

**An Investigation of the Effect of Mindfulness Training on Immunological
Biomarkers and Memory Recall**

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2018

MHSc in Psychology

**An Investigation of the Effect of Mindfulness Training on Immunological
Biomarkers and Memory Recall**

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A thesis submitted to Auckland University of Technology in fulfilment for the
requirements for the degree of Master of Health Science in Psychology
(Rehabilitation Psychology)

2018

Faculty of Health and Sciences

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgments), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institutions of higher learning.

Signed: *Ninad Patel*

Date: 12/12/2018

Acknowledgements

I would like to acknowledge and thank my supervisors Professor Richard Siegert and Dr. Grace Wang, for whom I am very grateful for all their advice, guidance, and input in this thesis. A heartfelt thanks to my study/support group and family who pushed me on and gave me encouragement and support throughout the process. I am very grateful to you all.

Abstract

Background: Pro-inflammatory cytokines have been implicated in the pathophysiology and maintenance of numerous diseases and disorders. Recently, the link between pro-inflammatory cytokines and cognition has also been found. Although studies have shown that mindfulness meditation can improve pro-inflammatory immune profiles and cognition, the link between improved cognitive function and pro-inflammatory immune profiles remains unclear. Furthermore, the existing studies have predominantly assessed populations with chronic illness (i.e. cancer), which makes it challenging to generalize the findings to the healthy population.

Objective: The present study aimed to examine 1) the effect of mindfulness on biomarkers of immune system and memory; and 2) the correlations between these immunological measures and memory in the healthy population.

Methods: Participants (n=26) undertook a 6-week mindfulness training intervention which was delivered via videoconferencing. Delayed and immediate memory recall was assessed utilising the computerised cognitive battery. CD4, CD8, CD69, Interleukin-6 (IL-6), C-reactive protein (CRP), and cortisol was examined with blood assays. An important involvement of CD4 and CD8 in short and long delay memory was further supported by logistical regression.

Results: There were significant improvements in immediate and long delay recall following mindfulness training, whereas immunological measures remained relatively stable and only significant change was found in CD69. Both CD4 and CD8 at baseline was found to be negatively correlated with long delay recall, together with a positive correlation between baseline CD8 and short delay recall.

Conclusion: Mindfulness training may improve memory and certain immunological biomarkers in the healthy population, and an association between memory recall and immunological measures was also found. In line with existing findings, our findings support an important role of immune system in memory and both could be improved with a brief mindfulness training.

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Chapter One: Introduction

The immune system is vital for well-being and human health, as it assists coordination of the body's reaction to infections and physical injuries, which if left unattended to, can cause illness or death (Slavich & Irwin, 2014). This system is commonly observed to be composed of two interconnected branches: innate immunity and adaptive immunity (Irwin & Cole, 2011). The innate immunity is the older evolutionary branch responsible for the body's first line of defense against microbial infection and tissue damage (Reiche, Nunes, & Morimoto, 2004). Innate immunity is comprised of immune cells, including dendritic cells and macrophages/monocytes that persistently circulate in the body and utilize invariant receptors to identify a broad range of pathogens (Medzhitov, 2007). These immune cells signal the incidence of infection or injury and initiate a cascade of inflammatory processes that facilitate aid to contain an infection and promote healing and recovery (Murphy, Slavich, Rohleder, & Miller, 2012).

In the event when the innate immune system defense is deemed insufficient, adaptive immunity is activated by these immune cells (Barton, 2008). Contrary to innate immunity, which is nonspecific and does not provide long-term protection, adaptive immunity encompasses the proliferation of microbial-specific white blood cells (i.e. lymphocytes) that attempt to eliminate or neutralize pathogens based on an immunological memory of having responded to the same specific pathogen previously (Gruys, Toussain, Niewold, & Koopmans, 2005). Whilst the innate immune response is fast, acting over minutes or hours, the adaptive immune response cultivates fully over several days (Chiu, von Hehn, & Woolf, 2012).

Cytokines play a significant role in immune system and inflammatory processes (Raison & Miller, 2011). Cytokines are glycoproteins that regulate the functions of the immune system (Zhang & An, 2007). Although 'cytokine' is the general name, it can vary depending on the cell that it is secreted from, for example, monokine (cytokines made by monocytes), lymphokine (cytokines made from lymphocytes), chemokine (cytokines made from chemotactic activities), and interleukin (cytokines made from one leukocyte and acting on other leukocytes) (Holdsworth & Gan, 2015). Amongst managing cell-to-cell communication, cytokines can change neuroendocrine and neurochemical

processes that have extensive effects on physiology and behaviour (Curfs, Meis, & Hoogkamp-Korstanje, 1997). Discharged from immune cells such as neutrophils, monocytes/macrophages, and dendritic cells, cytokines could be considered to function comparable to hormones and neurotransmitters in the sense that they facilitate physiological responses, rely on receptor-ligand interaction, and have distal (endocrine), self (autocrine), and local (paracrine) effects (Dhabhar, Malarkay, Neri, & McEwen, 2012). Cytokines have specific effects on the body that are generally known as signs of inflammation (Zalli, Jovanova, Hoogendijk, Tiemeier, & Carvalho, 2015). For example, at the sites of infection, cytokines cause swelling, redness, heat, and pain (Ricciotti & Fitzgerald, 2011).

At the more systemic level, specific cytokines (e.g. IL-6) stimulate the production of the acute-phase protein (key biomarker of inflammation) C-reactive protein (CRP), which, collectively with cytokines, can lead to increased fever, heart rate, body temperature, and respiratory rate (Poon, Ho, Chiu, & Chang, 2013). Together, these effects aid in accelerating wound healing, and constrain the spread of infection (Steptoe, Hamer, & Chida, 2007). The purpose of this process is to remove the inducing stimulus from the response and initiate local tissue recovery (Serra et al., 2017). Social-behavioral withdrawal is also promoted by these effects, which supports the organism to recover and recuperate, and reduces the probability of the infection spreading (Murphy et al., 2013). Cytokines that direct cell functions related to inflammation, and those that are responsible for increasing or up-regulating inflammation are called pro-inflammatory, while down-regulating cytokines are referred to as anti-inflammatory (Hiles, Baker, de Malmanche, & Attia, 2012).

Physiologically, it is clear that a fast-acting innate immune system and inflammatory response to a particular trigger and down-regulating the response after the pathogen has been neutralized are both vital for restoring tissue damage, combating infection, and reestablishing a state of homeostasis (Medzhitov, 2008). Nonetheless, recent literature has indicated that altered or prolonged inflammatory response can sometimes cause more damage to the organism than the pathogen (Barton, 2008; Radtke, MacDonal, & Tacchini-Cotter, 2013; Rivest, 2009). Certainly, it is now recognized the role chronic inflammation plays in numerous major diseases, including, diabetes,

asthma, certain cancers, arthritis, obesity, and Alzheimer's disease (Couzin-Frankel, 2010). Furthermore, cytokines such as tumor necrosis factor α (TNF- α) and interleukin-1 beta (IL-1B) have been observed to induce synaptic pruning, leading to impairments in neuroplasticity and changes in brain structure, which in turn can negatively influence cognition (Rosenblat, Cha, Mansur, & McIntyre, 2014). This cascade of events can be specifically detrimental to the sensitive hippocampal region, causing complications in memory and learning (Baune et al., 2012).

In recent years, mindfulness training has gained traction as a promising and feasible intervention for enhancing both physical and physiological health (Fountain-Zaragoza & Prakash, 2017). Broadly outlined, mindfulness can be defined as the cultivation of sustained attention in a framework of acceptance and non-reactivity (Kabat-Zinn, 1982). Extensive research documents the efficacy of mindfulness-based interventions (MBI) in the treatment of clinical disorders, such as, eating disorders (Tapper et al., 2009), major depression (Crane et al., 2015), multiple sclerosis (Simpson et al., 2014), anxiety (Hofmann, Sawyer, Witt, & Oh, 2010), certain aspects of cancer (i.e. fatigue) (Bower et al., 2010), and HIV pathogenesis (Creswell, Myers, Coles, & Irwin, 2009).

Furthermore, studies have also found mindfulness meditation to improve immune function (Carlson, Speca, Faris, & Patel, 2007), attention (van der Hurk, Gionmi, Gielen, Speckens, & Barendregt, 2010), memory (Wass, Scerif, & Johnson, 2012), and reduce cortisol and blood pressure levels (Davidson et al., 2003). Currently, there is a gap in knowledge on the relationship between inflammation and memory and the possible effects of mindfulness on these two variables. Furthermore, to knowledge, no studies have investigated the effects of mindfulness intervention on inflammation and memory in a non-clinical population. Especially considering that majority of studies use a traditional face-to-face mindfulness intervention, whereas, the present study utilizes a novel approach via webinar. Meaning, the therapy is given through the medium of the internet.

The present study attempts to address some of these gaps. This research is structured as per the following: Chapter 2 reviews the current literature on mindfulness,

inflammation, memory and the effect of each variable on each other. Chapter 3 covers the method and structure of the mindfulness intervention utilized in the current study. Next, along with descriptive statistics of the participants, the results from the study is summarized in Chapter 4. Finally, the findings of the experiment are interpreted and related to existing literature in Chapter 5, while also concluding with limitations of the study, research implications, future direction, and general overview of the research.

Chapter Two: Literature Review

Inflammation

Chronic inflammation plays an increasingly recognized role in the pathogenesis of numerous behavioural and neurological disorders including cognitive impairment and depression (Felger & Lotrich, 2013; McAfoose & Baune, 2009; Schiepers, Wichers, & Maes, 2005). Additionally, chronic inflammation contributes to the pathogenesis of various related metabolic disorders, and these disorders have been revealed to in turn exacerbate the elevated inflammatory state, thus producing a vicious cycle (Festa, D'Agostino, Howard, Mykkanen, Tracy, & Haffner, 2000; Hansson, 2001; Van Gaal, Mertens, & De Block, 2006). Numerous studies have shown the association between depression and inflammation (Capuron et al., 2003; Dowlati et al., 2010; Eisenberger, Berkman, & Inagaki, 2010) and how the two closely interlinked conditions can instigate and aggravate each other in a bidirectional pathway, in which inflammation promotes depressive behaviour, and depressive behaviour enhances inflammation (see Figure 1.) (Amodeo, Trusso, & Fagiolini, 2017; Dantzer, 2012; Howren, Lamkin, & Suls, 2009).

Communicatory pathways between systems allow for immune dysfunction to add to both endocrinal and neural impairment via various inflammatory mechanisms (see Figure 2.) (Amodeo et al., 2017). Pro-inflammatory mediators act on vagal afferents by their ability to directly influence the nervous system (Maier, Goeler, Fleshner, & Watkins, 1998), or by crossing the blood brain barrier (BBB) either through specialized active transporters (Bankz, Ortiz, Plotkin, & Kastin, 1991), or via leaky sites at the circumventricular organs (Watkins, Maier, & Goehler, 1995). Furthermore, pro-inflammatory cytokines have shown to directly act on receptors within the hypothalamic-pituitary-adrenal (HPA) axis by influencing hormone secretion (Chesnokova, Melmed, Angeles, & Angeles, 2014). Alternatively, various cytokines have demonstrated to indirectly effect endocrinal and neural disorders by varying the regulation of enzymes, leading to an imbalance in critical neuroactive compounds (Oxenburg, 2007).

