR) course on well-being, stress, and neurometabolites in the Posterior Cingulate Cortex (PCC) and the Anterior Cingulate Cortex (ACC) in typically ageing older adults, aged 60 and above. In particular, this study intended to investigate the feasibility of using Proton Magnetic Resonance Spectroscopy (¹H-MRS) longitudinally (before and after the MBSR course) and the acceptability of the MBSR course in this cohort. Feasibility of this study was assessed by participants' tolerance to complete the MRS scans at two time-points (Pre-Testing, Post-Testing) and quality of the acquired spectra data. A secondary aim of this study was to conduct a power analysis on effect sizes reported in this study. To this end, this study investigated the effects of an MBSR course on neurometabolites modulated in ageing and AD. Finally, this study aimed to examine the psychological effects, measured through self-reports of perceived stress, mindfulness, and well-being, of an MBSR course. Results indicated that the MBSR course was well-tolerated; participants reported high satisfaction and adherence to course practice. The use ¹H-MRS was also considered an acceptable method to measure neurochemical changes following an MBSR course in the PCC. However, findings indicated data from the ACC voxel was of poorer quality. While no significant changes in the concentration of neurometabolites was reported, a trend towards increases in myo-Inositol (mI) and decreases in Creatine (Cr) in the PCC were documented for the training group. Using effect sizes from analyses of mI and Cr, a sample size of 101.13 is recommended to achieve a power of 95%. No significant changes in self-reports of perceived stress and trait mindfulness were found, but significant improvements in well-being from pre-testing to post-testing was found for the training group.

Introduction

From a developmental perspective, typical ageing is associated with declines in executive function abilities (Buckner, 2004; Hedden & Gabrieli, 2004; Zelazo, Craik, & Booth, 2004) and memory processes including working memory (Buckner, 2004; Smith et al., 2001). At a neural level, these declines may be accompanied by volume reductions in the prefrontal cortex (Raz et al., 2004), decreases in the connectivity of default-mode network (DMN; Damoiseaux et al., 2008; Hafkemeijer, van der Grond, & Rombouts, 2012), and reduced volume of the hippocampus (Driscoll et al., 2003; Raz et al., 2005). In age-related degenerative diseases, such as Alzheimer's Disease (AD), similar neurocognitive changes have been documented (Buckner, 2004). However, these declines are more progressive in AD in comparison to typically ageing older adults (Fox, Cousensm Scahill, Harvey & Rossor, 2000).

Considering the negative effects of ageing and the more severe detrimental implications of age-related diseases such as AD, a growing body of research has begun to explore interventions that may be utilised to delay the onset of these declines and possibly prevent associated diseases (Reichman, Fiocca, & Rose, 2010; Solomon et al., 2014). One approach that has been identified, based on initial evidence (Larouche et al., 2015, Wells et al., 2013; Wong, Hassed, Chambers, & Coles, 2016), involves mindfulness-based interventions (MBIs). The concept and practices of mindfulness are rooted in Buddhist philosophy (Dorjee, 2010; Hanh, 1998; Grossman & Van Dam, 2011), yet there is limited agreement on a definition of mindfulness for research and practice. In the secular Western context, mindfulness is often characterised as an awareness resulting from self-regulation of attention, with an accepting and non-judgmental attitude, towards experiences in the present moment (Baer, 2003; Kabat-Zinn, 2003; Shapiro, Carlson, Astin, & Freedman, 2006). This conceptualization of mindfulness has been secularised and integrated into clinical interventions including Mindfulness-Based Stress

Reduction (MBSR; Kabat-Zinn, 1990) and Mindfulness-Based Cognitive Therapy (MBCT; Segal, Williams, & Teasdale, 2002).

While a relatively large body of evidence has documented moderate effects of MBSR and MBCT in young to middle-aged adults on anxiety and depression (Hofman, Sawyer, & Oh, 2010; Khoury, Sharma, Rush, & Fournier, 2015, Goyal et al., 2014), studies investigating the impact of MBIs in an ageing cohort are limited. However, initial research with older adults indicated that MBI training may impact well-being (Greiger et al., 2016) and risk factors (Splevins et al., 2009; Young & Baime, 2010) associated with age-related decline and AD, such as perceived stress (Peavy et al., 2012). Moreover, some studies have documented positive effects of MBIs on cognitive functions (Berk, van Oxtel, van Os, 2016) and neural substrates (Wells et al., 2013; Smart, Segalowitz, Mulligan, Koudys, Gawryluk, 2016; Malinowski, Moore, Mead, & Gruber, 2017) affected by ageing and AD. For example, a large randomised control trials on MBIs has reported improvements of executive function (Moynihan et al., 2013) for healthy older adults. In addition, smaller scale RCTs have documented increases in overall brain volume (Smart et al., 2016) for older adults with subjective cognitive decline, and increases in the connectivity of the DMN for Mild Cognitive Impairment (MCI) patients (Wells et al., 2013) following a MBI. While these findings are promising, more longitudinal multimethod research utilising imaging with older adults is necessary to examine the effectiveness and underlying mechanisms of MBIs as preventive tools.

In this context, Proton Magnetic Resonance Spectroscopy (¹H-MRS) may be a valuable method to track neurochemical changes resulting from MBIs. ¹H-MRS is a non-invasive imaging modality that quantifies the concentration of neurometabolites, such as Creatine, N-Acetyl-Aspartate, myo-Inositol, Glutamate, and gamma-Aminobutryric acid (Rae, 2014; Soares & Law, 2009). Creatine (Cr) is often used as a reference metabolite as it has been suggested to remain stable across pathologies (Condon, 2011). However, some studies have

indicated increases in Cr levels in parietal areas and frontal regions, such as the Anterior Cingulate Cortex (ACC), in healthy normal ageing (Chiu et al., 2014) (Haga, Khor, Farrall, & Wardlaw, 2009). N-Acetyl-Aspartate (NAA) is associated with cell neuronal viability (Soares & Law, 2009); and has been reported to decline in frontal brain regions with healthy ageing (Haga et al., 2009) and in grey matter in AD (Adalsteinsson, Sullivan, Kleinhans, Spielman, & Pferfferbaum, 2000). However, these changes in NAA may also be a result of changes in T2 Relaxation, reducing the visibility of NAA in normal MRS studies. Myo-Inositol (mI) often described as a marker of glial proliferation (Rosen & Lenkinski, 2007), has been reported to increase in the Posterior Cingulate Cortex (PCC) in AD (Kantarci et al., 2002). Glial proliferation refers to the increase in reactive glial cells, including astrocytes and microglia (Norton, Aquino, Hozumi, Chiu & Brosnan, 1992; Serrano-Pozo et al., 2013). Proliferation occurs as part of the reactive gliosis process in response to a brain injury (Burda & Sofroniew, 2014). In acute injuries, glial proliferation may be beneficial in repairing tissue damage (Burda & Sofroniew, 2014), and in early AD, reactive glial may play a role in clearing β -amyloid in early AD (Prokop, Miller, & Heppner, 2013). However, in the late stage of AD, an increase in reactive glial may promote neuroinflammation (Burda & Sofroniew, 2014; Neuroinflammation Working Group et al., 2000) and neural decline (Serrano-Pozo et al., 2013). Moreover, reactive glial may also be associated with β -amyloid buildup in the late stage of AD. For example, a post-mortem study on AD indicated that astrocytes, located in the enthorhinal cortex, showed increased levels of β-amyloid (1-42) (Nagel, & D'Andrea, Lee, Venkataraman, & Wang, 2003). In ageing, an increase in reactive glial (Hayakawa, Kato, & Araki, 2007; Lynch et al., 2010), accompanied by potential neuroinflammation (Lynch et al., 2010, Nije et al., 2010) may also be seen. Chronic stress may also promote reactive gliosis (Jauregi-Huerta et al., 2010; Nair & Bonneau, 2006), which may lead to neuroinflammation through the release of proinflammatory cytokines (Ricci, Ippoliti, & Businaro, 2011; Yirmiya & Goshen, 2010).

Interestingly, research with rats has reported an increase in reactive microglia in the hippocampus following restraint and water immersion (Sugama, Fujita, Hashimoto, & Conto, 2007). Considering this finding, researchers have postulated that stress-related increases in reactive microglia may impact the progression of neurodegeneration in diseases, such as AD (Sugama, 2009). However, few studies have specifically examined the link between stress-induced reactive gliosis and AD. Glutamate (Glu) is an excitatory neurotransmitter (Zhang et al., 2014) that is reduced in the PCC in AD (Fayed, Modrego, Rojas-Salinas, & Aguilar, 2011) and in a cognitively healthy ageing cohort (Suri et al., 2017). Gama-aminobutyric acid (GABA) is an inhibitory neurotransmitter (Zhang et al., 2014) that shows declines in frontal and parietal regions in healthy ageing (Gao et al., 2014), the PCC in MCI (Riese et al., 2015), and the temporal cortex in AD (Gueli & Taibi, 2013).

Cross-sectional research on Zen meditation has suggested that mindfulness-based training and practices may impact neurometabolites in the PCC and left thalamus (Fayed et al., 2013). More specifically, Fayed et al (2013) reported increased mI in the posterior cingulate gyrus and decreased NAA, Glu, and NAA/Cr ratio in the left thalamus for experienced meditators in comparison to healthy control participants. However, no studies, to our knowledge, have so far explored how MBIs may impact neurometabolite markers in relation to ageing and AD in older adults. Furthermore, few studies investigated how MBIs may affect well-being and risk factors in ageing, such as high levels of perceived stress, that are associated with an increased risk of developing AD (Peavy et al., 2012).

Consequently, this study aimed to pilot the use of MRS to examine the effect of an MBSR course on neurometabolites (NAA, mI, GABA, Glu, and Cr) in the PCC and the ACC in a typically ageing older adult population. The PCC is a common region examined in ¹H-MRS studies of AD (Kantarci, 2013) because it may show metabolic changes in early in AD (Minoshima et al., 1997), and ageing (Reyngoudt et al., 2012). Similar to the PCC, the ACC

may display age-related declines in neural activity (Pardo e al., 2007) and reductions in grey matter volume (Good et al., 2001). While limited ¹H-MRS studies have investigated the ACC in the context of ageing, initial research has indicated a positive link between increased age and concentration of Cho and Cr in the ACC (Chiu et al., 2014). For the current study, we predicted that NAA, GABA, and Glu levels would increase in the PCC and ACC following an MBSR course for the training group in comparison to a wait-list control (WLC) group, thus indicating MBSR training may reverse or prevent neurometabolite changes seen in ageing and AD. Given that Cr is considered a reference metabolite, no changes were predicted for Cr levels in the PCC and ACC. Finally, it was predicted that mI concentration in the PCC and ACC will decline following the MBSR course in the training group in comparison to the wait-list control group, indexing reduced glial proliferation following a MBSR course. In addition, it was hypothesized that for the training group following the MBSR course self-reports of perceived stress would show decreased scores, and self-reported well-being would increase as suggested by previous research on MBSR with adult populations. Given that this investigation was a pilot, primary objectives of this study were to examine the acceptability of the MBSR course and feasibility of using repeated MRS scans to assess the effects of MBSR in typically ageing older adults. Feasibility of this study considered the tolerance of participants' tolerance to undergo the ¹H-MRS scans at two time-points (Pre-Testing, Post-Testing) and the quality of spectra data. Spectra data was considered to be of a useable quality if the Signal to Noise Ratio (SNR) was above 20 and the Cramer-Rao Lower Bound (CRLB) percentage of the spectra was below 25. This also study aimed to conduct a power analysis to recommend sample sizes for future larger scale research using ¹H-MRS to examine the effects of MBIs on neurometabolites in ageing.

Methods

Ethics

This study received ethical approval by Bangor University School of Psychology Ethics Committee before data collection (See Appendix D). All participants provided informed consent before testing commenced. Prior to each testing session, the procedures were explained to the participants in a written information sheet and verbally. Participants were paid £10 towards travel expenses for each testing session, and offered a free MBSR course. Upon completion of the study, participants were debriefed.

Participants

Participants were recruited as part of a larger study (N = 49) which involved assessments using Event-Related Potentials (ERPs), magnetic resonance imaging (MRI), diffusion tensor functional MRI, heart-rate variability (HRV) imaging (DTI), measures, and neuropsychological assessments collected at two time points (pre-testing and post-testing) and questionnaires collected at 3 time points (pre-testing, post-testing, and at a 3-month followup). Thirty typically ageing older adult participants (9 males), aged 60 to 83 (M = 68.67, SD =6.99) were recruited by email advertisements to Bangor Psychology Research Panel, Bangor University Staff, and local community groups. Printed advertisements in common public places in Bangor, word of mouth, and Facebook/Twitter were also used for recruitment. From pretesting to post-testing, there was a 23.33% attrition rate - 7 (3 training group, 4 WLC group) participants withdrew (3 prior to pre-testing, 1 at the pre-testing session, and 3 after pre-testing) from the study. Therefore, results are reported from a sample of 23 participants (7 males), aged 60 to 83 (M = 67.65, SD = 6.71). Number of years in education varied across the sample with participants reporting 10 to 22 years in education (M = 15.52, SD = 3.22). See Table 5.1 for demographic characteristics at baseline.

All participants were pre-screened to ensure that they met inclusion criteria including 1) aged 60 and above, 2) no experience of formal mindfulness training, 3) normal or corrected to normal vison, 4) normal or corrected to normal hearing, 5) no experience of neurological conditions (i.e., stroke or seizures), 6) fluency in English, 7) no regular usage of painkillers, and 7) no MRI contraindications. Due to the design of the study, it was not possible to control for medication usage. List of medications regularly used by participants can be found in Appendix E. All participants scored within the normal range on the Mini-Mental Status (MMSE)-2 Standard Version, all total scores > 24 (Folstein, Folstein, White, & Messer, 2010; Tombaugh & MxIntyre, 1992).

As part of the larger study (involving ERP, heart rate variability measurements, questionnaires, and neuropsychological assessments), participants were pseudo-randomised into two groups (training group or wait-list control group) using Research Randomizer (Urbanaiak & Plous, 2015). Participants were matched (one to one) on age and number of years in education before randomisation. In addition, participants were matched before randomisation on their interest and/or ability to complete imaging measures to aim for an equal distribution of participants in both groups of this study Participants who identified themselves as partners were matched together to ensure that they were allocated to the same group. Following pseudo-randomisation, one extra participant in each group (Training group and WLC group) from the larger study, expressed interest in imaging measures, and therefore are included in the overall analyses of the 23 participants.

Between groups, no differences were noted for age, t(21) = 0.15, p = .881, number of years in education, t(21) = 0.49, p = .632, number of languages spoken fluently, t(21) = -0.95, p = .353, gender, $\chi^2(1, N = 23) = 0.77$, p = .382 and handiness, $\chi^2(2, N = 23) = 3.47$, p = .177. Finally, no differences were noted for MMSE scores at pre-testing, t(21) = 0.27, p = .790.
Table 5.1.

Demographic Characteristics at Baseline

| | MBSR Group | WLC Group |
|---|------------------|------------------|
| | (<i>N</i> = 10) | (<i>N</i> = 13) |
| Females, N (%) | 6 (60.00%) | 10 (76.90%) |
| Age (M years $\pm SD$) | 67.90 ± 7.61 | 67.46 ± 6.24 |
| Education (M years $\pm SD$) | 15.90 ± 2.42 | 15.23 ± 3.79 |
| Number of Languages Spoken (M years $\pm SD$) | 1.10 ± 0.32 | 1.31 ± 0.63 |
| Right Handiness, $N(\%)$ | 8 (80.00%) | 12 (92.30%) |
| Involvement in Group-Based Activities (%) | 70.00% | 92.3% |
| Involvement in Mental Training Activities (%) | 60.00% | 69.20% |
| Involvement in Stress-Reducing Activities (%) | 30.00% | 23.10% |

Mindfulness-Based Intervention

A standardised 8-week Mindfulness-Based Stress Reduction (MBSR) Course (Kabat-Zinn, 1990) was delivered by a teacher from the Centre for Mindfulness Research and Practice (CMRP) at Bangor University. The course met weekly for 2.5 hours each week, and focused on reducing stress and developing adaptive coping strategies (Baer, 2003; Kabat-Zinn, 1990). At each session, the teacher guided participants through practices, such as a body scan or mindful movement. Following the practices, participants completed guided discussions in which they considered thoughts, feelings, and sensations that arose during the practices. As part of the course, participants were encouraged to complete 45 minutes of daily mindfulness practice for six days of the week. CDs with guided meditations were provided each week to aid home practice. Each participant received a course workbook that detailed examples of practices for each week. In addition to weekly sessions, participants were invited to an orientation session before the start of the course and an optional full-day practice. The orientation session provided participants an opportunity to meet the course instructor and other group members, learn the aims and structure of the course, and ask questions prior to the course commencement. The full-day practice was offered after week 5 of the MBSR course. This 6-hour practice in participant silence aimed to deepen mindfulness skills and involved practices guided by the mindfulness teacher.

Imaging Parameters

All images were acquired using a 3T Phillips Achieva MRI System. A 5 echo T₁weighted image (slice thickness = 0.7 mm; TR/TE = 18/(3.5,5.1,6.7,8.5,10.1) milliseconds (ms), effective TE = 6.8 ms; FOV = $224 \times 224 \times 175$ mm; flip angle = 8°) in the sagittal plane was collected to act as an anatomical reference image to localize the single voxel in the PCC and ACC for ¹H-MRS acquisition, and to allow segmentation for partial volume correction of the ¹H-MRS spectra collected. ¹H-MRS data for GABA and Glu were collected utilising Mescher-Garwood Point-Resolved Spectroscopy (MEGA-PRESS) in a single voxel of the PCC (voxel size = 25 x 25 x 25 mm; TR/TE = 2000/68 ms; samples= 2048; shim voxel size = $30 \times 30 \times 30$ mm) and the ACC (voxel size = $25 \times 25 \times 25$ mm; TR/TE = 2000/68 ms; samples= 2048; shim voxel size = $30 \times 30 \times 30$ mm). For all other metabolites, the EDIT-OFF spectra from the MEGA-PRESS acquisition were analysed as a single voxel PRESS acquisition. Water suppression was achieved using a CHESS water suppression scheme. The voxel of interest (VOI) in the ACC and PCC was identified by using the Corpus Callosum as a neural landmark. All spectra were analysed with TARQUIN 4.3.10 (Wilson, Reynolds, Kauppinen, Arvanitis, & Peet, 2010), using the ¹H NAA, Cr, Cho, Lip option for internal referencing for preprocessing. Partial volume correction was employed to control for grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) concentration in the VOI as described by Gasparovic et al.(2006), with the relaxation time parameters adjusted for 3T (See Table 5.2).

Table 5.2.

| | Glu | GABA | NNA | Cho | Cr | MI | Water | Water | CSF |
|------------|------|------|------|------|------|------|-------|-------|------|
| | | | | | | | (GM) | (WM) | |
| T 1 | 1220 | 131 | 1403 | 1182 | 1320 | 1102 | 1488 | 781 | 4000 |
| T_2 | 169 | 88 | 247 | 254 | 160 | 200 | 71 | 58 | 200 |

Mean Literature Relaxation Values for Metabolites and Water

Notes. Values displayed are in milliseconds (ms).

Self-Report Questionnaires and Neuropsychological Assessment

Cognitive and Affective Mindfulness Scale-Revised (CAMS-R).

The CAMS-R (Feldman, Hayes, Kumar, Greeson, & Laurenceau, 2007) is a 12-item questionnaire that indexes trait mindfulness through four sub-scales including attention, present focus, awareness, and acceptance. Each sub-scale is measured using 3 statements that are rated on a 4-point Likert Scale (1 = Rarely/Not at all, 4 = Almost Always). Total mindfulness scores are calculated by summing all questions. Total scores can range from 12 to 48, with higher scores indicating greater trait mindfulness. This scale has been effectively utilized as pre-post measure (Greeson et al., 2011) with adults aged 18 and above. For the purpose of this study, only total mindfulness scores were analyzed. Cronbach alphas at pretesting ($\alpha = .76$) and post-testing ($\alpha = .80$) indicated good reliability of this measure.

Perceived Stress Scale (PSS).

The PSS (Cohen, Karmarck, & Mermelstein, 1983) is a 14-item questionnaire that assesses perceived stress experienced over a month. Each question is answered using a five-point Likert Scale (0 = Never, 4= Very Often). Scores range from 0 to 56, with higher scores reflecting greater levels of perceived stress. This measure has been effectively employed to index changes in perceived stress following MBSR for adults, aged 19 to 68 years (Carmody

& Baer, 2008). Cronbach alphas at pre-testing ($\alpha = .83$) and post-testing ($\alpha = .85$) suggested good reliability of this measure.

Warwick Edinburgh Mental Well-Being Scale (WEMWBS).

