Understanding the neurocognitive mechanisms and improving cognitive and emotional health in female survivors of breast cancer

Understanding the Neurocognitive Mechanisms and Improving Cognitive and Emotional Health in Female Survivors of Breast Cancer

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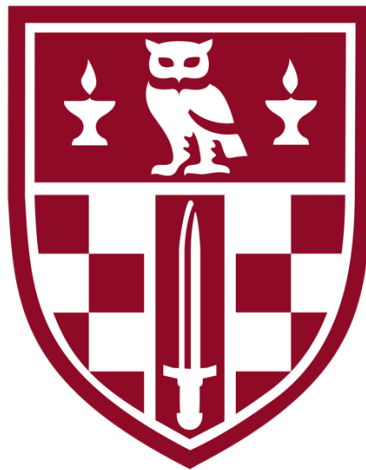
Declaration

'I, Jessica Swainston, declare that the work in this submitted thesis is my own'.

The thesis includes research that appears in the following articles:

Chapter 2: Swainston, J., & Derakshan, N. (2018). Training cognitive control to reduce emotional vulnerability in breast cancer. *Psycho-Oncology*, *27*(7), 1780-1786.

ABSTRACT

Breast cancer is the most prevalent cancer in women worldwide with incidence on the increase. Despite this, as a result of earlier detection and improvements in medical treatment outcomes, survival rates are improving. However, the longer term side effects of breast cancer can adversely affect an individual's social, cognitive and emotional functioning, profoundly impairing quality of life. As such, the primary aim of the present PhD thesis was to better understand the mechanisms involved in cognitive and emotional vulnerability in breast cancer and to develop and assess the efficacy of interventions that could better the lives of women in survivorship post diagnosis.

Findings from Experiment 1 firstly indicate that targeted neurocognitive interventions can improve cognitive control and processing efficiency in breast cancer survivors, establishing that this population is receptive to treatments that provoke brain neuroplasticity. Secondly, it demonstrates that as a result of engaging top down attentional control processes, such interventions can result in sustained reductions in emotional vulnerability. Following on, using an expressive writing intervention, Experiment 2 indicates a relationship between the use of words thought to reflect cognitive reappraisal, as well as affectively negative words, with improvements in perceived cognitive function, emotional vulnerability and quality of life. That said, refinement of expressive writing paradigms is required to optimise transfer outcomes. Experiment 3 outlines an intervention study demonstrating how both mindfulness meditation training, adaptive working memory training, and a combined course of both, can result in reductions in anxious symptomatology compared to an active control condition.

As a means to further understand the neurocognitive mechanisms affected by breast cancer, Experiment 4 adopts a neural approach exploring how breast cancer survivors respond to making cognitive errors in comparison to healthy controls. Findings

indicated that whilst performance effects were absent, neural differences were found between groups, indicating that compensatory processes were required in order to function efficiently.

Finally, whilst a large body of research now indicates that chemotherapy affects cognitive functioning post treatment, less is known about the effects of the estrogen reducing hormone therapy Tamoxifen, which is widely administered to breast cancer survivors for five to ten years post diagnosis. Study 5 employed qualitative methods to explore the lived experience of taking Tamoxifen in the absence of chemotherapy. Findings indicate that for this subset of breast cancer survivors, cognitive deficits are also present, and can greatly diminish quality of life.

Overall, findings have critical implications for informing researchers, clinicians and the breast cancer population alike on the underlying mechanisms surrounding cognitive and emotional vulnerability in breast cancer.

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Thesis Outline

The aims of the current PhD thesis are two-fold, and accordingly the project is divided into two main sections. Section A, incorporating chapters 1-5, primarily focuses on the emotional impact of breast cancer in survivorship, and presents a series of novel behavioural intervention studies aimed at reducing emotional vulnerability. Section B, incorporating chapters 6-9, is specifically centred around further exploring the phenomenon of cancer-related cognitive impairment (CRCI). First, a neural study investigating how breast cancer survivors monitor and respond to cognitive errors will be presented. In a second study employing qualitative methods, the impact of the estrogen depleting hormone therapy tamoxifen will be explored in relation to CRCIs and the consequential implications for quality of life in survivorship. Each section will begin with a general introduction presenting an overview of the current literature in each research area and will end with a general discussion based on the outcomes of the studies carried out in each chapter. The thesis will conclude with a general overview of the present findings and final comments for the direction of research across breast cancer survivorship.

Section A: Investigating Emotional Vulnerability in Breast Cancer

Chapter 1: General Introduction

1.1 Chapter Overview

Given the complexities of breast cancer, the current chapter will begin with a basic overview of diagnosis, etiology, epidemiology and treatment in order to contextualise the research project and facilitate comprehension of terminology throughout the succeeding chapters. The chapter will then proceed to summarize the current literature on emotional vulnerability in breast cancer in terms of type, prevalence and the trajectory of emotional change throughout survivorship. Following on, the chapter will present a prevailing theoretical position on targeting emotional vulnerability through improving cognitive control processes and discusses how we can leverage current research findings in psychopathology and apply them to populations such as breast cancer survivors who are at high risk of emotional disorder. Finally, the behavioural interventions that are employed in the studies situated in the following chapters of Section A will be presented, namely attentional control training, expressive writing and mindfulness. The dominant mechanistic theories for each intervention will be outlined along with a discussion of the efficacy of such treatments in psychopathology and emotional vulnerability in breast cancer to date. The chapter will conclude with a summary and research aims for the remaining chapters of Section A.

1.2 What is Breast Cancer?

Cancer is an overarching term for a class of diseases characterized by abnormal cells that grow and potentially invade other surrounding healthy tissue in the body. For a cancer to start, certain changes take place within the genes of a cell or a small group of cells. Mutations can cause cells to multiply and grow out of control, and approximately half a dozen different mutations will turn a normal cell into a cancerous cell. Breast

cancer occurs when such malignant tumors develop in the breast. Breast cancer most commonly begins in the cells that line the ducts of the breasts. There is a network of lymph glands (commonly referred to as lymph nodes) which are close to the breast and make up part of the lymphatic system that runs through the body. Lymph nodes contain a yellow fluid called lymph which runs through the lymphatic system collecting waste products and draining it into veins to be removed. Cancer cells released from the breast tissue can be trapped in nearby lymph nodes (Cancer Research UK, 2019). There are a number of different types of breast cancer including non-invasive, invasive and metastatic (secondary) breast cancers, along with the intrinsic or molecular subtypes of breast cancer. Ductal carcinoma in situ (DCIS) is the earliest from of breast cancer and develops when there are cancer cells contained (in situ) in the ducts of the breast. Invasive breast cancer (No Special Type; NST), is the most common form of breast cancer and indicates when cancer cells have grown through the lining of the ducts into the surrounding breast tissue. Other less common forms of breast cancer are classed as 'Special Type' and are identified by particular features. Special Type breast cancers include lobular breast cancer which starts in the lobes of the breast and other rare types of breast cancer (Macmillan Cancer Support, 2019). A breast cancer diagnosis is classified as a particular stage and grade which indicates how big the cancer is (stage), how fast the cancer is growing (grade) and whether it has metastasized (spread) to other organs of the body such as the liver, brain, lungs or bones (secondary breast cancer) making it incurable.

1.3 Epidemiology of Breast Cancer

Amongst women, breast cancer is the most commonly diagnosed and leading cause of cancer death worldwide. In the UK alone there are approximately 55,200 new cases diagnosed every year (Cancer Research UK, 2016). Since the early 1990s the incidence of breast cancer in women has increased by around a quarter (24%) and is

projected to continue rising. Nevertheless, the improvement of medical treatment has meant that significantly more women survive breast cancer, and around two thirds (65%) of women in the UK will now survive their disease for twenty years or more post diagnosis, (Cancer Research UK, 2016).

1.4 Etiology and risk factors

There is no singular cause of breast cancer however numerous risk factors have been identified. These include fixed risk factors such as genetic predisposition, ageing, ethnicity and increased breast tissue density, as well as risk factors which can be influenced by lifestyle factors including obesity, regular alcohol consumption and smoking. Exposure to estrogen throughout the lifespan can further increase the risk of breast cancer in women. For instance, early menarche (before the age of 12), late first pregnancy (over the age of 30), consumption of hormone replacement therapy (HRT) for longer than 5 years, and consumption of the contraceptive pill have all been identified as risk factors (Macmillan Cancer Support, 2019). That said, the research surrounding the etiology of breast cancer is inconclusive and whilst some people with multiple risk factors never develop breast cancer, others with minimal risk factors are diagnosed. Like many conditions, it is likely that breast cancer develops through a complex interaction of your genetic makeup and exposure to environmental factors.

1.5 Treatment

Breast cancer is frequently treated with multiple modalities. This can include a combination of surgical resection, systematic chemotherapy and radiation therapy. Chemotherapy may be neo-adjuvant whereby chemotherapy is initiated prior to surgery to reduce the tumour size, or adjuvant, in which case chemotherapy takes place after surgery in order to target the remaining cancer proliferation and occult cells that may have

metastasized to lymph nodes (Ahles & Root, 2018). Breast cancer can also be targeted through immunotherapy, a biological therapy that boosts the body's natural defences to fight cancer. To control for recurrence, hormonal (endocrine) therapy is also frequently administered to women with estrogen positive breast cancer for up to 10 years post diagnosis. This operates through either limiting estrogen binding (Tamoxifen) or blocking estrogen production (aromatase inhibitors).

1.6 Emotional Vulnerability in Breast Cancer

The improvement of medical treatment has meant that significantly more women survive breast cancer. In recent years this has prompted researchers to investigate the longer-term side effects of cancer diagnosis and treatment. Indeed, the acknowledgement that physical, cognitive and emotional complications can persist throughout the remaining lifespan is now well established. The long term side effects of breast cancer can adversely affect an individual's social, cognitive and emotional functioning, profoundly impairing quality of life. Not only can women experience longer term physical side effects such as fatigue, sleep disturbance, joint pain, heat flushes, and vaginal dryness (Hagen et al., 2016), but breast cancer can further leave individuals vulnerable to numerous psychological disorders such as anxiety, depression and post-traumatic stress (Härtl, Schennach, Müller, Engel, Reinecker, Sommer, & Friese 2010; Voigt et al., 2016). Emotional distress in cancer patients is a critical component of the cancer experience in that when severe, it has been associated with reduced treatment compliance (Greer, Pirl, Park, Lynch, & Temel, 2008) and increased risk of disease progression and mortality (Satin, Linden, & Phillips, 2009; Pinquart & Duberstein, 2010).

Onset can develop through the accumulation of a variety of anxieties and distressful changes surrounding their diagnosis such as fear of recurrence or mortality, altered self-image, changes in sexuality and the potential adverse impact on women's careers and relationships. Adjuvant chemotherapy and endocrine therapy i.e. tamoxifen

and aromatase inhibitors, which help prevent recurrence in estrogen receptor-positive breast cancer patients, cause early menopause, creating further stressors on young women who lose their fertility (Gorman, Malcarne, Roesch, Madlensky, & Pierce, 2010). Indeed a number of studies have indicated greater levels of psychological distress in younger compared to older women (Burgess, Cornelius, Love, Graham, Richards, & Ramirez, 2005; Bistrup, Johansen, Dalton, Deltour, Kehlet & Kroman, 2012).The phenomena of cancer-related cognitive impairment, which has gained increasing interest in recent years across cancer survivorship, has also been linked to psychological distress and impaired quality of life in survivors (Selamat, Loh, Mackenzie, & Vardy, 2014).

Adjustment to cancer-related changes is an adaptive process which involves managing emotional distress. Whilst some patients experience a handful of positive emotions such as gratitude and hope, many frequently experience negative affect such as anxiety, fear, sadness, anger and guilt (Conley, Bishop, & Andersen, 2016). Whilst such emotions are a natural response to diagnosis, for some they are disabling and may develop to reach clinical levels of emotional disorder. Indeed, considering psychological illness such and depression and anxiety are common, they are often a neglected component of the cancer experience.

1.6.1 Prevalence and Trajectory of Emotional Distress in Breast Cancer

Whilst numerous studies have assessed psychological disorder in breast cancer survivors, the exact prevalence of psychiatric conditions remains ambiguous. This in part is due to variability across outcome measures, different criteria for defining particular psychological disorders, as well as diversity across participant samples with respect to cancer type, stage and treatment modality (Tsaras, Papathanasiou, Mitsi, Veneti, Kelesi, Zyga & Fradelos, 2018). Moreover some of the typical side effects of cancer treatment such as fatigue, loss of appetite and sleep disturbance can resemble the neurovegetative

symptoms observed in certain psychological conditions such as depression, making detection diagnostically difficult (Krebber et al., 2014). Nevertheless, although variable, rates of clinically significant symptoms of psychological disorder typically exceed rates of the general population, particularly in the first year after diagnosis. Given the infancy of the research area, only a handful of studies have assessed psychological disorder beyond two-years post diagnosis. Burgess et al., (2005) found that approximately 50% of women with early breast cancer had anxiety, depression or both in the year after diagnosis, 25% in the second, third and fourth year and 15% in the fifth year, with previous psychological treatment, younger age and other stressful life experiences predicting longer term emotional disorder. Elsewhere research has started to investigate other emotional disorders in cancer, such as post-traumatic stress (PTSD). A recent study by (Voigt et al., 2017) investigated clinical levels of trauma in early breast cancer during their first diagnosis. Before treatment, 82.5% of participants experienced PTSD symptoms related to breast cancer, and at one year follow up this figure only decreased to 57.3%.

Overall, it is clear that the existing research on the emotional trajectory of breast cancer patients is limited in size and scope, with a particular need for longitudinal studies in this area.

1.6.2 Emotion Regulation in Breast Cancer

Given the level of emotionally distressing symptoms related to breast cancer, it is clear that the effective regulation of emotion is critical for survivors. By addressing negative affect at an early stage along the breast cancer trajectory, there is potential to limit its impact, and prevent the onset of anxious and depressive disorders. The particular strategies that women use in emotional regulation seem of critical importance in the context of breast cancer. For instance, breast cancer patients who have indicated using

less adaptive coping mechanisms to regulate their emotions, such as repressive emotional strategies, have also reported greater levels of anxious and depressive symptomatology, emotional distress, poorer quality of life as well as poorer physiological outcomes such as impaired cortical regulation and higher blood pressure (see Brandão, Tavares, Schulz, & Matos, 2016, for a review). Nevertheless, to date, the majority of research surrounding emotion regulation in breast cancer derives from the investigation of coping processes, and in fact, numerous studies utilize coping scales as a measure of emotion regulation (Conley et al., 2016). This is problematic in that much of the emotion regulation literature distinguishes emotion regulation from coping, positing that whilst emotion regulation is primarily the adaptation of emotional experience, coping involves multiple processes.

Research implementing a cognitive and affective behavioural and neuroscientific approach in the investigation of emotion regulation in breast cancer is uncommon, and as such forms the basis of the first section of the current thesis. By leveraging recent findings from current cognitive neuroscientific research into anxiety and depression, there is scope further our knowledge of emotional vulnerability in the breast cancer population.

1.7 Targeting Emotional Vulnerability in Breast Cancer

1.7.1 Attentional Control Theory

Attentional control is the ability to exercise and regulate attention towards relevant and away from irrelevant information, flexibly and efficiently (Eysenck, Derakshan, Santos & Calvo, 2007), and as such plays a vital role in everyday and complex activities and situational demands. Attentional control is a fundamental component of our working memory which is responsible for the inhibitory, shifting and updating functions that are critical for completing task goals effectively (Berggren & Derakshan, 2013). Here, inhibition refers to the capacity to inhibit task irrelevant information (i.e. intrusive thoughts), shifting refers to the ability to disengage attention from one task and direct it

to another, and updating refers to the transient storage of information (Eysenck et al., 2007). Recent models of working memory regard working memory capacity, a term considered synonymous with attentional control, to indicate the relative efficiency of these functions (Miyake, Friedman, Emerson, Witzki, Howerter, & Wager, 2000; Unsworth & Robison, 2019). Consequently, the efficient recruitment of attentional control is necessary for effective working memory functioning. Two attentional subsystems are thought to interact in order for attentional control to operate efficiently (Corbetta & Shulman, 2002). First, attention can be directed through a top-down volitional system, which is goal directed by nature, and highly influenced by experience, expectations and knowledge. Second, attention can be directed through a bottom up approach, which is stimulus driven and reflexive to external stimuli.

1.7.2 Attentional Control and Negative Affect

Emotion has critical impact on cognition and vice versa (Pessoa, 2008). Accordingly the two processes are inextricably linked and must be considered conjointly. The primary assumption of attentional control theory is that top-down attentional control processes that are necessary for task goals are highly disrupted by excessive negative affect that increase the dominance of stimulus driven bottom up processes (Eysenck at et al., 2007). This relationship is crucial in that it influences the extent to which individuals are able to inhibit disruptive stimuli in the environment and remain focused on current tasks.

Attentional control theory encompasses the assumption that anxiety related deficiency in attentional control processes are particularly influenced when stimuli in the environment is aversive/threat related (see Berggren & Derakshan, 2013, for a review). This is indicative of an implicit bias towards aversive information driven by the bottom up attentional system. It follows that anxiety is thought to drive the allocation of attentional resources to negative information, and as such leaves the remaining resources

available for goal-directed behaviour depleted. Nevertheless the relationship between high anxiety and impaired attentional control functions have also been observed in the absence of threat related stimuli pointing to general deficits in attentional control in anxious populations. Indeed numerous studies have indicated deficits in top-down attentional control mechanisms (i.e. the inhibition, shifting and updating functions of working memory) in individuals with high trait anxiety (Bishop, 2009; Pacheco-Unguetti, Acosta, Callejas, & Lupiáñez, 2010).

For instance, high levels of anxiety has been shown to increase reaction times in antisaccade tasks in which top down control processes are necessary to inhibit a reflective saccade towards a stimulus and instead make a conscious saccade to the opposite side of the target (see Derakshan and Eysenck, 2009, for a review). Greater antisaccade latencies in high anxious individuals are indicative of disrupted inhibition processes and reduced pre-frontal control. Similarly, a variety of paradigms have indicated the disruptive effects of anxiety on both the shifting and updating functions of working memory. In one commonly employed switching task, the Wisconsin Card Sorting Task, anxiety was shown to increase both error rate and reaction times (Goodwin & Sher, 1992; Caselli, Reiman, Hentz, Osborne, & Alexander, 2004). Similarly, Qi, Luo, Duan, Ding, Hu, & Li (2014) investigated the relationship between high anxiety and the monitoring and updating of information during a modified flanker task that manipulated working memory load. Results indicated that for high trait anxious individuals, increased working memory load interfered with participants ability to complete the task efficiently.

Whilst cognitive biases towards negative information have predominantly been linked to anxiety disorders (Cisler & Koster, 2010), they are also characteristic of depression (see Peckham, McHugh, & Otto, 2010 and Dolcos et al., 2019 for reviews). Indeed cognitive models of depression propose that depressed individuals display cognitive biases in all aspects of information processing including memory,

interpretation, perception and attention (see Gotlib & Joormann, 2010 and Everaert, Podina, & Koster, 2017 for reviews). Moreover deficits in cognitive control processes are thought to be broadly associated with depressive disorders (see Snyder, 2013, for a meta-analytic review). Difficulties in regulating the inhibitory, shifting and updating functions critical for task goals are thought to explain excessive negative information in working memory (Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017). This directly links cognitive control impairments to rumination (persistent negative thinking) a key risk factor for depression, (Joormann, Yoon, & Zetsche, 2007; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Indeed numerous studies of both clinically and at-risk depressive populations (high ruminators; dysphoric individuals) have indicated difficulties in inhibitory (Joormann, 2004; Derakshan, Salt, & Koster, 2009), shifting (Beckwé, Deroost, Koster, De Lissnyder, & De Raedt, 2014) and updating tasks (Levens & Gotlib, 2010), pointing to impaired cognitive control functions. Critically, it appears that such deficits are not simply correlates of depression, but can causally predict future rumination and depressive symptomatology in both healthy (Pe, Brose, Gotlib, & Kuppens, 2016) and remitted (Demeyer, De Lissnyder, Koster, & De Raedt, 2012) samples.

Neural studies further substantiate the association between regulatory top-down and bottom-up processes of attention and emotion. Specifically, prefrontal structures have been implicated in the effortful control of emotion regulation and simultaneous deactivation of subcortical regions associated with emotion (i.e. the amygdala). Using functional magnetic resonance imaging (FMRI) during a response-conflict task, Bishop (2009) found that high trait anxious individuals showed reduced prefrontal activation and slower target identification even when task demands on attention were low and threat-related stimuli were absent. The findings suggest that trait anxiety is associated with diminished recruitment of prefrontal mechanisms of attentional control pointing to a broad dysregulation of attentional control in anxiety disorders.

Similarly, numerous studies have indicated fronto-limbic alterations in depressive populations (Snyder, 2013; Palmer, Crewther, Carey, & Team, 2015). Neuroimaging studies demostrate that depression is linked to disrupted activity in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) (Etkin, Gyurak, & O'Hara, 2013) with reduced activation in prefrontal regions being associated with deficits in cognitive control processes (Collette & Van der Linden, 2002). This prefrontal hypoactivation has also been observed at resting state in patients with depressive disorders (see Fitzgerald, Laird, Maller, & Daskalakis, 2008, for a meta-analytic review). Conjointly, increased amygdala activity and decreased DLPFC activation in response to emotional information has been demonstrated in depressed individuals (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). As such, the altered patterns of activation in fronto-limbic neural pathways may be reflective of the key components observed in depression (e.g. impaired mood regulation, persistant rumination and avolition) (Nitschke & Mackiewicz, 2005; De Raedt & Koster, 2010). Similarly, ERP studies have demonstrated impaired attentional control processeses in at-risk depressive populations. Owens, Koster and Derakshan (2012), for example, found a sustained event-related potential asymmetry (referred to as contra-lateral delay activity) which was receptive to working memory capacity and the efficient filtering of irrelevant information in dysphoric vs non-dysphoric individuals. Taken together, these findings point to the fundamental role of attentional control processes in vulnerability to depressive disorders.

Attentional control theory further stipulates that whilst task performance in anxious populations is often equal to that of non-anxious individuals, this often comes at a neural cost in which greater cortical recruitment is required as a compensatory mechanism. An ERP study by Ansari and Derakshan (2011) investigated the neural correlates of cognitive effort/pre-target preparation (as measured by the contingent negative variation; CNV) in anxiety using an antisaccade task which manipulated the

interval between the offset of instructional cue and the target onset (CTI). High anxious individuals showed greater levels of CNV activity in pre-frontal areas during medium CTI indicating an exertion of greater cognitive effort and requiring more attentional resources in preparation for completing the task. This suggests that trait anxiety is linked to diminished pre-frontal recruitment of attentional control mechanisms due the compensatory resources that are required to reach task performance. Recent research has extended findings insofar as proposing a direct causal link between inefficient prefrontal attentional control mechanisms and amygdala response to affect. Ironside et al., (2017) used transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) in high-trait individuals to show that activation of this region reduced amygdala threat reactivity and simultaneous increased activity in cortical regions associated with attentional control and task performance.

1.8 Cognitive and Emotional Vulnerability Intervention Methods

1.8.1 Attentional Control Training and Emotional Vulnerability

Recent advancements in cognitive and affective neuroscience have shown that the key neural circuitries involved in attentional control processes can be targeted via computerized neurobehavioral cognitive training techniques (Jaeggi, Karbach, & Strobach, 2017). Findings indicate that, as a result of attentional control training, gains in working memory capacity can result in transfer to related cognitive capabilities that implicate related neural pathways, such as improvements in fluid intelligence (Jaeggi, Buschkuehl, Jonides, & Shah, 2011). The most frequent training task employed to date is that of the adaptive dual n-back task in which the central executive functions of working memory are exercised and engaged in a systematic and adaptive manner. Here participants are presented with continuous paired audio and visual stimuli and are required to decide whether the current stimuli pair is matched to the stimuli pair present

'n' trials before in the sequence. Based on performance, task difficulty adapts by increasing or decreasing the level of 'n'.

In light of a possible causal link emerging between efficient attentional control processes and the downregulation of emotion (Dolcos et al., 2019), the crucial role of cognitive functioning in emotional regulation is being investigated in recent interventions that target cognitive processes to improve well-being in anxiety and depression. A growing body of evidence now shows that training attentional control functioning can reduce and protect against anxiety and depressive vulnerability (Engen & Kanske, 2013). For instance, Sari, Koster, Pourtois, & Derakshan (2016) showed that a 3 week course of adaptive dual n-back training, resulted in reductions in anxiety for highly anxious individuals. Here task engagement was related to anxiety outcomes; high engagement with the task, as measured by the amount of n-back improvement, was positively correlated with greater reductions in trait-anxious symptomatology. Similarly in depressive research numerous studies indicate the efficacious impact of attentional control training in attenuating negative affect in both clinical and subclinical depressive disorders (see, Motter, Pimontel, Rindskopf, Devanand, Doraiswamy, & Sneed, 2016, and Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017, for meta-analytic and systematic reviews). For example, a group of participants with major depressive disorder took part in a 2-week course of attentional control training on an adaptive version of the PASAT (Paced Auditory Serial Addition Task) (Gronwell, 1977). Outcomes indicated significant reductions in rumination, a key predictor of depression, pre to post intervention (Siegle, Price, Jones, Ghinassi, Painter, & Thase, 2014).