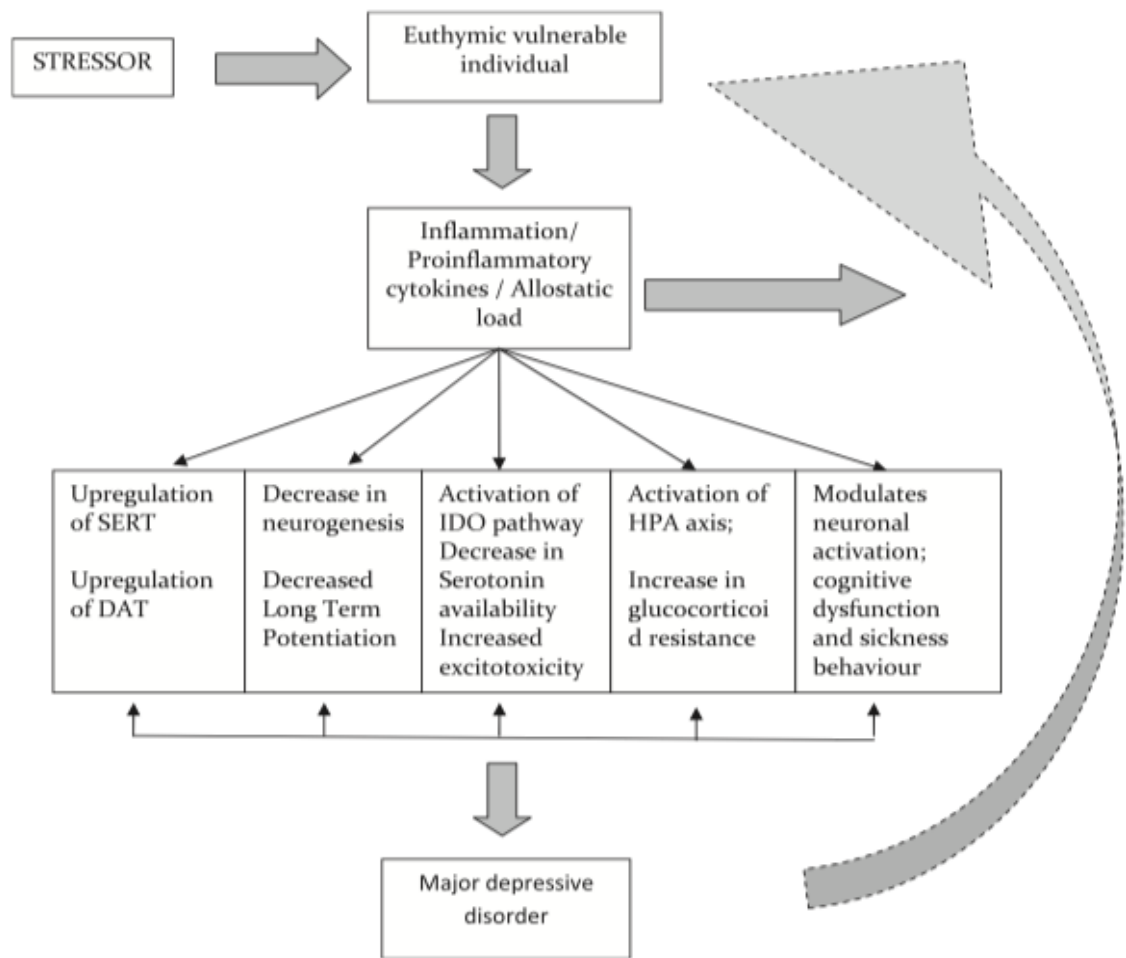


Figure 1. Potential pathways to which inflammation could contribute to the pathogenesis of major depression. Inflammation is induced in reaction to a stressor. Pro-inflammatory cytokines stimulate glia indoleamine dioxygenase, initiating the kynurenine pathway, which channels available tryptophan (substrate for serotonin synthesis) to form 3-hydroxy kynurenine (3HK), kynurenine (KYN), and quinolinic acid (QUIN), instead of serotonin (5TH). This accumulation of QUIN and 3HK contributes to calcium mediated cell death and excitotoxicity. Cytokines such as TNF- α induces glucocorticoid resistance via the prevention of cortisol-glucocorticoid receptor (GR) complex entry into the nucleus and also inhibiting the binding of cortisol-GR complex to DNA, leading to over-activation of the HPA-axis. DAT, dopamine transporter; HPA, hypothalamic-pituitary-adrenal; IDO, indoleamine dioxygenase; SERT, serotonin transporter (Krishnadas & Cavanagh, 2012).

The relationship between cognitive dysfunction and neuroinflammation is supported by studies demonstrating an association between markers of inflammation

and diseases like Alzheimer disease (AD), mild cognitive impairment, and Parkinson's disease (Amodeo et al., 2017; Eikelenboom & Van Gool, 2004). For example, beta-amyloid plaques in late stage Alzheimer's disease are frequently co-localized with pro-inflammatory cytokines (see Figure 3.) (Eikelenboom et al., 2006). The effect of chronic inflammation on HPA axis dysregulation and hippocampal volume could play a crucial role in the severity of cognitive impairment and depression (Allison & Ditor, 2014). Correlation between reduced scores in verbal recognition memory and hippocampal volume loss in the form of decreased grey matter density has been observed in depressed individuals (Shah, Ebmeier, Glabus, & Goodwin, 1998).

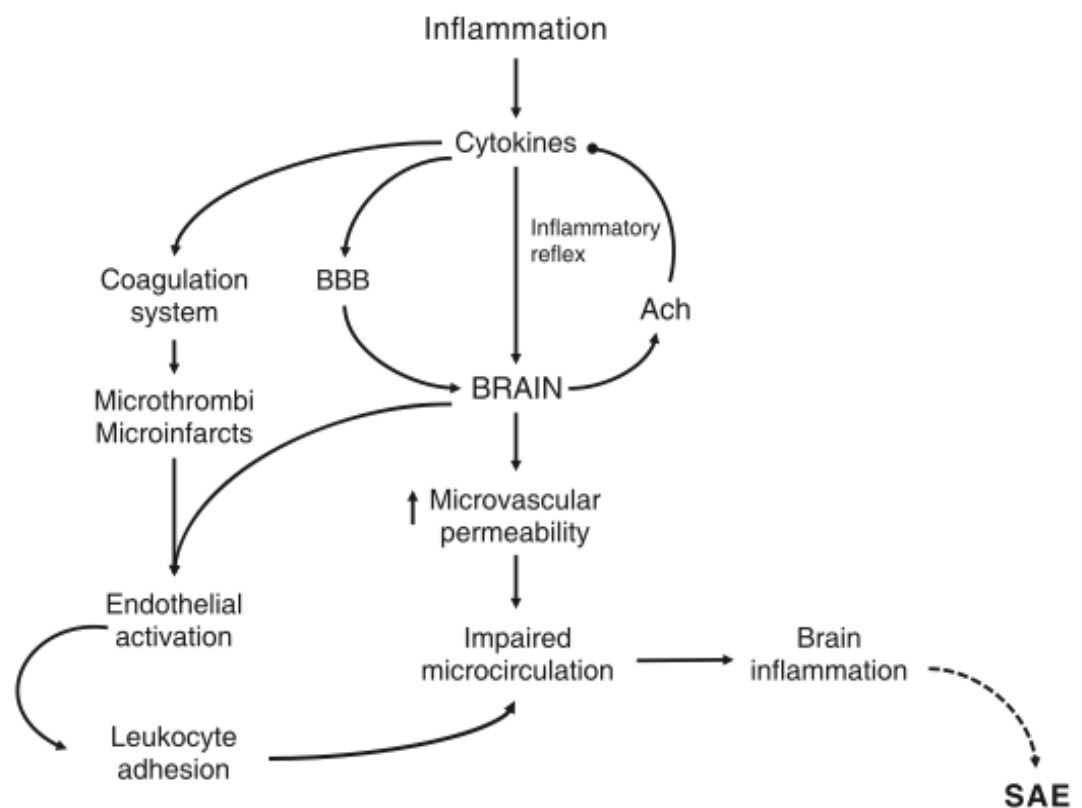


Figure 2. Pathway for cytokine-induced brain inflammation. Afferent signals to the brain are activated by cytokines produced in the infection site, and the subsequent vagal activation prevents cytokine synthesis via the “inflammatory reflex” of the cholinergic pathway. The structure and function of the blood-brain-barrier (BBB) is altered by inflammation, impairing microcirculatory blood flow, increasing microvascular permeability, and producing brain inflammation. During sepsis, changes in the coagulation system results in microinfarcts and microthrombus formation.

Activation of endothelial also impairs microcirculation and worsens brain inflammation, which in turn is linked to brain dysfunction. Ach, acetylcholine; BBB, blood-brain-barrier; SAE, sepsis-associated encephalopathy (Dal-Pizzol, Tomasi, & Ritter, 2014).

Numerous studies have found the presence of increased inflammatory cytokines in patients with disorders such as major depressive disorder (MDD) (Alesci et al., 2005; Danner, Kasl, Abramson, & Vaccarino, 2003; Musselman et al., 2001). Type 1 cytokines include interleukin (IL)-1, tumor necrosis factor- α (TNF- α), and interferon- γ , which serve the critical role of enhancing cellular immune responses (Amodeo et al., 2017). Type 2 cytokines are especially associated with antibody response and these include IL-6, IL-10, and IL-13 (Krishnadas & Cavanagh, 2012). Furthermore, acute phase proteins such as C-reactive protein (CRP) are also prompted by these cytokines to further activate the immune system (Miller, Maletic, & Raison, 2009).

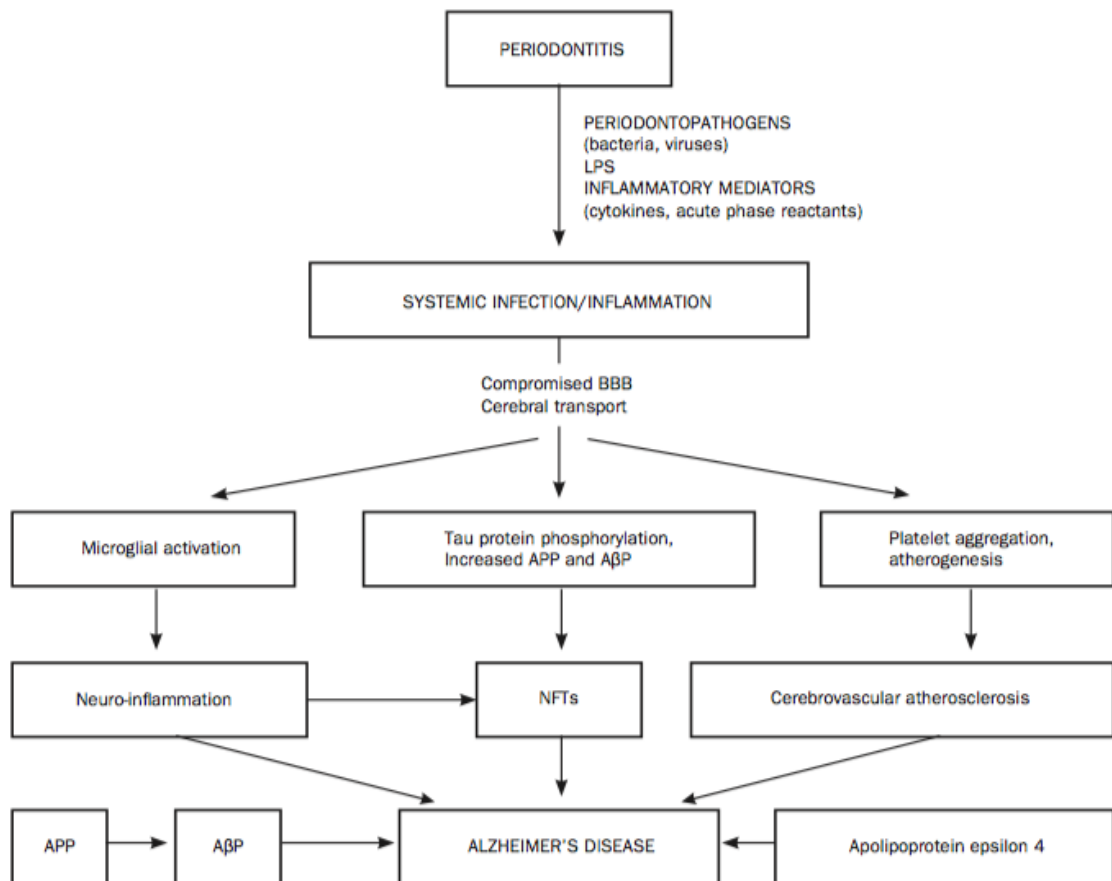


Figure 3. Two probable inflammatory mechanisms for the pathogenesis of AD:

1) periodontitis; 2) viral and bacterial influence. First mechanism involves host response and periodontal pathogens to increase levels of pro-inflammatory cytokines, leading to a range of pro-inflammatory agents and cytokines to surge into the systemic circulation. These pro-inflammatory molecules can deteriorate the blood-brain-barrier (BBB), gaining access to the cerebral regions and resulting in activation of microglial cells and adverse effects leading to neuronal damage. According to the second mechanism, bacteria and viruses residing in the dental plaque biofilm invade the brain directly through cerebral transport via peripheral nerves or via blood streams. This involves cytokines arbitrated interactions between glial cells and neurons. Cytokines such as TNF- α exacerbates demyelination, gliosis, inflammation, BBB deterioration and cell death. LPS, lipopolysaccharide; BBB, blood-brain-barrier; APP, amyloid precursor protein; A β P, amyloid beta protein; NFTs, neurofibrillary tangles (Gurav, 2014).