WEMWBS (Tennant et al., 2007) is a 14-item scale measuring mental well-being. Each item is rated on how best the statements describe a personal experience in the last 2-weeks using a five-point Likert-Scale (1 = none of the time, 5 = all of the time). Scores can range from 14 to 70; with higher scores implying higher levels of mental well-being. WEMWBS has been successfully used to assess pre-post changes in well-being in a longitudinal mindfulness intervention study with school teachers (Beshai, McSlpine, Weare, & Kuyken, 2015). Cronbach alphas at pre-testing (α = .91) and post-testing (α = .92) indicated good reliability of this measure.

Mini-Mental Status Examination (MMSE)-2.

The MMSE-2 (Folstein et al., 2010) is a valid and reliable assessment (Tombaugh & McIntyre, 1992) used to measure general cognitive functioning. It involves questions that index cognitive skills including: recall, registration, attention, calculation, language, and orientation to time and place (Folstein et al., 2010; Sheehan, 2012). Lower scores on the MMSE indicate possible cognitive impairment (Folstein et al., 2010; Tombaugh & McIntyre, 1992). The MMSE has been successful employed to measure longitudinal changes in cognitive function before and after a cognitive stimulation program for persons with dementia (Spector et al., 2003).

Acceptability Measure and Course Attendance.

To assess course satisfaction, an acceptability measure was employed. This measure was developed for a previous study involving a mindfulness training program in schools for adolescents (Sanger & Dorjee, 2016). It indexed the frequency of home practice using a 4-point Likert Scale (1 = Never, 4 = Every Day). In addition, course satisfaction was indexed with a 7

point Likert-Scale (1 = Not At All, 7 = Very Much). Participants were also asked whether they would continue with mindfulness practice. Participants' attendance of the course was recorded using a course register by the mindfulness teacher.

Procedure

Participants completed imaging measures at the Bangor University Brain Imaging Unit in Bangor, Wales before and after the MBSR course. The socio-demographic form, questionnaires, MMSE-2 (Folstein et al., 2010), and an acceptability measure were collected in a separate quiet lab space in the university. The socio-demographic form, questionnaires, and the MMSE-2 (Folstein et al., 2010) were completed at pre-testing and post-testing by all participants. At the post-testing session, training group participants completed the acceptability measure indicating their satisfaction with the MBSR course, amount of home practice, and willingness to partake in another MBSR course. Two different versions of the MMSE-2 (Folstein et al., 2010), coded as red and blue for the study, were administered at pre-testing and post-testing to control for practice effects. Regular medication usage was assessed with a brief question on the socio-demographic form at the 3-month follow-up.

Statistical Analysis

A mixed-factorial 2 (Group: Training Group, WLC Group) x 2 (Time: Pre, Post) ANOVA was employed to investigate the effects of the MBSR course on the concentration of neurometabolites (GABA, Glu, mI, Cr, NAA) and self-reports of mindfulness, perceived stress, and well-being. If the assumption of sphercitiy was not met, Greenhouse-Geisser was used. To replace missing data, multiple imputation analyses were conducted. Independent t-tests were conducted on pre-testing data to determine significant baseline differences. If baseline differences were noted, independent t-tests on difference scores (post-pre) and an ANCOVA (covariate = pre-testing scores) were performed. For significant interactions, follow-up paired sample t-tests were used. Given that this investigation was a pilot study, exploratory correlational analyses were conducted to provide insights into how the acceptability of the course may potentially influence neurometabolite measures in the PCC and self-report measures (e.g. trait mindfulness, perceived stress, and well-being). In particular, Pearson correlations were conducted to index the association between acceptability measures (e.g. course satisfaction and amount of home practice) and difference scores of all other measures. Outliers over three interquartile range from the mean were windsorised and included in the analysis. All analyses reported were twotailed.

Results

Self-Report Findings

Please refer to Table 5.3 for a summary of the means and standard deviations for each questionnaire. Figures 5.1 presents line graphs with group means for each questionnaire at pre-, post-, and follow-up testing. In all figures, 95% confidence intervals are shown.

Baseline Characteristics

In relation to normative data on trait mindfulness, previous research on university students (N = 212; $M_{age} = 18.74$) reported a mean value of 34.11 for total trait mindfulness scores measured through the CAMS-R (Feldman et al., 2007). In this study, the means of self-reported trait mindfulness at pre-testing for the WLC group (M = 35.80) and MBSR Group (M = 34.09) were similar to this norm. Normative data from a probability sample (N = 2, 387), aged 18 and above, in the United States indicated that the mean total for perceived levels of stress on the PSS-14 was 19.62 (Cohen & Williamson, 1988). Moreover, the mean total for perceived levels of stress on the PSS-14 declined with age. Specifically, the mean for adults, aged 55 to 64 was 18.30, and older adults, aged 65 and above, reported a mean of 18.50. In this study, the mean baseline levels of perceived stress were slightly higher for both the MBSR group (M = 19.70) and WLC Group (M = 21.31) in comparison to the reported norms. For

levels of self-reported well-being, as indexed by the WEMWBS, a large population-based study (N = 8011) in England reported a mean well-being score of 49.90 for adults, aged 16 and above (Morris, Earl, & NatCen Social Research, 2017). At baseline, mean levels of self-reported well-being were comparable to this published normed for the MBSR group (M = 49.90). However, the WLC group reported higher levels of self-reported well-being (M = 54.00) in comparison to the normative data on well-being.

Course Practice and Acceptability.

All training group participants, included in the analyses, attended at least 6 of the 8 MBSR sessions. Participants reported good adherence to daily practices outside of the MBSR course - 60% reported practicing mindfulness every day, 30% reported practicing mindfulness often, and only 10% reported practicing mindfulness rarely. Moreover, participants indicated high satisfaction with the MBSR Course (Mean Satisfaction Rating = 91.43%, Mean Likert Scale = 6.4 out of 7). In addition, 70% of the training group participants stated that they would carry on doing mindfulness and the remaining 30% stated that they may carry on doing mindfulness.

CAMS-R.

No significant between group differences were found at baseline for total mindfulness, t(21) = -0.29, p = .775, d = 0.12. No significant main effect of time, F(1, 21) = 1.18, p = .289, $\eta^2 = .05$ or group, F(1, 21) = .02, p = .903, $\eta^2 = .00$ was found. No significant interaction between time and group, F(1, 21) = 1.13, p = .300, $\eta^2 = .05$, was reported.

PSS.

No significant between-group differences were reported at baseline for perceived stress, t(21) = -0.62, p = .542, d = 0.25. No significant main effect of time, F(1, 21) = 3.01, p = .097, $\eta^2 = .12$, or group, $F(1, 21) = 1.25, p = .277, \eta^2 = .06$ was seen. In addition, no significant interaction between time and group, $F(1, 21) = 0.63, p = .437, \eta^2 = .03$, was found.

WEMWBS.

No significant between-group differences were found at baseline for well-being scores, t(21) = -1.27, p = .217, d = 0.53. No significant main effect of time, F(1, 21) = 1.62, p = .216, $\eta^2 = .04$ or group, F(1, 21) = 0.00, p = .958, $\eta^2 = .00$, was found. A significant interaction between time and group, F(1, 21) = 15.96, p = .001, $\eta^2 = .41$, with a large effect size, was reported. Paired-samples t-tests indicated a significant increase in self-reports of well-being for the training group, with a moderate effect size, t(9) = -3.41, p = .008, d = 0.68. No differences, with a small effect size, were noted for the WLC group, t(12) = 2.11, p = .057, d = 0.37.



Figure 5.1. Mean scores of A) Total Mindfulness, as measured by the CAMS-R, B)
Perceived Stress, as measured by the PSS, and C) Well-Being as measured by the
WEMWBS, at pre- and post-testing for Training Group and WLC Group. Error bars depicted in all graphs indicate 95% Confidence Intervals.

Table 5.3.

| | MBSR Group | WLC Group |
|-------------|------------------|------------------|
| | <i>N</i> = 10 | <i>N</i> = 13 |
| Pre- MMSE | 28.40 ± 1.17 | 28.23 ± 1.69 |
| Post- MMSE | 27.90 ± 1.10 | 27.77 ± 0.36 |
| Pre-CAMS | 34.09 ± 3.95 | 34.69 ± 5.56 |
| Post-CAMS | 35.80 ± 4.37 | 34.71 ± 5.69 |
| Pre-PSS | 19.70 ± 7.84 | 21.31 ± 4.55 |
| Post-PSS | 16.40 ± 5.99 | 20.08 ± 7.15 |
| Pre-WEMWBS | 49.90 ± 8.66 | 54.00 ± 6.81 |
| Post-WEMWBS | 55.10 ± 6.54 | 51.32 ± 7.60 |

Means and Standard Deviations $(M \pm SD)$ *of Self-Report Measures*

Magnetic Resonance Spectroscopy (¹H-MRS)

Imaging measures including the T1 weighted anatomical scan and MRS spectra acquisition were tolerated well by participants. Most spectra collected in the PCC were of usable quality, with an SNR above 20 and Cramer-Rao Lower Bound (CRLB) percentage below 25. Figure 5.2 displays an example of a MEGA-PRESS and PRESS Spectrum fit from Tarquin 4.3.10 program. However, data from one participant showed a low SNR for GABA measurements at pre-testing and a CRLB value above 25% at post-testing for Glu and mI. As such, data analyses for GABA, Glu, and mI were conducted and reported without this participant. See Table 5.5 for a summary of means and standard deviations of neurometabolite concentrations for the PCC. Figure 5.3 displays line graphs of mean neurometabolite levels for each group and time-point.

Approximately, 34.78% of the ACC spectra data (8 participants in total; 4 in the MBSR and 4 in WLC Group) were confounded with low SNR and/or high CRLB percentages across pre- and post-testing, thus indicating that the data was not of good usable quality. As such, means and standard deviations of ACC neurometabolite concentrations were calculated without confounded data, and are reported in Table 5.4. However, mixed factorial ANOVAs indicated no significant time x group interactions for neurometabolites (Glu, GABA, NAA, mI, Cr) in the ACC, all ps > .05.

Means and Standard Deviations of ACC Metabolite Concentration

| | MBSR Group | WLC Group |
|---------------------------|---------------------|----------------------|
| Pre-Glu, $N (M \pm SD)$ | $6(5.86 \pm 0.48)$ | 11 (6.39 ± 1.21) |
| Post-Glu, $N (M \pm SD)$ | $6 (6.17 \pm 0.58)$ | 11 (6.25 ± 1.08) |
| Pre-GABA, $N(M \pm SD)$ | 7 (2.99 ± 0.28) | $11 (2.97 \pm 0.50)$ |
| Post-GABA, $N (M \pm SD)$ | 7 (3.21 ± 0.47) | $11 (2.93 \pm 0.40)$ |
| Pre-NAA, $N(M \pm SD)$ | 7 (8.76 ± 0.19) | 11 (8.71 ± 0.72) |
| Post-NAA, $N(M \pm SD)$ | 7 (8.80 ± 0.29) | 11 (9.08 ± 0.99) |
| Pre-mI, $N (M \pm SD)$ | $6(3.47 \pm 0.69)$ | $10(3.82 \pm 0.98)$ |
| Post-mI, $N (M \pm SD)$ | $6(3.49 \pm 0.54)$ | 10 (4.04 ± 1.46) |
| Pre-Cr, $N (M \pm SD)$ | 7 (11.11 ± 0.73) | 11 (10.88 ± 1.04) |
| Post-Cr, $N(M \pm SD)$ | 7 (11.96 ± 1.00) | 11 (11.15 ± 1.35) |

Table 5.4.



Figure 5.2. PRESS (A) and MEGA-PRESS (B) Spectrum Fit of the PCC from Tarquin

Program.

B

Baseline Characteristics

In terms of ¹H-MRS, there is a lack of normative data on the concentrations of neurometabolites globally throughout the brain (Kantarci et al., 2013), and more specifically in the voxels of interest in this study (PCC and ACC). This may be due to a lack of standarised acquisition procedures used in ¹H-MRS studies (Kantarci et al., 2013). Therefore, baseline characteristics were compared to studies, with a similar acquisition methodology, on healthy younger adults. Given that data from the ACC was confounded with low SNR and/or high CRLB percentages, only mean values of the PCC will be considered. In an ¹H-MRS investigation with healthy adults (N = 13), aged 18-41, the mean concentration value for NAA in the PCC was 12.40 mM (Rusiak, 2016). This study also reported the mean concentration values of Cr (M = 11.90), Glu (M = 19.50), and mI (M = 6.70) for the healthy adult population. In the present study, the mean concentration value of NAA at pre-testing for the MBSR group (M = 10.44) and WLC group (M = 10.63) was lower than the aforementioned study. At pre-testing, means for Cr concentration levels were lower for both the MBSR Group (M = 9.17) and the WLC Group (M = 8.62). Mean concentration levels of Glu were also lower for both the MBSR Group (M = 4.95) and the WLC Group (M = 5.66) at pre-testing. In addition, mean concentration levels of mI were similar for the MBSR Group (M = 6.10) and higher for the WLC Group (M = 8.25) in comparison to unpublished data with healthy adults (Rusiak, 2016). In a separate ¹H-MRS investigation with healthy young adults (N = 19), aged 20-27, the mean concentration value of GABA in the PCC was 1.11 mM (Rusiak, 2016). In the present study, the mean concentration values of GABA were higher for both the MBSR (M = 2.83) and WLC group (M = 2.86).

Posterior Cingulate Cortex (PCC)

Glutamate (Glu).

A significant between-group difference was documented at baseline for Glu, t(20) = -2.99, p = .007, d = 1.29. Therefore, an ANCOVA and an independent t-test of difference scores (post-pre) were conducted to control for baseline differences. No significant effect of group was seen at post-testing, after controlling for concentrations of Glu at pre-testing, in the ANCOVA, F(1, 19) = 0.12, p = .730, partial $\eta^2 = .00$. In addition, no significant difference was noted for Glu difference scores between groups in the t-test, t(20) = 0.55, p = .591, d = 0.24.

Gama-aminobutyric acid (GABA).

No significant between-group difference was documented at baseline for GABA, t(20) = -0.23, p = .821, d = 0.10. No significant effect of time, F(1, 20) = 0.85, p = .368, $\eta^2 = .06$ or group, F(1, 20) = 0.06, p = .811, $\eta^2 = .00$, was reported. There was also no significant interaction between time and group, F(1, 20) = 0.70, p = .412, $\eta^2 = .05$.

N-Acetyl-Aspartate (NAA).

No significant between-group differences were noted at baseline for NAA, t(11.49) = -0.51, p = .621, d = 0.22. No significant effect of time, F(1, 21) = 0.15, p = .904, $\eta^2 = .00$, or group, F(1, 21) = 0.42, p = .523, $\eta^2 = .02$, was reported. In addition, no significant interaction between time and group was found, F(1, 21) = 0.04, p = .854, $\eta^2 = .00$.

myo-Inositol (mI).

A significant between-group difference was documented at baseline for mI, t(15.70) = -3.59, p = .002, d = 1.44. Therefore, an ANCOVA and an independent t-test of difference scores (pre-post) were conducted to control for baseline differences. No significant effect of Group was seen at post-testing, after controlling for mI concentrations at pre-testing, in the ANCOVA, F(19) = 0.31, p = .585, partial $\eta^2 = .02$. However, a marginally significant difference, with a large effect size, was noted for mI difference scores between groups in the t-test, t(20) = 1.88,

p = .074, d = 0.82. Means indicated that the training group had large difference scores (postpre) in comparison to the control group.

Creatine (Cr)

No significant between-group difference was documented at baseline for Cr, t(1, 21) = 1.15, p = .264, d = 0.51. No significant effect of time, F(1, 21) = 0.29, p = .597, $\eta^2 = .01$, or group, F(1, 21) = 0.02, p = .891, $\eta^2 = .00$ was reported. However, a significant interaction between time and group, with a large effect size, was found, F(1, 21) = 6.41, p = .019, $\eta^2 = .23$. Paired-sample t-tests indicated a marginally significant decrease in Cr levels at pre and post for the training group, with a moderate effect size, t(9) = 1.91, p = .089, d = 0.58. Furthermore, a marginally significant increase, with a moderate effect size, was seen for the WLC group, t(12) = -1.98, p = .072, d = 0.57.



Figure 5.3. Mean concentration levels of A) Glu, B) GABA, C) NAA, D) mI, and E) Cr in the Posterior Cingulate Cortex (PCC) measured at pre-testing and post-testing for the

Training Group and WLC Group. Error bars depicted in all graphs indicate 95% Confidence Intervals.

Table 5.5.

| Means and Standard Deviations of PCC | C Metabolite Concentration |
|--------------------------------------|----------------------------|
|--------------------------------------|----------------------------|

| | MBSR Group | WLC Group |
|--------------------------|-----------------------|-----------------------|
| Pre-Glu, $N(M \pm SD)$ | 9 (4.95 ± 0.56) | 13 (5.66 ± 0.54) |
| Post-Glu, $N(M \pm SD)$ | 9 (4.90 ± 0.86) | 13 (5.37 ± 1.14) |
| Pre-GABA, $N(M \pm SD)$ | 9 (2.83 ± 0.42) | 13 (2.86 ± 0.30) |
| Post-GABA, $N(M \pm SD)$ | 9 (2.82 ± 0.46) | 13 (2.72 ± 0.27) |
| Pre-NAA, $N(M \pm SD)$ | 10 (10.44 ± 1.06) | 13 (10.63 ± 0.90) |
| Post-NAA, $N(M \pm SD)$ | $10(10.39 \pm 01.07)$ | $13 (10.70 \pm 0.91)$ |
| Pre-mI, $N (M \pm SD)$ | 9 (6.10 ± 0.68) | 13 (8.25 ± 2.00) |
| Post-mI, $N(M \pm SD)$ | 9 (8.63 ± 2.12) | 13 (8.69 ± 1.35) |
| Pre-Cr, $N(M \pm SD)$ | $10 (9.17 \pm 0.75)$ | 13 (8.62 ± 1.34) |
| Post-Cr, $N(M \pm SD)$ | $10 (8.70 \pm 0.91)$ | 13 (9.35 ± 1.21) |

Home Practice and Course Satisfaction Correlation Analyses

No significant correlation between course satisfaction was found with change scores for self-report measures of perceived stress, well-being, and mindfulness, all ps > .05. In addition, no significant correlation was documented between course satisfaction and change scores of NAA, GAA, Glu, Cr, and mI in the PCC, all ps > .05. In regards to home practice, no significant correlation was seen between home practice and change scores for self-report measures of perceived stress, well-being, and mindfulness, all ps > .05. Moreover, no significant correlation was found for home practice and change scores of NAA, GABA, mI, and Cr in the PCC, all ps > .05. However, a significant positive correlation was documented between amount of home practice and changes in Glu concentration of the PCC, r(9) = .782, p = .013.

Power Analysis

To determine sample sizes for future longitudinal research involving ¹H-MRS of the PCC and MBIs with older adults, a power analysis was conducted using G*Power software (Faul, Erdelfer, Buchner, & Lang, 2009). Power at an 80% and 95% level was calculated using means and standard deviations from follow-up paired sample t-tests that indicated non-significant trends for changes in Cr for the training group and WLC group, and from the independent t-test indicating an approaching significant difference in mI. Recommended sample sizes from the power calculation at each level of power (80% and 95%) were then averaged across effects for mI and Cr. To account for attrition in this longitudinal study, we added 23.33% to the recommended sample size. As such, the sample size with a power of 80% for Cr was 65 (approximately 33 participants in each group) and 104 (52 participants in each group) for a 95% power level. The sample size with a power of 80% for mI was 60 (30 participants in each group) and 99 (approximately 50 participants in each group) for an 95% power level. In total, the average recommended sample size for a power of 80% is 63 participants and a power of 95% is 101.

Discussion

The results of this study indicated high acceptability of the standard MBSR course for typically ageing older adults. Moreover, this pilot study has shown that MRS measures using the PCC and ACC as the area of interest are a well-tolerated imaging approach for older adults, and that most spectra data was of usable quality in the PCC. However, caution should be taken when using the ACC as an area of interest, considering our findings of poorer quality data

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collected in the ACC. Findings also indicated improvements in self-reported well-being, with a medium effect size, for the training group following the MBSR course. Contrary to predictions, no effects of MBSR training were seen for self-reports of perceived stress and mindfulness. However, these findings of null results are similar to a small pilot study (Wells et al., 2013) that documented no significant changes in perceived stress and mindfulness following an MBSR course in comparison to treatment as usual for an overall sample of 14 MCI patients. In addition, a large RCT documented no significant changes in perceived stress following an MBSR course in comparison to a relaxation and reading intervention for healthy older adults (Mallya & Fiocco, 2015).