Similarly, promising results have emerged indicating improved resilience in students at risk for developing depression (Hoorelbeke, Faelens, Behiels, & Koster, 2015) and reduced symptoms of burnout as part of a stress rehabilitation program for individuals diagnosed with exhaustion disorder (Gavelin, Boraxbekk, Stenlund, Järvholm, & Neely,

2015). More broadly, cognitive training has shown to be effective in other areas of psychopathology such as schizophrenia, mood, and substance abuse disorders (see, Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014, for a review).

In neural studies, findings show that cognitive control training can directly modify emotion-related functional architecture in regions of the cortex that are implemented in the regulation of negative affect. Cohen et al., (2016) used FMRI during a flanker task to test the efficacy of executive control training on emotional reactivity. Results showed that frequent high intensity training sessions resulted in decreased behavioural interference of aversive pictures and a reduction in amygdala reactivity. Additionally, an interaction between changes in connectivity between right inferior frontal gyrus and the amygdala was found. Findings suggest that executive control training can result in altered amygdala-prefrontal connectivity and changes to amygdala activity to aversive information.

1.8.2 Cognitive Training in Cancer

A small number of studies have considered cognitive training in cancer survivorship. So far, results appear promising. Von Ah et al., (2012) trained breast cancer survivors on memory and speed of processing functions in ten 1-hour sessions across 6-8 weeks. Results indicated improvements in both functions to non-trained measures of cognitive performance at post-test as well as at 2 months follow up. Moreover training related gains resulted in improvements in perceived cognitive functioning, system distress, and quality of life for breast cancer survivors compared to a waitlist control group. Elsewhere, Kesler et al., (2013) found that executive functioning training resulted in improvements in cognitive flexibility, verbal fluency, processing speed and verbal memory, and Damholdt et al., (2016) found that web based cognitive training can result in improved objective and subjective measures of working memory and perceived

cognitive functioning respectively. In other cancer populations, Conklin et al., (2015) found that training in visual-spatial and verbal working memory exercises resulted in improvements in working memory, attention and processing speed in childhood survivors of cancer.

1.8.3 Expressive Writing

Expressive writing (EW) is a brief writing activity that requires the emotional disclosure of an individual's deepest thoughts and feelings about personally important experiences or situations in their lives (Arigo & Smyth, 2015). Whilst there is a long history of writing expressively in therapeutic settings, Pennebaker & Beall (1986) were the first to empirically test the effects of written disclosure by examining whether writing about traumatic events would influence short and long-term measures of wellbeing. Findings indicated that whilst immediately after writing about their trauma participants showed increased levels of negative mood and blood pressure, at 6 months follow up EW was associated with fewer physician visits and reduced health complaints. These preliminary findings initiated a body of research investigating the therapeutic effects of EW in both healthy and clinical populations. Whilst there remains ambiguity across findings, particularly relating to which populations it is most impactful, numerous studies indicate improved mental and physical outcomes as a result of EW (Pennebaker & Chung, 2011).

There is no clear consensus on the mechanisms by which EW works, however a number of theories have been put forward (see, Frattaroli, 2006 and Baikie & Wilhelm, 2005, for reviews). Early theories hypothesized that the effortful process of actively inhibiting distressing thoughts and feelings about one's trauma comes at a physical and psychological cost leading to increased physiological activity, ruminative thinking about past events and longer term disease (Pennebaker, 1985). It has been proposed that by

confronting trauma by writing about the experience and acknowledging the corresponding emotions connected to the events, a gradual process of disinhibition will occur and stressors on the mind and body will decrease. Empirical support for this theory is varied. Whilst some studies indicate improvements in immune functioning as a result of EW (Pennebaker, Kiecolt-Glaser, & Glaser, 1988; Booth, Petrie, & Pennebaker, 1997), suggesting that disclosure might reduce physical stress on the body, the idea that disinhibition is the causal mechanism that underlies this effect is equivocal. By contrast certain studies have indicated no differences in health outcomes for participants writing about previously undisclosed traumas compared to those who had previously disclosed theirs, or to participants who wrote about an imaginary trauma in which they could not have inhibited trauma-related thoughts and feelings to begin with (Greenberg & Stone, 1992; Greenberg, Wortman, & Stone, 1996).

Others have suggested that EW may prove beneficial through habituation. Supporting this theory are findings that show that repeated and prolonged exposure to one's traumas through EW results in the attenuation of negative affect and better physical outcomes (Sloan, Marx, & Epstein, 2005). Nevertheless similar benefits have been found across studies which allow participants to write about different traumas in the same session or across different sessions (Pennebaker & Chung, 2011).

Theories of self-regulation have further been put forward as a means to explain the mechanisms underlying EW effects, such that EW may promote feelings of self-efficacy, boosting an individual's ability to cope with challenges. Cameron & Nicholls (1998) for example found that participants who participated in a self-regulation task in which they expressed thoughts and feelings about starting college as well formulating coping plans showed improved mood state and college adjustment. Further studies have encouraged a positive expressive writing style. For instance, a number of studies have promoted 'benefit finding' in which participants are asked to try and find positive aspects

to adverse experiences. In a study with adults with lupus or rheumatoid arthritis, compared to a fact writing control group, benefit finding was shown to be effective in reducing pain for participants with high trait anxiety, whereas a typical EW task appeared effective in reducing pain for those with low trait-anxiety (Danoff-Burg, Agee, Romanoff, Kremer, & Strosberg, 2006). Both the benefit finding and EW groups also showed reductions in fatigue at 3 months follow up compared to the fact writing control. King, (2001) further found that participants who wrote about their 'best possible future self' and attaining life goals were less upset and indicated an increase in subjective wellbeing post-intervention compared to those who wrote about trauma. At 5 months follow up, both the trauma group and the 'best possible self' group showed decreased illness compared to those who wrote about an emotionally neutral topic. It was concluded that writing about self-regulatory topics can have comparable health-related benefits as writing about trauma. Recently, Smyth et al., (2018) found that positive affect journaling (PAJ), an emotion-focused self-regulation task, resulted in decreased mental distress and increased wellbeing relative to baseline in general medical patients with elevated anxious symptomatology. PAJ was also associated with decreased anxiety and depressive symptoms at 1-month follow up, and greater resilience after the first and second month.

Cognitive theories of EW have further emerged over recent decades. Typically studies have aimed to directly investigate cognitive processing as a potential mechanism, advocating the idea that writing may help the writer to organize and structure traumatic memories into coherent narratives, resulting in more adaptive integrated schemas about the self, the world and others (Baikie & Wilhelm, 2005). Empirically testing the cognitive processing hypothesis of EW has proved somewhat methodologically difficult due to difficulties assessing cognitive change. This led to the development of the Linguistic Inquiry and Word Count (LIWC), a computerized text analysis program which analyses writing excerpts by calculating the percentage word usage of predefined categories such

as positive emotion words, negative emotion words or 'cognitive mechanism' words that reflect insight (e.g. *understand, realize*) or causal words (e.g. *because, reason*). This has allowed researchers to assess how certain linguistic markers which may reflect cognitive and emotional processing may be associated with the health-related benefits of EW (Pennebaker, Boyd, Jordan, & Blackburn, 2015). Findings again appear mixed, however arguably the most consistent finding showing health improvements are participants who use increased positive emotion words, a moderate number of negative words and increased use of cognitive mechanism words which are thought to indicate cognitive processing and reappraisal of experiences (Pennebaker, 1997). Similarly Klein & Boals, (2001) found that the use of cognitive mechanism words and the use of negative words whilst writing about a personally negative experience was associated with greater working memory improvements and reductions in intrusive thinking. Similar effects were not found for individuals who wrote about a positive or trivial topic, opposing theories that point to the beneficial effects of positive word use in writing. Findings led the authors to develop a mechanistic theory for EW based on the idea that writing about a negative experience reduces intrusive and avoidant thinking about stressful topics, thus freeing up working memory capacity. Hinging on this hypothesis, Park, Ramirez, & Beilock (2014) investigated the impact of EW on students who suffer from high math anxiety, which is associated with reduced working memory capabilities. Results indicated that expressive writing boosts the performance of anxious students in Mathematics testing and that the use of anxiety-related and cognitive mechanism words were positively associated with performance. However, in a recent study by Shen, Yang, Zhang, & Zhang (2018), who found that long-term EW resulted in reduced test anxiety, it was the use of positive emotion words and insightful words that were associated with better outcomes. These contradictory findings suggest that perhaps it the use of cognitive mechanism words and affective words in general, irrespective of valence, that has influence.

1.8.4 Expressive Writing and Wellbeing

Whilst the underlying mechanisms involved remain equivocal, a growing body of research indicates that EW is related to a number of health-related outcomes, with benefits transferring at the biological, behavioural and affective levels. Biologically, activity of the autonomic nervous system is affected by EW, as observed by decreased levels of skin conductance and reductions of systolic blood pressure and heart rate (Pennebaker, Hughes, & O'Heeron, 1987; McGuire, Greenberg, & Gevirtz, 2005). This indicates that when writers reveal their emotions, their biological response is comparable to individuals attempting to relax (Pennebaker & Chung, 2011). Correspondingly, whilst cortisol levels have shown to increase during their first writing session relative to controls, this predicted better psychological but not physical outcomes at one-month follow up (Sloan & Marx, 2004). In a study including participants with clinical PTSD, whilst EW did not result in reduced PTSD symptomatology, at 3 months follow up reductions in cortisol levels were observed, as well as decreased negative mood state and increases in post-traumatic growth. However in a comprehensive meta-analysis by Frattaroli (2006), it was concluded that there is insufficient evidence for the association between EW and physiological improvements in blood glucose, blood lipids, lung function, blood pressure, stress-related measures and body composition. It did however find sufficient support for an association between EW and better immune functioning as shown by improved HIV viral load, liver function and dopamine levels.

Behavioural changes related to EW have also been identified. For instance lower rates of university staff work absence (Francis & Pennebaker, 1992), faster job finding for senior professionals who've been made unemployed (Spera, Buhrfeind, & Pennebaker, 1994) and improvements in student grades (Lumley & Provenzano, 2003) have all been associated with EW, but findings rarely extend to improving health related behaviours such as increased exercise or reduced smoking (Pennebaker & Chung, 2011).

In terms of the affective impact of EW, again findings appear mixed. In Frattaroli's (2006) meta-analysis it was concluded that EW was associated with improvements in the psychological categories of distress, depression, subjective well-being, anger and anxiety, however sufficient evidence for improved outcomes for grief/bereavement, stress, coping strategies, cognitive schemas, stress-related growth and eating disorders was lacking. However, a more recent meta-analysis concluded that there was indeed adequate evidence to infer that EW is associated with reductions in PTSD symptomatology, with effects being particularly strong across studies which required participants to have a clinical diagnosis (Pavlacic, Buchanan, Maxwell, Hopke, & Schulenberg, 2019), replicating an earlier meta-analysis by van Emmerik, Reijntjes, & Kamphuis (2013), who also found reductions in comorbid depressive symptoms. Findings did not extend, however, to measures of quality of life or post-traumatic growth. On the contrary, such benefits for subclinical populations have not always been found. Reinhold, Bürkner, & Holling (2018) recently conducted a meta-analysis specifically investigating depressive symptoms. Here, it was found that for healthy adults with varying degrees of psychological distress, brief EW interventions were not effective.

1.8.5 Expressive Writing and Wellbeing in Cancer

Marrying the aforementioned research into EW outcomes, the association between writing expressively and improved health related benefits across cancer survivorship is varied. Indeed, a recent meta-analysis (Zachariae & O'Toole, 2015) including different cancer types, revealed that overall, there were no statistically significant main effects of psychological or physical outcomes. A systematic review by Mertz and colleagues (2012) found that whilst the majority of intervention effects were null, there were several main effects of EW on sleep, pain and general physical and psychological symptoms. The analysis also identified a number of moderating factors suggesting that EW may have better or worse outcomes based on individual differences

or social constraints. Both studies noted that available studies were heterogenous in design, with many lacking methodological rigor, which may in part account for these findings. It was concluded that given the cost-effective and practical nature of the intervention further exploration is warranted, even if effects are only clinically relevant to specific sub-groups of patients.

A number of studies have specifically looked at the effects of EW in the breast cancer population. Predominantly, effects seem to be greater for physical rather than psychological symptoms (see Zhou, Wu, An, & Li, 2015, for a systematic review). Mosher et al., (2012) found that for metastatic breast cancer patients, EW was associated with increased use of mental health services, however no group differences were found in existential and psychological well-being, fatigue and sleep quality at 8 weeks post intervention. Similarly, in a study including women with early stage breast cancer, EW had no impact on cancer-related distress, depressive symptoms and mood compared to controls (Jensen-Johansen et al., 2013). On the contrary, Park & Yi (2012) found that for women with breast cancer, EW resulted in reduced physical symptoms and better quality of life. Stanton et al., (2002), who tested the efficacy of EW and benefit writing in relation to a woman's cancer-related avoidance (intentional avoidance of cancer-related thoughts and feelings), further produced some interesting developments in the field. They found that the typical EW intervention, in which women wrote about their deepest thoughts and feelings about cancer, was beneficial for women low in avoidance, whereas benefit writing was more useful for women high in avoidance on psychological outcome measures of distress. The authors reasoned that women low in avoidance may embrace an emotional disclosure intervention, leading to the full cognitive and emotional processing of events, whereas women high in avoidance may find generating positive factors from their diagnosis a less painful process, producing greater psychological effects. The authors commented however that interventions promoting positive thinking

styles in cancer patients must be approached with caution; not only may this approach be perceived as insensitive, but a focus on encouraging positive thinking may enable maladaptive forms of avoidance.

1.8.6 Mindfulness Meditation Training

Mindfulness, rooted in Buddhist philosophy, has been conceptualised as the awareness that arises through paying attention to one's moment by moment thoughts, feelings and bodily sensations, nonjudgmentally (Kabat-Zinn, 2006). Broadly, mindfulness may be cultivated through the regular practise of formal systematic meditation techniques, or through informal practises which aim to develop a continued awareness of the present moment across all activities daily (Kabat-Zinn, 2006). Over recent decades mindfulness has been adopted by clinicians, and increasingly has been a foci of empirical psychology, due to its potential capacity to increase awareness of, and improve response to mental processes that contribute to emotional distress and maladaptive behaviours (Bishop et al., 2006).

The most developed and commonly used mindfulness interventions are that of mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). MBSR aims to help individuals to develop a focused and accepting attitude towards their pain, sensations, emotions, thoughts and behaviour, leading to improved self-observation and coping skills. Extending on this technique, MBCT incorporates elements of cognitive therapy aiming to facilitate a detached view of ones thoughts, designed predominantly to prevent depressive relapse (Fjorback, Arendt, Ørnbøl, Fink, & Walach, 2011). The interventions are typically group-based and involve an 8-week course of mindfulness meditation with additional home practise sessions of up to 45 minutes per day. The programs are rigorous, and as such are considered a form of mental training to develop and exercise the mental capacity required to regulate emotion and

maintain cognitive health (Bishop et al., 2006). More recently, technological advances have ignited the emergence of online and mindfulness-based smartphone apps which, relative to in-person MMT interventions, are less time demanding, can reach a wider population, and may be more cost-effective and engaging (Plaza García, Sánchez, Espílez, García-Magariño, Guillén, & García-Campayo, 2017).

Accumulating evidence suggests the beneficial effects of mindfulness meditation training (MMT) on both physical and mental well-being. This has been the basis, in recent years, for a growing interest in MMT in the fields of cognitive and affective neuroscience, with an aim to further understand the underlying neuropsychological mechanisms at play, and develop more targeted interventions across psychopathology. Malinowski (2013) emphasises the critical role of attentional control mechanisms in the development of mindfulness meditation skills, underscoring previous research accentuating the central role of attention (Lutz, Slagter, Dunne, & Davidson, 2008; Tang & Posner, 2009; Hölzel, Lazar, Gard, Schuman-Olivier, Vago, & Ott, 2011). Studies implementing a variety of paradigms indicate that MMT improves the efficiency of attentional processes as demonstrated by improved performance on behavioural tasks and altered patterns of neural activity. Indeed findings show that MMT has been associated with improving sustained attention on the continuous performance test (Schmertz, Anderson, & Robins, 2009), as well as the attentional blink task. In an event-related potential (ERP) study employing the attentional blink task, performance improvement in meditators was shown alongside a decreased amplitude of the P3b, a component considered to index the allocation of attentional resources, pointing to an improved ability to sustain attentional engagement (Slagter, Lutz, Greischar, Francis, Nieuwenhuis, Davis & Davidson, 2007). Pertinently, the majority of tasks measuring sustained attention will necessitate the recruitment of attentional control processes such as the monitoring, updating, shifting and inhibitory processes required to direct attention and facilitate goal directed behaviours

(Miyake et al., 2000). Moreover, for a novice meditator, training will require the constant monitoring and adjustment of focus back to the present moment as such requires control processes. Other studies have considered attentional control functions more directly. For instance, studies have indicated enhanced response inhibition (Chan & Woollacott, 2007; Moore & Malinowski, 2009; Sahdra et al., 2011; Teper & Inzlicht, 2013), attentional switching (Chambers, Lo, & Allen, 2008), executive functioning (Tang, Yang, Leve, & Harold, 2012) and working memory capacity (Mrazek, Franklin, Phillips, Baird, & Schooler, 2013) as a result of MMT. Further, FMRI studies have shown that meditation has been associated with increased activation in the dorsolateral prefrontal cortex (DLPFC) which has been implemented in mechanisms of attentional control processes (Allen et al., 2012).

Although research into MMT has been accumulating rapidly, many studies have been criticised for methodological limitations. Studies have often lacked an active control group, varied greatly in terms of the length of MMT practise, and have utilised a variety of different measures to assess mindfulness. Whilst some research indicates that very short MMT interventions can be effective in improving health outcomes (Creswell, Pacilio, Lindsay, & Brown, 2014; Economides, Martman, Bell, & Sanderson, 2018), others posit that longer MMT interventions are required (Baer, Carmody, & Hunsinger, 2012). Additionally, studies have predominantly been cross-sectional by design and as such makes inferences about the efficacy of MMT over time difficult (Wolkin, 2015).

1.8.7 Mindfulness Meditation Training and Emotional Vulnerability

Studies employing various mindfulness meditation training programs have indicated a number of positive health outcomes in both healthy and affectively vulnerable populations. MMT has resulted in improved mental health in the general population (Freudenthaler, Turba, & Tran, 2017) as well as reductions in clinical levels of anxiety and depression (Baer, 2003; Hofmann, Sawyer, Witt, & Oh, 2010; Desrosiers, Vine,

Klemanski, & Nolen-Hoeksema, 2013). Rumination, a key facet of clinical depression characterized by repetitive affectively negative thoughts, has been shown to reduce after a course of MMT (Raes & Williams, 2010), with some findings indicating the mediating role that rumination may play in the association between MMT and reductions in depression and anxiety (Desrosiers et al., 2013; Alleva, Roelofs, Voncken, Meevissen, & Alberts, 2014). Similarly worry, which is characterised by uncontrollable affectively negative thoughts about the future, (Borkovec, Robinson, Pruzinsky, & DePree, 1983), and is often considered the core cognitive component of anxiety disorders, has been shown to decrease after a course of MMT (Lenze et al., 2014). Both rumination and worry are defined by their intrusive and persistent nature and as such have been associated with deficits in cognitive control capabilities (Beckwé, Deroost, Koster, De Lissnyder, & De Raedt, 2014; Hallion, Ruscio, & Jha, 2014).

Elsewhere studies have indicated the potential benefits of MMT for symptoms of numerous other psychopathological disorders including substance abuse, post-traumatic stress disorder, eating disorders, psychotic and bipolar disorders, and attention-deficit/hyperactive disorder (see Wielgosz, Goldberg, Kral, Dunne, & Davidson, 2019, for a review).

1.8.8 Mindfulness Meditation Training and Emotional Vulnerability in Cancer

Numerous studies across cancer care in the broader context as well as the breast cancer population point to the favourable effects of MMT in improving physical and emotional vulnerability. Improvements have been found for measures of stress and mood (Garland, Tamagawa, Todd, Speca, & Carlson, 2013), anxiety and depression (Zhang, Wen, Liu, Peng, Wu, & Liu, 2015), improved immune functioning and quality of life (Witek-Janusek, Albuquerque, Chroniak, Chroniak, Durazo-Arvizu & Mathews 2008), and reductions in fatigue (Johns, Brown, Beck-Coon, Monahan, Tong & Kroenke, 2015). However, recent reviews suggest that whilst mindfulness-based stress reduction (MBSR)

and mindfulness-based cognitive therapy (MBCT) have demonstrated efficacy in clinical populations of emotional disorder, the potential physical and mental health benefits of mindfulness in the wider context of cancer remains ambiguous. This predominantly arises from a lack of rigor across study design. A recent systematic review (Shaw, Sekelja, Frasca, Dhillon, & Price, 2018), found that a large portion of the 30 studies included failed to adhere fully to MBSR or MBCT protocol, with 5 studies reporting variants on MBCT and 1 using a combined MBSR/MBCT intervention method. Outcome measures were poorly justified and only 4 studies included an active therapeutic control group. Similarly, ambiguity is evident in consideration of the therapeutic benefits of MMT in the breast cancer population specifically. A recent meta-analysis (Haller, Winkler, Klose, Dobos, Kümmel & Cramer, 2017) revealed that whilst at post-intervention MMT was associated with improvements in quality of life and in reductions stress, fatigue, sleep, anxiety and depression, effects were only sustained for anxiety and depression at 6-months post-intervention, and anxiety at 12 months post-intervention. Moreover, compared to other active interventions, rather than wait-list control groups, significant effects were only found post intervention for anxiety and depression and effects remained below the threshold of minimal clinically significant important differences. It follows that whilst MMT interventions hold great promise for reducing emotional vulnerability in the cancer population, more stringent study designs must be implemented in order to fully validify its short- and long-term effectiveness in cancer populations.

1.9 Summary and Research Aims

In sum, a large body of research points to the debilitating nature of a breast cancer diagnosis, both physically and emotionally. Given that the number of women surviving breast cancer is increasing, this provides a strong rationale for developing efficacious treatments to improve longer term quality of life. Attentional control theory posits that

top down attentional control mechanisms are critical for the regulation of emotion through the efficient operation of the inhibitory, shifting and updating functions of working memory which assist in directing attention towards relevant information and away from disruptions. This, in effect, will facilitate goal directed behavior. Accordingly, this theoretical proposition has been applied to the development of recent behavioural intervention research.

Attentional control training, which aims to improve working memory capacity and processing efficiency via computerized techniques, has shown to be effective in reducing emotional vulnerability across varying populations. Similarly, whilst there remains disagreement regarding that exact underlying mechanisms involved, expressive writing has shown potential to improve working memory capacity and reduce anxiety, resulting in enhanced performance on cognitive tests. In addition, mindfulness meditation training, which is thought to require attentional control processes in order to attend to the present moment, has shown promising effects in targeting emotional disorder. Nevertheless, reviews point to methodological variability across studies which in some cases have led to conflicting results. This indicates that more research is required in order to elucidate which interventions are most beneficial to specific populations and develop and refine treatment programs.

In a recent paper by Czajkowski et al., (2015) the ORBIT model (see figure 1.1) was presented as a means to guide the development of evidence-based behavioral treatments for chronic disease and translate them to clinical application. Whilst advances in the understanding of processes such as emotion and cognition are critical to human behaviour, findings are often not applied, and early treatments that show promise are often abandoned rather than developed and refined incrementally over time. In the absence of early discovery and innovation, which is at the heart of basic science, the

potential for behavioural interventions to develop into robust treatments which produce clinically significant outcomes is undermined.