The relationship between inflammation and depression is evident throughout the adult lifespan (Bouhuys, Flentge, Oldehinkel, & Van den Berg, 2004; Kahl et al.,

2005), and even apparent in cases of individuals with mild depressive symptoms that do not meet the criteria for MDD (Suarez, Lewis, Krishnan, & Young, 2004). Additionally, evidence of inflammatory activation in healthy individuals has also been associated with even single depression-related symptoms (i.e. anger, fatigue, and insomnia) (Irwin et al., 2004; Suarez, Lewis, & Kuhn, 2002). A meta-analysis of over 50 studies found majority of research reported an elevation in pro-inflammatory cytokines, IL-6, IL-1B, and CRP among depressed patients (Howren, Lamkin, & Suls, 2009).

Effects of Neuroinflammation

Inflammation within the brain can have extensive acute and long term effects on cognition (Sartori, Vance, Slater, & Crowe, 2012). Supplemental to localized and immediate damage that follows in reaction to neurotoxic inflammatory enzymes, neuroinflammation over extended period of time is associated with risk of dementia and cardiovascular pathology, including stroke (Blasko et al., 2004, Kuo et al., 2005, Paul et al., 2004). Typically, neurodegeneration can be initiated by inflammation due to activation of the brain's resident immune cells – cytokines and microglia – which produce a great quantity of pro-inflammatory factors (Russo, Barlati, & Bosetti, 2010) and are detrimental to brain cells. According to Raz and Rodrigue (2006), the stimulation of neurotoxic products like reactive oxygen species and certain damaging enzymes from either acute or chronic inflammation processes, can cause brain tissue damage (Blasko et al., 2004). Brain structures such as basal ganglia and hippocampus (structures that play vital roles in cognitive processes such as perception, attention, emotion, and memory) contain more enzymes involved in an inflammatory response than do primary motor or sensory cortices; thus, these areas may sustain an increased risk of accumulative damage from subclinical inflammation (Raz & Rodrigue, 2006).

It is commonly accepted that humans' capability to learn, store, and retrieve information is supported by distinct memory systems (Squire, 2004). While distinct memory systems have been recognized, it is crucial to acknowledge that different memory systems compete and cooperate to support memory and learning (Packard & Knowlton, 2002; Squire, Stark, & Clark, 2004). Consequently, the skills and knowledge we acquire, including language, could be thought of as a result of these interacting memory systems rather than a set of systems working independently (Lum & Conti-Ramsden, 2013). Although there are several categories of memory, it can be classified generally into two categories: short-term memory (STM) and long-term memory (LTM) (Amin & Malik, 2013). STM refers to a temporary storage of limited amounts of information for a brief period, usually up to 15 seconds for approximately 7 items (Archibald & Gathercole, 2006). LTM is the collection of information over extensive period of time; includes unlimited amounts of information (Shrager, Levy, Hopkins, & Squire, 2008).

Several studies have examined the concept of working memory (WM), which refers to a capacity that stores limited quantity of material temporarily in the brain for manipulation in order to facilitate learning and reasoning abilities (Baddeley, 2003; Shrager, Levy, Hopkins, & Squire, 2008). Engle (2004) differentiated WM from STM by defining WM as the attention aspect of STM, whilst Cowan (2008) distinguished WM as a storage component comparable to STM, and provides additional processing mechanisms to support the use of STM. Nevertheless, both systems have frequently been used interchangeably in clinical research (Chang, Kinshuk, Chen, & Yu, 2012), suggesting a discrepancy of both constructs from a functional point of view (Aben, Stapert, & Blokland, 2012).

Various studies recognise the coexistence of both WM and STM (Gathercole & Alloway, 2006; Nadel & Hardt, 2010), but it is also asserted that the term STM has been replaced by WM (Gray, 2007) or that WM is a theoretical concept of STM (Davelaar, 2013). According to the original WM model, Baddeley and Hitch (1974) defined WM as the preservation and controlled manipulation of limited amount of information before

recall, nonetheless occasionally the distinction between STM (i.e. maintenance) and WM (i.e. maintenance plus manipulation) is not clearly defined in recent literature (Davidson, Amso, Anderson, & Diamond, 2006; Jensen, Kaiser, & Lachaux, 2007). Conclusively, both constructs have been suggested to represent the same cognitive process (Unsworth & Engle, 2007).

Immune proteins and signalling play various critical roles in the brain (Shatz, 2009). The central nervous system's own immune cells, astrocytes and microglia are necessary for regular synaptic functions such as synapse formation, synaptic pruning, and synaptic transmission (Papa, De Luca, Petta, Alberghina, & Cirillo, 2014; Stephan, Barres, & Stevens, 2014). Numerous studies in animal models of inflammation have found the causal role of inflammatory signalling in cognitive deficits and memory (Donzis & Tronson, 2014). As mentioned before, tumor necrosis factor- α (TNF α), Interleukin 6 (IL-6), and Interleukin 1 β (IL-1 β) are amongst the most common cytokines in the brain (Goehler, 2008). These proteins are heavily upregulated in the bloodstream after systemic inflammatory events including surgery (Terrando et al., 2011), sepsis model (Mina et al., 2013), lipopolysaccharide (LPS) injection (Skelly, Hennessy, Dansereau, & Cunningham, 2013), and other injuries (Bagdatoglu, Polat, Bagdatoglu, & Atik, 2008).

Systemic injection of lipopolysaccharide has shown to impair acquisition of operant conditioning (Aubert, Vega, Dantzer, & Goodall, 1995), memory consolidation (Pugh et al., 1998), and learning in Morris Water Maze tasks (Cunningham & Sanderson, 2008). Similarly, peripheral IL-6 levels are correlated with memory retrieval (Elderkin-Thompson, Irwin, Helleman, & Kumar, 2012). In humans, systemic triggers of inflammation, including major surgery (Hudetz et al., 2009), illness (Selnes et al., 2003), and injury (Shapira-Lichter et al., 2008) are associated with deficits in a range of memory and cognitive tasks. Patients with cancer, or after myocardial infarction, commonly develop cognitive deficits (Fredericks, 2012) or post-traumatic stress disorder (Meister et al., 2013) long after the illness, proposing an insistent role for immune function in alterations of memory.

The role of IL-6 is complex in memory, as it influences memory and learning in different, and even opposite ways under certain conditions (Trenova, Slavov, Miteva,

Manova, & Stanilova, 2016). IL-6 has been observed to be a regulator of neurogenesis, which is vital for modulating memory functions and cognitive functions, such as, memory consolidation and several types of hippocampal-dependent learning (Hryniewicz, Bialuk, Kaminski, & Winnicka, 2007). Furthermore, IL-6 has also shown to influence synaptic plasticity (Balschum et al., 2004; Jankowsky, Derrick, & Patterson, 2000; Tancredi et al., 2002) and memory improvements under impaired IL-6 signalling condition (Braidă et al., 2004). Hippocampal IL-6 levels have been observed to increase after learning (Del Rey, Balschum, Wetzel, Randolph, & Besedovsky, 2013), however, overexpression (Wei et al., 2012) or application of IL-6 has also shown signs of broad memory impairments (Tancredi et al., 2002).

Additionally, elevated levels have been associated with protection from memory loss (Heyser, Masliah, Samimi, Campbell, & Gold, 1997; Tha et al., 2000), nonetheless, IL-6 deficient mice show enhanced learning in mazes compared to control group mice (Braidă et al., 2004). Current research suggests the role of IL-6 depends heavily on certain conditions in which it is elevated, as well as on the duration (chronic or acute) and magnitude of the elevation (Yirmiya & Goshen, 2011). Findings propose that IL-6 is nonessential for memory and learning, yet contributes to cognitive impairments after an inflammatory event (Donzis & Tronson, 2014).

A two-year longitudinal study investigating global cognitive decline and inflammatory markers found participants with highest serum concentrations of C-reactive protein or IL-6 performed significantly worse at baseline and follow-up test, with a 24% increase of risk in cognitive decline compared to subjects with the lowest levels (Yaffe et al., 2003). A cross-sectional study by Wright et al. (2006) found negative correlation between Mini Mental State Examination score and serum IL-6. Maastricht Aging Study, 2003; Memory and Morbidity in Augsburg Elderly (MEMO) Study, 2008; and Health Aging and Body Composition (Health ABC) Study, 2009, found comparable results supporting the association between high concentrations of inflammatory factors and increased risk of cognitive decline, (Baune et al., 2008; Teunissen et al., 2003; Yaffe et al., 2009).

Contradictory results are presented when exploring the correlation between different cytokines and specific cognitive domain. For example, Elwan et al. (2003) found association between significant sensory memory and attention impairment and high IL-6 serum levels. The same cytokine exhibited negative correlation with executive functions (Mooijaart et al., 2013), working memory (Simpson et al., 2013), and IQ in healthy senior individuals (Krabbe et al., 2009). Contrastingly, Dik et al. (2005) and Baune et al. (2008) found no such relationship. The term “sickness behaviour” accompanied by temporary decrease in memory and attention functions is a well-established phenomenon in acute viral (i.e. influenza) infections (Trenova et al., 2016). An example of this phenomenon in action is the effect of administrated endotoxin in healthy individuals.

Reichenberg et al. (2001) found increased levels of IL-1ra, TNF-a, IL-6, cortisol, and soluble TNF receptors to produce a global decrease in memory functions, specifically, reduced delayed story recall, decreased immediate story recall, decreased performance in Word list learning, and deficit in delayed and immediate recall of figure items following 1, 3, and 9 hours post intravenous injection. Furthermore, the study found a significant positive correlation between delayed and immediate story recall impairments with the secretion of IL-1ra, IL-6, and TNF-a (Reichenberg et al., 2001).

Arnold et al. (2002) examined the causality between cytokine concentrations and cognitive impairments by assessing selective attention, executive control, and short-term memory after IL-6 administration. The study found observed improvements in short-term memory, with no global cognitive disturbances. This study expresses again the effects of elevated IL-6 levels are determined by various factors. In support of this theory are the results from studies assessing memory functions in patients with autoimmune diseases. Elevated serum levels of IL-6 were associated with higher learning scores in patients with systematic lupus erythematosus (Kozora, laudenslager, Lemieux, & West, 2001) and lower score for patients with relapsing-remitting multiple sclerosis in Mini Mental State Examination (Patanella et al., 2009).

Alzheimer’s disease (AD) patients show higher basal pro-inflammatory cytokine production in vitro (Rocha et al., 2012). A strong correlation has been found between

developing Alzheimer's disease and increased TNF- α serum levels, likewise, IL-18, IL-17, and IL-23 found in higher concentration in AD patient's serum compared to healthy individuals (Chen, Jiang, Li, Zhou, & Cheng, 2014). Samples obtained by post mortem or biopsy also display increased levels of IL-6, TNF- α , and IL-1 β in cerebro-spinal fluid in AD patients (Butchart & Holmes, 2011; Liu et al., 2013). CD69 is also associated with memory and found in monocytes derived from AD patients (Kusdra, Rempel, Yaffe, & Pulliam, 2000).

T cell-deficient mice injected with splenocytes display significantly higher performance in memory and learning compared to wild-type mice (Kipnis, Cohen, Cardon, Ziv, & Schwartz, 2004). Injecting T cell-depleted splenocytes in T cell-deficient mice found no performance change, signifying that cognitive improvement was T cell dependent (Brynskikh, Warren, Zhu, & Kipnis, 2008). Additionally, acute depletion of T cells through anti-CD3 antibodies administration results in cognitive impairment within five days, and that effect is facilitated by CD4 $^{+}$ but not CD8 $^{+}$ T cells (Wolf et al., 2009). Ruisenor-Escudero et al. (2016) found levels of CD8 $^{+}$ T cells to be associated with enhanced memory performance in children with HIV, reflected by higher receptive languages scores and higher total recall scores.

Mindfulness

Mindfulness based interventions (MBIs) have shown the capability to improve both immunological and psychosocial aspects of depression (Walsh, Eisenlohr-Moul, & Baer, 2016). Mindfulness is commonly defined 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). Practicing of such state has demonstrated to increase tolerance of aversive experiences, enhance attentional regulation (see Figure 4.), and disengagement from rumination (Baer, 2003). MBIs have gained empirical support for improving behavioural and neural metrics of cognition functioning, especially attentional control (Tang, Holzel, & Posner, 2015); regulating affective experiences (Chiesa, Serretti, & Jakobsen, 2013); reducing overall levels of systematic inflammation and perceived stress (Creswell et al., 2012; Rosenkraz et al., 2013); and overall psychological health and well-being (Baer, 2003).