Altogether the findings suggested that an MBSR course is an acceptable and possibly effective method to improve well-being in typically ageing older adults. This finding is particularly interesting considering that high levels of mental well-being may play an important protective role in physical health of ageing adults (Ostir, Markides, Peek, & Goodwin, 2001; Steptoe, Deaton, Stone, 2015). Indeed, previous longitudinal research has suggested that well-being, measured as positive affect, was associated with a decreased risk of stroke in older adults (Ostir et al., 2001. In addition, a longitudinal study with adults, aged 52 to 79, reported that increased mental well-being, measured through ecological momentary assessments on positive affect collected across an average of 5 years, may predict a lower mortality risk (Steptoe & Wardle, 2011). Therefore, the current finding on improvements in well-being for the training group following the MBSR course, could indicate that MBIs may be a useful in preventing physical decline by modulating mental well-being levels in older adults. However, further research would be necessary to determine the link between mindfulness practice, mental-well-being and physical health. Moreover, given the null results on self-reports of mindfulness and perceived stress, a question remains on how MBIs may improve well-being.

MRS results indicated no significant changes in neurometabolite concentrations in the ACC following the MBSR course. This finding may be due to the poor quality of data collected in the ACC voxel and thus removal of confounded data. As such, these results must be considered with caution. It could be hypothesised that data quality in the ACC was compromised due to volumetric changes, including white matter hyperintensities, seen in frontal lobe regions during ageing. Indeed, previous research has found declines in grey matter volume in the ACC as ageing occurs (Good et al., 2001; Mann et al., 2012). Moreover, a large population-based study (N = 1077) found a positive association between ageing and white matter lesions, with the frontal lobe showing the greatest amount of lesions (de Leeuw et al., 2001). The use of a larger voxel to improve SNR in the ACC may therefore be warranted for future studies, and while this will be at the expense of inclusion of adjacent regions that may not be of interest, this trade-off would be worth it to achieve more reliable results. Our results do indicate however that neurometabolite assessments in the ACC is problematic in ageing, and so care is needed if it is decided to use MRS measures from the ACC as indicators of the effects of MBI and other psychological interventions on neurochemistry.

While no significant effects of the MBSR course on neurometabolites were found in the PCC, marginally significant changes in mI and Cr were seen with medium-large effect sizes. In particular, difference scores for mI, with a large effect size, indicated a trend for increases in mI in the PCC for the training group. Similarly, follow-up analyses on Cr in the PCC showed increases in Cr levels for the WLC group and decreases for the training group that were approaching significance with medium effect sizes. While no previous research has investigated the impact of MBIs on neurometabolites in ageing, the finding of increased mI in the PCC is consistent with previous cross-sectional research involving Zen meditators (Fayed et al., 2013). The non-significant trend of increases in Cr indicate that MBSR could possibly positively affect neurometabolite markers linked with ageing (Haga et al., 2009). Specifically, previous research has suggested that increases in Cr levels may be associated with an increase of glial proliferation in ageing (Reyngoudt et al., 2012, Suri et al., 2017). As such the finding declines of Cr in the MBSR group and increases of Cr in the WLC group, may suggest that MBSR training protects against age-related proliferation. However, the trend of increases seen for mI, a marker of glial proliferation (Rosen & Lenkinski, 2007), for the MBSR group contradicts this theory.

Correlational analyses indicated no association between course satisfaction and difference scores (post-pre) of all measures (questionnaires and neurometabolite levels in the PCC). Also, no correlation between the amount of home practice and difference scores on questionnaire measures was found. Interestingly, a positive association between difference scores in Glu and amount of home practice for the training group was identified. This finding could suggest, although not seen in this study, significant changes in glutamate may be detected if a larger sample, practicing mindfulness more frequently, was included. In particular, it could be theorised that practicing mindfulness more frequently may be associated with increases in Glu in the PCC. Given that reduced levels of Glu have been found for ageing (Suri et al., 2017) and AD (Fayed et al., 2011), it could be suggested that practicing mindfulness more frequently may offset age-related declines in Glu in the PCC. However, further research would be necessary to confirm this. To further examine this correlation, exploratory analyses were conducted to investigate differences in Glu levels amongst those who practiced every day and those who practiced often or less. Paired-sample t-tests indicated no changes from pre-post for Glu levels for both practices groups. As such, this correlation may be a spurious finding. Finally, no correlation was found for the amount of home practice and differences scores of other neurometabolites.

The discrepancy in the findings of mI and Cr, and the lack of effect seen for perceived stress, NAA, and self-reported mindfulness may be due to the limited sample size in this study. Indeed, the power analysis conducted indicated that approximately 63 participants would be required to obtain an effect at an 80% power level. Furthermore, in this study, it was not possible to control for medication usage at pre- and post-testing. Moreover, regular medication usage was only measured at a 3-month follow-up for participants. As such, it could be that regular medication usage impacted neurometabolite levels at pre- and post-testing; however, limited studies have reported the specific impact of medication on neurometabolite measurements.

Another limitation of this study is the lack of active control group. Previous research with older adults has indicated that cognitively stimulating interventions may have a positive impact on cognitive functions and neural regions impacted by ageing and AD (Ball et al., 2002; Boyke, Driemeyer, Gaser, Büchel, & May, 2008; Lustig, Shah, Seidler, Reuter-Lorenz, 2009). As such, it could be argued that the trends of changes in neurometabolite levels reported in this study were not specific to mindfulness training, but were due to engaging in a cognitively stimulating activity. Indeed, we found no correlation between the amount of home practice, course satisfaction, and changes in mI and Cr.

It could also be postulated that improvements in well-being were due to the social elements of the group-based MBSR course. Indeed, empirical evidence has revealed a link between social contacts and well-being (Pinquart & Sörensen, 2000). Given that no changes in self-reports of mindfulness were documented, the question remains as to whether mindfulness is the key element evoking neural and psychological changes in older adults undertaking MBIs. As previously argued (Dorjee, 2016), it seems important not to equate the effects of MBIs with the effects of mindfulness practice as such.

Another limitation of this study that should be considered in relation to the findings of this study is the lack of payment required to complete the MBSR course by the participants. It could be argued that participants may have decreased motivation to adhere to the MBSR course in comparison to participants who may pay to join a course. Motivation plays a key role in psychological interventions, such as mindfulness practice. For example, Kabat-Zinn (2011) stressed that participants should be motivated to complete mindfulness practice in order to alleviate possible suffering. Indeed, a longitudinal randomised controlled trial (Seear & Vella-Brodrick, 2013) on positive psychology interventions, such as best possible selves intervention, found that high levels of self-reported retrospective motivation was associated with an increased frequency to practice according to the intervention. Moreover, increased motivation was associated with improvements in well-being for the training group participants.

In the current study, motivation was not specifically measured. However, participants did report on their adherence to course practice outside of the weekly-led course at post-testing. Results indicated good adherence to the course practice; 70% of course participants indicated that they practiced every day, and only 10% stated that they practiced rarely. Moreover, all participants attended 6 out of the 8 sessions. While these findings could suggest that participants had a high motivation to complete the MBSR course, future studies should employ a specific measure on the participants' motivation to complete the course.

An additional limitation of this study that should be considered is the absence of followup ¹H-MRS measurements. It could be that the positive neural impact of mindfulness is delayed (and/or requires more mindfulness practice), hence follow-up investigations might reveal significant changes in neurometabolite concentrations. Interestingly, a longitudinal study on a mindfulness-based intervention offered in school for children, aged 7-11, reported reductions in negative affect and improvements in metacognition at follow-up as opposed to post-testing (Vickery & Dorjee, 2015). While this study is weakly linked to the current investigation due to the sample characteristics, it does highlight the need for follow-up investigations in intervention research. Follow-up investigations could also show whether trends of changes in neurometabolite levels are sustained following the MBSR intervention, increased, or simply returned to baseline. Finally, while most participants were tested as close as possible to each other, there were some instances in which participants' testing session were rescheduled due to unforeseen circumstances. As such, results may be confounded due to differences in times of testing sessions.

While this pilot study did indicate that the standard MBSR course and the use of MRS imaging measures of the PCC are acceptable for a typically ageing older adult cohort, future research should consider and address limitations of this study. Specifically, further research utilising MRS measures should consider using a randomised controlled design with three arms including a mindfulness-based intervention, active control group, and wait-list control group. The active control intervention should be similar in duration to the MBSR course, group-based, and involve cognitively stimulating activities. A potential intervention that could be used as an active control condition is the Health Enhancement Program (HEP; MacCoon et al., 2011). The HEP course is similar in length to an MBSR course, and involves group-based classes and daily homework. HEP is designed to promote physical health and well-being (MacCoon et al., 2011). It incorporates physical activity, music therapy, imagery, and nutrition-based counselling. An initial validation study has indicated that the HEP course can be effectively employed as an active control condition for an MBSR course (MacCoon et al., 2012). Further research should also increase the sample size to ensure adequate power to detect effects in the study. A sample size of 63 (approximately 32 in each group) participants been recommended based on power calculations at 80% level in the current study.

Future studies should also incorporate follow-up imaging and questionnaire testing sessions - ideally at 3- months, 6 months, and 1 year. This may provide insights into the

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sustainability of initial effects on well-being and trends in neurometabolite changes due to an MBSR intervention. Moreover, such research may indicate whether longer term mindfulness practice may result in significant changes in neurometabolite markers, levels of perceived stress, and self-reports of mindfulness which might be non-significant at post-test.

Another interesting avenue for future research to investigate is the effect of an MBSR course with highly stressed ageing individuals. Although no effects were noted on perceived stress in this study, this might be due to ceiling effects. Thus, it could be hypothesised that an MBSR course is most effective for those who experience high levels of stress. Interestingly, previous research with older adults, aged 65 and above, who experienced cognitive impairments and clinically significant anxiety-related distress, reported significant improvements in cognitive assessments of memory and self-reports of trait mindfulness on the CAMS-R (Lenze et al., 2014).

In the current study, the baseline characteristics of the participant sample indicated that mean levels of self-reports of stress were slightly higher than published norms. Moreover, in the current study, stress scores ranged from 14.00 to 28.00 at pre-testing, and 8.00 to 31.00 at post-testing for the WLC group. Considering the baseline characteristics and ranges for the PSS-14 in the current study, it could be suggested that a portion of the participant sample in this study did experience mild to high levels of perceived stress. Thus, it could be argued that no true ceiling effect was seen in this study. Nevertheless, it may be worthwhile for future investigations to specifically include only individuals with high baseline levels of perceived stress in police constables suggested using a cut-off score of 28 or greater to indicate high levels of perceived stress (Walvekar, Ambekar, & Devaranavadagi, 2015). As such, future investigations on MBSR for highly stressed older adults should consider employing a similar cut-off value for the PSS-14 as an inclusion criteria.

Alternative methods to measure stress could also be utilised, such as experience sampling and real-time data collection of electrodermal activity, a measure associated with sympathetic system activity (Critchley, 2002), throughout the study to index changes in stress levels. Finally, to specifically address the argument of MBIs as preventive tools for AD, it is necessary to recruit individuals with subjective cognitive decline (SCD), MCI, and AD. It could be postulated that MBSR did not result in the expected changes in neurometabolite markers because there was little room for improvement amongst typically ageing older adults; in older adults with significant neurocognitive declines, an MBSR course may be more effective in impacting neurometabolites.

Conclusion

In conclusion, this pilot study provided tentative evidence that a standardised MBSR course is an acceptable intervention for improving well-being in typically ageing older adults, aged 60 to 83 years, and showed that collection of useable MRS measures pre-and post training is feasible. While no significant changes in neurometabolite concentrations were documented in this study, the non-significant trends of changes in neurometabolites (mI and Cr) in the PCC with medium to large effect sizes suggest that MBSR may lead to changes in neural markers associated with ageing and AD, and we have calculated the cohort sizes that should be used to investigate this further. Future research utilising these findings to design a study with a larger, more appropriately powered, sample size and including active control group would be necessary to truly identify neuro-metabolite changes in the PCC resulting from MBSR training.

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Chapter 6

The Impact of a Mindfulness-Based Stress Reduction (MBSR) Course on Well-Being and Event-Related Potential (ERP) Measures of Memory Processes

Abstract

In a pseudo-randomised longitudinal study with wait-list controlled design, the effects of a Mindfulness-Based Stress Reduction (MBSR) course on semantic/episodic memory processes and self-reports of mental health were examined in typically ageing older adults (N = 35), aged 60 to 82 years. Specifically, this study investigated modulations in two Event-Related Potential (ERP) components, the N400 and the P600, indexing memory processes from pre- to post-test. The self-report questionnaires examined changes in mindfulness, stress, depression, anxiety, well-being, personality factors, and cognitive emotion regulation strategies from before (pretesting) to after (post-testing, 3-month follow-up testing) MBSR. ERP data was acquired in a repetitive semantic categorization task. Contrary to predictions, no significant changes were documented for behavioural responses and ERP components. However, significant improvements in self-reports of well-being, and significant reductions in stress, depression, and neuroticism were reported for the training group after the MBSR course. Levels of course enjoyment correlated with increases in well-being and reductions in stress. Altogether, the findings of this study suggested that MBSR may have limited effects on measures of memory processes, as indexed by the N400 and P600 components, even though it may enhance selfreports of mental health in typically ageing older adults.

Introduction

Synapse loss (Reddy & Beal, 2008) in the prefrontal cortex (Raz, 2003; Terry et al., 1991) and hippocampus (Masliah et al., 1994) may underlie cognitive decline in ageing and Alzheimer's Disease (AD). Indeed, a longitudinal study indicated that synapse loss in the dentate gyrus correlated with reduced scores on the Mini-Mental Status Examination (MMSE) and neuropsychological tests on delayed recall (Scheff, Price, Schmitt, & Mufson, 2006) in older adults with no cognitive impairment (NCI), mild cognitive impairment (MCI) and AD. Scheff, Price, Schmitt, Scheff, and Mufson (2011) similarly found links between synapse loss in the inferior temporal gyrus and reduced scores on neuropsychological tests in older adults with NCI, MCI, and AD.

Event-Related Potentials (ERPs), a non-invasive measure of brain responses to stimuli, such as words, sounds, or pictures (Luck, 2005; Olichney, Yanh, Taylor, & Kutas, 2013), may provide a particularly useful index of cognitive changes seen in typical ageing and AD given its sensitivity to synaptic potentials. Indeed, researchers have suggested that ERPs allow for a precise and rapid detection of neural activity linked to memory processes (Olichney et al., 2013). In the context of ageing and age-related diseases, ERP components including the N400 and P600 have been identified as possible biomarkers of MCI and AD (Olichney et al., 2013).

The N400 is a brain wave that negatively peaks around 400 ms at central parietal sites (Kutas & Federmeier, 2011). An intracranial study has indicated that the anterior fusiform gyrus and the parahippocampal gyri are the neural substrates of the N400 (McCarthy, Nobre, Bentin, & Spencer, 1995). The N400 may index semantic processing, with a more negative N400 occurring when semantically incongruent items are presented (Kutas & Federmeier, 2011). In addition, the N400 is modulated by the repetition of items, and therefore may measure recognition memory (Friedman & Johnson, 2000; Kutas & Federmeier, 2011; Olichney et al., 2013).

In typical ageing, research has documented an attenuated N400 amplitude and increased latency of the N400 in a sentence processing task for older adults, aged 60-76 years in comparison to young adults, aged 18-24 years (Federmeier & Kutas, 2005). Iragui, Kutas, and Salmon (1996) also reported reduced N400 amplitude and longer latency for the N400 in healthy older adults, aged 62-81 years, in comparison to healthy young adults, aged 18-30 years. Moreover, in participants with AD, the N400 amplitude was further reduced and the latency delayed in comparison to older adults and young adults.

In repetitive semantic categorisation tasks, the N400 may be utilised to indicate the progression of cognitive decline. For example, Olichney et al. (2008) reported a less negative N400 amplitude to repeated incongruous items in comparison to new incongruous items in a repetitive semantic categorisation task for MCI participants who did not convert to AD (mean age = 71.10). However, in MCI patients who converted to AD (mean age = 75.20), no significant effect of repetition (old items versus new items) was seen for the N400 amplitude to incongruous items. Olichney et al. (2006) similarly found no effect of repetition (old items vs. new items) for the N400 amplitude to incongruous items in a repetitive semantic categorisation task for participants with mild AD (mean age = 79.40). Researchers of these studies suggested that the absence of the repetition effect (e.g. less negative N400 amplitude to repeated incongruous items) for the N400 amplitude could indicate impairments in semantic processing in cognitive decline.

The P600 is a positive occurring brain wave that peaks around 600 ms at central parietal sites (Coulson, King, & Kutas, 1998; Olichney et al., 2013). Intracranial investigations have suggested that the P600 may be linked with activation in the hippocampus (Fernández et al., 1995). The P600 is associated with memory encoding (Jackson & Snyder, 2008) and memory retrieval processing (Olichney et al., 2013). In healthy ageing older adults, research has indicated mixed findings on the P600 amplitude and latency. In particular, a study conducted

by Faustmann, Murdoch, Finnigan, and Copland (2007) indicated no changes in the P600 amplitude or latency to a semantic processing tasks for healthy ageing older adult, aged 60-79 years in comparison to middle-age adults, aged 52-59 years. However, Zhu, Hu, and Yhang (2018) reported increased latency of the P600 to a sentence reading task for healthy older adults, aged 56-79 years, in comparison to young adults, aged 18-27.

Similar to the N400 component, the P600 amplitude is sensitive to repetition; its amplitude reduces with repeated exposure to the same stimuli. However, the P600 has not been modulated by repetition in MCI and AD patients in repetitive semantic categorisation tasks (Olichney et al., 2008). Specifically, a 3-year longitudinal investigation documented no significant difference for the P600 amplitude to repeated congruous items in comparison to new items in a repetitive semantic categorisation task for MCI participants who converted to AD (mean age = 75.20). In non-converters (mean age = 71.10), the P600 amplitude was attenuated (less positive) to repeated congruous words. Interestingly, the P600 repetition effect (new congruous items-old congruous items) positively correlated with verbal memory, measured by the California Verbal Learning Test (CVLT). Similarly, Olichney et al. (2006) and Olichney et al. (2013) reported an absence of the P600 repetition effect (e.g. less positive P600 amplitude to repeated congruous items) for participants converting to AD (Olichney et al., 2013) or diagnosed with AD (Olichney et al., 2006). More specifically, both studies documented a larger P600 repetition effect to repeated congruous items in a repetitive semantic categorisation task for typically ageing older adults in comparison to participants who were converting to AD (mean age = 77.40) (Olichney et al., 2013) and were diagnosed with AD (mean age = 79.40) (Olichney et al., 2006). Olichney et al. (2013) suggested that the findings could indicate impairments in episodic or declarative memory processing.

Interestingly, Olichney et al. (2008) found that the absence of repetition effects on the N400 and P600 predicted an 87-88% likelihood of developing AD for MCI participants within

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3 years. As such, researchers have suggested that the P600 and N400 components could be sensitive to synaptic changes that may occur early in cognitive decline, and thus may be more useful measures of changes in AD as compared to volumetric changes of the brain (Olichney et al., 2008). However, future research is needed to examine methods that could modulate these biomarkers, and delay or prevent the onset of AD.

A potential mechanism that may play a key role in impacting these biomarkers by reducing synaptic dysfunction is chronic perceived stress. Stress can be defined as a threat that may impact the homeostasis and well-being of an individual (Ulrich-Lai & Herman, 2009). In response to stress, the Hypothalamic Pituitary Adrenocortical (HPA)- Axis is activated and releases cortisol. Cortisol helps to manage energy resources required for a stress response (de Kloet, Joëls, & Holsboer, 2005; Xiong & Zhang, 2013). While in low doses cortisol can have beneficial effects (Sapolksy, 2015), overexposure to cortisol can lead to neurodegeneration in the hippocampus and prefrontal cortex (Campbell & MacQueen, 2004; Frodl & O'Keane, 2013; Kremen et al., 2010; Sapolsky, Krey, &McEwan, 1986). Interestingly, research with rats has indicated synapse loss in the hippocampal CA3 area following corticosterone treatments (Tata, Marciano, & Anderson, 2006). While no research, to our knowledge, has specifically examined the effects of cortisol on synapse loss in humans, indirect research has documented an association between increased cortisol levels and hippocampal atrophy in older adults (Lupien et al., 1998).

Mindfulness-Based Interventions (MBIs) may be particularly effective in this context by attenuating stress-related pathways that possibly lead to synaptic dysfunction in ageing and AD. Indeed, empirical evidence has documented reductions in self-reports of stress measures following a Mindfulness-Based Stress Reduction (MBSR) intervention for clinical (Dobkin, 2008) and non-clinical adult populations (Shapiro, Astin, Bishop, & Cordova, 2005; Young & Baime, 2010). MBSR is an eight-week standarised course that develops mindful attention through weekly group meetings of 2.5 hours each and home-based practices (Kabat-Zinn, 1990). Moreover, declines in cortisol levels following an MBSR course have been reported for novice meditators (mean age = 40.20) (Brand, Holsboer-Trachsler, Naranjo, & Schmidt, 2012) and persons with breast and prostate cancer (mean age = 54.50) (Carlson, Speka, Faris, & Patel, 2007).