The ORBIT model aims to bridge this gap and provides a progressive, transdisciplinary framework to help optimize treatment development. With these concepts in mind, the studies outlined in chapters 2, 3 and 4 aim to investigate the effectiveness of novel intervention designs in the breast cancer population. In experiment 1 (chapter 2) the effects of working memory training on emotional vulnerability will be explored. Whilst studies have shown early promise in targeting clinical levels of psychopathology, this has yet to be examined in breast cancer survivorship. In experiments 2 and 3 (chapters 3 and 4) the concept of combining cognitive interventions thought to engage similar mechanisms will be considered. Specifically, the studies will examine whether working memory training can enhance the effectiveness of expressive writing and mindfulness meditation training respectfully.
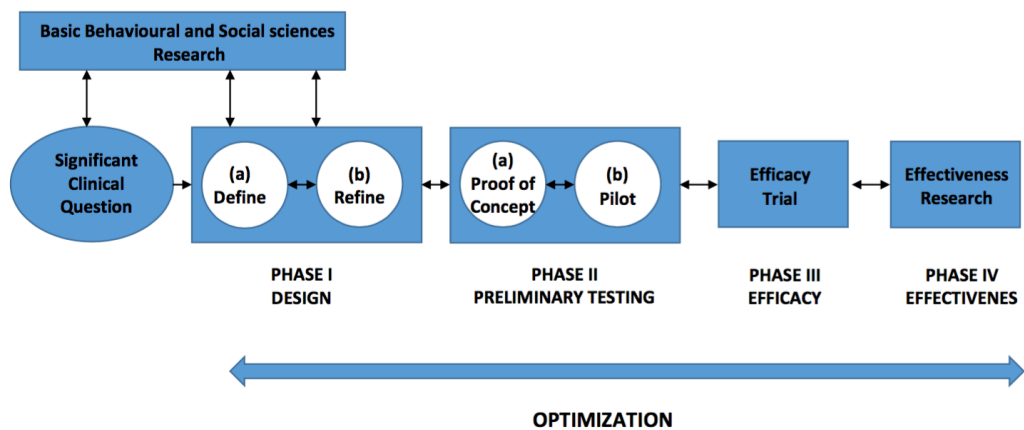
Figure 1.1. The Orbit Model for Developing Behavioural Treatments for Chronic Diseases

Chapter 2: Can Training Attentional Control Reduce Emotional Vulnerability in Breast Cancer?

2.1 Chapter Overview

Women affected by breast cancer are at high risk for developing cognitive and emotional disorder as a result of diagnosis and treatment. Accordingly, effective interventions targeting and preventing such deficits need to be developed and tested. Evidence from research into clinical affective disorders indicates that emotion can be regulated through improvement in attentional control mechanisms brought about by the neuroplastic effects of cognitive training. However, little research has explored this theory in the breast cancer population. As such, the first empirical study of the current thesis aims to explore how adaptive working memory training affects emotional vulnerability in a female group of breast cancer survivors.

2.2 Experiment 1: Training Cognitive Control to Reduce Emotional Vulnerability in Breast Cancer

2.2.1 Introduction

Based on recent theoretical breakthroughs in cognitive and clinical neuroscience advocating a causal role for attentional control in the onset, maintenance, and recurrence of anxiety and depressive vulnerability, increasing evidence shows that training cognitive control can reduce and protect against anxiety and depressive vulnerability (Sari et al., 2016; Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017). Attentional control is the ability to exercise and regulate attention towards relevant and away from irrelevant information, flexibly and efficiently (Berggren & Derakshan, 2013), playing a vital role in everyday goal-directed activities. Growing evidence supports predictions from

Attentional Control Theory (Eysenck et al., 2007) that top down attention necessary for completing tasks is disrupted by excessive negative affect reducing processing efficiency (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008; Stout, Shackman, Johnson, & Larson, 2015).

Research on reducing emotional vulnerability through the exercise of attentional control using engaging computerized cognitive tasks is growing in clinical research (see, Dolcos et al., 2019, for a review). Such techniques can target key neural circuits enabling transfer related benefits to a number of related cognitive capabilities (Jaeggi et al., 2011). Thus far, for women affected by breast cancer, transfer effects have been found to improve executive functioning (Kesler et al., 2013) and long term improvement in verbal learning and working memory (Von Ah et al., 2012), however findings are limited by the lack of an active control group. There are also improvements in working memory, attention and processing speed in childhood survivors of cancer (Conklin et al., 2015). Such improvements have the potential to greatly enhance quality of life in survivors through improving cognitive flexibility.

The hypothesis that improvements in attentional control via engaging cognitive training tasks can attenuate negative affect was addressed in a recent systematic review (Koster et al., 2017) and in a meta-analysis (Motter et al., 2016) of cognitive control training studies, with gains in working memory improvements associated with reductions in negative affect. Adaptive cognitive training has reduced rumination in clinical depression (Siegle et al., 2014) and anxious symptomatology in anxiety (Sari et al., 2016). Sari et al., (2016) showed that a 3 week course of adaptive dual n-back training, previously shown to increase fluid intelligence (Jaeggi et al., 2011) and processing efficiency in sub-clinically depressed individuals (Owens et al., 2013), can reduce anxiety in highly anxious individuals. In the adaptive dual n-back training, prefrontal functions of control are exercised and engaged in a systematic and adaptive manner. Adaptive

cognitive training can regulate prefrontal – amygdala activity (Cohen et al., 2015), so has the potential to modify the emotion-cognition prefrontal network crucial for emotion regulation.

The Current Investigation

Adaptive cognitive training holds the promise to help reduce emotional vulnerability by enhancing processing efficiency in breast cancer survivorship. Using the ORBIT Model (Czajkowski et al., 2015) for developing behavioural treatments for chronic diseases (see figure 1.1, general introduction) the current intervention sought to validate the effectiveness of the adaptive dual n-back training to translate basic behavioural scientific findings to clinical application.

In a former feasibility study, which acted as a preliminary/proof of concept study for the present investigation (Phase IIa along the ORBIT pathway), the adaptive dual n-back cognitive training showed promise in improving working memory performance and reducing anxiety related symptomatology in a small group (N = 17) of survivors with non-metastatic breast cancer who were recruited from The Breast Cancer Care (UK) charity. The current intervention sought to extend upon these effects in a larger sample of women with breast cancer (Phase IIb along the ORBIT pathway), the majority of whom had primary non-metastatic breast cancer. It was predicted that training related benefits would be associated with reductions in anxiety vulnerability post vs pre-intervention in the adaptive training compared with the active control group, with effects sustained at shorter and longer follow-up time points. In light of other promising findings indicating the promising effects of cognitive training on emotional vulnerability (Koster et al., 2017; Siegle et al., 2014; Hoorelbeke et al., 2015) we also included secondary measures of depression, rumination, worry and resilience. It was predicted that training related gains in working memory performance would be associated with better emotion-related outcomes for all measures. The study received ethical approval from the research ethics

committee of the Department of Psychological Sciences at Birkbeck University of London. Informed consent was obtained from participants prior to participation.

2.2.2 Methods

Participants

The study was advertised through the Centre for Building Psychological Resilience in Breast Cancer on various social media and breast cancer support network platforms using Facebook and Twitter. In total, 79 participants (40 Control, 39 Training) were recruited for the study. Participants must have had a diagnosis of breast cancer and be 6 months post active treatment to be eligible for participation. All participants received a fee of £100 upon testing at one-month follow-up, and a £7 Amazon voucher at the second follow-up. For participant demographics, clinical characteristics and psychiatric history (see table 2.1).

Materials and Experimental Tasks

Adaptive Dual N-Back Training Task (see figure 2.1): A standard dual n-back task was utilised, replicated from Owens et al (2013) Participants were presented with a 3x3 grid within which a green square appeared at one of eight different positions. Concurrently, one of 8 consonants (h, l, c, q, s, r, k and t) were presented audibly. Participants were asked to memorize the position of the green square and the letter spoken to them 'n' trials back within each trial and respond with appropriate keys on the keyboard to indicate a match or a non-match. Both sets of stimuli were presented at a rate of 500ms and each trial was separated by an interval of 2,500ms. Target stimuli appeared semi-randomly to ensure an equal number of audio and visual matches in each block (4 per block) and 2 trials of a simultaneous audio and visual match. Positions of target stimuli were randomly assigned so that the level of n was the same for both types of stimuli.

Tasks were programmed using php programming software, with a MYSQL database for data storage. Audio files were in mp3 format and were run on a Ununtu/apache server. Participants were told to complete the task as quickly and accurately as possible without stopping the task at any point; short breaks of 15s between blocks were given.
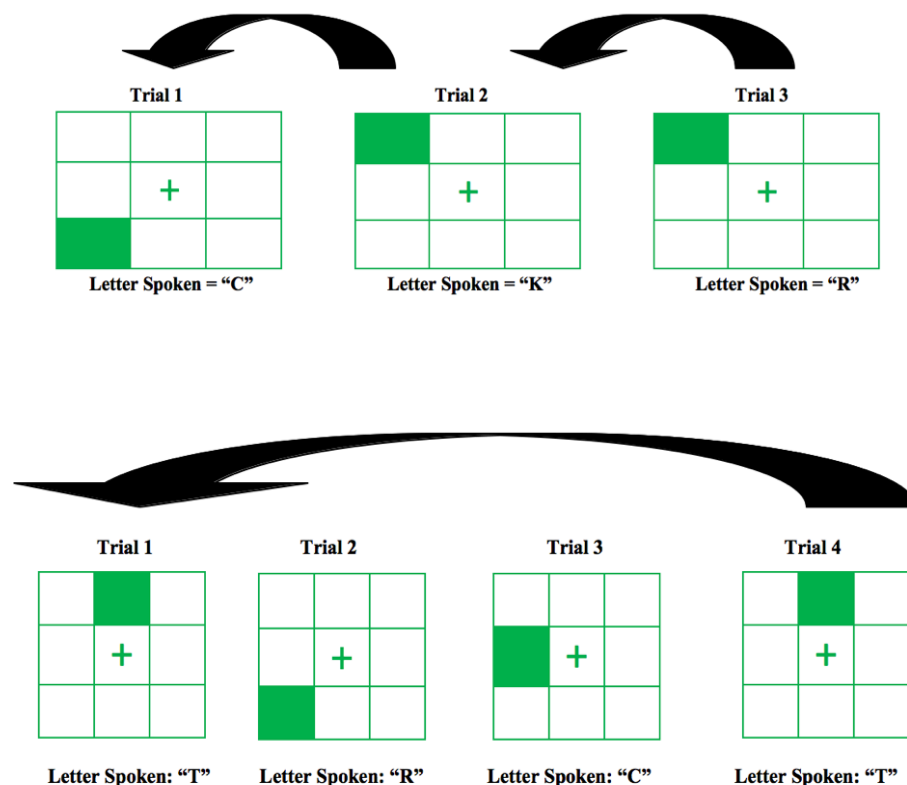
Figure 2.1: *An example of the 1-back (upper level) and 3-back (lower level) tasks. Audio and visual stimuli were presented simultaneously. For the 1-back task participants were instructed to remember the letter spoken and the position of the green square 1 trial back. In this example, the position of the square in Trial 3 is the same as it is in Trial 2 (1 trial back). Conversely the letter spoken in trials 1, 2 and 3 do not match. Consequently, the participants have to press button "A" for only a visual match. For the 3-back task participants were instructed to remember the letter spoken and the position of the green square 3 trials back. In this example, the position of the square in Trial 4 is the same as it is in Trial 1 (3 trials back). Similarly, the letter spoken in Trial 4 (T) matches the letter spoken in Trial 1. Therefore, the participants have to press buttons "A" and "L" simultaneously for both a visual and auditory match.*

Dual N-Back Task (Training): Participants in the training group completed 20 blocks of 20 + n trials per day whereby 'n' was determined by the level of n-back that the participant reached (e.g. 3-back, 20+3 = 23 trials). Participants started at the 1-back level for each training session. Difficulty level (level of n) was determined by average accuracy percentage scores for each block (hit minus false alarm rate) for each modality (auditory and visual). When accuracy on both modalities was 95% or above, level of n increased by 1, if less than 75% it decreased by 1, and if between 75% and 95%, level of n was maintained. Participants received feedback on their daily performance.

Dual 1-back Task (Active Control): Participants in the control group undertook a non-adaptive version of the task whereby the difficulty level remained unchanged. Participants began and remained on the 1-back level across 20 blocks per session.

Procedure

The design followed a pre-intervention, intervention, post-intervention, and two follow-ups design, the first at one-month post intervention and the second at approximately 15 months (11 – 18 months range) post intervention (see Figure 2.2, CONSORT diagram). Allocation to Training or Active Control conditions was achieved using a procedure that alternated participants sequentially to either of these conditions. Participants remained naive to the allocation to either the control or training groups and were emailed task instructions with verbal instructions over the phone. Participants accessed the task online in their homes on a secure and dedicated website, granting access only to the participant and the experimenter ensuring confidentiality. They firstly answered demographic questions on their breast cancer diagnosis, followed by the first set of questionnaires. They then continued on to the training task. Participants completed

each daily training session of 30 minutes, across 12 days, within a two-week period, at

approximately the same time each day. Performance was monitored by the experimenter

daily. On completion of training, participants completed the questionnaires, and again at

both follow-up time points.

Table 2.1. Participant demographics, clinical characteristics and psychiatric history for each group (Control, Training) for both the Intention to Treat (ITT) and Per Protocol (PP) populations.

	Intention to Treat			Per Protocol		
	Control (n= 40)	Training (n = 39)	P	Control (n= 28)	Training (n = 32)	P
Age (Years)[a]	48 (5.52)	51 (6.0)	.06	48 (5.82)	50 (6.34)	.2
Age at Diagnosis (Years)	44 (6.94)	47 (6.43)	.05*	45 (6.54)	47 (6.84)	.22
	No. (%)			No. (%)		
Diagnosis						
Primary	38 (95)	37 (94.9)	.98	27 (96.4)	31 (96.9)	.92
Secondary	2 (5)	2 (5.1)		1 (3.6)	1 (3.1)	
Grade of Cancer						
Low	- -	- -	.16			
Moderate	12 (30)	18 (46.2)		9 (32.1)	15 (46.9)	.25
High	27 (67.5)	21 (53.8)		19 (67.9)	17 (53.1)	
Chemotherapy						
Yes	37 (92.5)	36 (92.3)	.97	26 (92.9)	29 (90.6)	.76
Radiotherapy						
Yes	34 (85)	28 (71.8)	.15	22 (78.6)	21 (65.6)	.27
Surgery Type						
Mastectomy	25 (62.5)	30 (76.9)	.16	17 (60.7)	25 (78.1)	.14
Lumpectomy	15 (37.5)	9 (23.1)		11 (39.3)	7 (21.9)	
Endocrine Therapy [b]						
Yes	31 (79.5)	27 (69.2)	.3	21 (75)	21 (65.6)	.3
Current Psychological Medication [c]						
Yes	5 (12.5)	12 (30.8)	.05*	4 (14.3)	10 (31.3)	.1
No	27 (67.5)	20 (51.3)		21 (75)	18 (56.3)	
Previous Psychological [d] Condition						
Yes	8 (20)	11 (28.2)	.46	6 (21.4)	10 (31.3)	.4
No	23 (57.5)	21 (53.8)		18 (64.3)	18 (56.3)	
Alcohol Intake [e]						
None	18 (45)	11 (28.2)	.49	14 (50)	10 (31.3)	.69
1-5 units	6 (15)	8 (20.5)		4 (14.3)	6 (18.8)	
5-9- units	4 (10)	5 (12.8)		3 (10.7)	5 (15.6)	
10-14 units	3 (7.5)	6 (15.4)		3 (10.7)	5 (15.6)	
14+ units	1 (2.5)	2 (5.1)		1 (3.6)	2	

[a] Values indicate means and standard deviations unless indicated otherwise.
[b] 1 participant in the control group did not indicate whether they were taking endocrine therapy.
[c] Participants taking antidepressant or anti-anxiety medication. 8 control and 7 training participants were non- responsive.
[d] 9 participants in the control group and 7 in the training did not indicate a previous psychological condition.
[e] 8 participants in the control group and 7 in the training did not respond to alcohol intake.
*Significant between-group difference, P = .05.
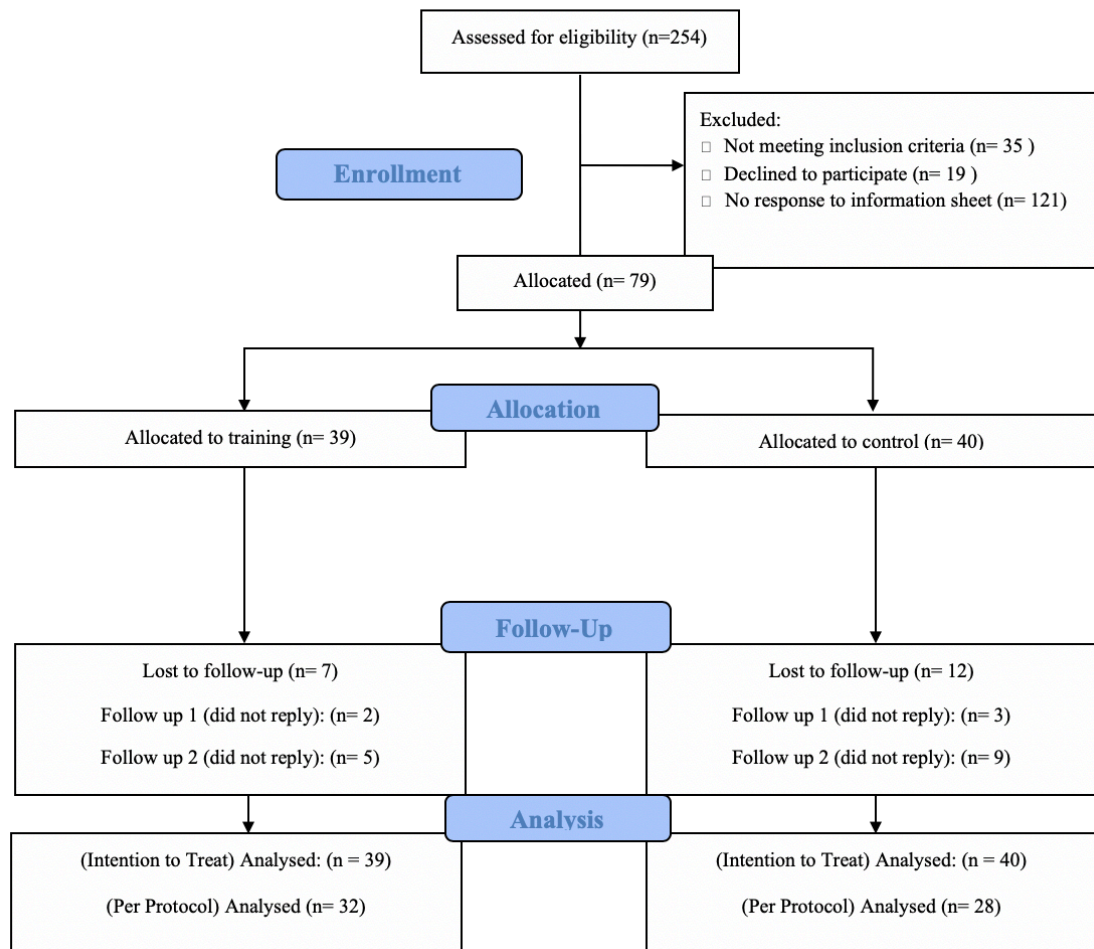
Figure 2.2. CONSORT diagram indicating participant enrolment, intervention allocation, follow-up and data analysis.

Outcome Measures

Primary Outcome: *Anxious symptomatology* was assessed by a composite score derived from the anxious and distress related subscales (Anxious Arousal, General Distress) of the Mood and Anxiety Scale Questionnaire (MASQ) (Watson, Clark, Weber, & Assenheimer, 1995), a 30-item inventory in which frequency of symptoms are indicated on a Likert scale ranging from 1 ('not at all') to 5 ('extremely'), as well as the anxious subscale (Hyperarousal) of the Cancer Impact of Events Scale (IOE) (Weiss,

2007), a 22-item inventory, whereby frequency of symptoms are indicated on a Likert scale ranging from 0 ('not at all') to 4 ('extremely'). Higher scores indicated higher anxiety. The scales demonstrated good reliability in the current study: all Cronbach's alphas >.75.

Secondary Outcomes: *Rumination,* a key predictor of depression, was assessed by the Ruminative Response Scale (Treynor, Gonzalez, & Nolen-Hoeksema, 2003,) a 22-item scale with a Likert scale ranging from 1 ('almost never') to 4 ('almost always)', with higher scores indicating higher levels of rumination. *Depression symptomatology* was assessed using the anhedonic depression subscale of the MASQ. *Worry* was assessed by the Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990), measuring trait worrying on a Likert scale ranging from 1 ('not typical of me') to 5 ('very typical of me') with higher scores indicating greater pathological worry. *Resilience* was assessed by the Connor Davidson Resilience Scale (CD-RISC) (Connor & Davidson, 2003) on a Likert scale ranging from 1 ('not true at all') to 5 ('true nearly all the time'), with higher scores indicating higher levels of resilience. All scales showed good reliability, all Cronbach alphas > .92**.**

Statistical methods

Data were analysed using IBM SPSS Statistics, Version 24.0. Chi-square tests were used to compare group demographics. T-tests were used to assess working memory improvement from pre- to post-intervention. 2 (Group: Active Control, Training) X 4 (Time: Pre-intervention, Post-intervention, 1st Follow-up, 2nd Follow-up) Linear Mixed Effect Models (MLMs) were used to compare groups on self-reported emotional vulnerability measures over time. Fixed effects were specified for Group (Active Control, Training), Time (Pre-intervention, Post-intervention, 1st Follow-up, 2nd Follow-up), and a Group x Time interaction. Data were analysed according to the intention-to-treat (ITT)

principle whereby the initial sample's ($n = 79$) data were analysed, irrespective of whether participants were compliant to the entire intervention. Models were estimated with the maximum likelihood method. Effect sizes were calculated by Cohen's d which was derived from the F- test and calculated as $d = 2*\sqrt{(F/\mathrm{df})}$. In addition, MLMs were conducted on a per protocol (PP) sample which included only the participants who completed the study in its entirety (Control, $n = 28$, Training, $n = 32$). Post hoc power analysis for the initial sample of 79, and the intended MLM analyses with a significance level of 0.05 (alpha), a small to moderate effect size of .3d, and with three time point measurements (pre, post, and first follow-up) was .83, For the final sample of 60, with four time point measurements (pre, post, first and second follow-ups), with the same specifications as above, the desired power was .79.

2.2.3 Results

Dual n-Back Performance

     1-back Control Group: There was a good average level of accuracy across the 12 days of training sessions ($M = 96.28$ %, $SD = 7.03$).

N-back Training Group: Figure 2.3 shows that working memory functioning, as measured by increasing levels of N, improved from Day 1 ($M = 1.49$, $SD = 7.03$) to Day 12 ($M = 2.78$, $SD = .62$), $t(31) = 14.27$, $p < .001$. The slope of this improvement was significantly different from zero $t(38) = 8.60$, $p < .001$.
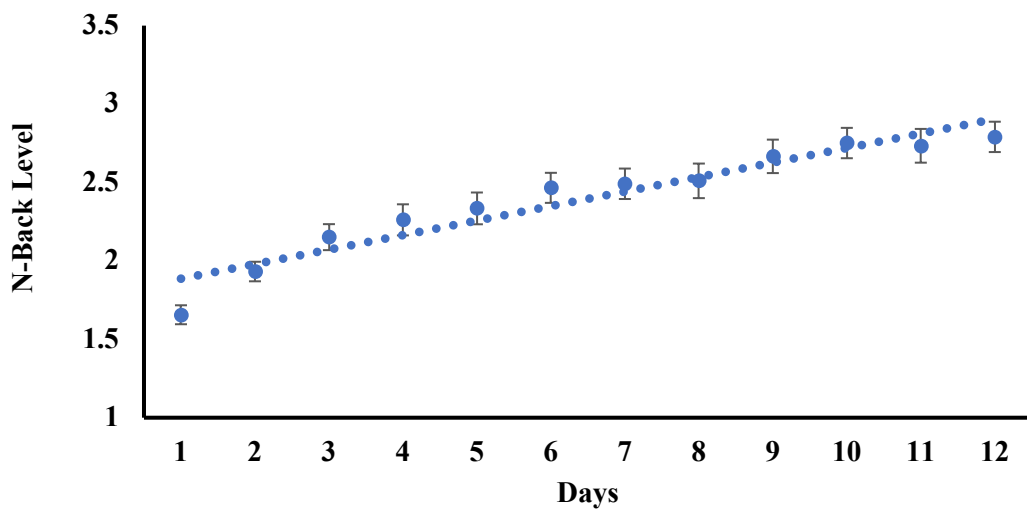
Figure 2.3 Mean dual n-back level for the training group across each day of training; lines indicate standard deviations.

Changes in Emotional Vulnerability

Mean self-reported symptomatology for each group at each time point is presented in Table 2.2 [1] The groups did not differ significantly at pre-intervention on any of the measures, all $t's < .95$, NS.

Table 2.2 Mean self-report symptomatology scores for each group (Training and Control) at pre, post and follow up time points.