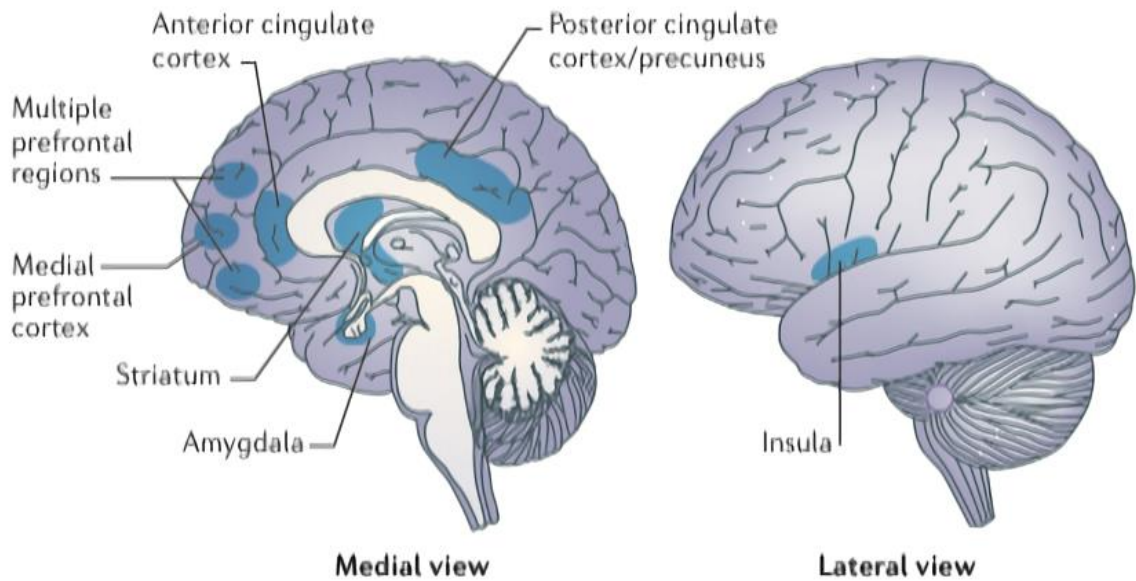


Figure 4. **Brain regions involved in the components of mindfulness meditation.**

Schematic view of several brain regions implicated in self-awareness (precuneus, the insula, posterior cingulate cortex and medial prefrontal cortex), attention control (the striatum and the anterior cingulate cortex), and emotional regulation (the striatum, limbic regions, and multiple prefrontal regions) (Tang, Holzel, & Posner, 2015).

Furthermore, recent evidence from studies have suggested that MBIs could be particularly beneficial for individuals with greater baseline depressive symptoms severity (Arch & Ayers, 2013; Greeson et al., 2015), and promote the development of skills that target cognitive-emotional processes important to severe or chronic depression (i.e. rumination), which in turn could mitigate the physiological stress reactivity that promotes chronic inflammation (Creswell & Lindsay, 2014).

In the last decades, several mindfulness interventions have been designed and widely integrated into numerous clinically oriented meditation programmes, such as Mindfulness Based Stress Reduction (MBSR) (Kabat-Zinn, 1990) and Mindfulness Based Cognitive Therapy (MBCT) (Segal, Williams, & Teasdale, 2002), and a number of psychological interventions, including Acceptance and Commitment Therapy (ACT) (Hayes, Strosahl, & Wilson, 1999) and Dialectical Behavior Therapy (DBT) (Linehan,

1993). However, such psychological interventions incorporate only partial conceptualizations of mindfulness, for example the emphasis of acceptance and change in the treatment process of ACT and DBT (Zenner, Herrnleben-Kurz, & Walach, 2014).

Integrating Cognitive Behavioral Therapy (CBT) (Beck, 1976) and mindful quality of awareness yields MBCT, which has shown to treat disorders such as generalized social anxiety disorder (Koszycki, Benger, Shlik, & Bradwejn, 2007), depression (Kuyken et al., 2008), bipolar disorder (Williams et al., 2008), hypochondriasis (Lovas & Barsky, 2010), and panic disorder (Kim et al., 2010). Similarly, combining relaxation techniques with body awareness forms MBSR, an intervention that has demonstrated competency in treating fibromyalgia (Alder-Neal & Zeidan, 2017), chronic pain (Hilton et al., 2016), rheumatoid arthritis (Fogarty, Booth, Gamble, Dalmath, & Consedine, 2014), and breast cancer (Cramer, Lauche, Paul, & Dobos, 2012).

Mindfulness and Inflammation

Mindfulness interventions have demonstrated promising effects on the immune system (Gouin & Kiecolt-Glaser, 2011), and this relationship represents a critical aspect of fighting disease given immune suppression is a hallmark symptom in chronic illnesses such as cancer (Tacon, Caldera, & Ronaghan, 2004) and HIV (Sibinga et al., 2008). Fang et al. (2010) examined MBSR effects on CRP in relation to changes of quality of life and psychological distress on heterogeneous patients. CRP is the most frequently utilized marker of inflammation, as it imitates the action of antibodies, except it has a broader array of possible pathogen molecules to attach (Webber, 2010). Signs of a systemic inflammatory response or infection is marked by increased levels of circulating CRP (Hapuarachchi, Chalmers, Winefield, & Blake-Mortimer, 2003). This increase in CRP is correlated with increased risk of diabetes (Freeman et al., 2002) and post-myocardial infarction (Liuzzo et al., 1994), but positive outcomes for cancer patients (Scott et al., 2002). Results from the study indicated no statistical significance in CRP levels from treatment-related changes, however decrease in CRP levels correlated with decrease in overall distress and anxiety. Therefore, the authors concluded that improvement in psychological wellbeing was associated with improved levels of CRP following MBSR intervention (Fang et al., 2010).

Witek-Janusek et al. (2008) assessed MBSR effects on IFN- γ , IL-4, IL-6, and IL-10 immune markers in cancer patients. IFN- γ is a critical cytokine for immunity against intracellular and viral bacterial infections, in addition to tumour control (Silva, Fonseca, Alvarez, & Lima, 2015). IL-4 initiates the proliferation of T-cells, and also the differentiation of CD4 cells into Th2 cells (T-helper cells), which in turn, generates additional IL-4 cells (Gadani, Cronk, Norris, & Kipnis, 2012). IL-6 has shown to act both pro-inflammatory and anti-inflammatory (Scheller, Chalaris, Schmidt-Arras, & Rose-John, 2011). As a pro-inflammatory cytokine, secretion of IL-6 by macrophages and T-cells in reaction to tissue damage leads to inflammation (Tanaka, Narazaki, & Kishimoto, 2014). Conversely, in an anti-inflammatory role it is mediated through its stimulating effects on IL-10, among inhibiting the effects of IL-1 and TNF- α (Schett, 2018).

IL-6 is involved in depression (Hodes, Menard, & Russo, 2016), breast cancer (Abana et al., 2017), atherosclerosis (Tousoulis, Oikonomou, Economou, Crea, & Kaski, 2016), lupus (Wallace et al., 2016), rheumatoid arthritis (Fleischmann, 2017), and diabetes (Qu, Liu, Lau, Huang, 2014). IL-10 has displayed the potential to inhibit pro-inflammatory cytokines, activate B-cells, T-cells, mast cells, and reduce antigen markers (Meng et al., 2018). Witek-Janusek et al. (2008) study contained three participant groups: MBSR early-stage cancer group, cancer-free comparison group, and early-stage assessment-only cancer group. The study found significant increase in production of IFN- γ cytokine in the MBSR cancer patient group, compared to the assessment-only cancer patient group. Moreover, at the 4-week post intervention follow up, the MBSR group had comparable levels of IFN- γ , IL-4, IL-6, and IL-10 to the cancer-free patient comparison group, but not for the assessment-only group (Witek-Janusek et al., 2008).

Carlson, Speca, Patel, and Goodey (2003) conducted a single group pre-post MBSR intervention on cancer patients, measuring immune functions involving B, T-helper, T-total, T-cytotoxic cell counts, IL-4, IL-10, and IFN- γ . The post-intervention results revealed no significant changes in overall number of lymphocytes or cell subsets. Nevertheless, there was a significant decrease in IL-10, pro-inflammatory IFN- γ , and significant increase in anti-inflammatory IL-4 production. There was also a substantial proliferation of eosinophils and reduction in monocytes, plus these changes persisted till the one-year follow up. These results indicate a change in cancer-related cytokine

production following MBSR intervention, however, the study found no significant correlation between immunological and psychological change scores (Carlson et al., 2003).

Robinson, Mathews, and Witek-Janusek (2003) studied the effects of MBSR on HIV patients. RANTES (regulated on activated, normal T-cell expressed and secreted) and SDF-1 (stromal-derived factor) immune markers were measured. RANTES are chemokines that contest with HIV for the chemokine receptor type 5 (CCR5) on lymphocytes (Crawford, Angelosanto, Nadwodny, Blackburn, & Wherry, 2011), whereas SDF-1 mediates the spread of HIV (Ding et al., 2018). Thus, an increase in RANTES and decrease in SDF-1 would suggest improvement in immunity (Zeicher, Kibler, & Zeicher, 2013). The results produced a significant increase in RANTES within the MBSR group, whilst SDF-1 levels remained stable across both groups. No changes were yielded for the assessment-only group for either measures of SDF-1 or RANTES. There were no significant between-group differences due to small sample size ($n = 24$ for MBSR intervention group, $n = 24$ for assessment-only group). This study offers limited evidence that MBSR could aid in immunity improvements among HIV patients (Robinson et al., 2003).

Davidson et al. (2003) investigated the effects of an 8-week MBSR intervention on healthy participants, measuring immune function. At the conclusion of the intervention, participants from both groups (MBSR group and wait-list control group) were injected with the influenza vaccine and antibody titer response levels were acquired after 4- and 8-weeks of completing the intervention. The MBSR group presented significantly greater increase in antibody titer compared to the control group, post week 4 and 8 of the vaccination (Davidson et al., 2003). These findings support positive effects of mindfulness intervention on immune function.

Mindfulness training practices emphasis on training various forms of attention, such as disengagement from distracting perceptual stimuli (attention switching), developing sustained attention on target stimuli, noticing when the mind wanders, redirection of attention to the chosen stimuli (selective attention), and learning to adopt an open accepting form of attention to avoid being caught up in emotions, thoughts, and body sensations (Baltar & Filgueiras, 2018; Lutz, Slagter, Dunne, & Davidson, 2008). Focused attention training has shown to enhance working memory performance with non-verbal (Maclean et al., 2010) and verbal materials (Chambers, Lo, & Allen, 2007; Jensen, Vangkilde, Frokjaer, & Hasselbach, 2012). Consistent with these findings, neuroimaging research has found mindfulness training to increase cortical thickness within attention-related sub regions of prefrontal cortex (Lazar et al., 2005) and improved connectivity in the anterior cingulate cortex (ACC) (Tang & Posner, 2009; Tang et al., 2010). Such results align with current theoretical understanding of mindfulness, in that attention, specifically the sustained attention cultivated in mindfulness training, could make stimulus representations in working memory more stable and less prone to decay (Rolle, Anguera, Skinner, Voytek, & Gazzaley, 2017).

Chambers, Chuen Yee Lo, and Allen (2007) evaluated the impact of mindfulness meditation training on non-clinical population, measuring affective and cognitive function. The participants undertook a 10-day intervention and were assessed via self-report scales on mindfulness, affect and rumination, sustained attention, attention switching, and working memory. Levels of mindfulness was measured with the Mindful Attention Awareness Scale (Brown & Ryan, 2003) and they found significant improvements in mindfulness scores among the meditation group. The Beck Depressive Inventory II (Beck, Rush, Shaw, & Emery, 1979; Beck & Steer, 1987) was utilized to assess depressive symptoms, results revealing significant decrease in depressive symptom scores across time for the meditators. Working memory was measured via the Digit Span Backward subscale of the Wechsler Adult Intelligence Scale, 3rd edition (The Psychological Corporation, 1997), similarly, the meditation group yielded significant improvements in working memory. Overall, the study results demonstrated significant

improvements in depressive symptoms, mindfulness, performance in working memory, sustained attention, and rumination (Chambers et al., 2007).

Jha, Stanley, Kiyonaga, Wong, and Gelfand (2010) investigated the potential effects of mindfulness training on preventing the loss of working memory abilities prior to exposure of stressful events. The Operation span (Ospan) task (Unsworth, Heitz, Schrock, & Engle, 2005) was used, which engages memory of non-affective stimuli for example, remembering letters over short intervals while solving simple arithmetic counts (McCabe, 2008). The study revealed improved Ospan scores in the meditators group, while scores deteriorated over time in the control group, and even in the meditation group with low meditation practice. Furthermore, overall decrease in negative affect and increase in positive affect on the Positive and Negative Scale (Watson, Clark, & Tellegen, 1988) was only observed in those with longer mindfulness practice, no such changes were recorded in those with shorter logged mindfulness practice sessions. The results signify the importance of persistent practice to attain greater results (Chiesa et al., 2013).