In addition, initial research with older adults (Lenze et al., 2014; Moynihan et al., 2013) and persons with MCI (Wells et al., 2013) has indicated that MBIs may modulate neurocognitive markers of ageing and AD. In particular, improvements in verbal memory, as measured by a paragraph recall task, have been reported after an MBSR course for older adults, aged 65 and above, who experienced self-reported anxiety and cognitive impairment (Lenze et al., 2014). Moynihan et al. (2013) also documented improvements in executive function, measured by the trail making Test A and B, for older adults, aged 65 and above, after an MBSR course in comparison to a wait-list control (WLC) group. From a neural perspective, Wells et al. (2013) found increases in the functional connectivity of the Default Mode Network (DMN) regions (Posterior Cingulate Cortex and Bilateral Medial Prefrontal Cortex; Posterior Cingulate Cortex and Left Hippocampus) following an MBSR course for persons with MCI (mean age = 73.00) in comparison to a treatment-as-usual group. The DMN, a network that is typically active at rest, shows reduced connectivity in healthy ageing (Damoiseaux et al., 2008), MCI (Wang et al., 2013), and AD (Greicius, Krasnow, Reiss, & Menon, 2004).

An ERP investigation of older adults, aged 65-80 years, with subjective cognitive decline reported increases in the P300 amplitude for a Go-NoGo task following an eight-week mindfulness training in comparison to five-week psychoeducation programme on memory and ageing (Smart, Seagalowitz, Mulligan, Koudys, & Gawryluck, 2016). The P300, a positive occurring component that peaks around 300 ms at frontoparietal sites (Johnson, 1993), may index attention allocation resources (Polich, 2007). Researchers of this study suggested that

their findings could indicate improvements of attention for persons with cognitive decline (Smart et al., 2016). Despite these promising findings, no research to date has examined the effects of MBIs on ERP biomarkers, such as N400 and P600, in an ageing population.

Therefore, this study aimed to investigate the effects of an eight-week standarised MBSR course on ERP markers including the N400 and the P600, that are associated with semantic memory and episodic memory processes, using a repetitive semantic categorization task in typically ageing older adults.

This study also aimed to examine possible psychological mechanisms, cultivated through mindfulness practice, that may impact the aforementioned ERP markers. Specifically, this study focused on how an MBSR course may modulate levels of stress, emotion regulation strategies, and personality traits. Previous research has indicated that MBIs may modulate emotion regulation strategies and personality factors, such as neuroticism and conscientiousness, that are associated in opposite directions with perceived stress (Ebstrup, Eplov, Pisinger, Jørgensen, 2011; Morrisson & O'Connor, 2005; Mroczek & Almedia, 2004). For example, a small randomized-pilot investigation found reductions in self-reports of neuroticism, a personality factor associated with perceived stress (Mrozcek & Almeida, 2004) for adults (mean age = 29.40) who completed a Mindfulness-Based Cognitive Therapy (MBCT) course in comparison to an active control group (mean age = 29.70) who completed an online self-help course (Armstrong & Rimes, 2016). MBCT is an MBI with similar structure to MBSR that includes element of Cognitive Behavioural Therapy (CBT; Segal, Williams, & Teasdale, 2002). Oken, Miller, Goodrich, and Wahbeh (2014) similarly documented reductions in neuroticism following a six-week adapted MBCT intervention for moderately stressed older adults, aged 50-85 years. In addition, significant decreases in difficulties of regulating emotions were reported for adults, aged 28-61 years, following an MBSR course in comparison to a WLC group, aged 28-71 years (Robins, Keng, Ekblad, & Brantley, 2011). Reductions in self reports of rumination, a maladaptive emotion regulation strategy (Nolen-Hoeksema, Wisco, & Lyubormirsky, 2008) that is associated with high levels of perceived stress (Morrison & O'Connor, 2005), were also found following an adapted MBSR course for university students, aged 18-61 years, in comparison to a control group (Jain et al., 2007).

Finally, this study aimed to examine the impact of an MBSR course on well-being of typically ageing older adults. A growing body of research has documented improvements in well-being following an MBI for older adults (Geiger et al., 2016). For example, Oken et al. (2017) documented improvements in a self-report measure of quality of life for stressed older adults, aged 50 to 75 years, following a six-week mindfulness meditation intervention.

It was predicted that the N400 and P600 would show enhanced repetition effects, as indexed by reduced amplitudes to repeated items, following an MBSR course for the training group in comparison to the WLC control group. This pattern of enhancement in the repetition effect could indicate that MBSR impacts ERP components linked with memory processes, including semantic and episodic memory, that decline in ageing (Burke, White, & Diaz, 1987; McDaniel, Einstein, & Jacoby, 2008) and AD (Dubois et al., 2010; Rogers, Ivanoui, Patterson, & Hodges, 2006). In addition, it was hypothesized that self-reported levels of stress, depression, anxiety, rumination, catastrophising, and neuroticism would decrease after the MBSR course for the training group in comparison to the control group. Conversely, it was postulated that increases in self-reports of positive reappraisal, acceptance, and well-being would be reported after the MBSR course for the training group in comparison to the wait-list control group.

Methods

Ethics

Ethics approval for the research study (See Appendix D) was obtained from Bangor University Psychology Ethics Committee prior to participant recruitment. Before data collection commenced, all study procedures were explained in a written and verbal form to the potential participants. All participants signed an informed consent, and upon completion of the study were debriefed. Participants received £10 to contribute towards travel expenses for each testing session. As part of the research study, training group participants were offered a free MBSR course. After completion of follow-up assessments, WLC group participants were offered to attend a free MBSR course.

Participants

Forty-nine typically ageing older adults (16 males), aged 60-83 years (M = 67.84, SD = 6.15), were recruited to complete an experimental task during which Event-Related Potentials (ERPs) were collected at two time points, pre-testing (before the intervention) and post-testing (after the intervention). Participants also completed questionnaires at 3 time points, pre-testing, post-testing, and at a 3-month follow-up. Participants were excluded if they reported 1) an age below 60, 2) an experience of formal mindfulness training, 3) a regular usage of medication that could impact performance on the experimental task, e.g. painkillers, and 4) an experience of neurological conditions (i.e., stroke or seizures). Participants were also pre-screened for self-reported 1) fluency in English, 2) normal or corrected to normal vison, and 3) normal or corrected to normal hearing.

Following recruitment, participants were pseudo-randomised into the training group or WLC group. First, participants were matched one to one on number of years in education and age. In addition, participants were matched on their eligibility and/or interest in completing neuroimaging as part of a separate study (Chapter 5). Partners were considered one participant

to make sure that they were allocated to the same group. After pairs were matched, each person in the pair was randomised, using a web-based programmed known as, Research Randomizer (Urbanaiak & Plous, 2015), into either the training group or WLC group.

From pre-testing to follow-up testing, six participants (5 training group, 1 WLC group) withdrew, and therefore were not included in data analysis. In addition, six participants' (2 training group, 4 WLC group) data were removed from analyses due to a high presence of EEG artifacts, and one participant's data from the training group was excluded due to low accuracy rate (< 75%) on the ERP task. Participants were also excluded post-hoc if the total score on the Mini-Mental Status Examination-2 (MMSE-2; Folstein, Folstein, White, & Messer, 2010) was below a normal range (Tombaugh & MxIntyre, 1992) of 24. Only one participant was excluded for this reason. Therefore, 35 (15 training group, 20 WLC group) typically ageing older adults (13 males), aged 60-82 years (M = 66.91, SD = 5.66) were included in the data analyses. See Table 6.1 for demographic characteristics at baseline.

Participants reported spending a varied number of years in education 10-25 years (*M* =15.89, SD = 3.31) No differences were reported between groups for age, t(33) = .28, p = .781, number of languages spoken, t(33) = 0.72, p = .478, and number of years in education, t(33) = -1.33, p = .194. In addition, no differences were noted between groups for handiness, $\chi^2(2, N = 35) = 3.85$, p = .146 and gender, $\chi^2(1, N = 35) = 0.09$, p = .762. No differences for MMSE-scores were reported at pre-testing, t(33) = -1.27, p = .213.

Table 6.1.

Demographic Characteristics at Baseline

| | MBSR Group | WLC Group |
|----------------------------|------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Females, $N(\%)$ | 9 (60.00%) | 13 (65.00%) |
| Age (M years $\pm SD$) | 66.60 ± 5.63 | 67.15 ± 5.82 |

Table 6.1 continued.

Demographic Characteristics at Baseline

| | MBSR Group | WLC Group |
|---|------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Education (M years $\pm SD$) | 16.73 ± 3.61 | 15.25 ± 3.01 |
| Number of Languages Spoken (M years $\pm SD$) | 1.13 ± 0.35 | 1.25 ± 0.55 |
| Right Handiness, N (%) | 11 (73.30%) | 18 (90.00%) |
| Involvement in Group-Based Activities (%) | 73.30% | 90.00% |
| Involvement in Mental Training Activities (%) | 26.70% | 40.00% |
| Involvement in Stress-Reducing Activities (%) | 66.70% | 70.00% |

Mindfulness-Based Intervention

A Mindfulness-Based Stress Reduction (MBSR) course designed by Kabat-Zinn (1990) was provided to participants at Bangor University by a mindfulness teacher who was trained by the Centre for Mindfulness Research and Practice (CMRP). A more detailed description of the course has been explained previously in Chapter 5.

Event-Related Potential (ERP) Recordings

EEG data was acquired using a 32 Ag/AgCI electrode cap (See Appendix B). To measure eye movements, two electrodes were placed above and below the right eye. The right mastoid served as the online reference, and FPz was the ground. During recording, all electrode impedance was kept below 7 kW. EEG data was sampled at the rate of 1 kHz using NeuroScan SynAmps, and bandpassed filtered at 0.01-200 Hz. Offline, all data was manually cleaned for motor movement, and then an alogorithm in NeuroScan Edit was applied to remove eye blinks. Data was filtered using a 0.1 Hz high pass filter and zero-shift low pass filter of 30 hz, 48 db/oct slopes. Data was epoched to 1100 ms epochs with 100 ms before the onset of the stimulus (e.g.

word) and 1000 ms after the onset of the stimulus (e.g. word). Data was baseline corrected using the pre-stimulus interval (100 ms) and averaged using correct trials only. In addition, data was re-referenced to the average mastoid. Grand averages were created by averaging ERPs for each participant and each condition.

Questionnaires and Neuropsychological Assessment

Cognitive and Affective Mindfulness Scale-Revised (CAMS-R).

The CAMS-R (Feldman, Hayes, Kumar, Greeson, & Laurenceau, 2007) questionnaire was utilised to index trait mindfulness. It consisted of 12 items that were rated on a four-point Likert Scale (1 = Rarely/Not at all, 4 = Almost always), and contained four sub-scales including attention, acceptance, awareness, and present focus. For this study, only total trait mindfulness scores were used. Total trait mindfulness scores can range from 12 to 48, with higher scores reflecting more trait mindfulness. Previous research with a pre-post design has effectively used this measure with adults, aged 18 and above (Greeson et al., 2011). Cronbach alphas at pretesting, post-testing, and follow-up testing indicated that this measure had good reliability (α = .68; α = .81; α = .80).

Perceived Stress Scale (PSS).

The PSS questionnaire (Cohen, Karmarck, & Mermelstein, 1983) was used to measure the experience of perceived stress over a month. The scale was composed of 14 items that were answered on a five-point Likert Scale (0 = Never, 4 = Very often). Scores can range from 0 to 56; a greater score on the PSS suggests higher level of perceived stress. Previous research with adults, aged 19-68 years, has effectively utilised this scale to assess changes in perceived stress following an MBSR course (Carmody & Baer, 2008). Cronbach alphas at pre-testing, posttesting, and follow-up testing indicated that this measure had good reliability ($\alpha = .87$; $\alpha = .86$; $\alpha = .92$).

Big Five Personality Inventory (BFI).

The BFI (John, Donahue, Kentle, 1991; Benet-Martinez & John, 1998; John, Naumann, & Soto, 2008) questionnaire was used to measure an individual's personality traits. The questionnaire is composed of 44 items with five sub-scales including extraversion, openness to experience, agreeableness, neuroticism, and conscientiousness. Participant rated statements on a five-point Likert Scale (1 = Disagree strongly, 5 = Agree strongly). Scores of neuroticism can range from 8 to 40, and scores of conscientiousness can range from 9 to 45. Higher scores on each sub-scale indicated a greater disposition to the personality trait. For the current study, only neuroticism and conscientiousness were examined, given their strong association with trait mindfulness (Giluk, 2009) and perceived stress (Ebstrup et al., 2010). The BFI has been effectively employed to index personality traits for adults, aged 21 to 60 years (Srivastava, John, Gosling, &Potter, 2003). Cronbach alphas indicated that this measure had good reliability at pre-testing, post-testing, and follow-up testing for neuroticism ($\alpha = .70$; $\alpha = .81$; $\alpha = .81$) and conscientiousness ($\alpha = .85$; $\alpha = .77$; $\alpha = .78$).

Depression Anxiety Stress Scale-21 (DASS-21)

The DASS-21 (Lovibond & Lovibond, 1995) questionnaire was employed to measure depression, anxiety, and stress experienced over a week. The scale was composed of 21 questions with three sub-scales including depression, anxiety, and stress. Each subscale consisted of seven items that were rated on four-point Likert Scale (0 = Did not apply to me at all, 3 = Applied to me very much or most of the time). Scores for each subscale can range from 0 to 42, with higher scores on each of the subscales indicating more severe depression, anxiety, and/or stress. DASS-21 has been effectively used to index changes in depression, stress, and anxiety for adults, aged 49 to 79 years, following a Mindfulness-Based Cognitive Therapy intervention (Splevins, Smith, & Simpson, 2009). Cronbach alphas indicated that this measure had moderate to good reliability at pre-testing, post-testing, and follow-up testing for the stress

subscale ($\alpha = .84$; $\alpha = .74$.; $\alpha = .83$), depression subscale ($\alpha = .93$; $\alpha = .90$; $\alpha = .91$), and anxiety subscale ($\alpha = .72$; $\alpha = .53$; $\alpha = .74$).

Warwick Edinburgh Mental Well-Being Scale (WEMWBS).

WEMWBS (Tennant et al., 2007) was used to index mental well-being experienced in the previous two weeks. The questionnaire was composed of 14 items, with each item answered on a five-point Likert Scale (1 = none of the time, 5 = all of the time). Scores on the WEMWBS can range from 14 to 70, with higher scores suggesting higher levels of self-reported mental well-being. Beshai, McAlpine, Weare, and Kuyken (2016) successfully utilised the WEMWBS to measure pre-post changes in well-being following a mindfulness intervention for school teachers. Cronbach alphas indicated good reliability at pre-testing, post-testing, and follow-up testing ($\alpha = .92$; $\alpha = .94$; $\alpha = .95$).

Cognitive Emotion Regulation Questionnaire (CERQ).

The CERQ (Garnefski, Kraaij, & Spinhoven, 2002) was utilised to index cognitive strategies employed to cope with stressful events. The questionnaire consisted of 36 items with nine sub-scales including self-blame, acceptance, rumination, positive refocusing, refocus on planning, positive reappraisal, putting into perspective, catastrophising, and other blame. Each sub-scale was composed of 4 items that were answered on a five-point Likert Scale (0 = Almost never, 5 = Almost always) Total scores for each subscale could range from 4 to 20, with higher scores on a sub-scale reflecting a greater usage of the emotion regulation strategy. For this study, adaptive emotion regulation strategies, including positive reappraisal and acceptance were analysed. These adaptive strategies were examined because they may be potentially impacted by mindfulness training (Baer, 2003; Hanley & Garland, 2014). In addition, maladaptive strategies, including rumination and catastrophising were analysed. These maladaptive strategies were selected based on previous research that suggests mindfulness training may lead to reductions in self-reports of rumination (Jain et al., 2007) and

catastrophising (Turner et al., 2016). In the context of reliability of this specific measure, previous research with high school students has successfully employed the CERQ to measure changes in cognitive emotion regulation strategies following an MBSR course (Shahidi, Akbari, & Zargar, 2017). Cronbach alphas indicated that this measure had good reliability at pre-testing, post-testing, and follow-up testing for the positive reappraisal scale ($\alpha = .81$; $\alpha = .84$; $\alpha = .88$), rumination ($\alpha = .89$; $\alpha = .79$; $\alpha = .79$), acceptance ($\alpha = .68$; $\alpha = .86$; $\alpha = .74$), and catastrophizing ($\alpha = .76$; $\alpha = .79$; $\alpha = .79$).

Mini-Mental Status Examination (MMSE)-2

The MMSE-2 (Folstein et al., 2010) was utilised to assess general cognitive functioning. It is composed of 30 questions that measure cognitive skills including recall, registration, attention, calculation, language, and orientation to time and place (Folstein et al., 2010; Sheehan, 2012). Lower scores on the MMSE could suggest possible cognitive impairment (Folstein et al., 2010; Tombaugh & McIntyre, 1992). Previous research has indicated that the MMSE is a valid and reliable assessment (Tombaugh & McIntyre, 1992) that can be used to measure changes in cognitive function following intervention for persons with dementia (Spector et al., 2003).

Acceptability Measure and Course Attendance.

The acceptability measure, completed at the post-testing session, was a 3-item questionnaire that indexed participants' satisfaction and adherence to the MBSR course. The first question on this measure indexed course satisfaction with a seven-point Likert scale (1 = Not at all, 7 = Very much. The second question on the acceptability questionnaire measured the frequency of home practice using a four-point Likert Scale (1 = Never, 4 = Every day). Finally, the third question on this questionnaire measured whether participants would like to continue with mindfulness practice after the MBSR course. The measure was developed and

successfully used in a longitudinal study on mindfulness training in schools (Sanger & Dorjee, 2016). Course attendance was recorded on the course registrar by the mindfulness teacher.

Repetitive Semantic Categorisation Task.

The computerised task was adapted from a study conducted by Olichney et al. (2008) on ERP components, including the N400 and P600, that are sensitive to cognitive changes in ageing and AD. The task was composed of three blocks with 160 trials presented in each block. Please refer to Appendix F for an example of a trial presented to participants. In each block, a total of 80 related and 80 unrelated items were randomly presented. Each item consisted of a semantic category, such as "A kitchen utensil", and a word that was either congruous "pot" or incongruous "tomb" with the category. Amongst the stimuli presented, 40 related and 40 unrelated target items always appeared in each of the three blocks. Thus, 80 (40 related and 40 unrelated) target items were repeated across three blocks. In addition, 80 (40 related and 40 unrelated) filler items were presented in each block. See Appendix A for a list of all target semantic categories and words.

Target semantic categories were taken from Van Overschelde et al. (2004), Battig & Montague (1969), and McEvoy & Nelson, 1982). All target categories were matched for number of syllables. All target words (related and unrelated) were matched for word length, frequency, imageability, and concreteness. The order of blocks were counterbalanced across participants. Participants first heard a semantic category via speakers. Then a related or unrelated answer was presented on the computer screen. Participants were asked to judge whether the word was related or unrelated to the preceding semantic category by pressing the z key on the keyboard if the word was related to the category.

Procedure

Participants completed questionnaires measures, the MMSE-2 (Folstein et al., 2010), and ERP recordings in a quiet lab space at Bangor University in Bangor, Wales. Questionnaires, including a socio-demographic form that collected information about age, gender, handeness, number of years in education, and involvement in extra-curricular activities, were completed at pre-testing (February-April 2016), at post-testing (May-June 2016), and follow-up testing (August-October 2016). ERP recordings and MMSE-2 (Folstein et al., 2010) were acquired at pre-testing and post-testing, and the acceptability measure was collected at post-testing only. effects. To reduce practice effects, different versions (colour coded red and blue) of the MMSE-2 (Folstein et al., 2010) were completed at pre-testing and post-testing.

Statistical Analysis

All questionnaire data was analysed using a mixed factorial 2 x 3 ANOVA with between- group (Group: Training Group, WLC Group) and within-group factors being (Time: Pre, Post Follow-up). Independent sample t-tests were conducted to determine baseline differences before conducting ANOVAs. If baseline differences were observed, an ANCOVA was conducted with pre-testing scores as the covariate If significant interaction effects were found, paired sample t-test and ANOVAs were then conducted. In addition, estimated marginal means and pairwise comparisons were used to interpret significant main effects.

For response time and trial numbers data to the repetitive semantic categorisation task, only target words were analysed. A mixed factorial 2 (Group: Training Group, WLC Group) x 2 (Time: Pre, Post) x 2 (Congruency: Congruent, Incongruent) x 3 (Repetition: 1, 2, 3) ANOVA was utilised to determine differences in trial numbers and response time between groups and conditions. To determine baseline differences, a mixed factorial 2 (Group: Training Group, WLC Group) x 2 (Congruency: Congruent, Incongruent) x 3 (Repetition: 1, 2, 3) ANOVA was first conducted for pre-testing measures. If a baseline difference was reported, difference scores (post-pre) were utilised for subsequent analyses. Paired sample t-test and ANOVAs were used to interpret significant interactions. Estimated marginal means and pairwise comparisons were also used to explore significant main effects.