	Pre-Test				Post-Test				Follow-Up 1				Follow-Up 2			
	Training		Control		Training		Control		Training		Control		Training		Control	
Rumination	41.46	(11.78)	41.53	(12.07)	40.13	(9.23)	40.64	(11.59)	36.94	(8.54)	40.21	(12.66)	35.72	(9.55)	41.28	(13.51)
Anxiety Symptomatology	6.11	(1.88)	6.28	(2.36)	5.09	(1.54)	6.12	(2.64)	5.03	(1.56)	6.1	(2.76)	5.11	(2.05)	6.01	(2.72)
Depression Symptomatology	3.19	(.83)	3.41	(.87)	3.05	(.83)	3.26	(.93)	3.12	(.87)	3.33	(.88)	3.0	(.83)	2.64	(.90)
Resilience	68.21	(12.60)	62.71	(18.71)	68.84	(11.83)	63.39	(15.13)	69.38	(13.21)	62.54	(18.22)	66.56	(14.99)	61.96	(18.13)
Worry	49.0	(16.11)	51.04	(15.19)	46.69	(15.55)	48.14	(13.76)	46.34	(15.37)	50.39	(17.41)	45.91	(16.27)	51.21	(16.27)

Note. Standard deviations are in parentheses.

---

[1] Mean emotional vulnerability scores reflect the per protocol population for all tables and graphs.

Effects on primary outcome

Anxiety symptomatology:

Composite scores were used in order to specifically test the primary outcome of anxiety and to protect against the risk of a false positive (Andrade, 2015). These were determined using a factor analysis, whereby each subscale (Anxious Arousal, General Distress and Hyperarousal) showed consistently high correlations with each other (>.6) across all time points. Figure 2.4 shows that participants in the Training group showed marked and sustained reductions in anxiety symptomatology relative to the Control group. The MLM confirmed this observation with a significant Group X Time interaction, $F(3, 68.43) = 2.81$, $p = .04$, Cohen's $d = 0.41$, (ITT); $F(3, 63.48) = 3.07$, $p = .03$, Cohen's $d = 0.44$ (PP).[2]
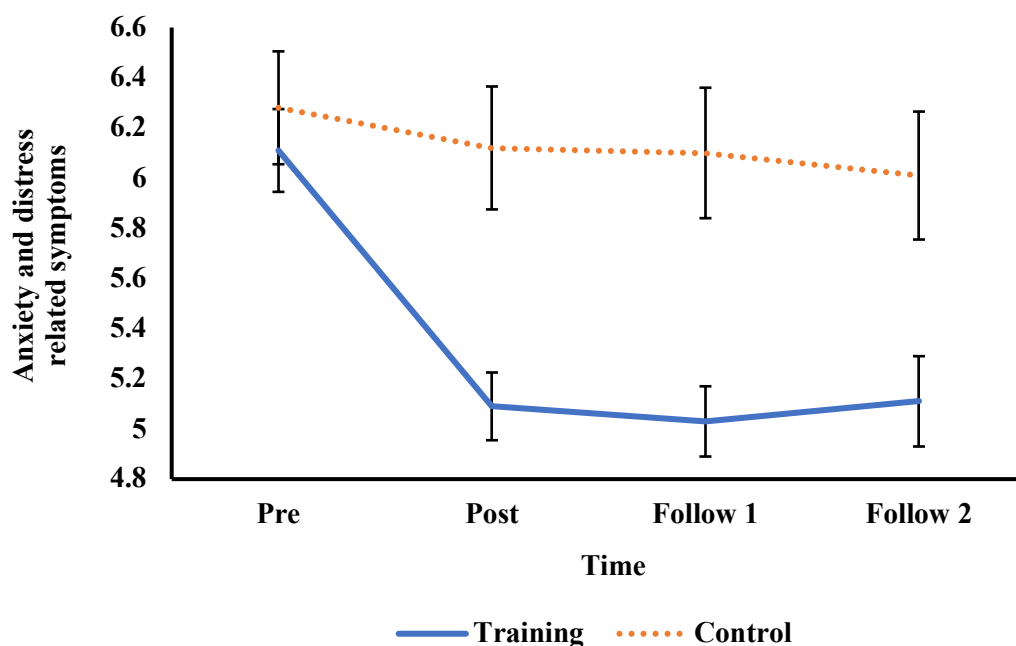
Figure 2.4 Mean anxiety symptomatology scores for each group (control, training) at pre, post and follow-up intervention time points.

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[2] Analyses on the subscales of intrusion and avoidance (Impact of Events) revealed no significant effects (all F's < 1, NS).

Effects on secondary outcomes

Rumination: Figure 2.5 shows that the Training group's scores decrease at follow-up times, but the Control group's scores remain consistent across time. This observation was supported by a Group X Time interaction, $F(3, 82.51) = 2.81$, $p = .04$, Cohen's $d = .39$ (ITT); $F(3, 75.54) = 2.82$, $p = .04$, Cohen's $d = .39$ (PP). *Depression symptomatology and Resilience:* No significant interactions were found, $Fs < 1$, NS. *Worry:* There was no significant interaction, $F(3, 74.48) = 1.21$, $p = .24$, Cohen's $d = .25$ (ITT); $F(3, 64.05) = 1.21$, $p = .32$, Cohen's $d = .27$ (PP).
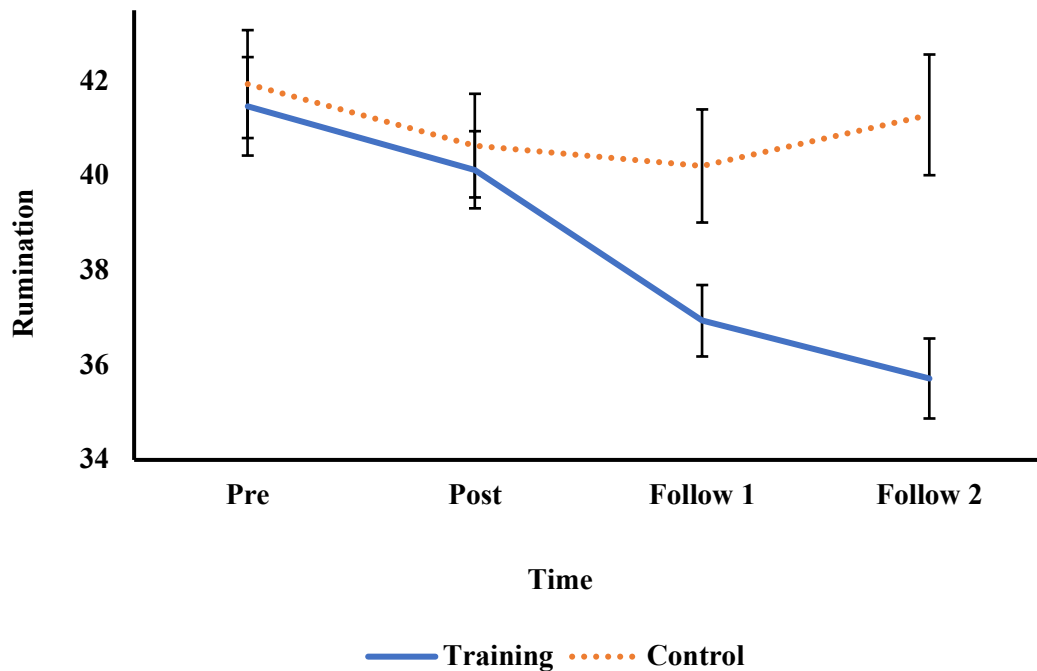
Figure 2.5 Mean rumination scores for each group (control, training) at pre, post and follow-up intervention time points.

Further Analyses

Table 2.1 indicates group characteristics on demographic variables for the initial sample of 79. Group differences were found for age at diagnosis (Training: $M = 47$, $SD = 6.43$, Control: $M = 44$, $SD = 6.94$), $t(77) = 2.02$, $p = .05$) and number of participants

taking psychiatric medication for anxiety and/or depression, X^2 (1) = 3.93, p = .05 (ITT), however these differences were not apparent in the final per protocol sample, (Age at diagnosis, Training: M = 47, SD = 6.84, Control: M = 45, SD = 6.54), t(58) = 1.23, p = .22; Psychiatric medication, X^2 (1) = 2.64, p = .1). No significant correlations were found between any demographic or medical variables and the slope of the primary and secondary outcome measures, (all r's < .26, all p's > .06).

Additional responses

Without elicitation, numerous participants expressed the positive impact of training on them. Participants spoke of how they would *'miss the daily challenge'* and how it had prompted them to give the *'brain a bit more of a workout on a regular basis'* because of the *'improvement in my memory'. Others commented* that it *'helped me in a funny way to stay concentrated on one thing'*, *'made me feel empowered and confident'*, and *'was just what I needed'*. Overall, participants enjoyed the training with improvement and completion igniting a sense of achievement and empowerment.

2.2.4 Discussion

The current study investigated how adaptive cognitive training via dual n-back training, previously shown to enhance cognitive efficiency and reduce emotional vulnerability in anxiety and depression, compared with an active control task, can help increase cognitive flexibility and reduce emotional vulnerability in breast cancer survivorship. As predicted, working memory performance improved in the training group pre to post intervention. Importantly, training-related benefits were associated with reductions in anxiety-related symptomatology as well as in rumination. Critically, these reductions were sustained across time to one-month follow-up and the longer period of 11 – 18 months follow-up testing intervals.

Transfer related gains on anxiety vulnerability imply a significant beneficial impact of training on physiological arousal symptoms such as anger, irritability, and difficulty concentrating due to cancer related traumatic experiences. Given the numerous physiological long-term side effects associated with breast cancer treatment (e.g., lymphedema, peripheral neuropathy, menopausal symptoms as well as fatigue and insomnia (Agrawal, 2014; Gorman, Malcarne, Roesch, Madlensky, & Pierce, 2010) this finding is particularly pertinent. Thus through remediating anxiety-related symptoms, there is potential for cognitive training to attenuate the distress caused by long term side effects that breast cancer survivors experience. These results have implications for better regulation of emotion and attenuation of cancer related thoughts, especially fear of recurrence, that frequently interrupt daily functioning (Mehnert, Berg, Henrich, & Herschbach, 2009).

Significant reductions in rumination in the training compared with the control group extend previous findings (Keshavan et al., 2014; Koster et al., 2017) of reduced ruminative thinking in major depression. Rumination is a key cognitive risk factor for depression (Nolen-Hoeksema et al., 2008) that involves top-down processes which can potentially benefit from training related gains as a result of brain neuroplasticity. By reducing rumination through improved cognitive control capabilities, it is possible to protect against depression. Rumination has also been linked to a delay in seeking diagnosis for breast cancer symptoms and motivational deficits that inhibit individuals from taking required action to solve problems (Lyubomirsky, Kasri, Chang, & Chung, 2006). This finding is thus key to this population who must remain vigilant for symptoms of recurrence and attend follow up appointments with medical practitioners.

Reductions in negative affective symptomatology in the adaptive training versus control group were not only apparent at post intervention but were sustained at one month as well as the longer time follow-up of an average of 15 months (11 – 18 month range)

post intervention. This finding is of key importance because we can infer that not only can adaptive training be of immediate benefit to reductions in emotional vulnerability in survivors of breast cancer, but through its potential effects on neuroplasticity, can encourage engagement with behaviours that can help sustain these effects at longer time periods. This suggests that attentional control processes remain plastic and can be targeted post treatment which holds important implications for cognitive health post diagnosis. Given the plethora of evidence on treatment induced cognitive decline in breast cancer survivors (Andryszak et al., 2017), adaptive cognitive training can improve cognitive efficiency instrumental to cognitive health and psychological well-being in breast cancer survivorship.

Training related gains did not significantly correlate with any demographic variables such as age, age at diagnosis or time elapsed since diagnosis suggesting that training is beneficial for a wider population, irrespective of particular demographic variables relating to both age and breast cancer diagnosis. Having said this, future work should systematically manipulate factors such as age at diagnosis and time since diagnosis to fully explore the modulating role of such individual difference variables.

Participants' positive responses indicated that they felt psychologically empowered. With increases in cognitive efficiency, individuals are better equipped and empowered to manage and reduce the impact of intrusive and troublesome anxieties through interventions that can pose less risk than current pharmaceutical treatments for psychopathology (Kelly, Juurlink, Gomes, Duong-Hua, Pritchard, Austin, & Paszat, 2010).

Limitations

The current study has a number of limitations. Participants were recruited via social media platforms and therefore may not be representative of the wider population

of breast cancer survivors. While such recruitment methods can access large numbers of participants, they do not provide data on reasons for refusing participation, and clinical characteristics of the sample. Future research should extend the current intervention using a registered RCT that fully randomizes group allocation of participants as well as including measures of cognitive vulnerability and participant demographics such as education. The current study did not measure cognitive transfer effects and further research should clarify the specific (cognitive) mechanisms underlying these beneficial emotional transfer effects of cognitive training. Finally, future research should systematically investigate the benefits of training in women with secondary and metastatic breast cancer, given that research in secondary breast cancer is sparse, this seems highly pertinent.

Clinical Implications

Attentional control training is a prosperous new technique targeting specific cognitive, behavioural and neural networks that play a crucial role in anxiety, stress and rumination (Keshavan et al., 2014). Improved processing efficiency via adaptive cognitive training and its associated longer-term effects in sustaining reduced emotional vulnerability indicates the potential to enhance the efficacy of therapies such as CBT and mindfulness that can be available on the NHS in breast cancer survivorship. The adaptive dual n-back training was recently shown to increase mindfulness meditation effects on reductions in worry over time, through its effects on processing efficiency (Course-Choi, Saville & Derakshan, 2017). In a recent Cochrane review of 28 studies (Jassim, Whitford, Hickey, & Carter, 2015), group Cognitive Behavioural Therapy helped reduce emotional vulnerability in non-metastatic breast cancer. CBT and mindfulness meditation effectiveness rely on processing efficiency, and as such the adaptive dual n-back may help sustain and enhance their effects if used in combination.

Chapter 3: Exploring the Combined Effects of Expressive Writing and Working Memory Training on Emotional Vulnerability in Breast Cancer

3.1 Chapter Overview

Chapter 2 demonstrated that a working memory training intervention targeting the neural networks requiring the recruitment of attentional control processes is associated with far transfer to reductions of anxiety and rumination in a group a female survivors of breast cancer. This finding was pivotal in that it established that women affected by breast cancer can be receptive to working memory training tasks, giving further emphasis to the hypothesis advocating a link between prefrontal mechanisms of cognitive control and their influential effects over emotion regulation. Accordingly, results from chapter 2 provide the foundation for the subsequent experimental intervention studies in the current thesis.

The exploration of combined cognitive and behavioural interventions to reduce emotional vulnerability is recent and thus limited. Preliminary findings indicate that by combining tasks that tap similar neural mechanisms of cognitive control, transfer effects to emotion regulation can be greater than each would achieve independently. So far, this has not been studied in breast cancer survivorship, and as such provided the catalyst for the succeeding empirical study.

3.2 Experiment 2: The Combined Effects of Expressive Writing and Working Memory Training on Emotional Vulnerability in Breast Cancer

3.2.1 Introduction

Breast cancer can result in a number of emotional and cognitive changes associated with diagnosis, leaving the everyday functioning of survivors highly compromised, even after treatment has finished. Given the complexities surrounding these vulnerabilities, an integrative approach applying recent findings surrounding anxiety and depression in the fields of cognitive and affective neuroscience seems appropriate. The contributive aspect of cognitive health in regulating emotional processes has now been established. Attentional Control Theory (Eysenck et al., 2007) posits that top down attentional processes critical for goal directed activity are compromised by disproportionate levels of negative affect which interrupt processing efficiency. Attentional control refers to the ability to direct attention towards task relevant information and away from task irrelevant interruptions efficiently. This theory has been corroborated by recent neurocognitive interventions that target cognitive functioning, specifically working memory, to reduce anxious and depressive symptomatology. A number of studies now indicate that a course of computerized adaptive cognitive control training which targets key attentional control neural networks can help attenuate negative affect as a result of cortical neuroplasticity (see, Motter et al., 2016, for a comprehensive meta-analysis). Beneficial emotion regulation transfer effects extend to a number of psychopathologies including anxiety, depression and PTSD (see Dolcos et al., 2019, for a review).

Within the breast cancer population, training related gains have resulted in improved executive functioning and better long term verbal learning and working memory function (Von Ah et al., 2012; Kesler et al., 2013). The adaptive dual n-back is

one task that has shown to be effective in generating this outcome and extending transfer effects to emotional vulnerability. For instance, recently, Sari et al., (2016) found that a 3 week course of adaptive dual n-back training resulted in reduced anxiety in a high anxious population. Pertinently, experiment 1 of the present thesis extended these effects to the breast cancer population, indicating that a 2 week course of adaptive dual n-back training can transfer to reductions in levels of anxiety and rumination.

One of the implications that can be taken from this finding relates to the idea that adaptive cognitive control training may aid in the efficacy of other cognitive therapies that target similar neural networks and which have also shown promise in reducing emotional vulnerability. One such intervention is that of Expressive Writing. In the face of adverse or important life events, expressing one's deepest thoughts and emotions in a brief writing activity may promote better well-being and functioning (Frattaroli, 2006). Indeed, whilst findings remain mixed, research indicates that relative to individuals who write about a neutral topic, writing expressively can result in improvements in a variety of mental and physical health outcomes. To date, the emotional benefits of expressive writing indicate a reduction in intrusive thoughts and anxious and depressive symptoms (Baikie et al., 2012, Gortner et al., 2006, Lee at al., 2016, Graf et al., 2008), improved cognitive functioning (Klein and Boals, 2001), decreased physician visits and greater immune competence (Pennebaker, Kielcolt-Glaser & Glaser, 1998), greater adaptive behaviour (Pennebaker, Mayne and Francis, 1997), reduced distress and levels of negative mood (Murray and Segal, 1994), improved self-esteem (O'Connor et al., 2011) and reductions in post-traumatic stress symptoms (Lange et al., 2000), (see Frattaroli 2006, for a meta-analytic review). The mechanism by which expressive writing operates remains inconclusive, however a number of theories have been proposed. Predominantly theories surround the cognitive changes that may initiate emotion regulation through writing expressively. Hypotheses include benefit pursuing, the redirecting of attention

towards more positive aspects of situations that are often overlooked, habituation, which involves repeated exposure to stressful situations or memories, encouraging individuals to habituate to aversive emotions surrounding their experiences, and cognitive reappraisal, which involves searching for causal explanations and reinterpretations of certain events to make them less traumatic (Kloss & Lisman, 2002; Gustella & Dadds, 2008; Pennebaker & Chung, 2011; King & Miner, 2000; Wang et al., 2015). Most in line with our own research is that of Klein and Boals (2001) who posit that the mechanism by which expressive writing reduces emotional vulnerability is via improving working memory capacity. This operates by the production of coherent narratives about stressful life events, reducing demands on attentional processes which may have been burdened with intrusive and ruminative thoughts about these situations. In the consideration of breast cancer diagnosis and survivorship, the regulation of emotion, in particular relating to the intensity of emotional expression, has been associated with patients' adaptation and wellbeing. The particular strategies that women use in emotional regulation seem of critical importance in the context of breast cancer. For instance, breast cancer patients who have indicated using less adaptive coping mechanisms to regulate their emotions, such as inhibition or repressive emotion strategies, have also reported greater levels of anxious and depressive symptomatology, emotional distress, poorer quality of life as well as poorer physiological outcomes such as impaired cortical regulation and higher blood pressure (see Brandao et al., 2016, for a review). It follows then that expressive writing, which encourages an expressive rather than repressive coping style, holds promise for improving psychological outcomes in breast cancer survivorship. Indeed, whilst studies utilizing the intervention are sparse in this population, expressive writing has been associated with decreased physical symptoms and fewer medical visits for cancer related morbidities (Stanton, Danoff-Burg, Sworowski, Collins, Branstetter, Rodriguez-Hanley, Kirk & Austenfeld, 2002).

The Current Investigation

The need for the translation of behavioral and neuroscientific findings to clinical application is becoming increasingly recognized. The ORBIT Model (Czajkowski et al., 2015) for developing behavioral treatments for chronic diseases (see figure 1.1, general introduction) attempts to bridge the gap between these disciplines, providing guidelines for the establishment of effective interventions. In line with this objective, the current study aims to extend on prior findings indicating the effectiveness of reducing emotional vulnerability via expressive writing and cognitive control training by investigating their combined effects in a female population of breast cancer survivors. Research into the combined effects of cognitive interventions is in its infancy, however preliminary studies show great promise. In a recent study by Course-Choi et al., (2017) findings indicated that a combined course of attentional control training and mindfulness meditation practice resulted in a reduction in worry pre to post intervention for a population of pre-selected high worriers. The current study, however, is one of the first to extend these findings to a cancer population. Hinging on the hypothesis that the mechanism by which attentional control training and expressive writing may reduce emotional vulnerability is through the engagement of neural networks that improve working memory functioning, and that both interventions have improved health related outcomes in the breast cancer population independently, it was predicted that a 12 day combined course of adaptive dual working memory training and expressive writing would result in greater transfer to reductions in anxious symptomatology than a course of expressive writing alone. Due to the complex nature of emotional and cognitive vulnerability in the breast cancer population, we also included exploratory measures of perceived cognitive function, quality of life, depression and resilience. In addition, it has been proposed that the construction of a narrative forms over time, with repeated writing moving from the vague to the cohesive, resulting in an insightful explanation of events (Pennebaker, Mayne, & Francis, 1997). As such, it has

been suggested that there should be an increase in causal or affective words across time reflective of this linguistic change. In line with this theory, it was predicted that individuals who used more causal, insightful or affective words across writing sessions (i.e. they used a higher proportion of insight, causal or affective words on the last 3 days of writing compared to the first 3) would show greater reduction in anxious symptomatology.

3.2.2 Method

Participants

The study was advertised through the Birkbeck Centre for Building Resilience in Breast Cancer (BRiC) and various breast cancer support networks via social media platforms such as Facebook and Twitter. In total, 84 participants (22 Expressive N-Back, 21 Non-Expressive N-Back, 21 Expressive, 20 Non-Expressive) were recruited for the study. Participants were required to have had a diagnosis of breast cancer and be 6 months post active treatment to partake in the study. For the combined groups (Training and Writing), which required a commitment of 50 minutes per day, participants received a fee of £140 upon completion of the study. For the writing groups, which required a commitment of 20 minutes per day, participants received a fee of £80. For participant demographics, clinical characteristics and psychiatric history, see Table 3.1.

Table 3.1. Participant demographics, clinical characteristics and psychiatric history.

	Expressive N-Back (n= 22)		Non-Expressive N-Back (n = 21)		Expressive (n= 21)		Non-Expressive (n = 20)		P
Age (Years)[a]	48 (6.89)		48 (6.38)		49 (4.95)		50 (8.88)		.83
Age at Diagnosis (Years)	45 (6.58)		45 (5.58)		46 (5.65)		45 (8.34)		.98
	No. (%)				No. (%)				
Diagnosis									
Primary	22	(100)	21	(100)	19	(90.5)	17	(85)	.1
Secondary	-	-	-	-	2	(9.5)	3	(15)	
Grade of Cancer									
Low	2	(9.1)	3	(14.3)	1	(4.8)	1	(5)	
Moderate	10	(45.5)	8	(38.1))	7	(33.3)	10	(50)	.79
High	10	(45.5)	10	(47.6)	13	(61.9)	9	(45)	
Chemotherapy									
Yes	22	(100)	15	(71.4)	15	(71.4)	16	(80)	.05*
Radiotherapy									
Yes	19	(86.4)	16	(76.2)	14	(66.7)	14	(70)	.46
Surgery Type									
Mastectomy	11	(50)	10	(47.6)	13	(61.9)	11	(55)	.61
Lumpectomy	11	(50)	11	(52.4)	7	(33.3)	9	(44)	
Both	-	-	-	-	1	(4.8)	-	-	
Endocrine Therapy [b]									
Yes	13	(59.1)	14	(66.7)	17	(81)	10	(50)	.26
Current Psychological Medication [c]									
Yes	6	(27.3)	3	(14.3)	7	(33.3)	7	(35)	.43
No	16	(72.7)	18	(85.7)	14	(66.7)	13	(65)	
Previous Psychological [d] **Condition**									
Yes	3	(13.6)	7	(33.3)	7	(33.3)	4	(20)	.38
No	19	(86.4)	14	(66.7)	14	(66.7)	16	(66.7)	
Alcohol Intake [e]									
None	1	(4.5)	3	(14.3)	4	(19)	8	(40)	.03*
1-5 units	9	(40.9)	11	(52.4)	11	(52.4)	8	(40)	
5-9- units	6	(27.3)	2	(9.5)	1	(4.8)	2	(10)	
10-14 units	4	(18.2)	-	-	1	(4.8)	-	-	
14+ units	2	(9.1)	5	(23.8)	4	(19)	2	(10)	

[a] *Values indicate means and standard deviations unless indicated otherwise.*

*Significant between-group difference, P = .05.