Williams, Teasdale, Segal, and Soulsby (2000) examined whether autobiographical memory could be affected by MCBT programme in formerly depressed individuals. The significance of memory specificity is based on recent findings indicating that individuals with a history of major depression display difficulties in retrieving specific autobiographical memories, and have the inclination to recall categorical overgeneralized memories (Kohler et al., 2015; Whalley, Rugg, & Brewin, 2012; Wilson & Gregory, 2017). Over-generality of memories is associated with increased risk of suicide attempts and episodes of depression in depressed individuals (Richard-Devantoy, Berlim, & Jollant, 2014). Furthermore, over-generalised memory is also correlated with higher occurrence of intrusions of past traumatic events, for example, sexual and physical abuse (Moore & Zoellner, 2007). Indicating, either the effort involved in avoiding or subduing unpleasant memories disturbs the mechanism for memory search at the stage where it transitions from specific events to general descriptions (El Haj, Daoudi, Gallouj, Moustafa, & Nandrino, 2018) or the individual strategically adopts an over-general retrieval approach as a process for confronting potentially emotional material (Abram, Picard, Navarro, & Piolino, 2014). Results from

the study found the mindfulness treatment group to report significantly fewer number of generic memories, compared to the control group (Williams et al., 2000). Subsequently, two studies replicated the same MBCT intervention on healthy patients, finding similar increase in ability to recall specific memories compared with the control group (Hargus, Crane, Barnhofer, & Williams, 2010; Heeran, Van Broeck, & Philippot, 2009).

Levy, Jennings, and Langer (2011) assessed the effectiveness of mindful intervention on attention and memory in an older adult population. Numerous studies have suggested that attention diminishes in old age, as the tendency for attention to wander begins (Muller-Oehring, Schuite, Rohlfing, Pfefferbaum, & Sullivan, 2013; Quigley & Muller, 2014; Lufi, Segev, Blum, Rosen, & Haimov, 2015). One the most popular theories explaining aging and attention, the inhibitory deficit theory of cognitive aging, proposing attention declines with age due to increasingly inefficient operation of an inhibitory mechanism that aids in suppressing irrelevant information (Askey & Playfoot, 2018; Park & Festini, 2016). The study divided the participants into four attention group, with each group given marginally different instructions: "Please note three distinctions in each of the following pictures" (Group 1); "Please note five distinctions in each of the following pictures" (Group 2); "Please turn the page" (Group 3); "Please pay attention to each of the following pictures" (Group 4). Thus, participants in the mindfulness groups (Group 1 and 2) were instructed to study the pictures and pay attention to the individual picture and detect distinctions. Both mindfulness groups reported remembering significantly more pictures than the controls (Levy et al., 2011).

Chiesa, Calati, and Serretti (2011) reviewed 15 randomized controlled studies and 8 case-control studies on the effects of mindfulness training on measures of memory, attention, executive functions, and other miscellaneous measures of cognition. The systematic review concluded that individuals in early stages of mindfulness training (i.e. minimal to no prior experience) can significantly increase selective, sustained, and executive attention, in addition to attention switching. The later phases of mindfulness training, which includes open monitoring of internal and external stimuli, was associated with enhanced unfocused sustained attention capability. The authors also indicated mindfulness training to improve working memory

capacity, plus prevent the loss of working memory prior to exposure of traumatic event. Finally, evidence supporting improvements of various executive functions, such as inhibition of cognitive responses, verbal fluency, meta-awareness, and emotional interference from distracting stimuli was also established (Chiesa et al., 2011).

Research rationale

Taken together, in addition to the positive effect on cognitive function, i.e. memory, MBIs also demonstrate capacity to change pro-inflammatory immune profiles, including reducing C-reactive protein and inflammatory cytokines (Carlson, Speca, Faris, & Patel, 2007, Malarkey, Jajoura, & Klatt, 2013, Witek-Janusek et al., 2008) and down-regulate genes related to expression of inflammation (Creswell et al., 2012). Nonetheless, the link between improved cognitive function and altered pro-inflammatory immune profiles remains unclear. Furthermore, the existing studies on the effect of MBIs on immune function have predominantly assessed populations with chronic illness (i.e. cancer), which makes it challenging to generalize the findings to the healthy population. The question of whether immune function changes found in studies were due to improvement in psychological health, illness, or both remains unanswered. Additionally, immune biomarkers are specifically relevant in the rehabilitation setting, given that immune system dynamics have been associated in numerous major mental and physical health problems, including rheumatoid arthritis, neurodegenerative disorders, asthma, metabolic disorders, certain types of cancer, and depression (Couzin-Frankel, 2010; Slavich, 2015). Thus, in the present study, we aimed to examine 1) the effect of mindfulness on biomarkers of immune system and memory; and 2) the correlations between these immunological measures and memory in the healthy population.

Chapter Three: Methods

Participants

Data for this study comprised a subset of the information collected from a large study. The study sample consisted of 26 participants, 13 secondary school students, 7 undergraduate students, 5 postgraduate students, and 1 post-doctoral student. 10 identified as male and 16 as female. The mean age was 30.2 (SD = 12.1) years. The sample comprised of NZ European (n = 11), Asian (n = 6), Indian (n = 2), Pacific Islander (n = 1), others or not specified (n = 7) (See Table 1.). The participants were recruited via emails and posters delivered through various university communication channels.

Memory Recall and Recognition Test

Testing for immediate, short, and long delay memory recall was taken during normal office hours (9 am-5 pm). Delayed and immediate memory recall was measured through a computerised cognitive battery 'IntegNeuro'. The test battery has good test-retest reliability and validity (Kemp et al., 2005; Paul et al., 2005; Williams et al., 2010) and meets standardised norms pre-established in 1000 healthy participants (Clark et al., 2006). Additionally, the test has been validated against traditional pencil and paper neurological tests of cognition (convergent validity measures > 0.53) (Paul et al., 2005). The test battery was distributed using an IBM screen interface platform with standardised visual and vocal instruments. Stereo headphones/microphones were utilised to convey instructions at the beginning of each test. To ensure the participants understood the instructions, a practice set was given for each test.

The first segment consisted of a list of 12 words being presented to the participants to which they had to memorise. The list was shown 4 times in total, and the participants were asked to recall as many words as possible after each presentation. Immediate recall was measured by averaging the number of words recalled immediately after each presentation. A second list of 12 distractor words was then presented to the participants, in which contained no words that were semantically or phonetically linked to the first list, and were asked to recall the second list. After the second distractor list,

the participants were immediately asked to recall the earlier words presented from the original list. Short delay was measured as the number of words recalled from the original list. Long delay recall was measured as the number of words recalled from the original list after a delay of approximately 25 minutes, during which other cognitive tests were completed by participants.

Blood Sample Collection/Analysis

Blood samples were taken between 10am and 12:30pm on a different day to that of which the cognitive tests were taken. This was done to minimise diurnal variation of circulating IL-6 (Nilsson, Lekander, Akerstedt, Axelsson, & Ingre, 2016) and avoid the effects of cognitive test on immune response. Moreover, after the early morning peak, cortisol levels are anticipated to be on the decline around this time (10:00-12:30) (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007). Nonetheless, research shows there is a significant consistency in immune responses to acute laboratory stressors prompted by cognitive tasks across similar tasks and time (Alder et al., 2002; Cohen & Hamrick, 2003).

Blood samples were collected via venepuncture in K2EDTA tubes and tubes with gel SST was utilized to separate serum (Surgical Supplies Ltd., Auckland, New Zealand.). Red and white blood cell count, haemoglobin and haematocrit concentration was immediately analysed from the EDTA samples via a Sysmex XT automated quantitative haematology analyser (Sysmex Corporation, Auckland, New Zealand). Tubes containing separating gels were centrifuged at 3000 rpm and at 4°C for 15 minutes. Immediately after, the serum was extracted and processed or preserved frozen at -20°C until later analysis.

CD69, CD4, and CD8 subpopulations of lymphocytes were measured with a Muse Cell Analyser (Merck Millipore, USA). Fast, reliable, and accurate quantitative cell analysis was viable through miniaturised fluorescence detection and microcapillary technology in the Muse Cell Analyser. The Muse Human CD4 T Cell Kit was used to detect and identify lymphocytes and CD4 T lymphocytes using a particular CD4 antibody that identifies human helper/inducer CD4⁺ T cell (HLA Class II reactive) and distinguishes a

60-kDa surface antigen. Similarly, the Muse Human CD8 T Cell Kit detects and recognises lymphocytes and CD8 T lymphocytes using a precise CD8 antibody that detects a 68-kDa transmembrane glycoprotein (HLA Class I restricted). Lastly, the Muse Human Lymphocyte CD69 Assay utilizes an anti-lymphocyte cocktail that recognises the total lymphocyte population and a precise antibody that binds to the CD69 early activation marker expressed on lymphocytes. T-cell percent of lymphocytes, T-cell concentration in cells/ μ L, and total lymphocyte concentration in cells/ μ L were acquired for all subpopulations testes. All kits were used following the specific manufacturers instruction for the whole process.

Precise assays on a cobas Modular E170 analyser (Roche Diagnostics, New Zealand) were used to calculate Interleukin-6 (IL-6) and Cortisol concentration. The total duration of assay was approximately 18 minutes established on the electrochemiluminesce principle using ruthenium-conjugated monoclonal antibodies. A cobas Modular P800 (Roche Diagnostics, New Zealand) was utilized to measure C-reactive protein (CRP), based on a Particle-enhanced immunoturbidimetric principle using latex particles coated with monoclonal anti-CRP antibodies. Quantitative results were determined through instrument-specific full point calibration curves for all assays.

Mindfulness Intervention

The mindfulness sessions were weekly based and for approximately 90 to 110 minutes on a weekday evening. The first session was delivered in person by the main facilitator. This was due to allow good rapport building between the participants and the main facilitator. The first session consisted of a brief discussion on the purpose of the course, a 10-minute guided meditation exercise, followed by an exercise on well-being. Session 2 and beyond was presented via a webinar using GoToMeeting™ (commercially available videoconferencing software). Session 2 comprised of approximately 10 to 15 minutes of physical exercise comparable to Taijichuan, breathing meditation exercises, and a PowerPoint presentation on the brain and mindfulness. The session concluded with a brief guided meditation exercise and a mindful eating exercise. Session 3 composed of the same guided breathing meditation and physical exercise,

together with the presentation on the types of awareness, negative bias, and advantages of walking meditation.

Session 4 included physical breathing exercises, breathing meditation, and a 450minute discussion on the fundamentals of mindfulness and emotion. Parallel to session 3, this session similarly concluded with a meditation exercise, particularly focusing on observing sound, body, and emotion. Session 5 comprised of physical movement exercise, concentration meditation, and a discussion on accepting and regulating emotions. Session 6 involved meditation practice, physical movement and breathing exercises, and a discussion on the four foundations of mindfulness and their purpose. A discussion by the main facilitator on loving kindness meditation concluded this session. All sessions concluded questions and answers between participants and facilitator. The same outline was followed by group 2. All participants were encouraged to practice for approximately 15 minutes per day from all material learnt in class or shown in an online link sent them via email (Krageloh et al., 2017). Baseline measures for both groups were taken during the week immediately prior to the beginning of the mindfulness programme. Ethical approval was attained from the authors' institutional ethics committee, and written informed consent was given by all participants. Ethics Approval Number: 16/147 'Mindfulness training – individual differences and mechanisms of change'.

Statistical Analyses

Descriptive (means and standard deviation) and ANOVA analysis was conducted. Data was inspected for normality, and where data showed non-normality, log transformations was applied. T-test were used to explore the change of cognition and immunological measures associated with mindfulness, as well as correlations. Spearman Rho correlations were used to test associations between the memory measures and immunological markers. Immunological (CD4, CD8, CD69, CRP and IL-6) and memory variables (immediate, short- and long delay recall scores) were included in the statistical analysis. When there was significant correlation, logistical regression was conducted to examine the predictability of immunological measures on memory. The choice of independent variables was directed by significant statistical significance in the

correlation analysis. Statistical Package for Social Sciences (SPSS) version 23 was used for all statistical procedures.