For ERP data, only target words were analysed. A mixed factorial 2 (Group: Training Group, WLC Group) x 2 (Congruency: Congruent, Incongruent) x 3 (Repetition: 1, 2, 3) ANOVA was first conducted for pre-testing measures to ensure that there were no baseline differences. If a baseline difference was found, all subsequent analyses were conducted using difference scores (post-pre). To examine an expected congruency effect on the mean amplitude and latency of the N400 and P600 with an average of selected electrodes, a mixed factorial 2 (Group: Training Group, WLC Group) x 2 (Time: Pre, Post) x 2 (Congruency: Congruent, Incongruent) x 3 (Repetition: 1, 2, 3) was conducted. To follow-up on effects of congruency, pairwise comparisons and estimated marginal means were employed.

Next, a mixed factorial 2 (Group: Training Group, WLC Group) x 2 (Time: Pre, Post) x 3 (Repetition, 1, 2, 3) ANOVA with an average of selected electrodes was conducted to investigate the impact of an MBSR course on repetition effects for the P600 and N400 mean amplitude and latency. Based on previous studies using this task (Olichney et al., 2006; Olichney et al., 2008), only incongruent items were included in the N400 mean amplitude and latency analyses. Moreover, only congruent items were included in the P600 mean amplitude and latency analyses. Given that specific hypotheses were formed in relation to the impact of an MBSR course on the N400 and P600 to this repetitive semantic categorisation task, only interactions between group, repetition, and time were discussed in the results section. To interpret a significant interaction between group, repetition, and time, t-tests and ANOVAs were employed. To explore significant main effects, pairwise comparisons and estimated marginal means were utilised.

If the assumption of spherecity was not met, Greenhouse-Geisser correction was employed. Correlational analyses were used to index the association between course enjoyment and home practice on significant changes in self-report and ERP measures. Missing data was replaced with multiple imputation analysis, and all outliers of (2.5 ICR) were windsorised and included in the data.

Analysed electrode sites and peak time windows for the N400 and P600 were selected through a visual inspection of grand average waveforms in NeuroScan and based on previous literature (Duncan et al., 2009; Regel, Meyer, & Gunter, 2014) on the ERP components. For the N400 mean amplitude analyses, electrode sites CP1, CP2, CPZ, CZ, and PZ with a peak time window between 350 to 500 ms was chosen. For the P600 mean amplitude analyses, electrode sites C1, C2, CP2, CP1, CPZ, and CZ with a time window between 540 to 710 ms was chosen. For latency analyses of the N400 and P600, electrode site CPZ was used. Only trials answered correctly and after the time window of 200 ms were included in the data analysis for N400 and P600 mean amplitude and latency.

Results

Self-Report Findings

Please refer to Table 6.2 for a summary of the means and standard deviations for each questionnaire. Figures 6.1, 6.2, and 6.3 display line graphs with group means for each questionnaire at pre-, post-, and follow-up testing. In all figures, 95% confidence intervals are shown.

Baseline Characteristics

The baseline levels of self-reported trait mindfulness, measured by the CAMS-R, for the MBSR Group (M = 33.98) and WLC Group (M = 34.63) were similar to the mean total of trait mindfulness (M = 34.11) reported in a previous study of university students (N = 212; $M_{age} = 18.74$; Feldman et al., 2007). Mean levels of perceived stress on the PSS-14, measured at pre-testing, for the MBSR Group (M = 18.67) were slightly lower than a reported normative mean value (M = 19.62) from a probability sample study (N = 2, 387) conducted in the United States (Cohen & Williamson, 1988). However, the WLC Group reported a higher mean level (M = 20.00) of perceived stress compared to the normative data. While there are no published norms for the Big Five Personality Inventory, a large study (N = 132, 515) conducted in the United States reported means of conscientiousness (M = 63.80) and neuroticism (M = 51.00) as percentage of maximum possible scores for adults aged 21 to 60 (Srivastava et al., 2003). To allow for comparison of the means, the means of neuroticism and conscientiousness in this current study were converted to percentage of maximum change scores. Mean levels of neuroticism at pre-testing were slightly lower for the MBSR Group (M = 40.83) and WLC Group (M = 41.72), as compared to the published study (Srivastava et al., 2003). In contrast, mean levels of conscientiousness at pre-testing were higher for the MBSR group (M = 72.22) and WLC Group (M = 70.56).

In relation to the DASS-21 measure, Lovibond & Lovibond (1995) reported cut-off scores for severity levels (normal to extremely severe) of each subscale (depression, anxiety, and stress. The means of depression for the MBSR Group (M = 6.13) and WLC Group (M = 7.20) were within normal ranges at pre-testing. In addition, the means of anxiety for the MBSR Group (M = 2.27) and WLC Group (M = 4.70) were within normal ranges at pre-testing. Finally, the means of stress for the MBSR Group (M = 11.51) and the WLC Group (M = 11.20) were within normal ranges at pre-testing.

Levels of self-reported well-being, as measured by the WEMWBS, were higher for the MBSR group (M = 52.80) and WLC group (M = 54.80) in comparison to the normative data (M = 49.90) acquired through a population-based study (N = 8011) of adults, aged 16 and above (Morris, Earl, & NatCen Social Research, 2017). For levels of cognitive emotion regulation strategies, measured by the CERQ, a study (Garnefski et al., 2002) involving a non-clinical

sample (N = 99; aged 18 to 68) reported means of rumination (M = 9.28), acceptance (M = 10.22), positive reappraisal (M = 12.73), and catastrophising (M = 5.37). In the current study, levels of self-reported rumination at pre-testing were higher for both the MBSR Group (M = 10.33) and WLC Group (M = 11.25) in comparison to these reported means (Garnefski et al., 2002). While levels of self-reported acceptance were lower for the MBSR Group (M = 9.27), the WLC group reported higher levels of acceptance (M = 13.35). In regards to positive reappraisal, the MBSR Group (M = 13.00) reported a similar level of self-reported positive reappraisal. However, the WLC group (M = 14.55) indicated a higher usage of self-reported positive reappraisal in comparison to reported means (Garnefski et al., 2002). Levels of self-reported means (M = 14.55) indicated a higher usage of self-reported positive reappraisal in comparison to reported means (Garnefski et al., 2002). Levels of self-reported means (M = 14.55) indicated a higher usage of self-reported positive reappraisal in comparison to reported means (Garnefski et al., 2002). Levels of self-reported catastrophising were higher for both the MBSR Group (M = 6.80) and WLC Group (M = 7.15) in comparison to reported means.

Course Practice and Acceptability.

Training group participants included in the ERP analysis (N = 15) had good course attendance; they attended at least six of the eight MBSR sessions. In addition, this subset of participants engaged in daily mindfulness practices as part of the course; 56.30% reported completing home practice every day, 31.30% reported completing home practice often, and 12.50% reported completing home practice rarely. Participants also indicated that they were satisfied with the MBSR course (Mean Satisfaction Rating = 89.29%, Mean Likert Scale = 6.25 out of 7). Finally of the participants included in the ERP analysis (N = 15), 68.80% reported that they would carry on with mindfulness practice, and 31.30% stated they may carry on with mindfulness practice.

CAMS-R.

No significant between group differences were found at baseline for total mindfulness scores, t(33) = -0.40, p = .695, d = 0.14. No significant main effect of time, F(2, 66) = 2.32, p

= .126, η^2 = .07 or group, F(1, 34) = .53, p = .425, $\eta^2 = .01$ was found. No significant interaction between time and group, F(2, 66) = 0.16, p = .769, $\eta^2 = .00$, was reported.

PSS.

No significant between group differences were documented at baseline for perceived stress, t(33) = 0.54, p = .594, d = 0.18. No significant main effect of time, F(2, 66) = 2.47, p = .092, $\eta^2 = .07$ or group, F(1, 33) = 2.45, p = .127, $\eta^2 = .71$ was reported. No significant interaction between time and group, F(2, 66) = 1.41, p = .253, $\eta^2 = .04$, was found.

BFI.

There were no significant group differences in self reports of conscientiousness at baseline, t(33) = -0.30, p = .770, d = -0.11. A significant main effect of time, F(2, 66) = 3.21, p = .047, $\eta^2 = .08$ was reported. Pairwise comparisons indicated a significant increase in conscientiousness from post-testing to follow-up testing, p = .031. No main effect of group, F(1, 33) = 0.01, p = .924, $\eta^2 = .00$, was found . A significant interaction between time and group was reported, F(2, 66) = 3.72, p = .029, $\eta^2 = .09$. Paired-sample t-tests indicated no changes in self-reports of conscientiousness across time points for the control group, all ps > .05. However, significant decreases in reports of conscientiousness from pre-testing to post-testing to follow-up testing for the training group, t(14) = -3.89, p = .002, d = -0.50. No significant changes were seen between pre-testing to follow-up testing for the training group, p > .05.

There was no significant group difference at baseline for neuroticism t(33) = 0.16, p = .871, d = .07. In addition, there was no significant main effect of time, F(2, 66) = 1.02, p = .365, $\eta^2 = .03$ or group, F(1, 33) = 0.49, p = .49, $\eta^2 = .01$. A significant interaction between time and group was found, F(2, 66) = 3.70, p = .030, $\eta^2 = .10$. Paired-sample t-tests indicated no significant changes for reports of neuroticism across time points for the control group, all

ps > .05. A significant decrease in self-report scores of neuroticism from pre-testing to followup testing was reported for the training group, t(14) = 2.38, p = .032, d = 0.59. However, there were no significant differences from pre-testing to post-testing or post-testing to follow-up testing for the training group, all ps > .05.



Figure 6.1. Mean scores of A) Total Mindfulness, as measured by the CAMS-R, B)
Perceived Stress, as measured by the PSS, and C) Conscientiousness as measured by the Big-Five, D) Neuroticism as measured by the Big-Five, at pre-, post-, and 3-month follow-up testing for Training Group and WLC Group. Error bars depicted in all graphs indicate 95%

Confidence Intervals.

DASS-21.

No significant between group differences were reported at baseline for stress, t(33) = -0.11, p = .912, d = -0.04. No significant main effect of time, F(2, 66) = 0.64, p = .532, $\eta^2 = .02$ was reported. A marginally significant main effect of group was found, F(1, 33) = 4.05, p = .052, $\eta^2 = .11$. Estimated marginal means indicated that the control group had higher levels of

reported stress in comparison to the training group. A significant interaction between time and group, F(2, 66) 4.29, p = .018, $\eta^2 = .11$, was also reported. Post-hoc paired-sample t-tests indicated no differences in self reports of stress from pre-testing to post-testing and post-testing to follow-up testing for the training group, all ps > .05. However, paired sample t-tests indicated significant decreases in self-reports of stress from pre-testing to follow-up testing for the training for the training of stress from pre-testing to follow-up testing for the training for the training for the training to follow-up testing to follow-up testing for the training for the t

No significant between group differences were documented at baseline for anxiety, t(33) = 1.56, p = .129, d = 0.46. No significant main effect of time, F(2, 66) = 0.49, p = .615, $\eta^2 = .01$ was found. A main effect of group was reported, F(1, 33) = 8.19, p = .007, $\eta^2 = .20$. Estimated marginal means indicated that the control group had higher levels of self-report anxiety. However, this main effect should be interpreted with caution due to the lack of homogeneity of variances as assessed by the Levene's Test. No significant interaction between time and group, F(2, 66) = 1.03, p = .364, $\eta^2 = .03$, was reported.

Finally, no significant between group differences were found at baseline for depression, t(33) = 0.44, p = .661, d = 0.16. No significant main effect of time, F(2, 66) = 1.03, p = .364, $\eta^2 = .03$ or group, $F(1, 33) = 2.72, p = .109, \eta^2 = .08$ was reported. A marginally significant interaction between time and group, $F(2, 66) = 2.75, p = .071, \eta^2 = .07$, was found. Post-hoc paired sampled t-tests indicated no significant differences in self-reports of depression across time points for the control group, all ps > .05. A significant decrease in self-reports of depression was reported from pre-testing to post-testing for the training group, t(14) = 3.07, p = .008, d = 0.82. No significant difference was noted from post-testing to follow-up testing and pre-testing to follow-up testing for the training group, all ps > .05.

WEMWBS.

No significant group differences were documented at baseline for well-being t(33) = 0.76, p = .450, d = 0.27. There was no significant main effect of time, F(2, 66) = 2.23, p = .116, $\eta^2 = .05$ or group, F(1, 33) = 1.52, p = .227, $\eta^2 = .05$. A significant interaction between time and group was found, F(2, 66) = 6.06, p = .004, $\eta^2 = .15$. Paired sample t-tests indicated no changes in well-being across time points for the control group, all ps> .05. However, a significant increase in well-being was reported from pre-testing to post-testing for the training group, t(14) = -3.96, p = .001, d = -1.01. In addition, a significant increase in well-being was found from pre-testing to follow-up testing for the training group, t(14) = -2.72, p = .017, d = -0.92. No significant changes in the training group were found from post-testing to follow-up testing, p > .05.



Figure 6.2. Mean scores of A) Stress, as measured by the DASS-21, B) Anxiety, as measured by the DASS-21, and C) Depression, as measured by the DASS-21, D) Well-being, as measured by the WEMWBS, at pre-, post-, and 3-month follow-up testing for Training Group and WLC Group. Error bars depicted in all graphs indicate 95% Confidence Intervals.

CERQ.

There were no significant between group differences documented at baseline for positive reappraisal, t(33) = 1.26, p = .218, d = 0.43. No significant main effect of time, F(2, 66) = 0.21, p = .980, $\eta^2 = .00$ or group, F(1, 33) = 0.36, p = .551, $\eta^2 = .01$ was found. Finally, a marginally significant interaction between time and group was reported, F(2, 68) = 2.66, p = .077, $\eta^2 = .07$. Exploratory post-hoc paired-sampled t-tests indicated no significant differences across time points for the WLC group and training group, all ps > .05.

No significant between group differences were documented at baseline for rumination, t(33) = 0.63, p = .532, d = 0.22. A significant main effect of time, $F(2, 66) = 4.89, p = .011, \eta^2$ = .13 was found. Pairwise comparisons documented higher reports of rumination at pre-testing in comparison to follow-up, p = .045. No significant main effect of group, F(1, 33) = 1.85, p = $.183, \eta^2 = .65$ was reported. No significant interaction between time and group, F(2, 66) = $0.95, p = .391, \eta^2 = .02$, was found.

No significant between group differences were found at baseline for acceptance, t(33) = 1.02, p = .317, d = 0.36. A significant main effect of time was reported, F(2, 66) = 3.55, p = .034, $\eta^2 = .10$. Pairwise comparisons indicated a significant increase in self reports of acceptance from post-testing to follow-up testing. No significant main effect of group was found, F(1, 33) = 1.24, p = .273, $\eta^2 = .04$. In addition, no interaction between time and group was found, F(2, 66) = 0.41, p = .094, $\eta^2 = .00$.

No significant between group differences were reported at baseline for catastrophising t(33) = 0.34, p = .738, d = 0.12. A significant main effect of time was reported, F(2, 66) = 5.46, p = .010, $\eta^2 = .14$. Pairwise comparisons indicated a significant decline in self-reports of catastrophising from pre-testing to post-testing, p = .008. No significant main effect of group, F(1, 33) = 2.76 p = .106, $\eta^2 = .08$, was found. Moreover, there was no significant interaction between time and group, F(2, 66) = 1.40, p = .254, $\eta^2 = .04$.



Figure 6.3. Mean scores of A) Positive Reappraisal, as measured by the CERQ, B) Rumination, as measured by the CERQ, and C) Acceptance as measured by the CERQ, D) Catastrophising as measured by the CERQ, at pre-, post-, and 3-month follow-up testing for Training Group and WLC Group. Error bars depicted in all graphs indicate 95% Confidence

Intervals.

Table 6.2.

| | MBSR Group | WLC Group |
|-----------------------------|------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Pre- MMSE Scores | 27.65 ± 1.63 | 28.33 ± 1.50 |
| Pre-CAMS | 34.63 ± 4.15 | 33.98 ± 5.24 |
| Post-CAMS | 35.73 ± 4.51 | 35.17 ± 6.02 |
| Follow-CAMS | 37.07 ± 4.65 | 35.55 ± 5.61 |
| Pre-PSS | 18.67 ± 6.95 | 20.00 ± 7.46 |
| Post-PSS | 15.27 ± 6.12 | 19.81 ± 6.90 |
| Follow-PSS | 14.93 ± 6.93 | 19.25 ± 8.77 |
| Pre-Stress | 11.51 ± 7.82 | 11.20 ± 8.42 |
| Post-Stress | 7.33 ± 4.51 | 13.80 ± 5.73 |
| Follow-Stress | 7.60 ± 4.67 | 12.40 ± 7.33 |
| Pre-Anxiety | 2.27 ± 2.91 | 4.70 ± 5.48 |
| Post-Anxiety | 0.93 ± 1.67 | 4.70 ± 4.01 |
| Follow-Anxiety | 1.07 ± 1.83 | 5.40 ± 6.16 |
| Pre-Depression | 6.13 ± 5.48 | 7.20 ± 8.04 |
| Post-Depression | 2.67 ± 2.35 | 8.10 ± 8.25 |
| Follow-Depression | 4.27 ± 4.33 | 7.10 ± 6.24 |
| Pre-Positive Reappraisal | 13.00 ± 3.36 | 14.55 ± 3.79 |
| Post-Positive Reappraisal | 12.96 ± 4.02 | 14.35 ± 3.67 |
| Follow-Positive Reappraisal | 14.20 ± 3.26 | 13.25 ± 4.53 |
| Pre-Rumination | 10.33 ± 3.85 | $11.25{\pm}4.52$ |
| Post-Rumination | 8.33 ± 2.64 | 10.60 ± 3.90 |

Means and Standard Deviations ($M \pm SD$) of Self-Report Measures

Table 6.2. continued.

| | MBSR Group | WLC Group |
|---------------------------|------------------|-------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Follow-Rumination | 8.73 ± 2.49 | $10.15{\pm}3.88$ |
| Pre-Catastrophizing | 6.80 ± 2.88 | 7.15 ± 3.15 |
| Post-Catastrophizing | 4.73 ± 0.80 | $6.35{\pm}2.21$ |
| Follow-Catastrophizing | 5.40 ± 1.30 | 7.00 ± 3.39 |
| Pre-Acceptance | 9.27 ± 3.45 | $13.35{\pm}3.76$ |
| Post-Acceptance | 11.27 ± 3.56 | 1260 ± 3.73 |
| Follow-Acceptance | 12.80 ± 2.73 | $13.70{\pm}3.59$ |
| Pre-Conscientiousness | 3.89 ± 0.67 | 3.82 ± 0.66 |
| Post- Conscientiousness | 3.70 ± 0.53 | $3.89{\pm}0.63$ |
| Follow- Conscientiousness | 3.99 ± 0.62 | 3.84 ± 0.70 |
| Pre-Neuroticism | 2.63 ± 0.43 | $2.67{\pm}0.75$ |
| Post- Neuroticism | 2.59 ± 0.51 | $2.64{\pm}0.92$ |
| Follow- Neuroticism | 2.35 ± 0.67 | $2.74{\pm}0.79$ |
| Pre-WEMWBS | 52.80 ± 6.62 | 54.80 ± 8.35 |
| Post-WEMWBS | 58.47 ± 5.44 | 53.50 ± 8.55 |
| Follow-WEMWBS | 58.92 ± 6.71 | 53.22 ± 10.24 |

Means and Standard Deviations ($M \pm SD$) of Self-Report Measures

Repetitive Semantic Categorisation Task

Trial numbers.

A baseline difference between groups was reported for trial numbers as indicated by a significant interaction with congruency and group, F(1,33) = 4.13, p = .050, $\eta^2 = .01$. Estimated

marginal means reported a larger number of trials for both congruent and incongruent items for the WLC group in comparison the training group. However, no main effect of group or other interactions were reported, all $p_s > .05$.

Given the baseline difference reported, a 2 (Group: Training Group, WLC Group) x 2 (Congruency: Congruent, Incongruent) x 3 (Repetition: 1, 2, 3) ANOVA with difference scores (post-pre) was conducted to examine differences in trial numbers across groups and conditions. No significant main effects of group, congruency, and repetition were found, all ps > .05. In addition, no interaction was documented between group, repetition, and congruency, all ps > .05. However, an interaction between congruency and repetition was noted, F(1,34) = 4.35, p = .045, $\eta^2 = .13$. A post-hoc repeated-measures ANOVA on repetition (1, 2, 3) was conducted for incongruent and congruent trials using difference scores (post-pre). A significant main effect of repetition was found for congruent trials, F(2,68) = 3.90, p = .025, $\eta^2 = .10$. Pairwise comparisons indicated a marginally smaller difference in trial numbers between the first presentation and second presentation of congruent items, p = .058. No other significant differences were noted between repetitions for trials numbers of congruent items, all ps > .05. No significant main effect of repetition was found for trials numbers of congruent trials, F(2,68) = 0.63, p = .536, $\eta^2 = .02$. Means and standard deviations for trial numbers can be seen in Table 6.3.