Materials and Experimental Tasks

Writing Tasks: Writing tasks were based on guidelines by and adapted from Pennebaker (2010). Based upon research indicating that greater effect sizes are achieved for three or more writing sessions (Frattaroli, 2006), participants in the writing groups completed 12 sessions of writing for 20 minutes per day. Writing was completed online via participants own dedicated link whereby the program would time out once the session was complete. Participants were asked to write about their day after 5.30pm.

Writing Tasks (Expressive): The instructions for the expressive writing groups were as follows: *"I would now like for you to write about your very deepest thoughts and feelings that you have felt during today. In your writing, I'd like you to really let go and explore your very deepest emotions and thoughts. You may explore your general emotions in relation to what you did today, or you may tie this to your cancer diagnosis and the feelings you have felt today in relation to this experience. This may include, for example, your feelings about your body, your health, your relationship with others, including family, friends and partners, and your feelings about work. You may include your feelings about the past, the present and the future, or to who you have been, who you would like to be, or who you are now. Please, don't worry about spelling, sentence structure, or grammar. The only rule is that you try to continue writing until your time is up (Approximately 20 mins)."*

Writing Tasks (Non-Expressive): The instructions for the non-expressive writing groups were as follows: *"I would like you to write about how you spent your time throughout today, in a cold and neutral way, without mentioning any of your emotions and feelings. In your writing, I want you to be as objective as possible. Feel free to be as detailed as possible in describing what you did today from the time you got up until the time you went to bed. Do not worry about spelling, sentence structure, or grammar. The only rule is that you try to continue writing until your time is up (Approximately 20 mins)."*

Working Memory Training Task: The same Adaptive Dual N-Back training task outlined in Experiment 1 was utilized for Experiment 2.

Procedure

The study followed a pre-intervention, intervention, post-intervention, and two follow-ups design. The first follow up took place one-month post intervention and the second at approximately 6 months post intervention (see CONSORT diagram, figure 3.1). Allocation to one of four conditions was achieved using a procedure that alternated participants sequentially to each of these conditions. Participants remained naive to the allocation to either a control (non-expressive writing) or experimental (expressive

writing) group and were emailed task instructions with verbal instructions over the phone. Participants accessed the task online in their homes on a secure and dedicated website, granting access only to the participant and the experimenter ensuring confidentiality. They firstly answered demographics questions on their breast cancer diagnosis, followed by the first set of questionnaires. They then continued on to their allocated task. Participants in the combined groups first completed their n-back training followed by their writing session. Participants completed each daily training session of 30 minutes, across 12 days, across a two-week period, at approximately the same time each day. This was followed by a writing session of 20 minutes per day whereby participants were asked to always complete their writing sessions after 5.30pm. Performance was monitored by the experimenter daily. On completion of training and writing sessions, participants completed the follow up questionnaires, and again at both follow-up time points.
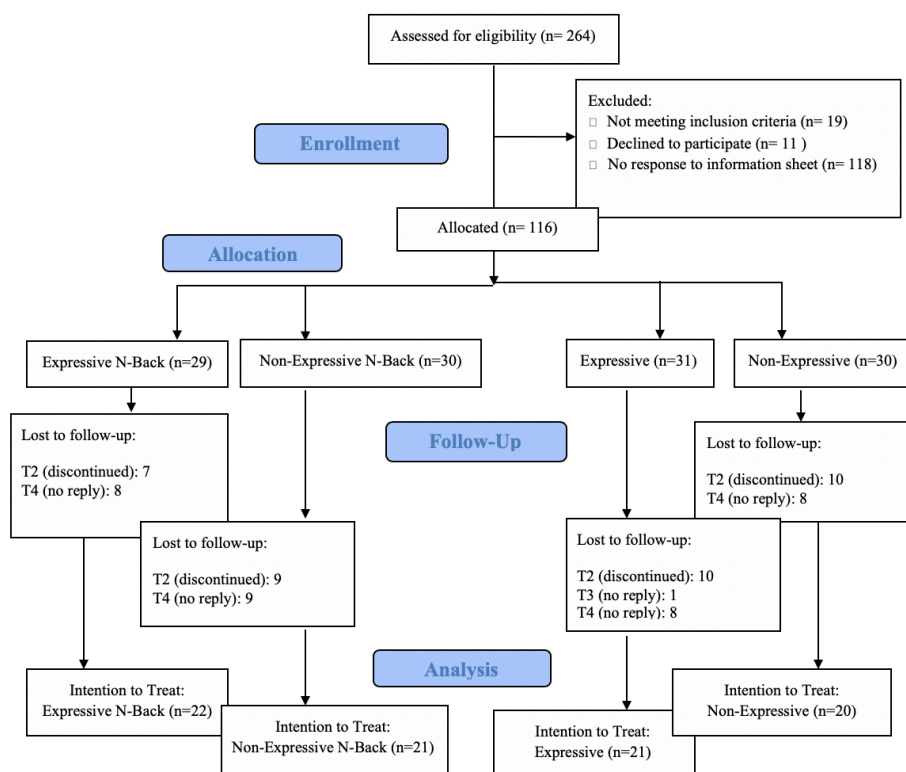
Figure 3.1. CONSORT diagram indicating participant enrolment, intervention allocation, follow-up and data analysis.

Outcome Measures

Primary Outcome: *Anxious symptomatology* was assessed by the anxiety subscale of the Hospital Anxiety and Depressions Scale (HADS), (Zigmond and Snaith, 1983). The HADS is a 14-item inventory assessing anxiety and depression, in which frequency of symptoms are indicated on a Likert scale ranging from 0 ('not at all') to 3 ('most of the time'). Higher scores indicated higher anxiety. The scale demonstrated good reliability in the current study: Cronbach's alpha =.77. We decided to use the HADS scale as opposed to the MASQ and Impact of Events Scale used in Experiment 1 (Chpater 2) in order to avoid a measure-specific effect.

Secondary Outcomes: *Depression* was assessed by the depression subscale of the Hospital Anxiety and Depressions Scale (HADS), (Zigmons and Snaith, 1983), (see above). Higher scores indicated higher depression. *Perceived Cognitive Function* was assessed by the FACT-Cog Version 3, (Wagner, Sweet, Butt, Lai, & Cella, 2009) a 37-item inventory assessing perceived cognitive abilities and perceived cognitive impairments. Scores are indicated on a Likert scale ranging from 0 ('never") to 4 ("several times a day"). Greater scores indicate better perceived cognitive functioning. *Resilience* was assessed by the Connor Davidson Resilience Scale (CD-RISC), (Connor& Davidson, 2003), as outlined in experiment 1 (chapter 2). Higher scores indicate higher levels of resilience. *Quality of Life* was assessed by the Quality of Life in Breast Cancer Patients Scale (Ferrell, 1997), which assesses the physical, psychological, social and spiritual dimensions of breast cancer patients. Scores are indicated on a Likert scale ranging from 0 ('no problem') to 10 ('severe problem'). Higher scores indicate better outcomes. Cancer related thoughts was assessed by the Cancer Impact of Events Scale (IOE), (Weiss et al., 2007), as outlined in experiment 1 (chapter 2). Higher scores indicated worse outcomes. All scales showed good reliability in the current study, all Cronbach alphas > .81.

Statistical methods

Data were analysed using IBM SPSS Statistics, Version 24.0. Chi-square tests were used to compare group demographics. T-tests were used to assess working memory improvement from pre- to post-intervention for the n-back training groups. Linear Mixed Effect Models (MLMs) were used to compare groups on self-reported emotional vulnerability measures over time. Fixed effects were specified for Group (Expressive N-Back, Non-Expressive N-Back, Expressive, Non-Expressive) Time (Pre-intervention, Post-intervention, 1st Follow-up, 2nd Follow-up), and a Group x Time interaction. Data were analysed according to the intention-to-treat (ITT) principle whereby the initial sample's ($n = 84$) data were analysed, irrespective of whether participants were compliant to the entire intervention. Models were estimated with the maximum likelihood method. Effect sizes were calculated by Cohen's d which was derived from the F- test and calculated as $d = 2*\sqrt{(F / \mathrm{df})}$. Post hoc power analysis for the initial sample of 84, and the intended MLM analyses with a significance level of 0.05 (alpha), a small to moderate effect size of .2d, with two time point measurements (pre and post) was .86. A sensitivity analysis was carried out to asertain the robustness of any findings; bivariate correlations were conducted for outcome measures and demographic variables to indicate whether the influence of potential moderating variables should be added as factors into the linear mixed effects model for each outcome factor.

The linguistic characteristics of the text for the writing groups was analyzed using the software program Linguistic Inquiry and Word Count (LIWC; Francis & Pennebaker, 1993). LIWC is a dictionary-based computerized text analysis program comprising of over 2000 words categorized under psychologically meaningful categories (eg. positive and negative affect), developed through previous writing samples. LIWC scans an excerpt of text and calculates the percentage of words that belong to a particular category. Previous studies indicate that increases in the use of affective words (positive and

negative emotional expression), causal words (e.g. because, hence, therefore) and insight words (e.g. know, think, believe, consider) which are recognised as important markers of emotional processing in the reappraisal process, are associated with reductions in emotional vulnerability (Pennebaker et al., 1997; Alparone et al., 2015; Lee et al., 2016). Discrepancies over the importance of valance utilised across writing essays exist; whilst some studies indicate that it is the use of negative emotion that improves outcomes (Klein & Boals, 2001; Lee et al., 2016) others suggest that it is the expression of positive emotion, utilising strategies such as self affirmation, that has the most impact (Niles, Byrne Haltom, Lieberman, Hur, & Stanton, 2016). Accordingly, the selected word categories of interest were emotional (positive, negative and anxiety) and cognitive (cause and insight). A series of One-way ANOVAs were used to assess differences in the percentage usage of word categories between groups. In addition, a series of bivariate correlations were used to assess the relationship between change in linguistic characteristics across excerpts (as measured by the amount of causal or affective used on the last 3 days of writing compared to the first 3 days) and changes in cognitive and emotional vulnerabilty.

3.2.3 Results

Dual n-Back Performance

N-back Training Groups: Figure 3.2 indicates that working memory functioning, as measured by increasing levels of N, improved for both groups across time, Day 1 ($M = 1.49$, $SD = .27$), Day 12 ($M = 2.73$, $SD = .32$), $t(19) = 16.77$, $p < .001$, (Expressive N-Back); Day 1 ($M = 1.41$, $SD = .42$), Day 12 ($M = 2.45$, $SD = .87$), $t(17) = 6. 46$, $p < .001$, (Non- Expressive N-Back). The slope of this improvement was significantly different from zero $t(21) = 4.33$, $p < .001$, (Expressive N-Back); $t(20) = 7.75$, $p < .001$, (Non- Expressive N-Back).
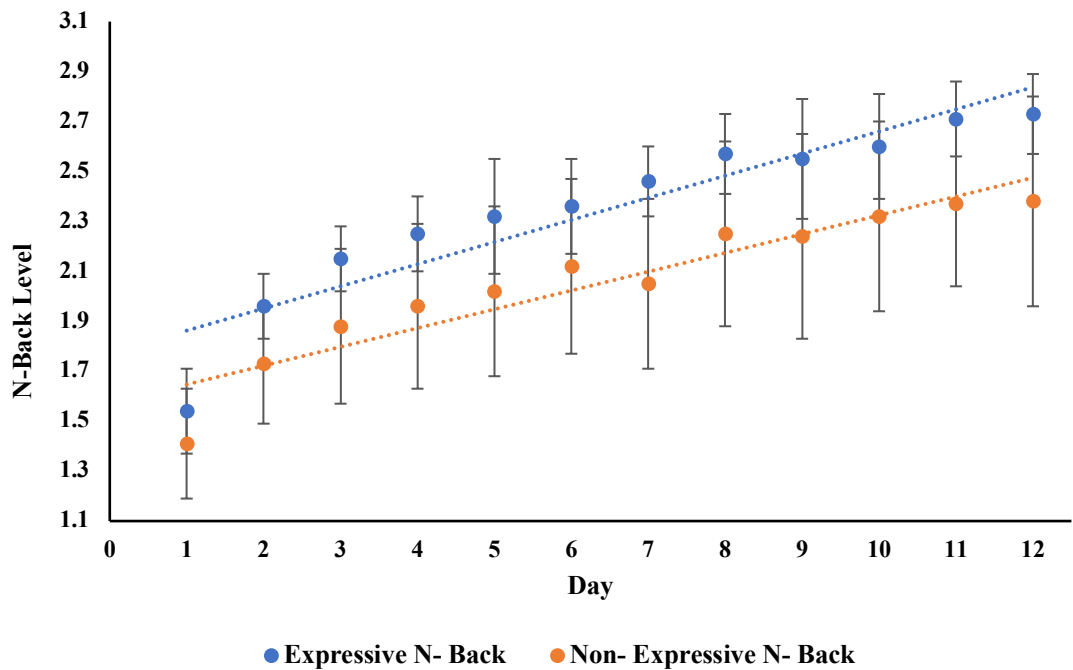
Figure 3.2. Mean dual n-back level for the training groups (Expressive N-Back and Non-Expressive N-Back) across each day of training; lines indicate standard deviations.

Changes in Emotional Vulnerability

Mean self-reported symptomatology for each group at each time point is presented in Table 3.2. The groups did not differ significantly at pre-intervention on any of the measures, all F's $< .79$, NS.

Table 3.2. Mean self-report symptomatology scores for each group (Expressive N-Back, Non-Expressive N-Back, Expressive, Non-Expressive) at pre, post and follow up time points.

	Expressive N-Back				Non-Expressive N-Back				Expressive				Non-Expressive			
Time	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Anxiety	8.82 (3.49)	9.36 (4.53)	8.05 (4.56)	9.50 (4.56)	9.67 (4.92)	8.24 (4.38)	8.19 (3.76)	7.92 (4.58)	9.33 (3.71)	8.38 (5.19)	9.05 (3.82)	8.69 (4.31)	9.75 (4.54)	8.85 (4.45)	7.95 (4.48)	8.17 (4.47)
Depression	6.50 (3.33)	6.09 (3.28)	5.50 (3.64)	7.14 (3.88)	6.71 (4.76)	5.57 (4.57)	5.71 (3.85)	5.83 (4.32)	7.29 (3.49)	6.52 (4.67)	6.80 (3.67)	6.92 (4.17)	5.70 (3.87)	5.95 (3.68)	4.80 (3.39)	6.83 (3.41)
Perceived Cognitive Function	71.5 (29.29)	77.09 (31.19)	78.27 (31.07)	75.36 (32.86)	70.62 (31.01)	83.05 (33.34)	84.81 (29.81)	89.67 (37.79)	72.62 (37.45)	78.75 (39.25)	79.05 (39.9)	80.38 (39.66)	84.6 (39.58)	81.3 (39.78)	88.5 (38.34)	83.67 (42.13)
Resilience	66.77 (12.71)	65.77 (15.95)	67.45 (15.95)	64.93 (18.5)	64.95 (13.59)	65.9 (16.8)	66.62 (15.17)	66.5 (15.37)	65.29 (12.71)	66.75 (18.34)	66.0 (14.96)	65.38 (16.43)	64.75 (13.76)	67.2 (16.55)	69.8 (15.85)	63.0 (10.75)
Quality of Life	195.91 (65.99)	205.18 (65.57)	215.41 (64.38)	195.5 (74.1)	211.86 (51.69)	212.29 (48.91)	208.81 (38.1)	221.17 (45.09)	195.86 (57.82)	202.86 (58.6)	209.65 (61.54)	202.31 (64.17)	218.6 (58.91)	211.95 (62.01)	223.9 (63.35)	224.77 (60.66
Cancer Related Thoughts	29.0 (16.49)	30.32 (17.46)	27.91 (17.82)	27.86 (20.07)	30.62 (15.08)	29.19 (16.15)	26.29 (10.16)	23.83 (16.15)	35.29 (12.53)	30.43 (14.17)	30.3 (14.18)	26.54 (14.38)	30.15 (18.91)	26.85 (17.53)	25.0 (16.42)	25.31 (15.11)

Note. Standard deviations are in parentheses.

Effects on primary outcome

Anxiety symptomatology:

Anxious symptomatology was assessed by the anxiety subscale of the HADS. The MLM indicated that there were no significant group differences for anxiety symptomatology across time, as shown by a non-significant Group X Time interaction, $F(9, 77.45) = 1.88$, $p = .32$, Cohen's $d = 0.31$.

Effects on secondary outcomes

Depression symptomatology: There was no significant interactions, $F(9, 77.47) = 1.11$, $p = .37$, Cohen's $d = .24$; *Resilience:* No significant interactions were found, $F < 1$, NS; *Perceived Cognitive Function:* There was no significant interactions, $F(9, 70.88) = 1.51$, $p = .16$, Cohen's $d = .29$; *Quality of Life:* There was no significant interactions, $F(9, 76.04) = 1.12$, $p = .16$, Cohen's $d = .24$; *Cancer Related Thoughts:* There was no significant interactions, $F(9, 79.24) = .59$, $p = .8$, Cohen's $d = .17$.

Expressive Writing Analysis

Mean percetange word usage for word categories are presented in Table 3.3. Whilst percentage scores may appear low, they are comparable to published norms (Pennebaker et al., 2001). There were no significant differences in the total amount of words written between groups ($p = .59$). As we would expect, due to the expressive vs non-expressive instructions, there were significant differences in the types of words used between groups, confirming that the Expressive N-Back and Expressive writing groups used more affective expression across writing excerpts. Bonferroni comparisons indicated that the Expressive N-Back group used significantly more affective words (positive, negative and anxiety) than the Non-Expressive N-Back and Non-Expressive groups (both p's $< .001$), however affective word usage was comparable to the Expressive

writing group ($p > .1$). A similar pattern across groups was found for the amount of insight and cause words utilized.

Table 3.3. Mean percentage of word frequency for each group across 12 writing sessions, as indicated by LIWC linguistic categories.

	Expressive N-Back (n= 22)		Non-Expressive N-Back (n = 21)		Expressive (n= 21)		Non-Expressive (n = 20)		F	P
Mean N° of Words	6095.27 (2139.16)		5393.95 (2376.06)		5430.43 (1949.53)		6075.3 (2262.94)		.64	.59
LIWC Categories		(%)					(%)			
Emotion Processes										
Positive Emotion	3.56	(.56)	1.58	(.71)	3.34	(.79)	1.51	(.64)	56.02	<.001*
Negative Emotion	2.37	(.73)	.58	(.28)	2.51	(.66)	.62	(.33)	79.54	<.001*
Anxiety	.73	(.19)	.16	(.09)	.86	(.36)	.17	(.09)	60.81	<.001*
Cognitive Processes										
Insight	3.47	(.81)	.96	(.53)	3.46	(.72)	.93	(.44)	107.57	<.001*
Cause	1.63	(.34)	1.18	(.24)	1.72	(.33)	1.14	(.26)	21.45	<.001*

[a] *Values indicate means and standard deviations unless indicated otherwise.*
Significant between-group difference, P = .05.
LIWC: Linguistic Inquiry and Word Count

Relationship between changes in word usage and changes in emotional vulnerability

As shown in Figure 3.3, exploratory analyses of the change in linguistic characterics across writing sessions indicated that for the Expressive Writing group, an increase in anxiety words acrosss writing sessions was related to reductions in depressive symptomatology $r(13) = -.71$, $p = .006$. A similar trend was found for the N-Back Expressive $r(14) = -.37$, $p = .19$ and N-Back Non-Expressive groups $r(12) = -.19$, $p = .54$, however they failed to reach significance. This pattern was not observed for the Non-Expressive writing group $r(12) = .12$, $p = .71$. Similarly, for the Expressive Writing group, an increase in anxiety words was associated with increased resilience $r(13) = .65$, $p = .01$, improvements in quality of life, $r(13) = .69$, $p = .01$, and reductions in cancer related thoughts $r(13) = -.64$, $p = .02$. This observation was not apparent for all other groups (all r's <.43, all p's >.13). For the Expressive Writing group further associations were found with the use of negative emotion words, such that increases in negative word usage across writing sessions was associated with better quality of life, $r(13) = .56$, $p = .04$ (see figure

3.4), better perceived cognitive functioning, $r(13) = .71, p = .007$, and reductions in cancer related thoughts $r(13) = -.62, p = .02$. These associations were not found for all other groups (all r's <.46, all p's >.11). Further, as shown in figure 3.5, for the Expressive Writing group an increase in cause and insight words across writing sessions was associated with an increase in perceived cognitive functioning $r(13) = .66, p = .01$. A comparable non-significant trend was observed for the N-Back Expressive and N-Back Non-Expressive groups, (both r's <.43, both p's >.12). This trend was not observed for the Non-Expressive writing group, $r(12) = .05, p = .85$.
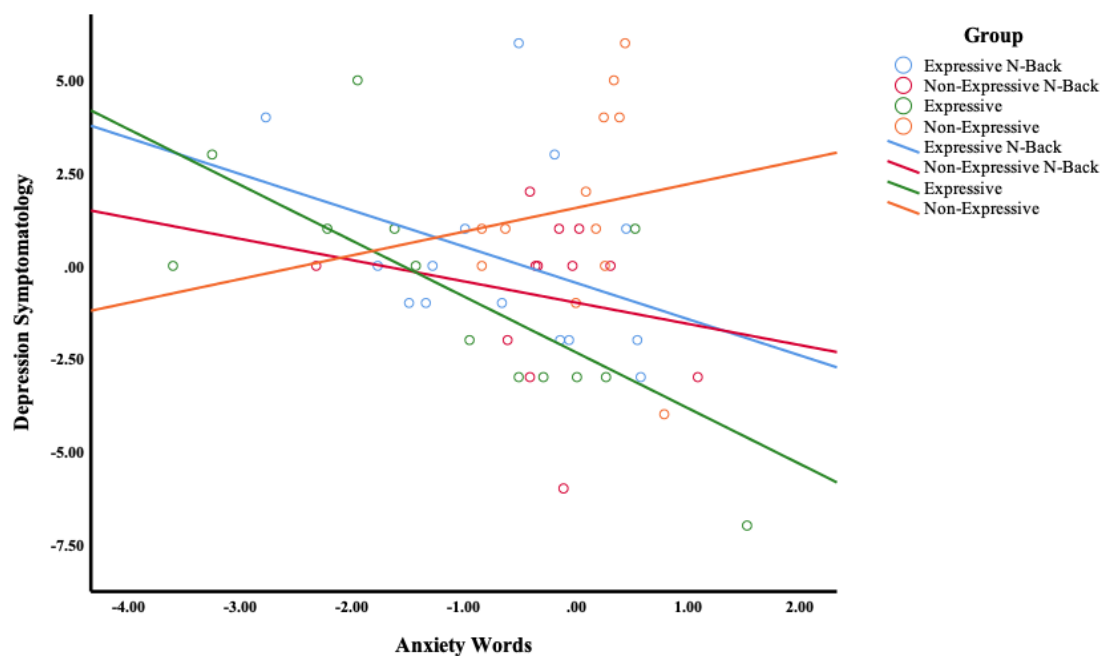
Figure 3.3 The association between change in use of anxiety words across writing sessions and reductions in depressive symptomatology for each group.
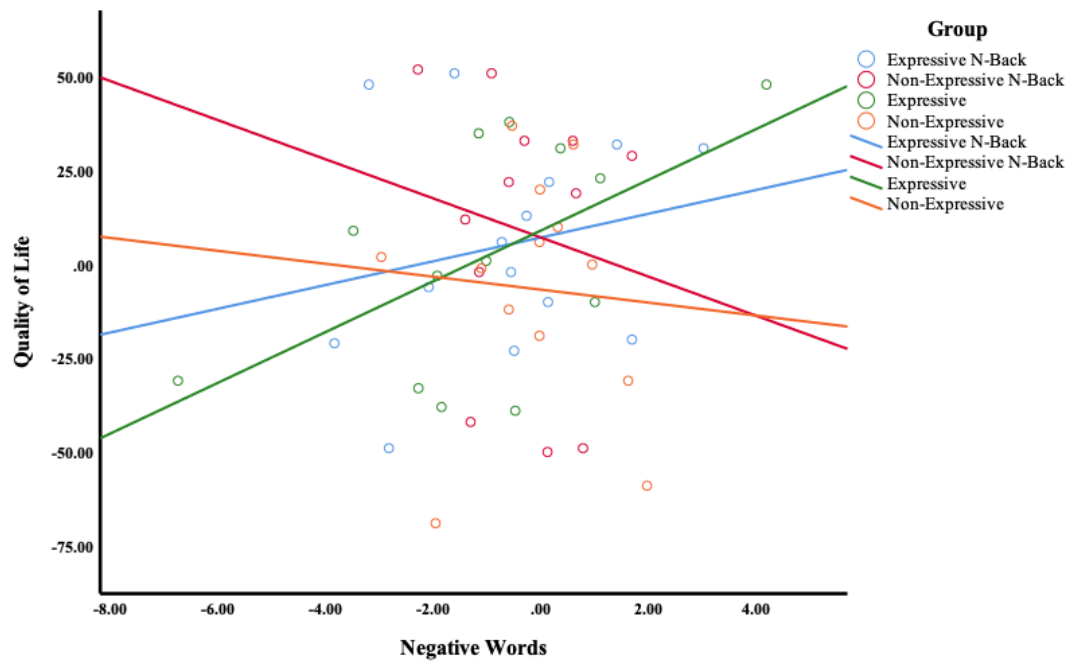
Figure 3.4 The association between change in use of negative words across writing sessions and improvements in quality of life for each group.
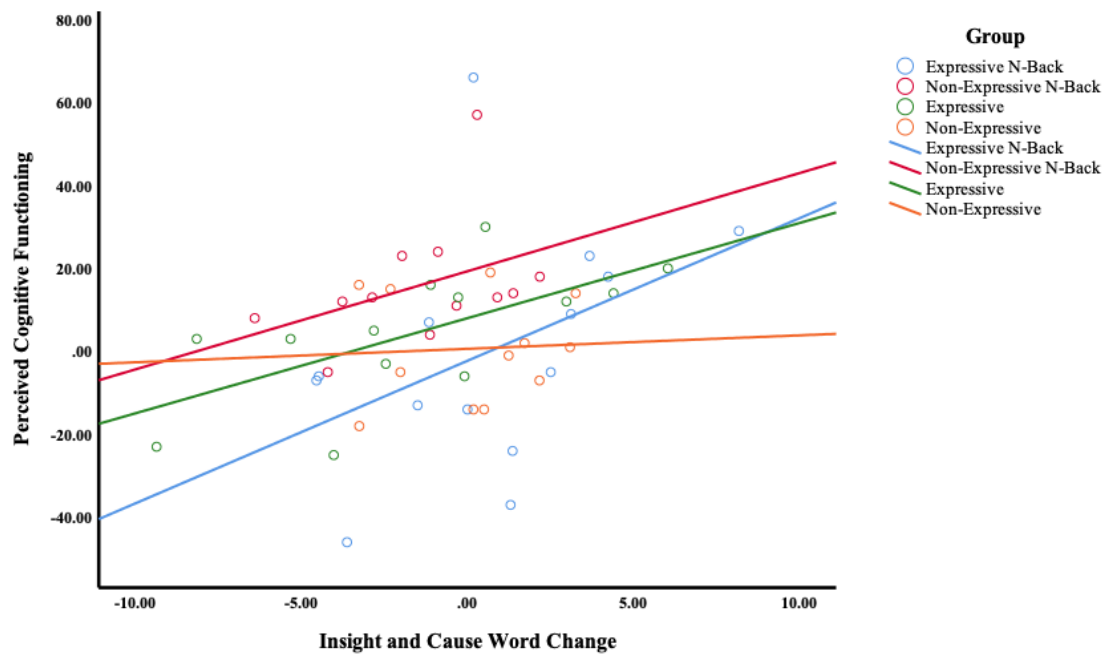
Figure 3.5 The association between change in insight and cause word usage across writing sessions and improvements in perceived cognitive functioning for each group.