Chapter Four: Results

Participants

The participant's descriptive statistics are presented in Table 1. Table 2 displays the pre and post-intervention memory task scores, with mean and standard deviation. Table 3 presents the Z scores and p-value for memory task following intervention. Table 4 shows the pre and post-intervention immunological measures, mean and standard deviation. Table 5 presents the Z scores and p-values for immunological measure following intervention. Pre- and post-intervention correlations between memory performance and immunological measure is shown in Table 6 and 7 respectively. A linear regression model between short delay recall and CD8 is displayed in Table 8. Finally, a linear regression model between long delay recall and CD4 and CD8 is presented in Table 9.

Table 1. Participants' descriptive statistics

	Sample (<i>n</i> =26,%)
Ethnicity	
NZ European	11 (42.3)
Pacific	1 (3.8)
Indian	2 (7.7)
Asian	5 (19.2)
Other/Not Specified	7 (26.9)
Education	
Secondary School	13 (50)
University Undergraduate	7 (26.9)
Post-Graduate	5 (19.2)
Post-Doctoral	1 (3.8)
Gender	
Female	16 (61.5)
Male	10 (38.5)
Mean Age in years	30.2 (<i>SD</i> =12.1)

Memory Recall Scores

There were significant changes in performance of immediate recall tests ($Z=-2.5$, $p=0.01$). Compared to the performance prior to mindfulness training, the total number of words immediately recalled across trials were significantly increased from average of 36 ($SD=4.24$) to 38 ($SD=4.46$). Significant improvement in performance was also found in the task measuring long delay recall ($Z=-2.3$, $p=0.02$). The mean for long delay recall task at baseline was 9.0 ($SD=2.04$) and increased to 9.9 ($SD=1.82$) after 6 weeks of training. However, there was no significant change in short delay recall task and memory recognition performance.

Table 2. Participants memory task performance following mindfulness intervention

Memory Task	Pre-Intervention ($n=26$) Mean (SD)	Post-Intervention ($n=23$) Mean (SD)
Immediate Recall	35.81 (4.24)	38.17 (4.46)
Long Delay Recall	8.92 (2.04)	9.93 (1.82)
Short Delay Recall	9.65 (1.61)	10.04 (1.51)
Memory Recognition	11.04 (1.12)	11.26 (1.11)

Table 3. Pre-post memory task Z. scores and p-values following mindfulness intervention

	Immediate Recall	Long Delay Recall	Short Delay Recall	Post-Memory Recognition
Z.	-2.497	-2.305	-0.633	-0.577
p	0.013	0.021	0.527	0.564

Immunological Measures Scores

Nevertheless, there was no significant change in measures of immunological measures, apart from CD69 ($Z=-4.2$, $P<0.001$). It appears that CD4, CD8, cortisol, IL-6 and CRP remained stable and were not significantly affected by mindfulness training. In contrast, CD69 was significantly increased following mindfulness training.

Table 4. Participants immunological measures following mindfulness intervention

Biomarkers	Pre-Intervention (n=26)	Post-Intervention (n=26)
	Mean (SD)	Mean (SD)
CD4	850.92 (277.41)	831.27 (288.43)
CD8	455.73 (144.81)	462.2 (123.05)
CD69	10.71 (7.14)	41.23 (31.56)
Cortisol	297.67 (136.29)	277 (98.74)
Interleukin 6	4.69 (1.22)	4.53 (1.24)
C-Reactive Protein	2.01 (3.62)	1.63 (3.09)

Table 5. Pre-post immunological measures Z. scores and p-values following mindfulness intervention

	CD4	CD8	CD69	Cortisol	Interleukin 6	C Reactive protein
Z.	-0.286	-0.986	-4.172	-0.714	-0.614	-0.327
p	0.775	0.324	0.000	0.475	0.539	0.743

Pre-Intervention Correlation

The correlations results displayed in Table 6 shows that immediate recall was significantly negatively correlated with CRP at baseline ($r=-0.39$) ($p<0.04$). No other correlations were found between memory performance and immunological measure in pre-intervention stage.

Table 6. Pre-Intervention correlation coefficients for memory performance and immunological measure

	CD4	CD8	CD69	Cortisol	IL-6	CRP	Immediate	Short-Delay	Long-Delay
CD8	0.261								
CD69	-0.067	-0.023							
Cortisol	-0.276	-0.172	-0.082						
IL-6	0.055	.476*	-0.102	-0.094					
CRP	-0.095	0.33	-0.032	-0.004	.762**				
Immediate Recall	-0.112	-0.199	-0.335	0.154	-0.182	-.399*			
Short-Delay Recall	-0.111	-0.131	-0.173	0.001	0.018	-0.108	.686**		
Long-Delay Recall	-0.091	0.042	-0.215	-0.168	0.176	0.083	.549**	.716**	
Memory Recognition	0.036	-0.096	-0.081	-0.324	-0.137	-0.328	0.159	0.311	0.021

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Post-Intervention Correlation

The results presented in Table 6 indicates that CD4 had a significant moderate negative correlation with long delay recall (-0.54) ($p < 0.01$). No other associations were discovered between immunology and memory.

Table 7. Post-Intervention correlation coefficients for memory performance and immunological measure

	CD4	CD8	CD69	Cortisol	IL-6	CRP	Immediate	Short-Delay	Long-Delay
CD8	0.109								
CD69	-0.023	0.059							
Cortisol	-0.028	0.045	0.002						
IL-6	0.028	0.179	.502**	-0.069					
CRP	-0.032	0.098	-0.081	0.276	0.339				
Immediate Recall	-0.379	0.083	-0.316	0.181	-0.283	0.059			
Short-Delay Recall	-0.337	0.153	-0.254	0.087	-0.052	0.199	.621**		
Long-Delay Recall	-.539**	0.094	-0.312	-0.007	-0.208	0.157	.650**	.854**	
Memory Recognition	0.009	0.236	-0.266	-0.314	0.071	-0.106	0.158	-0.007	0.006

** Correlation is significant at the 0.01 level (2-tailed).

Logistic Regression

Given the significant relationship between certain immunological measures at baseline and task performance after mindfulness training, logistical regression was run with CD4 and CD8 measured at baseline and memory performance following mindfulness. Table 8 shows the results of the multiple linear regression. CD8 explained 19.4% of the variance in short delay recall [model 1: adjusted $R^2 = 0.155$; $F(1, 21) = 5.05$, $p = 0.04$; sum of squares regression = 9.49, residual = 39.47].

Table 8. Linear regression model of short delay recall trials as predicted by CD8.

		B	SE	Beta	t	p	Tolerance	VIF
Model 1	(Constant)	7.96	0.96		8.22	<.001		
	CD8	0.005	0.002	0.44	2.247	0.036	1	1

When combining with CD4 and CD8, the model explained 38.4% of the variance in long delay recall [model 1: adjusted $R^2 = 0.322$; $F(2, 20) = 6.23$, $p = 0.008$; sum of squares regression = 28.02, residual = 44.94].

Table 9. Linear regression model for long delay recall trials as predicted by CD4 and CD8.

		B	SE	Beta	t	p	Tolerance	VIF
Model 1	(Constant)	10.42	1.39		7.48	<.001		
	CD4	-0.004	0.001	-0.503	-2.846	0.01	0.987	1.01
	CD8	-0.005	0.002	0.425	2.404	0.026	0.987	1.01

Chapter Five: Discussion

The aim of this study was to investigate the relationship between immunological biomarkers and memory recall following a mindfulness intervention programme in a non-clinical sample. The present study found increased mean scores in immediate recall and long-delay recall memory post mindfulness intervention. CD69 was observed to be the only immunological measure to change following the intervention, CD4, CD8, cortisol, IL-6, and CRP remained relatively stable. Results suggest that baseline CD8 has a moderate positive relationship with short delay recall and long delay, whilst baseline CD4 was negatively correlated with short delay recall (see Appendix. 1), which is consistent with previous research that has found increased levels of CD8 and decreased levels of CD4 to be associated with better memory performance (Ruisenor-Escudero et al., 2016; Serre-Miranda et al., 2014).

Mindfulness and Memory

Fairly consistent with the findings in this current study, improvements in memory capacity (Mrazek, Franklin, Phillips, Baird, & Schooler, 2013; Quach, Mano, & Alexander, 2016) and memory functioning (Zeidan, Johnson, Diamond, David, & Goolasian, 2010) have been observed following mindfulness interventions. Research indicates that the practice of mindfulness training can enhance attentional stability by promoting a vigilant and relaxed state of mind and therefore, heightening cognition through enhanced capacity to self-regulate emotions (Ching, Koo, Tsai, & Chen, 2015). Additionally, mindfulness training could increase cognitive performance by reducing mind wandering and improving mood (Morrison, Goolsarran, Rogers, & Jha, 2014). Mood disturbances and mind wandering have been linked to disrupt learning and memory (Morales, Landa, Criollo, 2015). The practice of mindfulness promotes a persistent effort to maintain focus on a single aspect of experience, especially sensations of breathing, regardless of constant interruptions of irrelevant perceptions or personal concerns (Lippelt, Hommel, & Colzato, 2014). This mindful ability has been shown to prevent the displacement of critical task-relevant information by distractions (Grabovac, Lau, & Willett, 2011).

Reduction in mind wandering through mindfulness training leads to decreased activation of the default mode network (Garrison, Zeffiro, Scheinost, Constable, & Brewer, 2015), a collection of brain regions that usually display greater activation during rest than through externally focused cognitive tasks (Raichle & Snyder, 2007). This network has been associated with autobiographical memory, reflecting the perspectives and thoughts of others, envisioning future events, and mind wandering (Mason et al., 2007; Sheline et al., 2009). Both beginner and experienced meditators have shown to reduce activation of the default network after completing a similar two-week mindfulness training intervention to the present study (Brefczynski-Lewis, Lutz, Schaefer, Levinson, & Davidson, 2007; Brewer et al., 2011). In functional magnetic resonance imaging (fMRI) studies, mindfulness training has displayed competency in decreasing activity in the posterior cingulate cortex, precuneus, inferior parietal cingulate cortex, lateral temporal cortex, and anterior medial prefrontal cortex (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner, Andrews-Hanna, Schacter, 2008), which are the core regions of the default mode network (Raichle & Mintun, 2006).

Contrastingly, increased activation has been observed in the brain regions involved in the dorsal and ventral attention network, for example, visual cortex, anterior insula, frontal eye field, and dorsolateral prefrontal cortex (Corbetta, Patel, & Shulman, 2008). Specifically, activation is detected prominently at moments when mind wandering is noticed by the meditator (Ranganath & Ritchey, 2012). Consequently, the recognition of mind wandering and redirection of attention to the present moment leads to increased activity in the caudate, and dorsolateral prefrontal cortex, and decreased activity in the anterior medial prefrontal cortex (Hasenkamp, Wilson-Mendelhall, Duncan, & Barsalou, 2012). Meaning, mindfulness training enhances intentional focused attention, which is associated with activity in the attention network and memory task performance (Fukino, Ueda, Mizuhara, Saiki, & Nomura, 2018). For example, decreased default mode network activity in depressed individuals is associated with subjective evaluation of emotional experience and self-referencing, allowing the individual to experience the present moment with reduced bias, and greater objectivity (Ives-Deliperi, Howells, Horn, Stein, & Meintjes, 2013).

A reduction in self-referential appraisal teaches the individual to abandon emotionally charged assessments of the external and internal world, therefore adjusting patterns of value assessment and self-judgment (Farb, Anderson, & Segal, 2012). The individual self-perception transitions from an enduring entity to a transient entity, thus the individual becomes less fixated and less prone to ruminating on mistakes and faults (Jackson, Malmstadt, Larson, & Davidson, 2000; Gross, 2002). These findings are consistent with the notion that the process of mindfulness meditation is characterized as an active cognitive regulation in novice meditators, who need to override the barrier of consistently internally reacting to one's emotions, and could consequently display greater prefrontal activation (Teper, Segal, & Inzlicht, 2013). Conversely, experienced meditators may not use this prefrontal control, rather, developing an automated accepting stance towards their experience (Sperduti, Martinelli, & Piolino, 2012). Therefore, they no longer employ top-down control, but instead exhibit enhanced bottom-up processing (Taylor et al., 2012).

Pagnoni and Cakic (2007) found evidence of neuroprotective effects and reduced cognitive decline associated with normal aging post mindfulness training. Utilizing MRI neuroimaging analysis technique, the participants in the study exhibited thicker gray matter volume, particularly in the putamen, a structure prominently implicated in attention processing (Max et al., 2002). Comparably, Hozel et al. (2011) discovered increased thickness of gray matter in brain regions responsible for emotional, cognitive, attention, and sensory processing (i.e. right hemisphere). The duration of time spent on meditation by the participants correlated with changes in brain cortical thickness. The researchers found meditation practice to slow down prefrontal cortex thinning associated with old-age (Hozel et al., 2011; Hurtz et al., 2014). Interestingly, studies have also reported increased volume of the hippocampus, which is implicated in memory (Desbordes et al., 2014; Luders, Thompson, & Kurth, 2015). The increased cortical thickness observed in meditators could be attributed to several mechanisms: formation of vessels, neuronal arborization, or multiplication of glial cells (Santarnecchi et al., 2014). These mechanisms suggest meditation could potentially lead to neurogeneration (Chau et al., 2018).