Table 6.3

| | MBSR Group | WLC Group |
|-------------------------------|------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Pre- Congruent Repetition 1 | 37.07 ± 1.87 | 38.15 ± 1.53 |
| Pre- Congruent Repetition 2 | 38.33 ± 1.80 | 38.65 ± 1.23 |
| Pre- Congruent Repetition 3 | 38.47 ± 1.41 | 38.70 ± 1.17 |
| Pre- Incongruent Repetition 1 | 38.33 ± 2.09 | 38.65 ± 1.31 |
| | | |

Means and Standard Deiation (Mean \pm SD) of Trials per Condition

Table 6.3. continued.

| | MBSR Group | WLC Group |
|--------------------------------|------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Pre- Incongruent Repetition 2 | 39.07 ± 1.28 | 38.95 ± 1.10 |
| Pre- Incongruent Repetition 3 | 38.53 ± 1.51 | 38.55 ± 1.47 |
| Post- Congruent Repetition 1 | 39.07 ± 1.28 | 38.70 ± 1.63 |
| Post- Congruent Repetition 2 | 39.00 ± 1.07 | 38.25 ± 2.29 |
| Post- Congruent Repetition 3 | 37.53 ± 6.31 | 37.95 ± 2.06 |
| Post- Incongruent Repetition 1 | 39.07 ± 1.10 | 38.35 ± 2.46 |
| Post- Incongruent Repetition 2 | 39.20 ± 1.08 | 38.65 ± 2.46 |
| Post- Incongruent Repetition 3 | 38.26 ± 4.57 | 37.85 ± 2.50 |

Means and Standard Deviations (Mean \pm SD) of Trials per Condition

Response Times.

A baseline difference between groups was reported for response time as indicated by a significant interaction with congruency and group, F(1,33) = 4.80, p = .036, $\eta^2 = .02$. Estimated marginal means indicated that response times were slower for the training group for congruent items, but the WLC group displayed slower response times for incongruent items. No main effect of group or other interactions were reported, all ps > .05

Considering the baseline difference, a 2 (Group: Training Group, WLC Group) x 2 (Congruency: Congruent, Incongruent) x 3 (Repetition: 1, 2, 3) ANOVA was conducted with difference scores (post-pre) to examine differences in response times across conditions and groups. While no interaction between group, congruency, and repetition was found, F(2, 66) = 1.05, p = .357, $\eta^2 = .01$, a main effect of congruency, F(1, 33) = 6.72, p = .014, $\eta^2 = .05$, was noted. Pairwise comparisons indicated a larger difference in response time (post-pre) for

congruent items in comparison to incongruent items, p = .014. No main effect of repetition or group was reported, all ps > .05. Table 6.4 presents means and standard deviations for response times.

Table 6.4.

Means and Standard Deviations (Mean \pm SD) of Response Times (ms) per Condition

| | MBSR Group | WLC Group |
|--------------------------------|---------------------|--------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Pre- Congruent Repetition 1 | 865.42 ± 140.24 | 838.13 ± 118.70 |
| Pre- Congruent Repetition 2 | 727.19 ± 118.84 | 719.23 ± 81.91 |
| Pre- Congruent Repetition 3 | 688.96 ± 111.32 | 702.87 ± 98.43 |
| Pre- Incongruent Repetition 1 | 825.97 ± 161.94 | 849.79 ± 100.69 |
| Pre- Incongruent Repetition 2 | 761.76 ± 151.24 | 798.28 ± 57.69 |
| Pre- Incongruent Repetition 3 | 771.97 ± 123.65 | 811.70 ± 112.88 |
| Post- Congruent Repetition 1 | 818.82 ± 103.47 | 818.65 ± 125.29 |
| Post- Congruent Repetition 2 | 720.87 ± 116.32 | 714.12 ± 85.38 |
| Post- Congruent Repetition 3 | 665.19 ± 97.34 | 687.00±117.41 |
| Post- Incongruent Repetition 1 | 823.56 ± 104.35 | 856.49 ± 130.97 |
| Post- Incongruent Repetition 2 | 794.76 ± 133.29 | 800.21 ± 119.64 |
| Post- Incongruent Repetition 3 | 767.53 ± 107.00 | 828.80 ± 152.00 |

N400 Mean Amplitude

No baseline difference between groups was reported as indicated by a non-significant main effect of group and non-significant interactions with group, all ps > .05. As expected for an N400 amplitude, a main effect of congruency was found, F(1,33) = 109.065, p < .001, $\eta^2 = .39$. Pairwise comparisons indicated a less negative mean amplitude for congruent items in

comparison to incongruent items, p < .001. Similar to Olichney et al. (2006), subsequent analyses were conducted with incongruent items only. There was no main effect of time, $F(1,33) = 0.80, p = .377, \eta^2 = .01$, or group, $F(1,33) = .0.00 \ p = .987, \eta^2 = .00$. A main effect of repetition was found, $F(2,66) = 15.09, p < .001, \eta^2 = .16$. Pairwise comparisons indicated a less negative amplitude for repetition two, p < .001, and three, p = .001, in comparison to repetition one. There was no significant difference in mean amplitude between repetition two and three, p > .05. No significant interaction was reported between time, group, and repetition, $F(2,66) = 0.25 \ p = .208, \ \eta^2 = .00$. Please refer to Table 6.5 for means and standard deviations of the N400 mean amplitude.

Table 6.5.

Means and Standard Deviations (Mean \pm *SD) of N400 Mean Amplitude*

| | MBSR Group | WLC Group |
|--------------------------------|------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Pre- Congruent Repetition 1 | 4.66 ± 3.42 | 4.25 ± 3.65 |
| Pre- Congruent Repetition 2 | 6.76 ± 3.56 | 5.55 ± 2.65 |
| Pre- Congruent Repetition 3 | 7.33 ± 3.38 | 6.25 ± 3.21 |
| Pre- Incongruent Repetition 1 | 2.04 ± 2.56 | 2.29 ± 3.81 |
| Pre- Incongruent Repetition 2 | 3.39 ± 2.16 | 3.48 ± 3.48 |
| Pre- Incongruent Repetition 3 | 3.45 ± 2.36 | 3.02 ± 2.41 |
| Post- Congruent Repetition 1 | 4.68± 3.20 | 4.05 ± 4.04 |
| Post- Congruent Repetition 2 | 6.87 ± 3.93 | 5.30 ± 2.88 |
| Post- Congruent Repetition 3 | 7.44 ± 3.57 | 6.94 ± 3.29 |
| Post- Incongruent Repetition 1 | 1.66± 2.69 | $2.03{\pm}4.15$ |
| Post- Incongruent Repetition 2 | 3.03 ± 2.83 | $2.88{\pm}2.47$ |
| Post- Incongruent Repetition 3 | 3.41 ± 2.80 | 3.21 ± 3.29 |
N400 Latency

A summary of means and standard deviations for the N400 latency are reported in Table 6.6. No baseline difference between groups was reported as indicated by a non-significant main effect of group and non-significant interactions with group, all ps > .05. A main effect of congruency was reported, F(1,33) = 12.55, p = .001, $\eta^2 = .08$. Pairwise comparisons indicated a longer latency for incongruent items, p = .001. Based on previous research, the following analyses were conducted with incongruent items only (Olichney et al., 2006). No main effects of repetition, F(2,66) = 1.91, p = .157, $\eta^2 = .02$ or time, F(1,33) = 0.95, p = .338, $\eta^2 = .01$ were documented. In addition, no main effect of group was found, F(1,33) = 0.24, p = .395, $\eta^2 = .01$. Finally, there was no interaction between time, repetition, congruency, and group, F(2, 66) = 1.11, p = .335, $\eta^2 = .01$.

Table 6.6.

Means and Standard Deviations (Mean \pm SD) of N400 Latency

| | MBSR Group | WLC Group |
|-------------------------------|--------------------|--------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Pre- Congruent Repetition 1 | 401.27 ± 48.79 | 422.95 ± 51.36 |
| Pre- Congruent Repetition 2 | 401.60 ± 50.25 | 430.40 ± 55.07 |
| Pre- Congruent Repetition 3 | 424.93 ± 66.83 | 427.20 ± 52.79 |
| Pre- Incongruent Repetition 1 | 433.20 ± 51.29 | 444.10 ± 46.32 |
| Pre- Incongruent Repetition 2 | 435.73 ± 40.74 | 442.55 ± 48.31 |
| Pre- Incongruent Repetition 3 | 439.53 ± 43.42 | 445.05 ± 46.17 |
| Post- Congruent Repetition 1 | 401.73 ± 42.65 | 418.65 ± 59.47 |
| Post- Congruent Repetition 2 | 408.80 ± 52.07 | 417.50 ± 57.06 |
| Post- Congruent Repetition 3 | $430.27{\pm}57.28$ | 406.75 ± 64.05 |
| | | |

Table 6.6. continued.

 $Mean \pm SD$ of N400 Latency

| | MBSR Group | WLC Group |
|--------------------------------|--------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Post- Incongruent Repetition 1 | 430.73 ± 44.52 | 426.10 ± 52.89 |
| Post- Incongruent Repetition 2 | 423.53 ± 39.78 | 446.70 ± 49.63 |
| Post- Incongruent Repetition 3 | 446.73 ± 42.83 | 441.15 ± 41.23 |



Figure 6.4. Graphs A-D display the Grand averaged (GAV) waveform at the electrode site CPZ for incongruent items across testing time points (pre-, post-) and groups (training Group, WLC Group). The selected time window for the N400 component (350-500 ms) is shown in each graph.



Figure 6.5. shows the topography graphs of the N400 component at the electrode site CPz for incongruent items across repetition (1, 2, 3) and testing time-points (pre-, post-) in the Training Group.



Figure 6.6. displays the topography graphs of the N400 component at the electrode site CPz for incongruent items across repetition (1, 2, 3) and testing time-points (pre-, post-) in the WLC Group.

P600 Mean Amplitude

There was no main effect of group or interaction with group, all ps > .05; therefore indicating that there was no baseline difference for the P600 mean amplitude. A main effect of congruency was noted for the P600 mean amplitude, F(1,33) = 16.09, p < .001, $\eta^2 = .09$. Pairwise comparisons indicated a more positive amplitude for incongruent items in comparison to congruent items, p < .001. Like previous research using a repetitive semantic categorization task (Olichney et al., 2006), the following tests were conducted with congruent items only. No main effect of time, F(1,33) = 1.20, p = .281, $\eta^2 = .01$, or group, F(1,33) = 0.66, p = .424, η^2 = .02, was reported. A main effect of repetition was noted, F(2,66) = 9.43, p = .001, $\eta^2 = .09$. Pairwise comparisons indicated a more positive amplitude for repetition two, p = .010, and three, p = .004, in comparison to repetition one. However, no significant difference in mean amplitude between repetition two and three was documented, p > .05. There was no significant interaction between time, group, and repetition, F(2,66) = 0.01 p = .992, $\eta^2 = .00$. Refer to Table 6.7 for means and standard deviations of the P600 mean amplitude.

Table 6.7.

| | MBSR Group | WLC Group |
|-----------------------------|------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Pre- Congruent Repetition 1 | 5.56 ± 2.66 | 4.60 ± 2.61 |
| Pre- Congruent Repetition 2 | 6.48 ± 3.14 | 5.37 ± 2.97 |
| Pre- Congruent Repetition 3 | 6.43 ± 3.57 | 5.58 ± 3.20 |

Means and Standard Deviations (Mean ± SD) of P600 Mean Amplitude

Table 6.7. continued

| | MBSR Group | WLC Group |
|--------------------------------|------------------|------------------|
| | (<i>N</i> = 15) | (<i>N</i> = 20) |
| Pre- Congruent Repetition 1 | 5.56 ± 2.66 | 4.60 ± 2.61 |
| Pre- Congruent Repetition 2 | 6.48 ± 3.14 | 5.37 ± 2.97 |
| Pre- Congruent Repetition 3 | 6.43 ± 3.57 | 5.58 ± 3.20 |
| Pre- Incongruent Repetition 1 | 5.72 ± 2.74 | 5.42 ± 2.79 |
| Pre- Incongruent Repetition 2 | $8.61{\pm}3.18$ | 7.81 ± 3.25 |
| Pre- Incongruent Repetition 3 | 8.20 ± 3.48 | 7.23 ± 2.97 |
| Post- Congruent Repetition 1 | 5.35 ± 2.76 | 4.91 ± 3.10 |
| Post- Congruent Repetition 2 | 6.61 ± 4.48 | $5.97{\pm}2.74$ |
| Post- Congruent Repetition 3 | 6.84 ± 3.81 | $6.38{\pm}2.80$ |
| Post- Incongruent Repetition 1 | 5.78 ± 3.39 | 6.09 ± 3.86 |
| Post- Incongruent Repetition 2 | 8.33 ± 4.76 | 7.18 ± 3.18 |
| Post- Incongruent Repetition 3 | 8.55 ± 3.93 | 7.17 ± 3.99 |

Means and Standard Deviations (Mean ± SD) of P600 Mean Amplitude

P600 Latency

A main effect of group was documented at pre-testing thus indicating baseline differences for the P600 latency, F(1,33) = 6.25, p = .018, $\eta^2 = .16$. Estimated marginal means indicated that the Training Group had a longer latency in comparison to the WLC Group. Therefore, a mixed 2 (Group: Training Group, WLC Group) x 2 (Congruency: Congruent, Incongruent) x 3 (Repetition: 1, 2, 3) ANOVA was conducted with difference scores (postpre). A marginally significant main effect of congruency was noted for the P600 latency, F(1,33) = 3.61, p = .066, $\eta^2 = .02$. Estimated marginal means indicated a greater difference in

latency times for incongruent trials than congruent trials. In line with previous research using a similar task (Olichney et al., 2006, the subsequent analyses were conducted with congruent items only. No main effect of repetition was documented, F(2, 66) = 0.51, p = .604, $\eta^2 = .01$. Moreover, no main effect of group was found, F(1,33) = 2.38, p = .132, $\eta^2 = .07$. Finally, no interaction between repetition and group was reported, F(2, 66) = 1.31, p = .277, $\eta^2 = .04$. Table 6.8 displays means and standard deviations of the P600 latency.

Table 6.8.

| | MBSR Group | WLC Group |
|--------------------------------|--------------------|--------------------|
| | (<i>N</i> = 16) | (<i>N</i> = 20) |
| Pre- Congruent Repetition 1 | 658.80 ± 56.55 | 641.10 ± 61.45 |
| Pre- Congruent Repetition 2 | 665.20 ± 57.09 | 619.55 ± 69.37 |
| Pre- Congruent Repetition 3 | 695.67 ± 14.18 | 643.50 ± 62.84 |
| Pre- Incongruent Repetition 1 | 619.00 ± 82.91 | 592.30 ± 70.01 |
| Pre- Incongruent Repetition 2 | 628.33 ± 82.30 | 588.85 ± 70.90 |
| Pre- Incongruent Repetition 3 | 642.20 ± 83.37 | 598.65 ± 74.81 |
| Post- Congruent Repetition 1 | 681.47 ± 28.10 | 614.85 ± 70.71 |
| Post- Congruent Repetition 2 | 664.87 ± 56.55 | 617.60 ± 57.41 |
| Post- Congruent Repetition 3 | 679.93 ± 41.40 | $626.70{\pm}73.35$ |
| Post- Incongruent Repetition 1 | 607.27 ± 78.30 | 585.65 ± 69.48 |
| Post- Incongruent Repetition 2 | 608.60 ± 82.01 | 550.15 ± 11.13 |
| Post- Incongruent Repetition 3 | 622.93 ± 79.07 | 562.75 ± 35.27 |
| | | |

Mean ± SD of P600 Latency



Figure 6.7. Graphs A-D display the Grand averaged (GAV) waveform at the electrode siteCPZ for congruent items across testing time points (pre-, post-) and groups (training Group,WLC Group). The selected time window for the P600 component (540-710 ms) is shown in each graph.



Figure 6.8. shows the topography graphs of the P600 component at the electrode site CPz for congruent items across repetition (1, 2, 3) and testing time-points (pre-, post-) in the WLC



Group.

Figure 6.9. shows the topography graphs of the P600 component at the electrode site CPz for congruent items across repetition (1, 2, 3) and testing time-points (pre-, post-) in the WLC

Group.

Home Practice and Course Satisfaction Analyses

A correlational analysis was completed to determine the strength of the relationship between course enjoyment and significant changes in self-report questionnaires, as well as home practice and significant changes in self-reports. The amount of home practice completed by the training group during the mindfulness-intervention course did not significantly correlate with change scores (post-pre) in neuroticism, conscientiousness, stress as measured by the DASS-21, depression, and well-being. Moreover, no significant associations were documented between enjoyment of the course and change scores (post-pre) on self-reports including depression, neuroticism, and conscientiousness. However, a significant positive correlation was found between enjoyment of the course and change scores (post-pre) of well-being for the training group, r(15) = .57, p = .027. Therefore, those who enjoyed the course more, showed the greatest improvements in self-reports of well-being. In addition, a significant negative correlation was noted between enjoyment of the course and change scores (post-pre) of stress, as measured by the DASS-21, for the training group, r(15) = -.52, p = .049. As such, those participants who enjoyed the course more, reported greater decreases in stress.

Discussion

Self-report findings of this study indicated significant decreases in stress, measured by DASS-21, from pre-testing to follow-up testing with a medium effect size for the training group. In addition, significant decreases in neuroticism with a medium effect size from pretesting to follow-up testing for the training group were reported. While initial decreases in conscientiousness were reported from pre-testing to post-testing with small effect size for the training group, an increase in conscientiousness was found from post-testing to follow-up testing with a medium effect size for the training group. Increases in self-reports of well-being from pre-testing to post-testing were also documented for the training group with a large effect size. Post-hoc analyses indicated a significant decrease in self-reports of depression for the training group from pre-testing to post-testing with a large effect size. While it was hypothesized that the training group would display decreases in self-reports of depression, the post-hoc analyses should be considered exploratory because only a marginally significant interaction (Group x Time) was found for self-reports of depression. Interestingly, the improvements in well-being and decreases in stress were associated with enjoyment of the MBSR course. No other significant changes were documented for questionnaire measures including trait mindfulness, anxiety, positive reappraisal, acceptance, catastrophising, and rumination.

In relation the repetitive semantic categorization task, results indicated that a marginally smaller difference in trial numbers for congruent items at first presentation in comparison to congruous items that were repeated once. For response times, a larger difference (post-pre) in response times was documented for congruent items in comparison to incongruent items. Finally, results showed no significant changes were seen for mean amplitude and latency of the P600 and N400 mean.

The findings of this study are mostly consistent with previous research on MBSR courses. For example, previous studies with adults that has found decreases in self-reports of depression (Würtzen et al., 2012), stress (Shapiro et al., 2005) and well-being (Carmody & Baer, 2009) following an MBSR course (Shapiro et al., 2005). Previous research with middleaged and older adults (Berk, Hotterbeekx, Os, van Boxtel, 2017) also found no changes in trait mindfulness. Furthermore, Wells, Kerr, et al. (2013) also documented no changes in levels of perceived stress, measured through the PSS, for persons with MCI following an MBSR course. Contradictory to previous studies on MBSR with adults, no changes were seen for anxiety (Würtzen et al., 2012) and cognitive emotion regulation strategies (Garland, Gaylord, & Frederickson, 2011; Jain et al., 2007). Moreover, Oken et al. (2017) similarly documented decreases in neuroticism in stressed older adults, aged 50 to 75 years. Interestingly, a growing body of research has documented significant changes in neuroticism following an MBI, such as MBSR or Mindfulness-Based Cognitive Therapy (MBCT; Armstrong & Rimes, 2016; Eberth & Sedlmeier, 2012; Spinhoven, Huijbers, Ormel, & Speckens, 2017). While no studies have specifically examined the impact of an MBSR course on the N400 and P600 ERP components, previous research involving older adults with subjective cognitive decline similarly found no changes in response times to a Go/NoGo task after an eight-week mindfulness course (Smart et al., 2017).

In total, the results of this study indicated that MBSR is most effective in improving self-report measures of well-being, perceived stress, and depression in typically ageing older adults. Moreover, the results suggested that MBSR may modulate stable personality factors associated with regulation of stress, such as neuroticism (Mroczek & Almedia, 2004), in

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typically ageing older adults. The finding of reductions in neuroticism are particularly interesting, as neuroticism is thought to be a stable factor across the lifespan (McCrae & Costa, 1994). However, more recent research suggests that personality traits may change across age (Srivastava et al., 2003) and due to psychological interventions (Barlow et al., 2014; Roberts et al., 2017). Therefore, the current study adds further support on the flexibility of personality factors, such as neuroticism. Considering these results, it could be suggested that mindfulness practice may promote positive changes in mental health in an ageing population. However, reductions in stress, measured by DASS-21, must be interpreted with caution, given the lack of convergence with the PSS measure.