Further Analyses

Table 3.1 indicates group characteristics on demographic variables for the initial sample of 84. Group differences were apparent for chemotherapy treatment such that more participants in the Expressive N-Back group had chemotharapy compared to the other 3 groups, X^2 (3) = 7.66, p = .05. Group differences were also apparent for alcohol intake, X^2 (12) = 22.87, p = .03. No significant correlations were found between any demographic or medical variables and the slope of change for the outcome mesures, (all r's < .15, all p's > .3), and thus demographic variables were not included as factors in the linear mixed effect model.

3.2.4 Discussion

This investigation aimed to assess the combined effects of adaptive working memory training and expressive writing on emotional vulnerability in a female population of women affected by breast cancer. Whilst the isolate effects of working memory training and expressive writing have been highlighted in numerous studies investigating emotional vulnerability (Frattaroli et al., 2006; Motter et al., 2016), combined effects have yet to be assessed in a single study within the breast cancer population.

Firstly, in line with the findings from the first study in Chapter 1, marked improvements in working memory performance were found for the training groups (Expressive N-Back, Non-Expressive N-Back) indicating that this population are receptive to this type of intervention. Given the plethrora of evidence indicating cancer related cognitive decline (Andryszak et al., 2017) this finding was important to replicate, substantiating that through neural plasticity, attentional control processes can be targeted post cancer active treatment. Secondly, analysis of the writing excerpts indicated that the expressive writing groups (Expressive N-Back and Expressive) used significantly more emotional (positive, negative, anxiety) and cognitive (cause, insight) words across writing

excerpts, indicating that participants adhered to experimentor instructions and that emotional expression was used where appropriate. Consistent with other studies (Mosher et al., 2012; Jensen-Johansen et al., 2013) our main analysis did not indicate significant group differences in psychological outcomes across time. Exploratory correlational analyses however indicated that for the Expressive Writing group, increased use of anxiety words across writing sessions was associated with reduced depressive symptomatolgy, reductions in cancer related thoughts and improved resilience and quality of life. Similarly, results indicated that increased use of negtive emotion words was related to better quality of life, improvements in perceived cognitive functioning, and reductions in cancer related thoughts. In addition, increased use of cause and insight words were associated with better pereceived cognitive functioning. Importantly, the effects were observed in the Expressive writing group alone, and were not apparent for the Expressive N-Back, Non-Expressive N-Back and Non-Expressive groups.

It is important to consider why no transfer effects onto emotional vulnerability were found across groups. Whilst a number of other studies have found effects previously on emotional vulnerabilty in non-cancer populations (Frattaroli, 2006), the efficacy of the intervention, particularly relating to its effectiveness for treating clinical levels of emotional disorder, is still undertermined. Indeed a number of other studies found no significant effects of expressive writing on psychological outcomes in clinical populations (see Frisina et al., 2004, for a meta-analytic review). Moreover, a recent meta-analysis specifically focusing on the cancer population indicated no main effects of psychological or physical outcomes, mirroing our findings (Zachariae & O'Toole, 2015).

It appears that working memory training added no beneficial value to expressive writing intervention outcomes in terms of reductions in emotional vulnerability across time, and vice versa. Both the Expressive N-Back and Non-Expressive N-Back group differs from other studies that have found beneficial effects of n-back training on

emotional vulnerability (Sari et al., 2016; Swainston & Derakshan, 2018) in that participants were additionaly asked to either tap into their emotions and write expressively about their lives, or they were instructed to inhibit emotional expression in their writing essays. This suggests that expressive writing may in fact counter the impact of working memory training indicating that perhaps the two interventions do not function via similar mechanisms. Our study is limited in that for the purposes of this study, we did not administer a second cognitive task to assess whether expressive writing in itself results in marked improvements in working memory performance, thus it is difficult to fully assess whether expressive writing itself can increase working memory capacity as argued by Klein & Boals (2001). Administration of a second cognitive task should however be taken into consideration for future studies in order to fully explore this theory. For the Non-Expressive N-Back group, who were asked to write emotionlessly, a repressive coping style was encouraged. Considering the aforemementioned research that indicates that for the breast cancer population, less adaptive coping mechanisms such as avoidance and inhibition have been associated with poorer heath outcomes (Brandao et al., 2016), it follows that no reductions in negative affect were found.

Nevertheless, analysis of the linguistic characteristics of writing excerpts across time revealed that the types of words used in expressive writing are related to changes in emotional and cognitive vulnerabilty. Results indicated that increased use of negative emotion, anxiety and cognitive mechanism words (indicating cause or insight) across writing sessions was associated with better outcomes on measures of perceived cognitive function, emotional vulnerabilty and quality of life. This substantiates and extends research by Klein & Boals (2001) who found that the use of cognitive mechanism and negative words was related to reductions in intrusive thinking and improved working memory capacity. Whilst the current study did not use a second working memory task to measure transfer, we did find that the use of cognitive mechnism words was linked to

improvements in perceived cognitive functioning, pointing to improved cognition. Findings further corroborate research by Park et al., (2014) who found that increased anxiety and cognitive mechanims words was related to improved math performance, research by Alparone, Pagliaro, & Rizzo (2015) who found that increased use of cognitive mechanism words across writing sessions is linked to decreases in anxiety symptomatology, and research by Zheng, Lu, & Gan (2019) who found that the use of cognitive mechanism words was related to increases in post-traumatic growth. In contrast to other studies, we found no association between the use of positive emotion words and improved psychological outcomes. This may be because for our manipulation we did not instruct participants to write about either positive or negative feelings across writing sessions (as in Shen et al., 2019, where particpants were told to write about positive emotions), but allowed partcipants to write freely about their emotions.

Findings from the current study suggest that for expressive writing to be effective as an intervention, perhaps a more structured approach to writing sessions which encourages the specific use of affect and cognitive mechanism words will result in greater change in cognitive and emotional vulnerabilty. For instance, it could be argued that the expressive writing instructions did not encourage reappraisal strategies sufficiently. Moreover, the improtance of moderating factors based on individual differences and social constraints may be critical in determining the effectiveness of an expressive writing intervention (Mertz et al., 2012). The importance of individual differences was reported in a study by Stanton and collegues (2002) who tested the efficacy of expressive writing and benefit writing in relation to a woman's cancer-related avoidance (intentional avoidance of cancer-related thoughts and feelings). Benefits of writing on psychological outcomes varied as a function of participants' avoidant coping styles; induced expressive disclosure was found to be more effective for women with low cancer-related avoidance, whereas benefit finding resulted in betters outcomes for more avoidant women. The

authors reasoned that women low in avoidance may embrace an emotional disclosure intervention, leading to the full cognitive and emotional processing of events, whereas women high in avoidance may find generating positive factors that they can take from their diagnosis a less painful process, producing greater psychological effects. It must be noted that interventions promoting positive thinking styles in cancer patients must be approached with caution; not only may this approach be perceived as insensitive, but a focus on encouraging positive thinking may enable maladaptive forms of avoidance (Stanton et al., 2002). It seems however, that overall perhaps a more nuanced approach is necessary for expressive writing of any form to be benefical to the psychological state of breast cancer patients. Lee et al., (2016) suggest that a more formal/well structured writing template that not only encourages further reappraisal but is additionally personalised to individuals specifically, would maximise writing outomes. Indeed, perhaps a structured writing template which focuses on a reconstructive approach to specific vulnerabilities relating to an individuals unique concerns about their cancer diagnosis, treatment and life situation would be more beneficial. Admittedly, this would need oversight and greater input from a clinician.

Limitations

The current study has a number of limitations. Firstly participants were recruited via social media platforms and therefore may not be representative of the wider popultaion of breast cancer survivors. Consequently reasons for participation refusal and clinical charaterstics of the sample are unknown. Secondly, the study did not measure the cognitive transfer effects of adaptive cognitive training or expressive writing to a second working memory task. An inclusion of such task may assist in undrestanding the exact mechanisms that are at play in such interventions. Finally, the influence of participant

demographic variables such as education and marital status were not considered in this investigation, therefore future research should consider these factors.

Clinical Implications and Conclusions

Expressive Writing is a well-known technique that is thought to lessen the burden on working memory resources leading to more effective coping. Attentional control training is an exciting new intervention that targets key cognitive and neural networks that are considered key in emotion regulation. The current study indicated that combining expressive writing and working memory training did not result in improved psychological outcomes for breast cancer survivors. For the independent expressive writing group, increases in the the use of emotionally negative words, anxiety words and cognitive mechanism words were associated with improvements in perceievd cognitive functioning, reduced depressive symptomatology, reductions in cancer related thoughts and better quality of life. Expressive writing can be administered online, offering a cost-effective and accessible route of reaching a wider popultation. In addition, it can be accessed anonymously, which may appeal more to individuals concerned with the stigma often attached to seeking help for psychological and emotional disorder. Going forward, more research is necessary to establish whether a more nuanced approach to expressive writing in cancer patient samples would produce more promising outcomes for psychological vulnerability in breast cancer survivorship. Future reaserach may also consider the effects of adaptive n-back training in combination with other ineterventions such as CBT and mindfulness that have previously had a more encouranging impact on psychological distress in breast cancer.

Chapter 4: Exploring the Combined Effects of Mindfulness and Working Memory Training on Emotional Vulnerability in Breast Cancer

4.1 Chapter Overview

So far, experiment 1 (chapter 2) showed that computerised working memory training targeting attentional control processes can be associated with far transfer effects to measures of emotional vulnerability. This indicates a critical link between cognitive health and the downregulation of emotion. In chapter 3, the effects of combining interventions that potentially engage similar mechanisms in order to regulate emotion was explored. In experiment 2 working memory training was combined with expressive writing, a technique thought to aid in creating coherent narratives related to trauma, resulting in reduced burden on working memory processes and consequently improved emotion regulation. The study indicated that combined expressive writing and working memory training did not result in any greater transfer to emotional vulnerability than expressive writing did independently. Moreover main analyses did not indicate any group differences in emotional and cognitive vulnerability across time as a result of expressive writing. That said, exploratory correlational analyses pointed to the importance of linguistic predictors for changing emotional and cognitive states. Results showed that as the use of negative, anxious and cognitive mechanism words increased across writing sessions, the better the outcomes for emotional vulnerability and perceived cognitive functioning.

Whilst combined expressive writing and working memory training did not result in significant improvements in emotional vulnerability, recent studies have indicated that combined mindfulness meditation training and working memory training can reduce anxious symptomatology in high trait anxious populations. As discussed in chapter 1,

there is growing behavioural and neuroscientific evidence that indicates that mindfulness meditation recruits attentional control processes much like that of working memory training. Accordingly, the purpose of current chapter is to investigate whether the combined benefits of mindfulness meditation practise and working memory training can extend to women affected by breast cancer.

4.2 Experiment 3: The Combined Effects of Mindfulness and Working Memory Training on Emotional Vulnerability in Breast Cancer

4.2.1 Introduction

Breast cancer is a debilitating and emotionally distressing disease which can result in increased risk to anxiety, depression, stress disorders and suicide, compared with women with no prior cancer (see Carreira et al., 2018, for a systematic review). Inefficient emotion regulation mechanisms is a central facet of psychopathologies (Gross, 2013). Accordingly, the development of better, more cost-effective interventions targeting emotion regulation could result in considerable benefit to individuals and society at large, including the breast cancer population. Research has indicated an association between more efficient attentional control processes and reduced emotional vulnerability. Attentional control represents the capacity to attend to target related information and inhibit interference from distractions, in order to assist goal directed behaviour (Eysenck et al., 2007). With this in mind, targeted interventions that train attentional control processes have recently been developed, with the aim to achieve robust transfer effects to more generalised improvements in emotion regulation (Engen & Kanske, 2013). Intervention research utilising attentional control training techniques have so far indicated promising results, with studies showing better mental health outcomes across a range of psychopathologies (see Dolcos et al., 2020, for a review), as well as in healthy individuals

(Takeuchi et al., 2014). A frequently employed attentional control training technique that recruits prefrontal mechanisms of control is that of working memory training (WMT). Working memory capacity, a term used interchangeably with attentional control (Kane, Bleckley, Conway, & Engle, 2001), is responsible for the inhibitory, shifting and updating of information in working memory critical for facilitating task completion. Numerous studies now show that WMT can result in reduced anxious and depressive symptomatology in both subclinical and clinical populations (Peckham & Johnson, 2018; Koster et al., 2017). This is supported by recent neural studies that show that prefrontal cortical structures necessary for attentional control processes have been implicated in the downregulation of emotion (Cohen et al., 2016b).

Importantly, in chapter 2 of the current thesis, findings show that transfer effects to emotion regulation through WMT can extend to the breast cancer population, whereby reductions in anxiety and rumination were observed (Swainston & Derakshan, 2018).

Another intervention that requires the engagement of attentional control mechanisms is that of Mindfulness Meditation Training (MMT). Mindfulness, grounded in Buddhist philosophy, is developed through meditation techniques that aim to build a continued awareness of the present moment throughout daily life (Kabat-Zinn, 2006). At the heart of mindfulness is the capacity to cultivate an observant state of mind whereby arising thoughts and emotions are recognised as a series of mental events without ascribing specific value to them (Malinowski, 2008). The most commonly employed mindfulness intervention techniques are that of mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). Both aim to promote a state of mindfulness that can translate to daily life, with the latter incorporating elements of cognitive therapy to achieve this goal. More recently, online MMT interventions have been developed with the view that they are cost-effective and easily accessible to a wider population (Plaza García et al., 2017).

Mindfulness requires sustained attention to the present moment and as such necessitates the engagement of attentional control processes to inhibit surrounding distractions and remain focused. It follows then that numerous studies indicate that MMT can result in transfer to attentional control processes such as inhibition, switching, executive functioning and working memory capacity (Teper & Inzlicht, 2013; Tang et al., 2012; Mrazek et al., 2013), which are further substantiated by neural studies that indicate the recruitment of neural networks associated with attentional control mechanisms (Allen et al., 2012). Studies employing MMT have indicated favourable mental health outcomes across clinical populations as well as healthy individuals (see Wielgosz et al., 2019, for a review). Like WMT, it has been proposed that the mechanisms by which this takes effect is through the downregulation of emotion through the improved functioning of attentional control processes (see Guendelman, Medeiros, & Rampes, 2017, for a review).

The Current Investigation

A per experiments 1 and 2 of the current thesis, the ORBIT Model (Czajkowski et al., 2015) for developing behavioural treatments for chronic diseases (see figure 1.1, general introduction) formed the foundation of the current study; for efficacious interventions to emerge, they must be grounded in fundamental behavioural research and be developed and refined over time.

Building upon this goal, the current investigation aims to extend on prior findings indicating the effectiveness of reducing emotional vulnerability via WMT and MMT by investigating their independent and combined effects in a female population of breast cancer survivors. To date, research considering combined interventions is sparse, however preliminary studies show promise. For instance, Course-Choi et al., (2017) found that a combined course of working memory training and mindfulness meditation practice resulted in reductions in worry pre to post intervention for a population of pre-

selected high worriers. The current study is novel in that it is the first to consider combined mindfulness and working memory training in cancer survivorship. In addition, the lack of an active control group has been highlighted as a major limitation throughout cognitive training research, and in particular across the MMT literature (Davidson & Kaszniak, 2015). Here, an active control condition which requires continued low level prefrontal engagement was employed in order to further elucidate to efficacy of MMT and WMT.

MMT and WMT have both shown to improve attentional control processes (Sood & Jones, 2013; Blacker, Negoita, Ewen, & Courtney, 2017). Considering accumulating evidence that suggests that prefrontal mechanisms of control can causally affect emotional response (see Dolcos et al., 2019), it was predicted that a 10 day combined course of MMT and WMT would result in greater transfer to reductions in anxious symptomatology than a course of MMT or WMT would independently. To extend upon findings from Experiment 1 (Chapter 2) we also included a measure of rumination. It was predicted that a 10 day combined course of MMT and WMT would result in greater transfer to reductions in ruminative symptomatology than a course of MMT or WMT would independently. Finally, we felt that it was important to include some exploratory cancer-specific measures of cognitive and emotional vulnerability and as such assessed fear of recurrence, perceived cognitive functioning, quality of life and cancer related thoughts.

4.2.2 Methods

Participants

The study was advertised through the Birkbeck Centre for Building Resilience in Breast Cancer (BRiC) and various breast cancer support networks via social media platforms such as Facebook and Twitter. In total, 84 participants (23 Mindfulness, 22 Mindfulness N-Back, 19 N-Back, 20 1-Back) were recruited for the study. Participants were required to have had a diagnosis of breast cancer and be 6 months post active treatment to partake in the study. For the combined groups (MMT and N-Back) which required a commitment of approximately 40-50 minutes per day, participants received a fee of £140 upon completion of the study. For the Mindfulness group which required a commitment of 10-20 minutes per day participants received a fee of £80, and for the working memory training groups (N-Back and 1-Back) which required a commitment of 20-30 minutes per day, participants received a fee of £90. For participant demographics, clinical characteristics and psychiatric history see Table 4.1

Materials and Experimental Tasks

Dual N-Back Task (Training): As outlined in experiments 1 and 2 of the current thesis, a standard dual n-back task replicated from Owens et al., (2013) was utilized whereby difficulty increased based on task performance (see, chapter 2, experiment 1, for a comprehensive description).

Dual 1-back Task (Active Control): Participants in the control group undertook a non-adaptive version of the task whereby the difficulty level remained unchanged, (see, chapter 2, experiment 1, for a comprehensive description).

Table 4.1. Participant demographics, clinical characteristics and psychiatric history.

	Mindfulness (n= 23)		Mindfulness N-Back (n = 22)		N-Back (n= 19)		1-Back (n = 20)		*P*
Age (Years)[a]	49 (9.57)		47 (7.70)		48 (10.22)		42 (9.35)		.14
Age at Diagnosis (Years)	46 (8.58)		44 (8.13)		45 (10.09)		40 (9.29)		.21
	No. (%)				No. (%)				
Diagnosis									
Primary	17	(73.9)	16	(72.7)	19	(100)	19	(95)	.02*
Secondary	6	(26.1)	6	(27.3)	-	-	1	(5)	
Grade of Cancer [b]									
Low	6	(26.1)	1	(4.5)	2	(10.5)	1	(5)	
Moderate	9	(39.1)	8	(36.4)	8	(42.1)	7	(35)	.31
High	8	(43.8)	11	(50)	9	(47.4)	12	(60)	
Chemotherapy [c]									
Yes	12	(52.2)	18	(81.8)	13	(68.4)	16	(80)	.11
Radiotherapy									
Yes	19	(82.6)	16	(72.7)	14	(73.7)	15	(75)	.74
Surgery Type [d]									
Mastectomy	9	(39.1)	10	(45.5)	9	(47.4)	9	(45)	.79
Lumpectomy	12	(52.2)	10	(55.5)	10	(52.6)	11	(55)	
Both	-	-	1	(4.5)	-	-	-	-	
Endocrine Therapy [e]									
Yes	15	(65.2)	14	(63.6)	14	(73.7)	14	(70)	.97
Current Psychological Medication									
Yes	3	(13)	-	-	5	(26.3)	6	(30)	.04*
No	20	(87)	22	(100)	14	(73.7)	14	(70)	
Previous Psychological Condition									
Yes	4	(17.4)	3	(13.6)	4	(21.1)	5	(25)	.81
No	19	(82.6)	19	(86.4)	15	(78.9)	15	(75)	
Alcohol Intake [f]									
None	6	(26.1)	4	(18.2)	7	(36.8)	3	(15)	.68
1-5 units	11	(47.8)	10	(45.5)	5	(26.3)	9	(45)	
6-9- units	1	(4.3)	5	(22.7)	4	(21.1)	2	(10)	
10-14 units	3	(13)	1	(4.5)	1	(5.3)	2	(10)	
15+ units	1	(4.3)	1	(4.5)	1	(5.3)	2	(10)	

[a] *Values indicate means and standard deviations unless indicated otherwise.*

[b] *2 participants from the Mindfulness N-Back group did not indicate grade of cancer.*

[c] *1 participant from the Mindfulness group and 1 participant from the Mindfulness N-Back group did not indicate chemotherapy or radiotherapy treatment.*

[d] *2 participants from the Mindfulness group and 1 participant from the Mindfulness N-Back group did not indicate surgery treatment.*

[e] *2 participants from the Mindfulness group and 1 participant from the Mindfulness N-Back group did not indicate endocrine therapy.*

[f] *1 participant from the Mindfulness, Mindfulness N-Back and N-Back groups, and 2 participants from the 1-Back group did not indicate alcohol intake.*

*Significant between-group difference, P = .05.

Mindfulness Meditation Training

The mindfulness meditation training was delivered via the Headspace, commercially available, mindfulness-based smartphone app. The decision to utilize the Headspace app for the current study was based upon scientific review of commercially available mindfulness-based apps in which it deemed favorable in terms of engagement,

functionality, information and satisfaction, compared to others on the market (Mani, Kavanagh, Hides, & Stoyanov, 2015). Use of the Headspace app has been associated with reductions in stress, affect and irritability (Economides et al., 2018), reductions in mind wandering (Bennike, Wieghorst, & Kirk, 2017) and most importantly, improvements to quality of life outcomes in women diagnosed with breast cancer, (Rosen, Paniagua, Kazanis, Jones, & Potter, 2018).

The mindfulness meditation training intervention is part of Headspace's basic foundation sessions which are intended to act as an introduction to mindfulness meditation, focusing on the core techniques involved in mindfulness such as awareness of the present moment. The course consists of 10 sessions for a duration of approximately 10 minutes daily and is delivered by former Buddhist monk Andy Puddicombe.