Newberg, Wintering, Khalsa, Roggenkamp, and Waldmanb (2010) examined the effects of mindfulness training on individuals with memory loss difficulties (i.e. early Dementia and Alzheimer's disease). The meditation intervention resulted in significant increase in baseline cerebral blood flow levels in the superior frontal, prefrontal, and superior parietal cortices. Scores on neuropsychological tests of logical memory, and verbal fluency also showed improvements following the intervention. Moss et al. (2012) presented equivalent results showing memory loss associated with positive changes in anxiety and mood, and these changes correlated with changes in cerebral blood flow. Singleton et al. (2010) found an increase in gray matter concentration in the temporo-parietal junction, posterior cingulate cortex, and cerebellum in participant's post-mindfulness training. These results indicate that mindfulness is associated with changes in gray matter concentration in brain regions linked with emotion regulation, perspective evaluation, self-referential processing, and learning and memory processing (Schmidtman, Hurley, & Taber, 2017).

Research has suggested that mindful meditation can affect multiple pathways that can play a vital role in brain aging and mental fitness (Kurth, Cherbuin, & Luders, 2017). For instance, similar to the cortisol reduction found in the present study, mindful meditation has shown to reduced stress-induced cortisol secretion and this could potentially have neuroprotective effects by elevating brain derived neurotrophic factor (BDNF) levels (Xiong & Doraiswamy, 2009). BDNF stimulates and controls growth of new neurons from neural stem cells (neurogenesis) (Bathina & Das, 2015), and exhibits a neuroprotective effect under adverse conditions, for example cerebral ischemia, neurotoxicity, and hypoglycemia (Scalza, Kummer, Bretas, Cardoso, & Teixeira, 2009). Meditation has also presented beneficial effects on lipid profiles and decreasing oxidative stress, both of which are associated with increased risk of age-related neurodegeneration and cerebrovascular disease (Shantakumari, Sequera, & El deeb, 2013).

Although CD4, CD8, CRP, IL-6, and Cortisol observed a group mean difference in the present study, CD69 was the only one with significant change among the immunology measures following the mindfulness intervention. While CD69 exerts a pro-inflammatory effect, recent research suggests it can act like a 'brake' to control inflammatory responses (Gonzalez-Amaro, Cortes, Sanchez-Madrid, & Martin, 2013). Animals with collagen-induced arthritis in the absence of CD69 display exacerbated inflammatory response and causes damaging effect in the affected joints (Sancho et al., 2003). Additionally, these animals also present increased production of Th1 lymphocytes, which enhances the synthesis of soluble inflammatory mediators, including IL-1B, and the chemokines RANTES (Gomez et al., 2008). CD-69 deficient mice have been observed to develop an aggravated form of ovalbumin-induced allergic airway inflammation, with increased levels of eosinophils, and enhanced synthesis of cytokines (i.e. Th2) in the lung tissue (Martin et al., 2010). In cardiomyopathy, deficiency in CD69 can accelerate the progress of heart failure via aggravated tissue damage mediated by increased production of Th17 lymphocytes (Cruz-Adalia et al., 2010). Therefore, the significant increase observed in CD69 levels in the present study could potentially be perceived as a protective effect against any exacerbated inflammatory response (Cibrian & Sanchez-Madrid, 2017; Miki-Hosokawa et al., 2009), however further research should be conducted to explain the precise mechanism behind the increased levels of CD69 following mindfulness training.

Numerous studies have suggested that stress can initiate an inflammatory response in the brain and peripherally (Calcia et al., 2016; Rohleder, 2014), and psychosomatic interventions such as mindfulness meditation that incorporate a stress-reduction mechanism and psychophysiological self-regulation, have demonstrated anti-inflammatory benefits (Bower & Irwin, 2015). Psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis via the hypothalamic secretion of corticotropin-releasing hormone (CRH), which typically suppresses immune responses by the release of glucocorticoids (GCs) from the adrenals (Quan and Backs, 2007). GCs possess anti-inflammatory and immunosuppressive properties, such as their ability to inhibit lymphocyte proliferation and cytotoxicity (Coutinho & Chapman, 2011), in

addition to increasing the expression of anti-inflammatory cytokines (i.e. IL-10) and decreasing the expression of pro-inflammatory cytokines (i.e. IL-6) (Sorells, Caso, Munhoz, & Sapolsky, 2009). However, recent research has discovered that GCs also have a pro-inflammatory effect on the immune system (Perez-Nievas, Garcis-Beuno, Caso, Menchen, & Leza, 2007).

GCs increase the function and expression of inflammasomes, which are cytoplasmic multi-protein complexes that sense endogenous and exogenous signals and slice pro-inflammatory cytokines into mature cytokines (Busillo, Azzam, & Cidlowski, 2012). Circulating pro-inflammatory cytokines such as IL-1 and IL-6 directly stimulate the pituitary-adrenal axis (Danese, Pariente, Caspi, Taylor, & Poulton, 2007), causing an increase serum levels of GCs and adrenocorticotrophic hormone (ATCH), resulting in the inhibition of the production of pro-inflammatory factors (Miller et al., 2008). The endocrine negative feedback loop is formed from the interaction between HPA axis and the immune system (Taghvafard, Proskurnikov, & Cao, 2017).

Nonetheless, in cases of cytokine overstimulation such as in inflammatory diseases or chronic stress, this negative loop can be weakened by decreased cytoplasmic GC-receptor (GR) level and reduced expression of GR driven anti-inflammatory genes, therefore leading to GC low-responsiveness (Yaribeygi, Panahi, Saharael, Johnston, & Sahebkar, 2017). Both anti-inflammatory and pro-inflammatory mechanisms rely on the intensity and type of stressors, as chronic stressors have shown to suppress immune function, whereas acute stressors enhance (Segerstrom & Miller, 2004). Over-activation of the immune system due to prolonged intense stressors lead to the imbalance of inflammation and anti-inflammation (Mariotti, 2015).

Mindfulness training has been shown to buffer this stress-processing pathway by two methods: increase recruitment of prefrontal regulatory regions that inhibit activity in stress-processing regions, and/or a directly effect on the modulation of the reactivity of those regions (Kadziolka, Pierdomenico, & Miller, 2015). Supporting the first method, mindfulness training has shown to increase recruitment of stress-regulatory regions of the prefrontal cortex (e.g. dorsal and ventral regions of the lateral prefrontal cortex), especially in settings in which the meditators are requested to engage in active

emotion-regulatory tasks (i.e. reappraisal or affect labeling) (Mordinos, Ormel, & Aleman, 2010). Additionally, enhances in prefrontal cortical activation during mindfulness training predicts improvements in clinical symptoms (i.e. reduction in anxiety and stress) (Holzel et al., 2013; Monoz et al., 2018). In support of the second method, mindfulness has shown to decrease the reactivity of central stress-processing regions responsible for signaling peripheral stress-response cascades (i.e. hypothalamus, amygdala, parabrachial pons, and anterior cingulate cortex) (Arnsten, 2009).

Earlier fMRI studies found mindfulness to alter the structure and function of the amygdala, a region essential for mediating flight-or-fight responses and emotion processing (Way, Creswell, Eisenberger, & Lieberman, 2010). Recent studies suggest mindful meditators have lower resting-state amygdala activity, and decreased right-amygdala volume (Taren, Creswell, & Gianaros, 2013). Furthermore, mindfulness reduces the connectivity between right-amygdala in resting state and subgenual anterior cingulate cortex, which decreases the strength of the connectivity of brain networks driving stress reactivity (Taren et al., 2015). Certain research has indicated that mindfulness increases parasympathetic nervous-system activation (Ditto, Eclache, & Goldman, 2006), whilst other studies suggest mindfulness training to buffer sympathetic-nervous-system reactivity to stressors (i.e. blood pressure) (Nyklicek, Mommersteeg, van Beugen, Ramakers, van Boxtel, 2013).

The lack of significant change observed in immunological measures in the present study apart from CD69 could possibly be attributed to the healthy participants. As the participants had relatively normal levels of cytokines at baseline, the six week mindfulness intervention may not have been extensive enough to cause any significant change or due to the ceiling/floor effect, there was a limited amount the cytokines levels could fluctuate within. Nonetheless, Gonzalez-Garcia et al. (2013) found mindfulness training to increase CD4 cell count in individuals with HIV, and also observed reduction in depressive and anxious symptoms, and enhanced quality of life. Alinaghi et al. (2012) presented similar results with increased CD4 cell count and lower levels of psychological distress in 171 adults diagnosed with HIV. Although the results contradict the findings of decreased CD4 cell count in the present study, it should be noted that individuals with

HIV have abnormally low levels of CD4, therefore an increase of CD4 to normal levels is desirable in these individuals (Sulaiman, 2012). Lengacher et al. (2013) examined the effects of MBSR on breast cancer patients, finding increased levels in CD8 and decreased levels in CD4 in the intervention group compared to the control.

Fang et al. (2010) followed a similar protocol for MBSR in cancer patients. The study found decreased levels of CRP post-mindfulness intervention and a correlation with overall reduced anxiety and stress. A study assessing the effects of mindfulness training on medical students found significant reduction in cortisol serum levels, which correlated with overall stress reduction (Turakitwanakan, Mekseepralard, & Busarakumtragul, 2013). Pace et al. (2009) investigated the outcome of 61 healthy adults in IL-6 serum levels following mindfulness intervention. The researchers reported significantly lower IL-6 levels and distress scores in participants that meditated above the group median practice time, indicating that only high levels of engagement in the intervention may be necessary to produce positive stress-induced immune and affective outcomes (Vibe et al., 2018).

Memory and Inflammation

In the present study, CD4 was negatively correlated with long delay recall and CD8 was positively correlated with short delay recall (see Appendix 1.). These findings are moderately consistent with previous research, e.g., Ruisenor-Escudero et al. (2016) study on HIV children found higher levels of CD8 to be associated with better memory performance, reflecting in higher total recall scores on The Color Object Association Test (COAT) and with higher Receptive Language scores. However, another study found higher CD8 level to correlate with neurodevelopment delay, significant psychiatric symptoms, and poorer behavioral and emotional outcomes (Ruisenor-Escudero et al., 2015). A study on healthy aging discovered low blood-derived CD4 levels to be associated with better memory performance (Serre-Miranda et al., 2014). The researchers suggested that high levels of CD4 could produce poorer memory performance by increasing the pro-inflammatory profile.

In line with our findings, evidence shows that the immune system plays a vital role in neural plasticity and neurogenesis, which can significantly affect cognitive functions such as memory (Lekander, 2002). For example, animals injected with bacterial cytokines present difficulties with the Morris water maze, however this effect dissipates if IL-1 is blocked (Gibertini, Newton, Klein, & Friedman, 1995), suggesting that the hippocampal function can be affected by immune stimulation (Marin & Kipnis, 2013). The hippocampus is involved in several aspects of learning, for instance, spatial learning and conditioning to a context rather than to a simple sensory stimulus (Dhikav & Anand, 2012). In the hippocampus, the neuro-biological model of memory (long-term potentiation; LTP) has been demonstrated consistently (Bliss, Collingridge, Morris, & Reymann, 2018; Fedulov et al., 2007). LTP is the main form of synaptic plasticity reflecting the activity of synaptic information storage process, and has been recognized as the primary cellular correlate of learning and memory (Stuchlik, 2014). LTP suggests that neural pathways are highly sensitive to previous activity, and high-frequency stimulation of afferent fibers leads to a persistent enhancement of synaptic transmission in target neurons (Smolem, 2007).

Conversely, the administration of pro-inflammatory cytokines has been observed to abolish LTP in the hippocampus (Khairova, Machado-Vieira, Du, & Minji, 2009). Research on contextual conditioning indicates that the process of memory consolidation to long-term storage can be disrupted by immune activation (Bjorkstrand et al., 2016). The high density of cytokine receptors in the hippocampus could be mediating this effect on memory (Head, Rodrigue, Kennedy, & Raz, 2008). Healthy humans present impaired memory functions following administration of bacterial toxins (Capuron, Lamarque, Dantzer, & Goodall, 1999; Capuron et al., 2003), in addition to suffering from flu-like symptoms (Burton, Sparkman, & Johnson, 2011). Cytokines are also associated with neurodegeneration in diseases, such as HIV (Catalfamo, Le Saout, & Lane, 2012), Alzheimer's disease (Zheng, Zhou, & Wang, 2016), and multiple sclerosis (Gobel, Ruck, & Meuth, 2018).