In addition to these findings, decreases in self-reported levels of conscientiousness were documented from pre-testing to post-testing. However, the reductions in this measure was not maintained at follow-up. Given that previous research has documented that persons low in conscientiousness reported low levels of well-being (Keyes, Shmotkin, & Ryff, 2002), it could be argued that declines in conscientiousness following the MBSR course may have negative implications for well-being. However, this is contradictory to the findings of improved levels of well-being for the training group following the MBSR group. As such, the declines in conscientiousness could be considered a spurious finding.

Unlike self-report measures, no significant changes were found for objective measures of cognition including behavioural results and ERP components to the repetitive semantic categorization task. Therefore, it could be suggested that mindfulness practice has limited effects on cognitive processes measured in this study. This finding may be due to the design of the repetitive semantic categorization task, which was originally developed to measure cognitive changes in older adults with identified cognitive impairment (Olichney et al., 2006; Olichney et al., 2008, Olichney et al., 2013). However, as outlined in Chapter 3, it was hypothesised that the task would be sensitive to modulations in semantic and episodic memory in this cohort because it potentially involved increased attention and working memory resources. Thus, it could be argued that that the task did not tax attention and working memory processes sufficiently enough to detect changes in memory processes in typically ageing older adults.

It could also be argued that the lack of effects on the semantic task is not unexpected; mindfulness practice may encourage the inhibition of semantic processing by bringing attention to the present moment (Bishop et al., 2004; Pagnoni, Cekik, & Guo, 2008). Although limited investigations have specifically examined the link between mindfulness and semantic processing, initial studies provide tentative support in this context. For example, Pagnoni et al. (2008) found decreases in activity of default mode network regions (superior frontal gyrus, left angular gyrus, rostral anterior cingulate cortex, and inferior temporal gyrus) to a lexical decision task for meditators in comparison to non-meditators. Researchers of this study suggested that these findings may indicate that meditators disengage from semantic or conceptual processing through shifting attention to a physical anchor, such as the breath. An ERP investigation of the N400 and the P600 has also reported an association between trait mindfulness and semantic processing (Dorjee, Lally, Darall-Rew, & Thierry, 2015). More specifically, Dorjee et al. (2015) documented a more negative N400 amplitude to negative target words in a semantic affective word task for high trait mindfulness individuals. In addition, a less positive P600 amplitude was found for both positive and negative target words for high trait mindfulness participants. It was concluded that the modulations of the N400 amplitude could indicate an increase in cognitive effort to semantically process negative words. It was theorised that through the inhibition of ruminative elaborative processing, mindfulness may lead to less semantic access to negative words. In relation to modulations of the P600, researchers of this study suggested that the less positive P600 amplitude could indicate reductions in attentional and elaborative ruminative processing of emotional words.

In the context of the current study, it could be suggested that the MBSR course led to less semantic processing involved in rumination. Therefore, MBSR group participants may not have displayed enhanced reductions in the N400 and P600 amplitudes to repeated items because they had less semantic access to target words. However, no significant reductions in self-reports of rumination were found in this study.

Moreover, the absence of significant changes in objective measures may also be due to the short duration of the mindfulness training course. Specifically, it could be posited that extensive mindfulness practice may lead to modulations in the ERP markers and behavioural results to a repetitive semantic categorisation task. However, future longitudinal research involving a mindfulness course with a longer duration is necessary to examine this hypothesis.

The findings of this study must be considered in light of several limitations. In particular, in this study it was not possible to control for regular medication usage. Although participants were excluded if they reported regular usage of painkillers, it could be argued that other medication may influence behavioural and physiological measurements, such as response times and the ERP components. However, limited research, to our knowledge, has documented the effects of medication on the N400 and P600.

The smaller sample size of this study may also be considered a limitation. Although, Luck (2014) suggested that a typical sample size for an ERP study includes 10-20 participants. Moreover, previous ERP research on mindfulness interventions and ageing, used a similar sample size to the current study (Smart et al., 2017). As such, while the sample size may be underpowered for questionnaire measures, the ERP assessments including an adequate sample size.

In addition, the lack of a longer follow-up for self-report measures, and no follow-up for ERP measures could be considered a limitation. Specifically, follow-up testing beyond 3 months may help to establish the sustainability of improvements in well-being, stress,

depression, and neuroticism. Moreover, follow-up measures may reveal the positive effects of an MBSR course on self-report and ERP measures that are delayed and/or require further mindfulness practice.

Another limitation of this study is the absence of an active control group, which could help to ascertain whether the positive outcomes on stress, depression, neuroticism, and wellbeing were due to the MBSR course. Interestingly, this study documented no association between the amount of home practice and significant changes in self-report measures. Moreover, no significant changes on self-reports of mindfulness were reported. As such, it could be suggested that the improvements in the aforementioned measures are not specific to mindfulness training. In particular, the MBSR course involves social elements (e.g. groupbased weekly meetings), which may contribute to improvements in well-being, stress, and depression. Indeed, previous research has found an association between social contact and higher levels of well-being (Pinquart & Sörensen, 2000) in older adults. In addition, Glass, Mendes de Leon, Bassuk, and Berkman (2006) report a link between social engagement and lower self-reported levels of depressive symptoms.

In addition to the absence of an active control group, it could be suggested that participants in the MBSR group had decreased motivation to adhere to the course because they were not required to pay the course fees. Motivation may impact the efficacy of an MBSR course, with participants who are more motivated, adhering to the course practice. Interestingly, Seear and Vella-Brodrick (2013) found an association between higher levels of self-report motivation and increases in self-report well-being following a positive psychology intervention. While motivation was not specifically measured in this study, course attendance and practice completed outside of the MBSR course were measured. All participants attended at least 6 out of 8 courses. However, only 56.30% participants reported practicing every day. Thus, it could be suggested that participants may have lacked motivation to complete

mindfulness practice outside of the MBSR course. Future research should consider using a selfreport measure of motivation to further understand how motivation may play a role in the effectiveness of the MBSR course.

Considering these limitations, future longitudinal research should ideally include three arms including a mindfulness-based intervention wait-list control group, and active control group. As stated in a previous chapter (Chapter 5), the Health Enhancement Program (HEP; MacCoon et al., 2011) may be a viable program to utilise for the active control condition given it is similar in length to MBSR and incorporates group-based practices. Alternatively, future investigations may consider using a shorter, more potent practice of mindfulness, such as a mindfulness breath exercise, as utilised in Malinowski et al. (2017) study on cognitive and emotional function in older adults. According to Malinowski et al. (2017), standarised MBIs involve multiple components beyond mindfulness practice, and thus it is difficult to establish whether positive changes are specific to mindfulness training. By using a particular mindfulness practice, future research may be able to determine whether improvements in wellbeing, depression, stress, and neuroticism are due to mindfulness practice alone.

Future studies on MBIs should also incorporate longer follow-up periods (3 months, 6 months, 1 year) to determine if significant effects are maintained following the MBSR intervention, and whether changes in ERP markers might surface after more extensive duration of mindfulness practice. In addition, it is recommended that future empirical investigations employ both a self-report and physiological measure of stress to increase the convergent validity of potential reductions in stress. Physiological measures, such as cortisol tests, may highlight how MBSR affects the HPA-axis in older adult populations. Finally, future studies may consider is the use of both quantitative and qualitative methods. Qualitative methods may provide insight into the mechanisms by which mindfulness training may impact impacts self-reports levels of stress, depression, neuroticism, and well-being in typically ageing older adults.

Conclusion

In summary, the current study indicated that MBSR may be have a beneficial impact on self-report measurements of stress, well-being, depression, and neuroticism, in typically ageing older adults. Interestingly, the study also found that enjoyment in the course correlated with reductions in stress and improvements in well-being. Thus, suggesting that participant satisfaction plays a key role in promoting positive outcomes of the MBSR course. However, no significant changes were found for more objective measures, including the ERP components, N400 and P600 to the semantic categorization task. Thus, it could be concluded that an MBSR course does not modify ERP markers associated with semantic and episodic memory processes in a typically ageing cohort. Despite the mixed findings of this study, future investigations, using a longer follow-up period, are warranted to elucidate the role of mindfulness-based practice on cognitive function in ageing.

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Zhu, Z., Hou, X., & Yang, Y. (2018). Reduced syntactic processing efficiency in older adults during sentence comprehension. *Frontiers in Psychology*, 9, 243. doi:10.3389/fpsyg.2018.00243 **Chapter Seven**

Discussion

Introduction

This PhD study aimed to explore how mindfulness-based interventions (MBIs) may impact neural-based markers associated with cognitive decline in ageing and age-related diseases, such as Alzheimer's Disease (AD). In Chapter 1, the neural and cognitive changes that can occur in ageing and AD were discussed, in addition to theories of cognitive ageing. MBIs were introduced as promising methods to reduce cognitive and neural declines across the aging spectrum, and relevant empirical evidence in this context was considered. In Chapter 2 and 3, the methodology employed in this PhD study, including electroencephalography (EEG)/ Event-Related Potentials (ERPs) and proton magnetic resonance spectroscopy (1H-MRS), was outlined with a specific focus on the underlying psychophysiology of these measures. Moreover, the methodological parameters of EEG and ¹H-MRS in this study were reviewed. Chapter 4 presented a critical theoretical review of mindfulness-based approaches and AD. A neurocognitive and psychological model was proposed that focused on the stressrelated pathways by which mindfulness practice may prevent or delay the onset of AD. Chapter 5 and 6 detailed investigations on the effects a Mindfulness-Based Stress Reduction (MBSR) on neurocognitive markers of aging and AD. Moreover, both chapters presented findings on the impact of MBSR on psychological mechanisms, measured through self-report of wellbeing, stress, and stress-regulation. This final chapter summarizes the findings from chapters 4, 5, and 6, and will consider the overall implications of the results from the experimental studies. The limitations of the experimental studies will be discussed, and recommendations for future research will be presented.

Chapter 4: The Potential of Mindfulness-Based Approaches in the Prevention of Dementia: A Neurocognitive Review

This chapter introduced the global prevalence of dementia and the importance of preventive techniques that may reduce the risk and delay the onset of dementia. While there

are different causes of dementia, the review focused on AD, the leading cause of dementia (Sheehan, Karim, & Burns, 2009). Clinically, AD is characterized by the presence of amyloid plaques and neurofibrillary tangles (Jack et al., 2013; Perl, 2010; Sheehan et al., 2009). In addition to presenting with short-term (Jahn, 2013; Sheehan et al., 2009) and long-term memory loss, AD is associated with atrophy in the medial temporal lobe (MTL; Jack et al., 1997), hippocampus (Dickerson et al., 2001), entorhinal cortex (EC; Dickerson et al., 2001), precuneus (Scahill, Schott, Stevens, Rossor, & Fox, 2002), and posterior cingulate cortex (PCC; Scahill et al., 2002). Moreover, reduced connectivity of the default-mode network (DMN) is reported in AD (Greicius, Krasnow, Reiss, & Menon, 2004). Although there are many risk factors to AD, including increased age (Wimo & Prince, 2010; Lindsay et al., 2002) and APOE ɛ4 allele (Kim, Basak, & Holtzman, 2009; Reinvang, Espeseth, & Westlye, 2013), the role of stress in AD pathology was specifically considered throughout the review.

In research, a link between increased levels of perceived stress and dementia risk has been identified. Indeed, Johansson et al. (2013) documented a heightened risk of AD for individuals who reported multiple stressors in midlife. This might be due to the stress process particularly impacting neural regions sensitive to AD pathology. Specifically, increased perceived stress may lead to the release of cortisol from the Hypothalamic-Pituitary Adrenocorticol (HPA) Axis (Oken, Chamine, & Wakeleand, 2015). In overabundance, cortisol is reported to lead to atrophy in the hippocampus and prefrontal cortex (Campbell & MacQueen, 2004; Frodl & O'Keane, 2013; Kremen et al., 2010; Sapolsky et al., 1986), two areas implicated in the development of dementia (Salat, Kaye, & Janowsky, 2001; Scahill et al., 2002).

Given that MBIs may promote an adaptive regulation of stress (Carlson et al., 2007; Epel, Daubenmier, Moskowitz, Folkman, & Blackburn, 2009), it was hypothesized that mindfulness practice may potentially serve as a preventive intervention for AD. The review therefore explored the mechanisms by which mindfulness may impact the stress process, and proposed recommendations for future research in this context. In particular, it considered the impact of MBIs on the cognitive appraisal process in stress responses. Based on relevant research, it was suggested that mindfulness practice may encourage a more adaptive cognitive appraisal of stressors by decreasing stress reactivity (Hoge et al., 2014) and improving adaptive coping resources (Dobkin, 2008) used to process threatening stimuli. Moreover, it was theorised that mindfulness practice may modify the cognitive appraisal process by promoting self-regulation of attention (Tang, Lu, Feng, Tang, & Posner, 2015), with a decentered perspective (Carmody, Baer, Lykins, & Olendzki, 2009).

In addition to the cognitive appraisal of stress, the review investigated the effects of mindfulness practice on neural pathways associated with the stress process. It was suggested that mindfulness practice may down-regulate the release of cortisol by attenuating the amygdalae activity, a neural region linked with the activation of the HPA axis to threatening stimuli (Smith & Vale, 2006). Specifically, mindfulness training may promote cognitive reappraisal strategies, which is reflected neurally in increased prefrontal cortex activity and decreased amygdalae activity (Chiesa, Serretti, & Jackobsen, 2013; Modinos, Ormel, & Aleman, 2010). Alternatively, mindfulness training may cultivate an accepting awareness of emotional responses to stressors (Chiesa et al., 2013). This is characterised neurally by increased recruitment of sensory processing areas and decreased recruitment of the amygdalae (Taylor et al., 2011).

Other pathways of stress-related changes that were examined include the parasympathetic response and inhibitory brain regions. It was posited that mindfulness practice may enhance parasympathetic axis activity (Ditto, Eclache, & Goldman, 2006), which results in the down-regulation of the sympathetic axis (Ulrich-Lai & Herman, 2009) and decreases in cortisol levels. The sympathetic axis is thought to innervate the adrenal cortex of the HPA-axis

(Ulrich-Lai & Engeland, 2005; Ulrich-Lai & Herman, 2009), and thus could be indirectly involved in the regulation of cortisol. Finally, it was hypothesised that mindfulness training regulates cortisol release by promoting neuroplasticity in the hippocampus (Hölzel et al., 2011), a neural region involved in the negative feedback loop of cortisol (Frodl & O'Kean, 2013).

In total, the review highlighted the need for further multi-method research in this area, and identified possible research questions for future investigations. Event-Related Potential (ERP) tasks and ¹H-MRS were identified as neuroimaging tools of potential use in providing novel insights into the effect an MBI has on markers of ageing and AD. This prompted the use of these methodologies in Chapters 5 and 6 to examine the effect of MBSR with typically ageing older adults.

Chapter 5: The Effects of a Mindfulness-Based Stress Reduction (MBSR) Course on Well-Being, Perceived Stress, and Neurometabolite Markers of Dementia and Ageing

This chapter presented a feasibility-pilot investigation (N = 23) of the use of ¹H-MRS in examining the effects of an MBSR course on neurometabolites in the Posterior Cingulate Cortex (PCC) and Anterior Cingulate Cortex (ACC) within typically ageing older adults. The main aim of this study was to investigate the acceptability of the MBSR course, and the feasibility of using ¹H-MRS before and after an MBSR intervention in this cohort. Feasibility was conceptualised as the tolerance of participants to undergo the ¹H-MRS scan at two timepoints (Pre-Testing and Post-Testing). Feasibility also considered the quality of acquired spectra, as indexed by Signal to Noise Ratio and Cramer-Rao Lower Bound (CRLB) percentage of the spectra. Spectra data that had SNR above 20 and Cramer-Rao Lower Bound (CRLB) percentage below 25 data was identified as useable quality.

As a pilot study, the second aim was to investigate effect sizes for changes in neurometabolites so a power calculation could be conducted for future studies. To address this
secondary aim, the study analysed the effects of the MBSR intervention on neurometabolites reported to change with ageing and AD, such as myo-Inositol (mI), Creatine (Cr), N-Acetyl-Aspartate (NAA), gamma-Aminobutryric acid (GABA), and glutamate (Glu). Finally, the study aimed to investigate the impact of an MBSR course on psychological measures, including trait mindfulness, perceived stress and well-being.

It was predicted that levels of NAA, GABA, and Glu would increase in the PCC and ACC for the training group following the MBSR intervention in comparison to a wait-list control (WLC) group. In addition, it was postulated that levels of mI would decrease in the PCC and ACC for the training group following the MBSR training in comparison to the WLC group. In relation to self-report measures, it was hypothesised that the training group would report increases in well-being and trait mindfulness following the MBSR course in comparison to the WLC group. Conversely, it was expected that levels of perceived stress would decline following the MBSR intervention for the training group in comparison to the WLC group.

The results of this study indicated that the training group participants rated the MBSR course with high satisfaction (91.87% mean satisfaction rating). Moreover, most participants reported a good adherence to home practice for the course (60% reported practicing every day), and that they would like to carry on doing mindfulness (70% stated they would continue mindfulness practice). In this respect, the feasibility pilot study showed good compliance for the intervention. The employment of ¹H-MRS at two time points (pre- and post-testing) was also deemed acceptable with participants tolerating the scans well. In addition, most spectra data collected from the PCC was of usable quality. As such the feasibility of the study design and measurement techniques was demonstrated, and the primary objective of the study was achieved.

While ¹H-MRS was deemed effective in tracking changes in neurometabolites in the PCC, results from the ACC were confounded with high variability in fitting (e.g. high Cramer-

Rao Lower Bound (CRLB) and/or low Signal to Noise Ratios). As such, the rest of the chapter focused on the analyses of the PCC. Within the PCC, no significant changes were noted for NAA, Glu, and GABA. However, contrary to predictions, marginally significant decreases in Cr were noted for the training group with a medium effect size. For the control group, marginally significant increases in Cr were found with a medium effect size. Moreover, a marginally significant difference was noted for difference scores (post-pre) between groups for mI with a large effect size. Means showed that the training group showed larger difference scores in comparison to the control group. Thus, it was suggested that the training group showed a trend for increases in mI in the PCC. Using the effect sizes of Cr and mI analyses, the secondary aim of performing a power calculation was achieved, suggesting 101 (approximately 51 in each group) participants should be recruited for future research with a 95% power level.

While self-report findings showed no changes in perceived stress and trait mindfulness, significant increases in well-being were reported for the training group from pre-testing to post-testing with a large effect size. There were no significant correlations between change scores of neurometabolites or self-report measures with course enjoyment. However, change scores (post-pre) of Glu positively correlated with course practice.

Based on the findings it was concluded that MBSR is an acceptable treatment regimen, and may be an effective method for improving well-being in typically ageing older adults. However, given that self-reports of mindfulness did not increase, there is question as to whether the changes in well-being were due to mindfulness itself. It could be argued that the active ingredient leading to changes in well-being was the group-based aspect of the training or its psychoeducational elements. As such future investigations, should incorporate an active control group which involves group weekly meetings and psychoeducation. While no significant findings were reported for neurometabolite measures, marginally significant effects for mI and Cr suggested that MBSR may impact neural markers of ageing and AD. Thus, future research with recommended sample size of 101 participants is warranted to confirm the replicability of these findings.

Chapter 6: The Impact of a Mindfulness-Based Stress Reduction (MBSR) Course on

Event-Related Potential (ERP) Measures of Memory Processes

This chapter reported on a longitudinal study (N = 35) of ERP markers associated with cognitive decline (Olichney et al, 2008), specifically the N400 and P600. The N400 component is associated with semantic processing (Kutas & Federmeier, 2011) and recognition memory (Friedman & Johnson, 2000; Kutas & Federmeier, 2011; Olichney et al., 2013). It is modulated by repetition, with the N400 amplitude attenuating to repetitive items. The P600 component is linked with memory encoding (Jackson & Snyder, 2008) and memory retrieval processes (Olichney et al., 2013). Previous research has indicated that it is modulated by repetition, with the P600 amplitude attenuating to repeated items (Olichney et al., 2008). Both components have been studied in relation to Mild Cognitive Impairment (MCI; Olichney et al., 2008) and AD (Olichney et al., 2006), and researchers have suggested these components may help to predict cognitive decline (Olichney et al., 2008).