Procedure

The study followed a pre-intervention, intervention, post-intervention, and two follow-ups design. The first follow up took place one-month post intervention and the second at approximately 6 months post intervention (see, figure 4.1 for CONSORT diagram). Allocation to one of four conditions was achieved using a procedure that alternated participants sequentially to each of these conditions. Participants remained naive to the allocation to either an experimental (Mindfulness, Mindfulness N-Back, N-Back,) or control (1-Back) group and were emailed task instructions with verbal instructions over the phone. For all groups participants accessed the task online in their homes on a secure and dedicated website, granting access only to the participant and the experimenter ensuring confidentiality. They firstly answered demographic questions on their breast cancer diagnosis, followed by the first set of questionnaires. The Mindfulness-N-Back, N-Back and 1-Back groups then continued on to complete their allocated task. The Mindfulness and Mindfulness N-Back groups, were also provided with a unique code

to access their mindfulness training along with instructions on how to download the app and redeem the code. Participants completed their daily tasks for 10 days, across a two-week period, at approximately the same time each day. The N-Back and 1-Back tasks took approximately 20 minutes and the Mindulness task took approximately 10 minutes. Performance and adherence to the tasks was monitored by the experimenter daily. On completion of the tasks, participants completed the follow up questionnaires, and again at both follow-up time points.
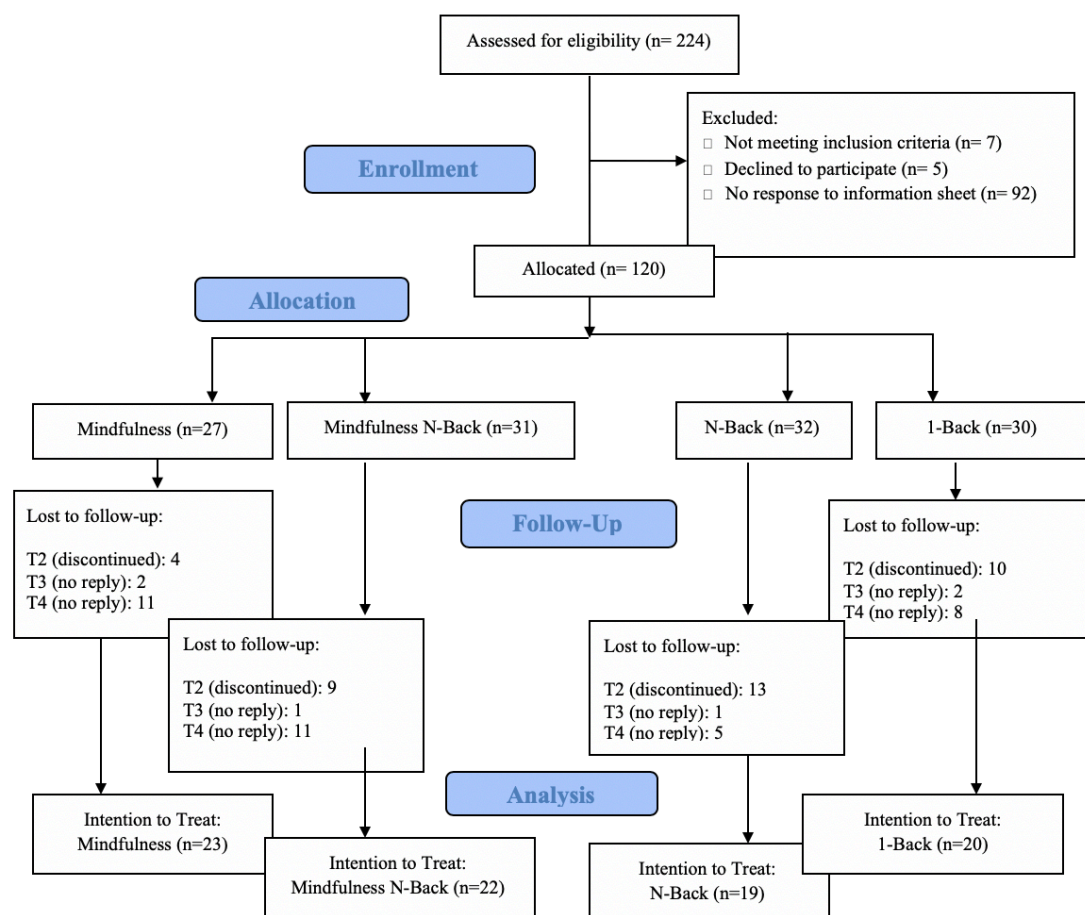
Figure 4.1. CONSORT diagram indicating participant enrolment, intervention allocation, follow-up and data analysis.

Outcome Measures

Primary Outcome: *Anxious symptomatology* was assessed by the anxiety subscale of the Hospital Anxiety and Depressions Scale (HADS), (Zigmond and Snaith, 1983), as

outlined in experiement 2 (chapter 3) of the current thesis. Higher scores indicated higher anxiety.

Secondary Outcomes: *Rumination,* a key predictor of depression, was assessed by the Ruminative Response Scale (Treynor et al., 2003) (as outlined in experiment 1, chapter 2). Higher scores indicated higher rumination. ***Perceived Cognitive Function*** was assessed by the FACT-Cog Version 3 (Wagner et al., 2009), (as outlined in experiment 2, chapter 3). Greater scores indicate better perceived cognitive functioning. ***Quality of Life*** was assessed by the Quality of Life in Breast Cancer Patients Scale (Ferrell, 1997) (as outlined in experiment 2, chapter 3). Higher scores indicate better outcomes. ***Cancer Related Thoughts*** was assessed by the Cancer Impact of Events Scale (IOE) (Weiss et al., 2007), (as outlined in experiment 1, chapter 2). Higher scores indicate worse outcomes. ***Fear of Recurrence*** was assessed by the Fear of Cancer Recurrence Scale (Simard & Savard, 2009), a 42 item inventory which assesses cancer recurrence fears. Fears are scored on a Likert scale ranging from 0 ("never") to 4 ("all the time"). Greater scores indicate higher levels of fear. All scales demonstrated good reliability in the current study: all cronbach's alpha = .89.

Statistical methods

Data were analysed using IBM SPSS Statistics, Version 24.0. Chi-square tests were used to compare group demographics. T-tests were used to assess working memory improvement from pre- to post-intervention for the n-back training groups. Linear Mixed Effect Models (MLMs) were used to compare groups on self-reported emotional vulnerability measures over time. Fixed effects were specified for Group (Mindfulness, Mindfulness N-Back, N-Back, 1-Back), Time (Pre-intervention, Post-intervention, 1st Follow-up, 2nd Follow-up), and a Group x Time interaction. Data were analysed according to the intention-to-treat (ITT) principle whereby the initial sample's ($n = 84$)

data were analysed, irrespective of whether participants were compliant to the entire intervention. Models were estimated with the maximum likelihood method. Effect sizes were calculated by Cohen's *d* which was derived from the *F-* test and calculated as $d = 2*\sqrt{(F/df)}$. Post hoc power analysis for the initial sample of 84, and the intended MLM analyses with a significance level of 0.05 (alpha), a small to moderate effect size of .2, and with two time point measurements (pre and post) was .86. A sensitivity analysis was carried out to asertain the robustness of any findings; bivariate correlations were conducted for outcome measures and demographic variables to indicate whether the influence of potential moderating variables should be added as factors into the linear mixed effects model for each outcome factor.

4.2.3 Results

Dual n-Back Performance

N-back Training Groups: Figure 4.2 indicates that working memory functioning, as measured by increasing levels of N, improved across time for both groups (Mindfulness N-Back: Day 1, *M* = 1.59, *SD* = .39 to Day 10, *M* = 2.54, *SD* = .61, *t(21)* = 11.12, *p* < .001; N-Back: Day 1, *M* = 1.71, *SD* = .36 to Day 10, *M* = 2.57, *SD* = .57, *t(18)* = 8.28, *p* < .001). The slope of this improvement was significantly different from zero, Mindfulness N-Back: *t(21)* = 9.53, *p* <.001, N-Back: *t(18)* = 8.18, *p* <.001.

1-back Control Group: There was a good average level of accuracy across the 10 days of training sessions (*M* = 98.63 %, *SD* = .95).
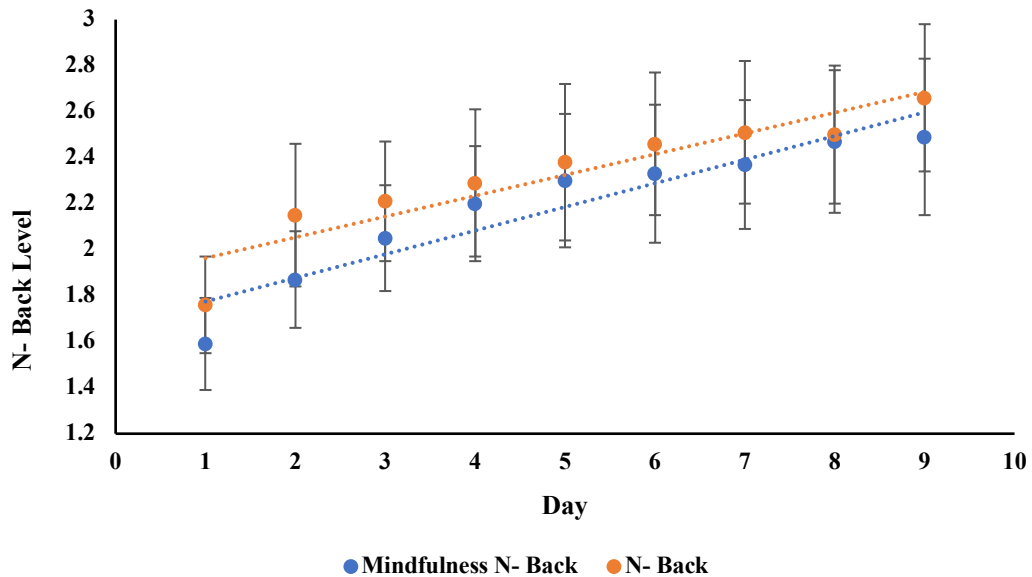
Figure 4.2. Mean dual n-back level for the training groups (Mindfulness N-Back and N-Back) across each day of training; lines indicate standard errors of the mean.

Changes in Emotional Vulnerability

Mean self-reported symptomatology for each group at each time point is presented in Table 2. The groups did not differ significantly at pre-intervention on any of the measures, all F's < 2.16, all p's > .1.

Table 4.2. Mean self-report symptomatology scores for each group (Mindfulness, Mindfulness N-Back, N-Back, 1-Back) at pre, post and follow up time points.

	Mindfulness				Mindfulness N-Back				N-Back				1-Back			
Time	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Anxiety	9.91 (4.29)	7.76 (3.83)	7.76 (4.08)	6.80 (2.85)	8.95 (4.01)	6.31 (3.72)	5.81 (2.91)	9.2 (2.44)	9.0 (4.24)	7.79 (3.86)	7.38 (4.01)	7.33 (3.02)	8.75 (4.24)	8.70 (3.68)	7.66 (3.91)	8.3 (4.39)
Rumination	47.22 (12.14)	44.0 (13.09)	40.25 (9.67)	39.1 (9.62)	41.18 (10.73)	41.0 (14.25)	41.33 (15.09)	43.0 (12.53)	42.0 (12.08)	39.63 (10.36)	40.05 (8.48)	34.39 (8.06)	44.15 (11.14)	42.55 (11.27)	41.35 (13.15)	39.27 (11.64)
Perceived Cognitive Function	85.13 (31.92)	92.09 (26.46)	95.41 (26.34)	105.12 (30.05)	85.86 (30.09)	102.72 (39.40)	99.90 (30.41)	95.00 (28.73)	84.68 (23.55)	93.94 (25.30)	96.44 (22.04)	99.14 (17.37)	86.05 (31.94)	93.65 (23.40)	99.12 (25.09)	92.0 (29.60)
Fear of Cancer Recurrence	87.82 (17.47)	74.06 (19.66)	76.63 (20.11)	82.43 (10.51)	81.5 (20.13)	78.5 (20.21)	71.25 (12.02)	83.13 (17.06)	85.89 (13.56)	79.53 (14.36)	77.11 (12.02)	75.97 (11.38)	84.94 (24.13)	84.11 (25.95)	78.59 (27.51)	76.18 (36.54)
Quality of Life	198.61 (39.53)	231.23 (50.89)	229.90 (53.51)	219.20 (41.64)	200.54 (51.31)	227.14 (77.44)	220.29 (48.61)	212.20 (49.26)	217.26 (48.55)	229.32 (51.14)	228.72 (42.35)	234.46 (35.88)	208.00 (50.87)	211.70 (51.17)	224.64 (61.29)	211.55 (72.91)
Cancer Related Thoughts	37.74 (14.65)	29.65 (15.18)	25.5 (15.51)	22.33 (12.51)	29.41 (15.03)	24.45 (14.40)	24.29 (17.93)	28.56 (13.94)	26.95 (11.75)	22.47 (12.39)	23.06 (13.29)	22.15 (10.96)	33.79 (15.19)	32.68 (18.48)	25.5 (15.64)	26.60 (16.41)

Note. Standard deviations are in parentheses.

Effects on primary outcome

Anxiety symptomatology: Anxious symptomatology was assessed by the anxiety subscale of the HADS. Figure 4.3 shows that participants in the Mindfulness, Mindfulness N-Back and N-Back groups showed marked and sustained reductions in anxiety symptomatology relative to the 1-Back control group. The MLM confirmed this observation with a significant Group X Time interaction, $F(9, 65.51) = 2.23$, $p = .03$, Cohen's $d = 0.4$. Whilst the Mindfulness N-Back intervention appeared to lead to the greatest reductions in anxiety at one-month follow up, at 6 months post-intervention anxiety scores reverted to baseline. On the contrary for the independent Mindfulness and N-Back groups, reductions in anxiety were sustained at 6 months follow up. No significant correlations were found between any demographic or medical variables and the slope of the primary measure of anxiety, (all r's < .23, all p's > .14), and thus demographic variables were not included as factors in the linear mixed effect model.
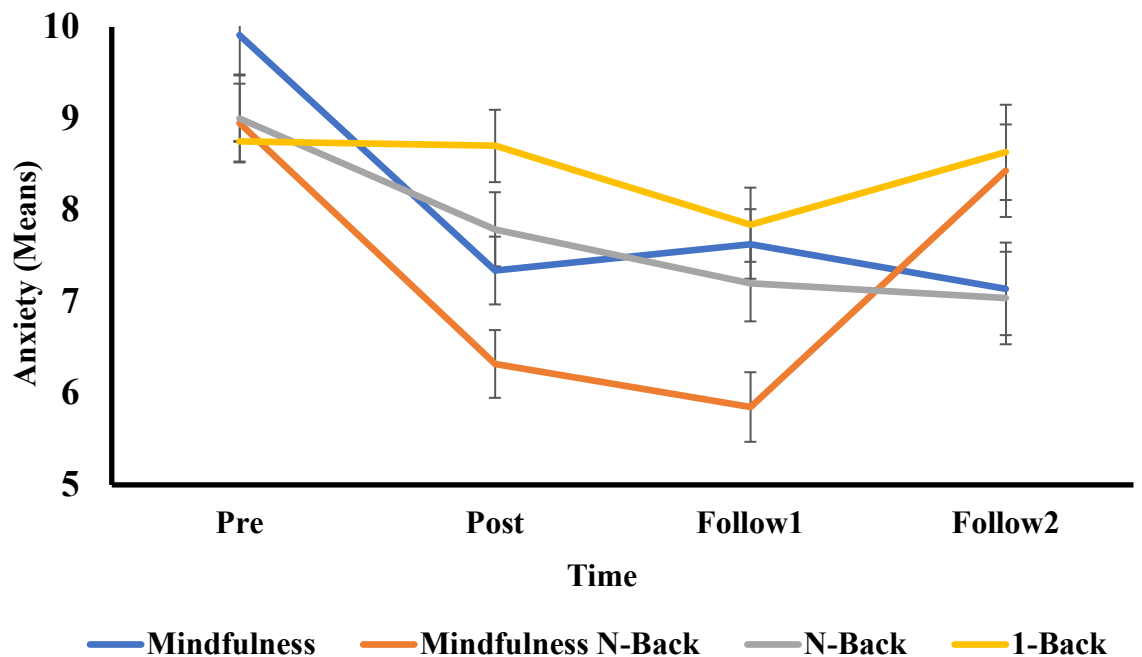
Figure 4.3. Mean anxiety symptomatology scores for each group (Mindfulness, Mindfulness N-Back, N-Back, 1-Back) at pre, post and follow up time points.

Effects on secondary outcomes

Rumination: The greatest reductions in rumination were observed for the N-back group (T1 (Time 1): M = 42.0 (12.08), T4 (Time 4): M = 34.39 (8.06), followed by the Mindfulness group (T1: M = 47.22 (12.14), T4: M = 40.25 (9.62), and changes in the 1-Back Group (T1: M = 44.15 (11.14), T4: M = 39.64 (11.64), and Mindfulness N-Back Group (T1: M = 39.1 (9.62), T4: M = 43 (12.53), however the MLM failed to reach significance, $F(9, 68.77) = 1.31$, $p = .24$, Cohen's $d = .28$. ***Perceived Cognitive Function:*** All groups improved their perceived cognitive functioning, reflected by a non-significant interaction, $F < 1$, NS. ***Quality of Life:*** The greatest improvements in quality of life were observed for the Mindfulness group (T1: M = 198.61 (39.53), T4: M = 219.20 (41.64), and the N-Back group (T1: M = 217.26 (48.53), T4: M = 234.46 (35.88), followed by the Mindfulness N-Back group (T1: M = 200.54 (51.31), T4: M = 212.20 (49.26), and 1-back group (T1: M = 208.46 (20.17), T4: M = 211.55 (72.91), however the MLM failed to reach significance, $F(9, 73.69) = 1.22$, $p = .3$, Cohen's $d = .26$. ***Cancer Related Thoughts:*** The greatest reductions in cancer related thoughts were observed for the Mindfulness group (T1: M = 37.74 (14.65), T4: M = 22.33 (12.51), followed by the 1-Back group, (T1: M = 33.79 (15.19), T4: M = 26.60 (16.4), N-Back group (T1: M = 26.95 (11.75), T4: M = 22.15 (10.96), and Mindfulness N-Back group (T1: M = 29.41 (15.03), T4: M = 28.56 (13.94). The MLM was non-significant significance, $F(9, 66.96) = 1.12$, $p = .26$, Cohen's $d = .26$. ***Fear of Cancer Recurrence:*** The greatest reductions in fear of cancer recurrence were observed for the N-back group (T1: M = 85.89 (13.56), T4: M = 75.97 (11.38), followed by the 1-Back group (T1: M = 84.94 (24.13), T4: M = 76.18 (36.54), the Mindfulness group (T1: M = 87.82 (17.47), T4: M = 82.43 (10.51), and the Mindfulness N-Back Group (T1: M = 81.5 (20.13), T4: M = 83.13 (17.06). The MLM was non-significant, $F(9, 59.43) = 1.66$, $p = .19$, Cohen's $d = .33$.

Further Analyses

Table 4.1 indicates group characteristics on demographic variables for the initial sample of 84. Differences were found for diagnosis status (primary or secondary) X^2 (3) = 9.48, p = .02, such that more women in the Mindfulness and Mindfulness N-Back group had secondary breast cancer compared to the N-Back and 1-Back groups. Group differences were also apparent for current psychological medication, X^2 (3) = 8.45, p = .03, such that fewer partcipants in the Mindfulness N-Back group were taking psychological medication compared to the Mindfulness, N-Back and 1-Back groups.

4.2.4 Discussion

The current study investigated how the independent and combined effects of adaptive Working Memory Training (WMT) and Mindfulness Meditation Training (MMT) can affect emotional and cognitive vulnerability in a group of female breast cancer survivors. The fundamental role of attentional control processes has been advocated in recent theoretical models of emotion regulation, based on the premise that top down mechanisms causally influence affective response (Berggren & Derakshan, 2013). Both WMT and MMT have been associated with improvements in attentional control processes (Sood & Jones, 2013; Blacker, Negoita, Ewen, & Courtney, 2017) and a recent study by Course-Choi et al., (2017) indicated that combined WMT and MMT resulted in greater reductions in worry relative to those who completed WMT or MMT independently for a preselected high worry population. Whilst WMT and MMT have shown to be associated with regulating emotional vulnerability in breast cancer independently (Experiment 1 of the current thesis, Swainston & Derakshan, 2018; Haller et al., 2017), their combined effects have not yet been explored in the breast cancer population.

As per experiments 1 (chapter 2) and 2 (chapter 3) of the current thesis, results indicated that working memory performance significantly improved pre to post

intervention for the groups who carried out WMT (Mindfulness N-Back and N-Back) substantiating the notion that through neuroplastic mechanisms, working memory functioning can be targeted in the breast cancer population, despite the prevalence of cancer related cognitive impairments consistently reported (Ahles & Root, 2018). In line with our predictions and the aforementioned research elsewhere, further findings showed that both the independent WMT and MMT groups and the combined Mindfulness N-Back group showed reductions in anxious symptomatology at post intervention relative to the 1-Back control group whereby reductions were negligible. Importantly, effects were sustained at 1-month follow up for all 3 groups. Whilst from pre intervention to 1-month follow up, the combined WMT and MMT groups showed the greatest reductions in anxiety, effects were not sustained at 6 months post intervention. On the contrary, for the independent WMT and MMT groups, effects continued to sustain after approximately 6 months. The comparable effects of both the independent and combined WMT and MMT groups give weight to the theory that both interventions may operate through similar mechanisms which necessitate attentional control processes (Bishop et al., 2006; Engen & Kanske, 2013; Xiu, Zhou, & Jiang, 2016). Moreover effects support the findings for experiment 1, chapter 2, of the current thesis (Swainston & Derakshan, 2018) which indicated that adaptive dual n-back training is associated with reduced anxious symptomatology in breast cancer survivors. Similarly, MMT showed similar effects to WMT, indicating marked and sustained reductions in anxiety. Given the lack of appropriate control conditions apparent across the MMT literature (Davidson & Kaszniak, 2015), this finding is pertinant. Whilst the majority of MMT research have used wait-list control groups, the current study utilised an active control condition in which low level recruitment of attentional control processes are required. Therefore the current study further validates MMT as an effective intervention for treating anxious symptomatology in the breast cancer population. In addition, research investigating the

effects of MMT via a smartphone app, rather than typical in-person mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) interventions, are relatively novel. As such the current study corroborates and extends preliminary findings indicating that app-based MMT can improve affect and stress in non-clinical samples (Economides et al., 2018) and quality of life in the breast cancer population (Rosen et al., 2018).

Whilst the Mindfulness N-Back group indicated greater transfer effects than independent groups at post-test and 1 month follow up, effects did not sustain to 6 months. It might be suggested that participants felt overwhelmed by the time commitment necessary to complete both tasks daily, and therefore were unlikely to engage in WMT or MMT post intervention. On the other hand a shorter intervention may have encouraged participants to engage in some form of WMT or MMT post-intervention. Further research should account for and measure these factors in order to further elucidate the sustained effects of WMT and MMT.

Limitations

The current study had a number of limitations. First, whilst the MMT groups continued to have easy access to the commercial Headspace application if desired, this was not the case for the N-Back task. The current study did not take this into account and therefore did not measure continued engagement of MMT and its potential influences from 1-month to 6 months post intervention. Second, given the commercial and well-known nature of the Headspace application, this may have created some bias in that participants may have held optimistic expectations about mindfulness outcomes prior to the intervention. Thirdly, participants were recruited via social media platforms and therefore may not be representative of the wider popultaion of breast cancer survivors. Lastly, cognitive transfer effects to a second measure of attentional control was not

measured. Future studies should consider the inclusion of another task in order to fully elucidate the mechanisms at play in WMT and MMT.

Clinical Implications

MMT is a prominent intervention frequently used to improve health related outcomes in both clinical and non-clinical populations. WMT is a relatively novel intervention in which a growing body of research points to the potential benefits it may transfer to emotional vulnerability. The current study indicated that an independent course of either MMT and WMT or a combined course of MMT and WMT can result in reductions in anxious symptomatology compared to an active control group. Whilst effects were sustained for all groups at 1-month post intervention, at 6-months follow up effects were only apparent for the independent MMT and WMT groups. Both interventions hold promising clinical implications in that they can be delivered online and thus are easily accessible at any time and are therefore available to a wider population.