Interestingly, the development stage of the cell in culture dictates whether the cytokine will contribute to neuronal cell death or survival (Garlet, 2010). In mature neurons, IL-1 induces cell death; in immature neurons, IL-1 plays a neurotropic factor

role that prevents cell death (Moudgil & Choubey, 2011). As several cytokines possess anti-tumoral properties, cognitive impairments can occur in cancer patients as side effects of the treatment (Floros & Tarhini, 2015). For instance, IL-2 administration can cause severe confusion and picture amnesia in cancer patients, resembling the cognitive impairments observed in Alzheimer's disease (Walker et al., 1996). IL-2 is also implicated in psychiatric disorders, as it has been proposed as a mediator in schizophrenia (Boerrigter et al., 2017).

Nevertheless, we did not find any significant association between IL-6 levels and memory recall. However, absence of significant correlations may only indicate a lack of linear relationship between these measured variables. It has been shown that the role of IL-6 is complex in learning and plasticity. The genetic deletion of IL-6 fails to disrupt memory and learning (Braidia et al., 2004), whilst application or overexpression of IL-6 can cause extensive memory impairments and impede LTP (Li, Katafuchi, Oda, Hori, & Oomura, 1997). Suggesting, IL-6 is not necessary for memory and learning, although it can contribute to impairments in cognitive function following an inflammatory response (Bradburn, Sarginson, & Murgatrod, 2018). Inversely, IL-6 has shown to be a regulator of neurogenesis, which is crucial for memory consolidation and hippocampal-dependent learning (Erta, Quitana, & Hidalgo, 2012). Hippocampal IL-6 levels have also been observed to increase after learning, which has been associated with protection from memory loss (Baune et al., 2012). On the other hand, IL-6 deficient mice exhibit enhanced learning in the radial arm maze compared to the wild type mice (Bialuk, Taranta, & Winnicka, 2018). The exact role of IL-6 on memory is not conclusive, however according to some current research, the role of IL-6 depends entirely on the specific condition under which it is elevated, together with the duration (i.e. chronic or acute) and magnitude of the elevation (Donzis & Tronson, 2014).

The relationship between cognitive performance and T-cell function has primarily been described in rodent studies, finding hippocampus-dependent learning to be impaired in T-cell deficient mice (Kipnis, Derecki, Yang, & Scrable, 2008; Ron-Harel & Schwartz, 2009; Ziv et al., 2006). It is proposed that T-cells regulate neural plasticity (Kuhn, Dickinson-Anson, & Gage, 1996), particularly hippocampal neurogenesis, the process of immature neurons migrating into the granule layer of the dentate gyrus and

develop into functional neurons (van Praag et al., 2002). In agreement of this hypothesis, T-cell deficient mice exhibit decreased neurogenesis, and the transfer of T-cells back into the mice reveal recovered neurogenesis and greater performance in a water maze (Ziv et al., 2006). Cytokine-induced modulation of memory processes is a complex phenomenon, including both beneficial and detrimental effects, depending on the specific cytokine, its levels within the brain, and the particular condition that changes the cytokine secretion (Tan, Cao, Zhang, & Zuo, 2014).

Limitations

Limitations of the study include the relatively small sample size, which limits the statistical power to discover statistically significant associations between intervention and measures. Additionally, the small sample size limits the generalizability of the results, therefore the findings should be interpreted with caution. There was also moderate attrition in the study, as there were originally 33 participants in the beginning of the study. However, a meta-analysis of 40 studies on computer-based psychological interventions found that unsupported treatments have approximately a dropout rate of 75%, compared to 38% for those treatments with administrative support, and 28% with therapist support (Richards & Richardson, 2012). Additionally, face-to-face psychological therapy dropout rate is roughly 30 to 60% (Richards & Richardson, 2012), thus the dropout rate in this study (26%) is not too different from traditional face-to-face approaches. Also, the participants were not checked for their day-to-day health status, therefore a participant with a common cold/flu may present skewed immunological measures. Furthermore, as the participants were non-clinical, it is possible that only participants under psychological stress or with an inflammatory condition will reveal changes in the immune markers measures in response to the mindfulness intervention. Lastly, there was a lack of active control group, thus a direct comparison of effectiveness could not be made with traditional face-to-face therapy (Kinser & Robins, 2013).

A growing amount of clinical research point to the critical involvement of inflammation in the pathogenesis of several neurological, immune system, and behavioral disorders, including cognitive impairment, depression, and autoimmune and metabolic diseases (Hunter, 2012). Thus, therapies designed to restore a balance in inflammatory mediators should be considered as conceivable methods of treatment and prevention (Tabas & Glass, 2013). While the efficacy of modern drug treatments should not be undervalued, combining them with behavioural intervention strategies (i.e. mindfulness training) that target inflammatory processes could enhance the outcome of drug treatments for diseases effected by chronic inflammation (Omid, Hamidian, Mousavinasab, & Naziri, 2016). For example, an inflammatory perspective on depression provides novel insights into adequacies of current treatment options. Antidepressants have shown to inhibit the release and/or production of inflammatory cytokines in humans and stimulate the proliferation of anti-inflammatory cytokines (i.e. IL-10) (Kenis & Maes, 2002).

These effects could contribute to therapeutic effectiveness, particularly as the effect of desipramine (tricyclic antidepressant) in the forced swim test (frequently used animal model method to assess antidepressant efficacy) relies on the capability of the drug to inhibit TNF- α production (Hestad, Tonseth, Steen, Ueland, & Aukrust, 2003; Reynolds, Ignatowski, Sud, & Sprengler, 2004). In humans, a selection of antidepressant strategies (including psychotherapy, medication, and electro-convulsion shock therapy) appear to reduce inflammatory activity in concert with improvements in depressive symptoms, indicating that attenuation of inflammation may contribute to treatment response (Lanquillon, Krieg, Shach, & Vegger, 2000; Tuglu, Kara, Caliyurt, Vardar, & Abay, 2003).

However, patients with a history of non-responsiveness towards antidepressants have been shown to present with increased plasma concentrations of IL-6 when compared with treatment-responsive patients (Maes et al., 1997). Comparably, patients with symptoms of increased inflammatory activity prior to treatment have been reported to be less responsive to antidepressants, sleep deprivation (effective short-

term mood elevator), and lithium (Benedetti, Lucca, Brambilla, Colombo, & Smeraldi, 2002; Sluzewska, Sobieska, & Rybakowski, 1997). Additionally, in the context of cytokine exposure, antidepressants may only effect selected symptoms domains (i.e. anxiety or depressed mood) (Capuron et al., 2002), whilst leaving numerous symptoms comparatively unaffected (i.e. psychomotor slowing or fatigue) (Morrow et al., 2003). Interestingly, this pattern of symptom response has also been documented in the antidepressant treatment of medically healthy patients with depression (Greco, Eckert, & Kroenke, 2004).

These observations indicate that inhibition of pro-inflammatory cytokine signaling represents a viable strategy for the treatment of depression, specifically in patients with symptoms of increased inflammatory activity prior to therapy who may be less likely to respond to conventional agents (Raison, Capuron, & Miller, 2006). In support of these observations, research in laboratory animals demonstrates that cytokine-induced sickness syndromes (parallel symptomatically with depression) can be reversed by the administration of anti-inflammatory cytokines (i.e. IL-10) (Maier & Watkins, 1995) or specific cytokine antagonists (i.e. IL-1a) directly into the brain (Pugh et al., 1999). Furthermore, cytokine antagonists have shown to have antidepressant-like effects, even in the absence of an immune challenge. For instance, IL-1a intracerebro-ventricular administration in mice prevents memory deficits following the psychological stress of social isolation (Katsouri et al., 2013), and reduction of depressive symptoms have been reported in humans (Lichtenstein, Bala, Han, Woody, & Schaible, 2002; Mathias et al., 2000).

Likewise, depression is a highly prevalent co-morbidity in inflammatory conditions such as multiple sclerosis (Kobelt & Giovannoni, 2017) and rheumatoid arthritis (Lin et al., 2015). Intriguingly, improvements in mood in patients with these conditions often appear before improvements in the underlying disease and is associated with better health outcomes (Raison et al., 2006). Mindfulness training has repeatedly demonstrated efficacy in decreasing depressive symptoms (Blanck et al., 2018) and improved immune system activity (Black & Slavich, 2016), therefore mindfulness training could be a valuable adjunct treatment with pharmacotherapy, especially for those patients who have been found to be resistant to establishment

forms of treatment (Eisendrath et al., 2008; Kenny & Williams, 2007). For the general population, countering effects of mindfulness training on hypersensitive or dysregulated immune system profiles could theoretically enhance immune defenses against common bacterial and viral infection (Morgan, Irwin, Chung, & Wang, 2014), in addition to improved cognitive function (Berk, Boxtel, & Os, 2016). Future research should investigate the effects of mindfulness on a larger sample size with active control group, and compare across both clinical and non-clinical populations.

Conclusion

To knowledge, this is one of the first study to investigate the effect of mindfulness training on immunological measures and memory, and the relationship between these immunological biomarkers and memory in the healthy population. The results from the study highlight significant improvements in immediate and long delay recall, and modest change in immunological measures with only significant change in CD69. Both CD4 and CD8 was found to be negatively correlated with long delay recall, together with a positive correlation between CD8 and short delay recall. In summary, the findings suggest there are associations between immunological biomarkers and memory in the general healthy population, thus providing evidence that mindfulness training is associated with changes in certain biomarkers of the immune system and memory function.

Appendix 1. Pre-Post Intervention correlation coefficients for memory performance and immunological measure

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Pre-CD4	-																			
2. Pre-CD8	0.261	-																		
3. Pre-CD69	-0.067	-0.023	-																	
4. Pre-Cortisol	-0.276	-0.172	-0.08	-																
5. Pre-IL6	0.055	.476*	-0.102	-0.094	-															
6. Pre-CRP	-0.095	0.33	-0.032	-0.004	.762*	-														
7. Pre-Immediate Recall	-0.112	-0.199	-0.335	0.154	-0.182	-.399*	-													
8. Pre-Short Delay Recall	-0.111	-0.131	-0.173	0.001	0.018	-0.108	.686**	-												
9. Pre-Long Delay Recall	-0.09	0.042	-0.215	-0.168	0.176	0.083	.549**	.716**	-											
10. Pre-Recognition	0.036	-0.096	-0.081	-0.324	-0.137	-0.328	0.159	0.31	0.02	-										
11. Post-CD4	.568**	-0.218	-0.053	0.042	-0.172	-0.087	-0.236	-0.17	0.055	-0.077	-									
12. Post-CD8	-0.031	0.345	-0.347	0.067	0.218	0.148	-0.093	-0.032	0.066	0.352	0.109	-								
13. Post-CD69	-0.11	0.124	0.127	0.133	.449*	0.37	-.569**	-.436*	.411*	-0.326	-0.023	0.059	-							
14. Post-Cortisol	-0.145	-0.039	-0.16	.729**	-0.083	0.025	0.358	0.081	0.137	-0.383	-0.028	0.045	0.002	-						
15. Post-IL6	0.117	0.353	0.18	-0.239	*	.662**	-.491*	-0.27	0.066	-0.246	0.028	0.179	.502**	0.069	-					
16. Post-CRP	-0.144	0.245	0.054	0.135	0.125	.483*	-0.103	0.081	0.217	-0.257	-0.032	0.098	-0.081	0.276	0.339	-				
17. Post-Immediate Recall	-0.219	0.002	-0.262	0.021	-0.141	-0.311	.605**	0.189	0.272	0.055	-0.379	0.083	-0.316	0.181	-0.283	0.059	-			
18. Post-Short Delay Recall	-0.222	.440*	-0.295	-0.044	0.141	0.015	.473*	0.207	0.377	-0.034	-0.337	0.153	-0.254	0.087	-0.052	0.199	.621**	-		
19. Post-Long Delay Recall	-.454*	0.367	-0.251	0.016	0.138	0.063	0.412	0.179	0.236	0.052	.539**	0.094	-0.312	0.007	-0.208	0.157	.650**	.854**	-	
20. Post-Recognition	0.284	-0.055	-0.265	-.555**	0.032	-0.006	0.23	0.311	0.168	.663**	0.009	0.236	-0.266	0.314	0.07	0.106	0.158	-0.007	0.006	-

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