Therefore, this study utilised a repetitive semantic categorisation task, adapted from Olichney et al. (2008), to examine how an MBSR course may modulate repetition effects on the P600 and N400 components in typically ageing older adults. This task was chosen to measure semantic memory and episodic memory processes in typically ageing older adults. While episodic memory declines are typically reported in healthy ageing (McDaniel, Einstein, & Jacoby, 2008), healthy older adults may display limited decrements in semantic memory (Balota, Dolan, & Ducheck, 2000). However, it is argued that tasks that require a higher level of attention processing may reveal subtle changes in semantic memory in healthy ageing (Balota et al., 2000; Park & Festini, 2017). This task involved semantic judgements and

repetition of items, thus it was hypothesised that the task may recruit attention and working memory processes. As such, it could be sensitive to semantic memory changes in a typically ageing cohort. In addition to analysing ERP markers, the study intended to examine the psychological mechanisms of mindfulness that may lead to changes in these ERP components. In this context, the study focused on how MBSR may impact self-reports of perceived stress, trait mindfulness, depression, anxiety, well-being and stress-related measures, such as personality traits and cognitive emotion regulation strategies.

It was predicted that the training group would show enhanced repetition effects (e.g. attenuation of amplitude to repeated items) on the N400 and P600 components to the repetitive semantic categorisation task, which could indicate improvements in semantic and memory processes. For self-report measures, it was hypothesised that the training group would report reductions in stress, depression, anxiety, neuroticism, and maladaptive coping strategies (catastrophising and rumination). In addition, it was predicted that the training group would display increases in adaptive coping strategies (acceptance and positive reappraisal), wellbeing, and conscientiousness were also expected. These changes were expected both from pre to post (after the MBSR intervention, 3-month follow-up) and in between group (training group, WLC group) comparisons.

Results from this study indicated no significant changes in the mean amplitude or latency of the N400 and the P600 following the MBSR course for training group or control group participants. Moreover, no changes were noted in response times to the repetitive semantic categorisation task. For self-report measures, no significant changes in trait mindfulness, rumination, acceptance, catastrophising, positive rumination, and anxiety were documented for the training group or control group following the MBSR intervention. However, a significant increase in well-being was noted for the training group from pre-testing to post-testing, with a large effect size. Interestingly, this effect was maintained at the 3-month follow-up with no significant difference reported in levels of well-being from post-testing to follow-up testing for the training group. Although no significant changes in perceived stress were noted for the Perceived Stress Scale (Cohen, Karmarck, & Mermelstein, 1983) a significant decrease in stress, with a medium effect size, was found for the training group from pre-testing to follow-up testing on the Depression Anxiety and Stress Scale-21 (Lovibond & Lovibond, 1995). In addition, a significant decrease in neuroticism from pre-testing to followup testing, with a medium effect size, was reported for the training group. A significant decline in self-report levels conscientiousness, with a small effect size, from pre-testing to post-testing was also found for the training group. However, self-report levels of conscientiousness significantly increased at follow-up testing, with a medium reported effect size, for the training group participants. Given that there was no difference between pre-testing and post-testing levels of conscientiousness for the training group, it could be suggested that conscientiousness returned to baseline at follow-up testing after the initial decline reported at post-testing. Posthoc exploratory analyses also indicated significant declines in self-reports of depression, with

Interestingly, no correlation was found between the amount of mindfulness practice completed outside of the course and self-report measures, including depression, stress, wellbeing, neuroticism, and conscientiousness. However, a significant positive correlation was reported between course satisfaction and change scores (post-pre) of well-being. This suggested those who enjoyed the course more reported increased improvement in self-reports of well-being. Moreover, change scores (post-pre) of stress were found to negatively correlate with course satisfaction. This indicated that participants who enjoyed the course, displayed greater decreases in self-reports of stress.

In summary, the findings of this study indicated that an MBSR course may have limited effects on ERP and behavioural measures of memory processes, as assessed to the repetitive

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semantic categorisation task. However, results showed that an MBSR course may positively impact self-report measures of well-being, depression, stress, and neuroticism in typically ageing older adults. As such, it can be postulated that MBSR is most effective in improving mental health in a typically ageing cohort.

The findings of this study should be considered in relation to some limitations. Specifically, the study did not involve an active control group, which could help to identify if the effects are specific to mindfulness training. Interestingly, no significant changes in self-reports of mindfulness were found for the training group following the MBSR course. Therefore, it could be argued that other components of the MBSR course, such as the psychoeducational elements of the course, may have led to improvements in well-being, stress, depression, and neuroticism. Moreover, the study did not involve follow-up assessments for ERP measurements, which could show whether the effects of mindfulness training are delayed. Longer follow-up periods for questionnaires may also indicate the sustainability of improvements in self-report measures. Future longitudinal research, using an active control group and longer follow-up periods, should consider utilising physiological measures of stress, such as cortisol, to provide converging evidence on the stress-reducing effects of an MBSR course in typically ageing older adults.

General Discussion

This doctoral research project examined the effects of an MBI on neurocognitive markers of ageing and AD through a critical, theoretical review (Chapter 4) and a pseudo-randomised longitudinal study (Chapter 5 and Chapter 6). The review provided a theoretical discussion for the role of MBIs as a preventive intervention for AD, and suggested recommendations for future research on MBIs in an ageing population. Based on these recommendations and relevant neuroscientific research presented in the review, the predictions of this doctoral research project were developed. The predictions were tested in a pseudo-

randomised longitudinal study with a wait-list controlled design using self-report measures, EEG/ERPs, and ¹H-MRS.

The results of this pseudo-randomised longitudinal study indicated that an MBSR course may have limited effects on the neural markers, associated with ageing and AD, measured in this doctoral research study. In particular, the ¹H-MRS study (Chapter 5) only found marginally significant decreases for levels of Cr and increases of mI in the PCC for the training group following the MBSR course. These findings were contrary to the hypothesis; as it was predicted that Cr levels would not change following the MBSR intervention, and that mI levels would decline for the training group after the MBSR intervention. In ageing, increases in Cr levels may indicate glial proliferation (Reyngoudt et al., 2012, Suri et al., 2017), thus it could be suggested that mindfulness practice may reduce age-related gliosis. However, the training group displayed a trend for increases in mI, a neurometabolite that is also potentially associated with glial proliferation (Rosen & Lenkinski, 2007). Therefore, the argument that mindfulness training leads to reductions in age-related gliosis could be considered tenuous.

While no previous research has utilised ¹H-MRS to examine the effects of an MBSR course, a cross-sectional study with meditators and healthy controls similarly documented increased mI in the PCC for meditators (Fayed et al., 2013). In light of findings from Fayed et al. (2013) and given that some researchers state that mI may not index glial proliferation specifically ($\ddot{O}z$ et al., 2010; Stagg & Rotham, 2014), the trend towards an increase in mI in the mindfulness group cannot be easily interpreted as suggesting cognitive decline. Future longitudinal research, with an adequate sample size (N = 101.00) is necessary to determine if the trend for increases in mI following an MBSR intervention can be replicated and linked to other markers of cognitive decline.

In relation to the ERP study (Chapter 6), no significant effects of an MBSR course were documented for the mean amplitude/latency of the P600 and N400 to the repetitive semantic

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categorisation task. In addition, no significant changes were shown for response times to this task. This was contrary to predictions that the N400 and the P600 would should enhanced repetition suppression effects, as indexed by attenuated amplitudes to repeated items, following the MBSR course. Given that the N400 and P600 are associated with memory processes, including semantic and episodic memory, it could be argued that an MBSR course does not directly impact these memory processes. However, this interpretation is contradictory to previous research on MBIs, which has found improvements in episodic memory, as measured by cognitive assessments (Brown, Goodman, Ryan, & Anãlayo, 2016).

Therefore, future research on MBIs and memory processes may consider employing neuropsychological assessments to index possible changes in memory for the training group.

In regards to the self-report measures, the results showed positive effects for an MBSR course on stress, depression, well-being, and neuroticism. Specifically, a significant decrease in depression, stress, and neuroticism was documented for the training group following the MBSR intervention. These findings are in line with previous investigations of MBIs (Oken et al., 2017; Shapiro, Astin, Bishop, & Cordova, 20051 Würtzen et al., 2012). Also similar to a previous study (Carmody & Baer, 2008), a significant improvement in well-being was reported for the training group after the MBSR intervention.

Self-report measurements also showed that a standardised eight-week MBSR course is acceptable for typically ageing older adult participants. Across both experimental studies, training group participants rated the course with high satisfaction. However, it was also noted that only approximately 56.30% to 60.00% of the participants reported completing home practice every day, which could have an impact on the cultivation of mindfulness skills. Therefore, future investigations may consider adapting the home-based practices to shorter sessions to encourage more practice outside of the weekly group-based sessions.

Interestingly, the reductions in stress and improvements in well-being correlated with course satisfaction. This highlights the importance of ensuring that an intervention is appropriate and well-suited for the population. In terms of home practice, only change scores (post-pre) of Glu correlated with home practice, which could imply that significant changes in Glu would be seen in a larger sample of participants who practiced frequently.

In addition to self-report measures, findings of this study indicated that neuroimaging measures (e.g. ¹H-MRS) can be feasibly employed to longitudinally examine neurochemical changes in the PCC before and after an MBSR intervention. As such, future studies should consider employing ¹H-MRS to understand the neurochemical effects of an MBI. Based on recommendations from the power calculations, future investigations using this methodology should recruit a large sample size of 101.13 participants in total.

Considering the outcomes to the pseudo-randomised longitudinal study, it could be concluded that the MBSR course is more effective in modulating participants' reports of wellbeing, depression, neuroticism, and stress in comparison to physiological measures associated with ageing and AD. This interpretation is contradictory to prior research that has suggested that MBIs may modify neural and cognitive markers of decline seen in ageing and AD (Gard, Hölzel, & Lazar, 2014; Larouche et al., 2014; Wells, Yeh et al., 2013). However, a recent review conducted by Berk et al. (2017) stressed that the evidence for effects of MBIs on cognitive measures in the context of ageing is mixed and inconclusive. Furthermore, a randomised controlled trial (RCT) with stressed older adults, aged 50 to 85 years, similarly documented limited effects of a mindfulness meditation intervention on neuropsychological assessments and physiological measures, such as heart-rate variability and salivary cortisol (Oken et al., 2017). However, significant improvements in self-report measures of stress, neuroticism, and mental health quality of life were reported for the training group at post-testing in comparison to the WLC group. As such, combined with the results reported in this thesis, the results of the study conducted by Oken et al. (2017) support the theory that MBSR is more suited for improving well-being and stress than improving cognitive function directly in a typically ageing population.

The improvement in well-being, depression, and stress-related measures following an MBSR course for typically aging older adults may have clinical implications for the overall health of an ageing population. In particular, increased levels of well-being may have a protective influence on the physical health of older adults (Friedman & Ryff, 2012; Ostir, Markides, Peek, & Goodwin, 2001; Steptoe, Deaton, Stone, 2015). For example, Ostir et al. (2001) reported an association between higher levels of self-reports of positive affect and a lower incidence of stroke in adults, aged 65 years and older. In contrast, increased levels of self-reported stress, neuroticism, and depression may be damaging to the physical health of older adults (Henderson et al., 2012). Indeed, Henderson et al. (2012) found that higher levels of self-reported distress, measured by stress, depression, life satisfaction, and neuroticism scales, were associated with an increased risk of haemorrhagic stroke in older adults, aged 65 years and above. As such, it could be theorised that an MBSR intervention may impact well-being and thereby improve physical health in older adults. Future research should therefore include measures of physical health to investigate this theory.

Limitations, Interesting Complications, and Future Research

Several limitations were identified in the experimental studies. More specifically, the smaller size in the experimental studies could be considered a limitation. While the sample size used in the feasibility pilot investigation of ¹H-MRS (Chapter 5) was appropriate for the study aims, a larger sample size would be required for a full study. Based on the power analysis conducted in this study a sample size of 63 participants are recommend to achieve a power of 80%. To achieve a 95% power level, a 101 participants are needed. Therefore, future studies should consider recruiting at least 31 participants per condition. In regards to the ERP study (Chapter 6), the sample size was suitable for ERP measurements. Indeed, Luck (2014) recommended that ERP investigations include 10 to 20 participants. However, a larger sample size may be necessary for questionnaire measures.

Other limitations of these studies are the lack of a longitudinal follow-up period for neurocognitive measures and the limited follow-up period for questionnaires. Interestingly, in Chapter 6, self-report measures of stress and neuroticism only showed changes from pre-testing to follow-up testing. Thus, it is possible that positive effects of an MBSR course are delayed, and/or requires more mindfulness practice. Follow-up testing, using ¹H-MRS and ERPs, could reveal a positive impact of mindfulness-based training on neurometabolites and ERP components. In addition, a longer follow-up period could indicate whether changes in self-report and neurocognitive measures are maintained. It is therefore recommended that future research utilise 3-month, 6-month, 1-year, and 2-year follow-up testing to determine the sustainability of effects of an MBSR course.

The absence of an active control group in both experimental studies is also a limitation. Without an active control group, it is difficult to ascertain whether the findings of this study are specific to the MBSR course. As highlighted in Chapter 5 and Chapter 6, the group-based and psychoeducational aspect of the MBSR course may impact the changes documented in self-report and neurometabolite measures. For example, Williams et al. (2014) reported no significant difference in the risk of depression relapse between a Mindfulness-Based Cognitive Therapy (MBCT) intervention and a cognitive psychoeducation intervention that was structured similarly to MBCT, but involved no mindfulness practice. In addition, it could be suggested that as MBSR is a cognitively stimulating activity, it is this cognitive stimulation itself which may lead to the increases in mI and decreases in Cr. Previous studies have suggested that activities which involve cognitive stimulation may lead to neuroplasticity (Boyke, Driemeyer, Gaser, Büchel, & May, 2008) and cognitive improvements (Ball et al.,

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2002) in older adults. Therefore, future investigations should utilise both an active control group, that involves a cognitively engaging task, in addition to a WLC group, to determine if modulations in mI, Cr, depression, well-being and stress-related measures are specific to mindfulness training. As discussed in Chapter 5, a potential intervention that could be used is the Health Enhancement Program (MacCoon et al., 2011), which is similar in design and length to an MBSR course.

The use of the repetitive semantic categorisation task for the ERP study (Chapter 6) is another area that should be considered a potential limitation. It could be argued that this task was specifically designed for participants with cognitive impairment (Olichey et al., 2006), and thus may not effectively assess neurocognitive changes in typically ageing older adults. However, it was hypothesised that this task would be appropriate to detect modulations in semantic and episodic memory processes in a typically ageing cohort. In particular, it was postulated that the task would tax attention and working memory processes sufficiently enough to detect changes in semantic memory. Nevertheless, it may be prudent for future studies to employ other, more appropriate tasks, to measure the impact of an MBSR course on ERP markers in a typically ageing population. Although this study was particularly interested in semantic and episodic memory, a potential ERP task that could be used in future studies is the Go/NoGo task, which measures inhibitory processes (Falkenstein, Hoorman, & Hohnsbein, 1999; Jodo & Kayama, 1992). In healthy ageing, declines of inhibition have been reported (Persad, Abeles, Zacks, & Denburg, 2002). Thus, investigations with typically ageing older adults could measure changes in the amplitude of the N200, an ERP component associated with response inhibition (Falkenstein et al., 1999), to No-Go stimuli after an MBSR course.

The characteristics of the participant sample should also be considered when interpreting the findings of this PhD study. In particular, it could be argued that the participant sample for both experimental studies is not representative of a typical ageing population in the

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UK. In this PhD study, it was the responsibility of the participant to express interest in the investigation. Participants also had to commit to completing multiple testing sessions, and to possibly participating in an eight-week MBSR course. As such, it could be suggested that as participants were self-selected, they may have an interest in psychological research and mindfulness-based practices. Moreover, they may be at the higher end of the range of cognitive function abilities in comparison to a typically ageing population. Alternatively, it could be argued that participants may have expressed interest in the study because they experienced subjective cognitive decline.

In this PhD study, it was not possible to control for medication usage and previous meditation experience, such as yoga, because of difficulties in recruiting older adults. While limited studies have specifically examined the effects of medication on neurometabolites and ERP components, a potential criticism is that medication could influence these measures. Although, it should be stated that participants were excluded if they reported a regular usage of painkillers. In relation to meditation experience, previous research has indicated that yoga practice may influence quality of life (Oken et al., 2008), executive function (Gothe, Karmer, & McAuley, 2014), and perceived stress (Hewett, Randsell, Gao, Petlichkoff, & Lucas, 2011). Thus, it could be suggested that potential differences in previous meditation experiences between the training group and WLC group impacted results. However, a counter argument could be made for not excluding participants who use medication and/or have previous meditation experience. Specifically, the sample may be more representative of an older adult population, and thus have higher ecological validity. For example, a large population-based study in the UK reported that only 7.8% of older adults, aged 65 and above, take no medication (Gao et al., 2017). However, this study did exclude participants with medical diagnoses, thus it could include participants with cognitive decline.

Another potential criticism of both studies is that did not involve participants with cognitive impairment. Consequently, only tentative implications can be proposed in relation to how an MBSR course may affect individuals with MCI or AD. Another limitation of this study is the lower reliability of some self-report measures; the cronbach alpha for the anxiety subscale of the DASS-21 indicated lower reliability at post-testing. However, all other measures showcased good reliability across testing sessions.

In addition to the limitations of these studies, several interesting findings were reported that could impact the interpretation of the results. Specifically, in both experimental studies, no significant changes to self-report measures of trait mindfulness were reported.

This could indicate that mindfulness does not play a key role in the impact of neurometabolites, well-being, depression, and stress-related measures in an MBSR course for typically ageing older adults. Alternatively, it could be argued that self-report measures do not accurately index changes in mindfulness. Therefore, future research may consider employing ecological momentary assessments (EMA), which involves real-time assessment completed outside a labtesting environment across multiple time periods (Shiffman, Stone, & Hufford, 2008). Previous research with older adults, aged 65 years and older, indicated that EMA may be more sensitive to changes in trait mindfulness after an MBSR course in comparison to a self-report measure (Moore, Depp, Wetherhell, & Lenze, 2017). Another recommendation for future studies is to utilise a more specific type of mindfulness training that is known to elicit mindfulness. For example, a longitudinal ERP investigation on cognitive and emotion processing with older adult participants, aged 55 years to 75 years, used a shortened mindful breath awareness task as a form of mindfulness training (Malinowski, Moore, Mead, & Gruber, 2017). While overall scores of mindfulness did not change following the intervention, a sub-scale of the mindfulness measure did showcase improvements for the training group at post-testing. Thus, future studies could employ a similar mindfulness training program.

Another potentially interesting finding that should be considered is the contradictory findings on the PSS (Cohen et al., 1983) and the stress sub-scale of the DASS-21 (Lovibond & Lovibond, 1995). While no significant changes of perceived stress were noted on the PSS (Cohen et al., 1983), the DASS-21 (Lovibond & Lovibond, 1995) measure revealed significant reductions in stress for the training group from pre-testing to follow-up testing. This could be due to differences in how stress is operationalised and assessed by both measures. For example, the PSS questionnaire indexed the level to which events are evaluated as stressful in the past month (Cohen et al., 1983). However, the stress-subscale of the DASS-21 (Lovibond & Lovibond, 21) measured more arousal and tension that is experienced in the past week. Therefore, it could be concluded that while training group participants reported decreases in arousal following the MBSR course, this was not coupled with declines in perceived stress. To provide converging evidence for the stress-reducing effects of mindfulness training, future longitudinal research should consider employing both self-report measures of stress and a physiological measure of stress, such as salivary cortisol. Cortisol measurement may provide a more objective measure of stress, and provide insights into the HPA-axis response to stressors. In addition, EMAs could be utilised to index modulations in stress levels after an MBSR course.

Future studies on the effects of MBIs on neurocognitive markers of ageing and AD may also consider alternative avenues for investigating this question. Specifically, studies should examine whether MBSR is more effective for highly stressed older adults or older adults with subjective cognitive decline. Given that midlife stress is associated with a greater risk for cognitive decline (Johansson et al., 2013), longitudinal research introducing an MBSR course to middle-aged adults could be useful to track how an MBSR course impacts projected neurocognitive decline in ageing.

Conclusion

Overall, the findings of this study contribute to the growing body of literature on mindfulness and ageing. Specifically, the findings tentatively indicate that an MBSR course may have a limited impact on the neurocognitive markers of ageing and AD that were measured in this study using ¹H-MRS and ERPs. However, the findings suggest it is feasible to use ¹H-MRS longitudinally to examine neurochemical changes resulting from a mindfulness intervention. Moreover, the results indicate that an MBSR training is an acceptable intervention with good compliance amongst this study's cohort. Self-report findings showed that an MBSR course may significantly improve depression, well-being, and stress-related measures in typically ageing older adults. As such, MBSR could be proposed as an alternative intervention for promoting well-being in an ageing population. In total, it is hoped that the findings of this PhD study will both stimulate and provide some guidance as to participant numbers required for future multi-method longitudinal RCTs using different imaging techniques, self-report measures, physiological measures of stress, and EMAs, to assess the effects of MBIs on typical ageing and age-related diseases.

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