Chapter 5: General Discussion

5.1 General Overview of Section A

Breast cancer is the most common cancer amongst women, with a new case being diagnosed every 10 minutes in the UK (Breast Cancer Care, 2018). Cancer is a debilitating disease that often involves a number of negative physical, psychological, cognitive and emotional side effects both during and post treatment (Hagen et al., 2016; Härtl et al., 2010). Unsurprisingly, this can leave breast cancer survivors vulnerable to affective disorders such as anxiety, depression and post-traumatic stress disorder (PTSD), which may often develop through a patients' psychological reaction to diagnosis, treatment, survivorship, relapse or end of life care. Indeed recent estimates indicate that depression affects up to 20% and anxiety 10% of patients with cancer, compared to figures of 5% and 7% prevalence in the general population (Pitman, Suleman, Hyde, & Hodgkiss, 2018). In addition, cancer diagnosis has further been associated with increased risk of suicide (Carreira et al., 2018; Henson et al., 2019). Despite this, psychiatric illness, which can affect adherence to treatment, cancer survival, treatment costs and quality of life, is an often neglected complication of cancer (Stark & House, 2000; Smith, 2015). Accordingly, the development of evidence-based emotion regulation interventions is a critical need.

Section A of the current thesis set out to explore how emotional vulnerability in breast cancer can be targeted through a series of cognitive intervention studies. Recent research indicates that cognition-emotion interactions are critical in maintaining affective wellbeing. Accumulating evidence indicates that alterations of the fronto-limbic system assists the modulation of attention towards emotional stimuli in individuals with anxiety and depression (Dolcos et al., 2019). Indeed multiple studies demonstrate implicit attentional biases towards affectively negative information which may contribute to the onset of emotional disorder. Similarly inefficient top-down attentional control

mechanisms have been associated with the dominance of stimulus driven bottom up processes, and excessive negative affect. Findings are further emphasized by neural studies including populations with emotional disorder which indicate that diminished activation of the prefrontal cortical regions implicated in attentional control is associated with increased activation of the subcortical regions involved in emotion processing.

In light of the established cognition-emotion relationship, it follows that recent research has capitalised on such findings to further develop efficacious treatments for affective disorder. Developments in the field of cognitive and affective neuroscience demonstrate that by targeting attentional control processes through computerised training techniques, we can optimise emotion-attention interactions. Indeed emerging evidence indicates that cognitive training can result in reductions in negative affect for both anxious and depressive populations, (see Motter et al., 2016 and Koster et al., 2017, for reviews).

Building upon this research, the primary aim of Section A of the current thesis was to extend findings to the breast cancer population. The first empirical study in chapter 2 explored whether a course of working memory training would result in improved emotional vulnerability in a group of female survivors of breast cancer. Following on, experiments 2 (chapter 3) and 3 (chapter 4) investigated the combined effects of working memory training with other interventions thought to engage attentional control processes, namely expressive writing and mindfulness meditation.

5.2 Summary and Discussion of the Main Findings

5.2.1 Cognitive Training to Reduce Emotional Vulnerability in Breast Cancer

The aim of experiment 1 (chapter 2) was to investigate whether a course of dual n-back working memory training (WMT) could improve cognitive flexibility and reduce emotional vulnerability in breast cancer survivorship, compared to an active control group. Findings firstly demonstrated that for the training group, working memory performance improved from pre to post intervention indicating that the neuroplastic mechanisms of cognitive training are effective in the breast cancer population. This was a critical finding, given the accumulating evidence demonstrating cognitive dysfunction in cancer survivors (Ahles & Root, 2018). Secondly results showed that training related gains transferred to reductions in anxiety and rumination symptomatology, which were sustained for up to 18 months post-intervention.

Attenuation of anxiety through cognitive training builds upon other recent research in anxious populations (Sari et al., 2016). Our findings indicate that reductions were particularly evident for physiological arousal symptoms of anxiety. This finding is particularly pertinent for the breast cancer population given the multitude of short- and long-term physiological side effects associated with breast cancer (e.g., lymphedema, peripheral neuropathy, menopausal symptoms as well as fatigue and insomnia (Agrawal, 2014; Abrahams et al., 2016). Reductions in rumination, a critical risk factor for depression were also found, extending previous findings in clinical populations (Koster et al., 2017). Rumination has been associated with motivational deficits and the deferring of medical assessment for cancer symptoms (Lyubomirsky et al., 2006). Accordingly this finding is fundamental to the breast cancer population who must attend follow up medical appointments and remain attentive to bodily changes for signs of recurrence.

Findings extend upon previous cognitive training research in breast cancer which have shown transfer to both cognitive and emotional measures (Von Ah et al., 2012; Kesler et al., 2013; Damholdt et al., 2016). However a fundamental difference between previous cognitive training research in breast cancer and the current study is the use of an active, rather than waitlist, control group. The lack of an active control group has been highlighted as a criticism in the overarching, ongoing debate surrounding the efficacy of working memory training (Shipstead, Redick, & Engle, 2012; Pergher et al., 2019). Here, through the use of an active control group which engages the same mechanisms as the training group, but at a lower inflexible level, we can infer that the mechanism by which emotional vulnerability is reduced is through the improvement of attentional control processes.

5.2.2 Combined Effects of Expressive Writing and Cognitive Training on Emotional Vulnerability in Breast Cancer

The aim of experiment 2 (chapter 3) was to build upon the findings from experiment 1 which established the validity of attentional control training as an effective intervention for attenuating negative affect. Here, we explored the combined effects of expressive writing and working memory training on emotional vulnerability. It has been hypothesized that the mechanism by which expressive writing operates is through the freeing up of working memory capacity, through the consolidation of past events into a cohesive explanatory narrative, developed over the course of writing sessions. Research indicates that the specific types of words used, such as those that reflect cognitive reappraisal (i.e. cause or insight words), is an important factor in generating positive health outcomes through writing. These theories were further explored in experiment 2, in which participants took part in a course of Expressive Writing, Non-Expressive

Writing, combined Expressive Writing and N-Back or combined Non-Expressive Writing and N-Back.

Firstly, findings from experiment 2 replicate results from experiment 1 which demonstrate that the breast cancer population is receptive to working memory training, with participants showing significant improvement on an adaptive dual n-back task from pre to post intervention. To reiterate, given the punishing impact that anti-cancer treatments can have, and considering the body of evidence that indicates neurocognitive decline in cancer, this finding is substantial. The main analysis, however, showed no significant group differences for transfer effects on psychological and emotional outcomes across time. This finding is consistent with other research employing an expressive writing paradigm in cancer populations which have typically found transfer to physiological rather than psychological health outcomes (Frisina et al., 2004). Notwithstanding this finding, further investigation of the linguistic characteristics of writing excerpts indicated that the types of words used during expressive writing were related to changes in cognitive and emotional vulnerability outcomes. Specifically, findings showed that increased use of negative emotion, anxiety and cognitive mechanisms words (i.e. cause and insight words thought to reflect reappraisal) was associated with improvements in perceived cognitive function, emotional vulnerability and quality of life. Results substantiate previous studies that have found associations between increased use of anxiety and cognitive mechanism words and better maths performance (Park et al.,2014) and reductions in anxiety symptamotology (Zheng et al., 2019).

5.2.3 Combined Effects of Mindfulness and Cognitive Training on Emotional Vulnerability in Breast Cancer

The main objective of experiment 3 (chapter 4) was to explore the combined effects of mindfulness mediation training (MMT) and working memory training. Mindfulness is cultivated through the focusing of one's attention on the present moment, whilst observing and accepting one's thoughts and emotions without judgement (Kabat-Zinn, 2006). Mindfulness, by definition, requires sustained attention, and as such the engagement of attentional control processes to inhibit environmental distractions. It follows that theorists have proposed that the mechanism by which MMT operates is through a process of emotional regulation that is achieved by improving the control of attention allocation. In light of the similar mechanisms implicated in MMT and WMT, experiment 3 considered both the independent and combined effects of both intervention techniques.

In line with experiments 1 (chapter 2) and 2 (chapter 3) of the current thesis, results demonstrated that for the groups that completed working memory training, performance significantly improved pre to post intervention indicating neuroplastic effects. Findings further showed that gains from MMT and WMT can translate to reductions in anxious symptomatology, both as an independent and combined intervention, supporting previous studies (Swainston & Derakshan, 2018; Rosen et al., 2018; Course-Choi et al., 2017). Results further give weight to preliminary studies demonstrating the effectiveness of app-based, rather than in-person, MMT inteventions (Economides et al., 2018).

5.3 Limitations

The investigations in Section A are subject to limitations which may constrain the interpretation of results. Firstly, participants were recruited via social media platforms

and therefore may not be representative of the wider population of breast cancer survivors. Depending on self-selection, our results may not be generalizable, as the participant population may typically only include those who are interested in gaining psychological help, and not those who are less likely to actively seek out support or take part in research.

The studies did not investigate cognitive transfer effects to a second measure of attentional control. The inferences that we can make regarding broader improvements in attentional control abilities from training is therefore confined. However, this was not the main goal of the current research. As a first step, we wanted to investigate the potential effectiveness of working memory training as an intervention for emotional vulnerability in the breast cancer population. Due to the online nature of our studies, administration of a second cognitive task within a controlled environment was restricted. Future studies however should consider using a second lab-based cognitive task, to further validate the theory that training reduces negative affect through improving attentional control mechanisms. In addition, in order to avoid measure specific effects, we decided to use different self-report measures of anxiety across the intervention studies. Whilst we believe that the significant findings across different anxiety measures indicates the strength of the cognitive training intervention, it may be suggested that different aspects of anxiety have been assessed, and thus findings are not fully comparable across studies.

Furthermore, whilst engagement in tasks employing working memory processes (WMT and MMT) was associated with reductions in anxious and ruminative symptomatology, this was not apparent for all measures of emotional vulnerability. Indeed, no groups differences were apparent for change in measures of depression, worry, resilience, fear of cancer recurrence, perceived cognitive functioning and quality of life. It is therefore a challenge of future research to better understand which variables may predict beneficial outcomes from cognitive training on different measures. It has been

suggested, for instance, that inconsistencies across cognitive training findings may at least partly be due to differences in an individuals' ability to benefit from the intervention in general, and from specific types of training in particular (Shani et al., 2019). One approach to addressing this limitation is the movement towards personalised medicine and the adoption of machine learning approaches to optimise cognitive training outcomes. Specifically, training may be more beneficial if the type of training intervention is firstly selected according to baseline characteristics of cognitive and emotional strengths and vulnerabilities as well as variables such as age and personality traits. Secondly, an individual's performance trajectory can be used to continuously tailor the training parameters (training type, number of sessions, overall training hours, time intervals between sessions) in order to achieve optimal performance. Indeed, the idea of intervention selection and intervention adaptation is being adopted elsewhere in personalised medicine, for example in the investigation of the utility of antidepressant medication, where typically medication is ineffective for approximately half of the patients (Cipriani et al., 2018). It follows that investigation into the efficacy of psychological interventions adopts a similar approach; the use of machine learning may help in the development of personalised cognitive training interventions which optimize outcomes.

There are further limitations associated with the software program Linguistic Inquiry and Word Count (LIWC; Francis & Pennebaker, 1993), used to examine the linguistic characteristics of writing excerpts in expriment 2 (chapter 3). Specifically, LIWC ignores context and is unable able to detect linguistic nuances such as sarcasm, irony or idioms (Tausczik & Pennebaker, 2010). For instance, if an individual was to write 'she's as mad as a hatter' or 'I'm mad about him', the meaning of these phrases will be coded incorrectly. It is thus important to remember that the development of LIWC, in terms of the broader investigation of word use as a reflection of psychological state, is in

its infancy. Accordingly, further refinement is required and findings must be interpreted with caution due to the inprecise measurement of word meaning and psychological states.

Limitations extend to experiment 3 (chapter 4). Here the commercially available app Headspace was used and therefore findings cannot extent to other mindfulness based applications that are currenty available. In addition, variation in the device operating system and software may have influenced app utilisation.

Across studies it is important to note that findings must be interpreted with caution, in particular for our secondary outcome measures, due to the testing of multiple hypotheses. In all studies, based on Attentional Control Theory (Eysenck et al., 2007), the primary outcome measure of anxiety was outlined a priori in order to reduce the risk of false-positive errors resulting from the statistical testing of many outcomes. However, statistical testing of secondary outcomes is associated with an increased risk of both false-positive and false-negative errors (Andrade, 2015). Similarly a power analysis should be conducted prior to the commencement of the studies in order to determine an adequate sample size. That said, post-hoc power analyses for the current studies indicated that the sample was sufficient for all three investigations.

Finally, future studies would benefit from pre-registration to an appropriate journal outlining the proposed research rationale, hypotheses, design and analytic strategy for peer review prior to commencement. It is becoming increasingly recognised that pre-registration may help minimise problematic research practises such as hypothesizing after the results are known ("HARKing;" Kerr, 1998) and "p-hacking" (i.e. manipulating data analyses in order to obtain significant effects; Simmons et al., 2011). Similarly, pre-registration aims to reduce the publication bias for results that are novel and statistically significant with an overall aim to improve the scientific contributions of research.

5.4 General Implications of Findings and Future Directions

There are a number of implications from the findings of Section A of the current thesis. First, findings corroborate the main assumptions of attentional control theory (ACT) which emphasize the fundamental relationship between cognition and emotion. ACT marks the importance of attentional control (i.e., cognitive flexibility) in the onset, maintenance and recurrence of emotional disorder, indicating a possible causal link (Tausczik & Pennebaker, 2010). Our findings show that through targeting the prefrontal top-down mechanisms involved in attention allocation, there is potential to attenuate negative affect, substantiating a growing body of evidence advocating the emotion-related benefits observed from cognitive training (Dolcos et al., 2019). As such, findings hold implications for the field of cognitive and affective neuroscience which has most frequently employed cognitive training paradigms. Specifically, results further validate cognitive training as a technique that is able to target working memory function which translates to improved attentional control and reductions in emotional vulnerability (Keshavan et al., 2014; Koster et al., 2017).

Moreover, findings from the current thesis have significant implications for further developing emotion-targeted interventions for the breast cancer population which may reduce the risk of clinical affective disorder in spite of the numerous adversities that survivors face. As per the Orbit model for developing behavioural treatments for chronic disease, (Czajkowski et al., 2015), presented in the introduction of section A, the current studies have furthered the development of psychological interventions for the breast cancer population by applying basic science to behavioural research. It is suggested that the current studies fall under the 'phase II preliminary testing' stage of the Orbit Model continuum. Given that findings demonstrated that online working memory training and app-based mindfulness meditation training showed promise for improving anxious and

depressive symptomatology in breast cancer (experiment 1, chapter 2; experiment 2, chapter 3), it is suggested that the interventions are now ready for randomised phase III efficacy testing with larger sample sizes. Conversely, for the expressive writing and WMT intervention (experiment 2, chapter 3) the main analysis did not show significant group differences for cognitive and emotional health outcomes. That said, exploratory analyses indicated that the linguistic characteristics of writing excerpts was related to changes in cognitive and emotional vulnerability. Specifically, the use of negative emotion, anxiety and cognitive mechanisms words (i.e. cause and insight words thought to reflect reappraisal) was associated with improvements in perceived cognitive function, emotional vulnerability and quality of life. This suggests that there is potential for expressive writing to develop into a successful intervention if it is refined and adjusted based on these findings. For instance, perhaps writing tasks can be designed in such a way as to encourage cognitive reappraisal and expression of negative emotions and anxieties. Accordingly, for the expressive writing paradigm, it is advisable to revert back to the 'phase I' design stage of the Orbit Model for further optimisation of the intervention.

The accessibility and affordability of the intervention techniques used in the current thesis should be acknowledged. The current availability of specialist psychological therapy for cancer patients with comorbid anxiety or depression varies geographically. For instance major cancer centres in the UK, US, Australia, France and Germany may offer integrated psychological support services, however they are often unavailable outside of large cities (Pitman et al., 2018). Therefore findings have significant implications for offering psychological support for breast cancer, irrespective of personal, financial, social or geographical circumstances. Moreover, the interventions can be administered immediately after diagnosis. Research indicates that the elevated risk of suicide in cancer patients is greatest within the first 6 months of diagnosis, pointing to

an unmet need for psychological support during this period (Henson et al., 2019). Treatments that can be offered quickly, and that can be accessed at any time, may aid in the prevention of unmanageable psychological distress which may lead to more serious psychological outcomes.

Future research investigating potential treatments for cognitive and emotional vulnerability in breast cancer may wish to consider other promising interventions. For instance, Attention Bias Modification (ABM) training paradigms have been developed in the field of cognitive and affective neuroscience with the aim to reduce the maladaptive negative information processing biases often observed in anxiety and depression (see Hirsch, Meeten, Krahé, & Reeder, 2016, for a review). The idea here is that through repetitive computer-based techniques, anxiety-related attentional biases towards threatening information can be altered through training individuals to repeatedly shift their attention towards more neutral or positive information. A number of studies indicate that when the intended ABM training manipulation has been successful, reductions in anxiety-related pathology were observed (see MacLeod & Clarke, 2015, for a review). Research into the role of attentional bias as well as interpretation bias (interpreting ambiguity as threatening) in adjustment to cancer diagnosis is in its infancy. Initial studies indicate, however, that highly anxious breast cancer patients are more likely to overinterpret ambiguous information negatively, leading to worsened illness representation and a heightened risk for developing clinical psychopathologies (Lam et al., 2018). This indicates that modifying biases may be a beneficial intervention technique in reducing fear of cancer recurrence, for example. Whilst breast cancer survivors must remain vigilant for signs of recurrence, maladaptive levels of fear can be debilitating. Indeed, fear of cancer recurrence is one of the most distressing psychological factors involved in breast cancer with prevalence reports ranging from 25% to 97% (Koch et al., 2014). Research indicates that cancer recurrence fears are associated with impaired

quality of life and wellbeing, poor mental health, and physiological disruptions such as sleep disturbance and fatigue (Koch et al., 2014; Cohee et al., 2017; Sun et al., 2019). As such, it is critical that effective interventions are developed to help manage disabling fears.

In some cases, breast cancer survivors may not have access to a computer, be computer literate, or be able to attend regular psychological treatments sessions. For this subset of survivors, other promising interventions must be considered. An emerging area of research in cancer survivorship relates to activation of the vagus nerve. The vagus nerve is the primary nerve of the parasympathetic system and plays an important role in several diseases including cancer and its progression. Specifically, research indicates that vagus nerve stimulation (VNS) can reduce oxidative stress, inform the brain about inflammation, inhibit inflammation, and inhibit sympathetic nerve activity (see De Couck, Caers, Spiegel, & Gidron, 2018, for a review). Each one of these factors is important in cancer progression and as such accumulating evidence points to the association between high vagus nerve activity and the slowing of tumorigenesis and longer survival (Giese-Davis et al., 2015; Reijmen, Vannucci, De Couck, De Grève, & Gidron, 2018). Simultaneously, accumulating evidence points to the therapeutic value of VNS in the treatment of depression and more recently, anxiety and post-traumatic stress (Rong et al., 2016; Müller et al., 2018). This is potentially due to the etiopathogenisis of depression which may involve chronic inflammation of the brain and peripheral tissues (Ondicova, Pecenák, & Mravec, 2010). Moving on from past methods involving surgery, VNS can now be achieved through transcutaneous auricular VNS (tVNS) which is non-invasive and can be achieved placing two earclips/electrodes to the ear area (auricular concha) where there is a rich vagus nerve branch distribution. This is then stimulated via transcutaneous electrical nerve stimulation. Taken together initial findings suggest that tVNS may serve as a beneficial treatment for emotion disorders in cancer in addition to

the critical role it may play in cancer progression. More research is required to further explore its efficacy.

Finally, considering other future directions in the wider context of cancer survivorship, the findings of the current thesis may further be extended to other cancer populations and family caregivers. Research indicates that family caregivers of cancer patients can also experience excessive levels of anxiety and depression, and as such, deserve recognition and help (Li, Lin, Xu, & Zhou, 2018).

SECTION B: Exploring Cancer-Related Cognitive Impairments in Breast Cancer

Chapter 6: General Introduction

6.1 Chapter Overview

Section A of the current thesis outlined three novel intervention studies predominantly focusing on the impactful effects of cognitive functioning on emotional vulnerability in breast cancer. Findings from Chapter 2 firstly indicate that targeted neurocognitive interventions can improve cognitive control and processing efficiency in breast cancer survivors, establishing that this population is receptive to treatments that provoke brain neuroplasticity. Secondly, findings demonstrate that as a result of engaging top down cognitive processes such as attentional control, such interventions can result in reduced levels of emotional vulnerability, specifically anxiety and rumination. Chapter 3 showed that whilst combined expressive writing and working memory training did not result in transfer to measures of emotional vulnerability, increased use of affective and cognitive mechanism words thought to reflect reappraisal resulted in associated reductions in depressive symptomatology and cancer related thoughts aswell as improvements in perceievd cognitive functioning and quality of life for the independent expressive writing group. Chapter 4 however indicated that both an independent course of working memory training and mindfulness meditation training, aswell as a combined course of both, can result in transfer to reductions in anxious symptamotolgy. Findings further substantiate working memory training and mindfulness meditation training as efficacious interventions for the breast cancer population in targeting emotional vulnerability.

In light of the established relationship between cognitive function and emotion regulation, it is imperative to further our understanding of the neurocognitive mechanisms affected by breast cancer as a means to develop more targeted interventions moving forward. To that end, it is important to consider the wider context of cognition in relation

to cancer. The acknowledgement of cancer-related cognitive impairments (CRCIs) is now well established across the literature surrounding cancer survivorship with increasing evidence emerging that indicates the detrimental effects such deficits can have on quality of life. That said, there remains ambiguity across the literature in identifying the exact etiology and underlying mechanisms at work in CRCIs. In addition, whilst a substantial amount of research has now been conducted investigating CRCIs in patients treated with chemotherapy, less is known about CRCIs in the subgroups of patients who did not undergo chemotherapy. That said, preliminary findings indicate that the estrogen depleting hormone therapy tamoxifen may be a contributing factor in CRCIs. Accordingly the current chapter gives an overarching outline of the current evidence for CRCIs across the breast cancer literature considering behavioural, neuroscientific and qualitative research. This is followed with an overview of studies, though sparse, that specifically consider the impact of tamoxifen. Finally, the research aims of the final two studies of the current thesis will be laid out.

6.2 Cancer Related Cognitive Impairment (CRCI)

Whilst research indicates that the majority of breast cancer patients are affected by cognitive deficits during active treatment, longitudinal studies now indicate that a subset of survivors (approximately 20-30%) report problems with cognition for up to 20 years post treatment (Koppelmans et al., 2012). In some instances, whilst cognitive dysfunction was absent shortly after active treatment, a subset of survivors reported decline at follow-up assessments indicating that there may be a subgroup of breast cancer survivors who have a delayed onset of cognitive decline (Wefel et al., 2010). Originally coined 'chemobrain' the presence of such impairments was initially thought to derive solely from the neurotoxic effects of chemotherapy, however increasingly this notion is disputed. Whilst it is clear that chemotherapy may play a large role in impacting cognitive

function, it is becoming clear that it is not the sole contributing factor (see Ahles & Root, 2018, for a review). This complication partly arises from the multiple modalities in which breast cancer is treated, making it difficult to isolate the most critical components that affect cognition. For instance, studies now show that hormonal therapies such as tamoxifen and aromatase inhibitors which decrease estrogen levels in the body may be a contributive factor (Castellon et al., 2004; Schilder et al., 2010). Conjointly, whilst radiotherapy is considered localized, it induces chronic fatigue, a systematic immune response, and possible cognitive deficits (Shibayama et al., 2014). Moreover, cancer treatment can interact with multiple other factors including those which are predisposed (genetic, sociodemographic, cancer type) and those that can be modified (physiological, psychological, allostatic load and lifestyle). Indeed a number of biological theories surrounding potential mechanisms for cognitive decline in cancer are also emerging including inflammation (Ganz et al., 2013) and the predictive value of allostatic load (McEwen, 2015). Additionally, psychological theories such as that of cognitive reserve, which indicates an innate and developed cognitive capacity influenced by genetics, education, lifestyle, genetics, occupation and cognitively stimulating activities etc., are beginning to be considered. This follows from research into neurocognitive decline in other populations in which low cognitive reserve has been associated with the risk and severity of neurocognitive disorders such as Alzheimer's, cognitive decline in aging and cognitive decline following brain injury (Barulli & Stern, 2013). So far in breast cancer research, Ahles et al., (2010) found that lower cognitive reserve, older age, chemotherapy treatment and the use of endocrine therapy was related to increased post-treatment cognitive decline. Correspondingly, Mandelblatt et al., (2014) found that lower education, a key component of cognitive reserve, and older age were associated with increased cognitive impairment prior to the onset of adjuvant treatment.

Critically for survivors, it is important to understand to what extent cancer treatments can impact brain structure and function, which cognitive processes are most likely to be affected, and how such changes are manageable. Whilst cognitive changes may appear to be subtle on standard neuropsychological tests, for many survivors functional impairments are common, with many reporting difficulty returning to and maintaining performance at work, as well as finding that cognitive deficits negatively impact social relationships and feelings of self-confidence (Von Ah, Habermann, Carpenter, & Schneider, 2013; Selamat, Loh, Mackenzie, & Vardy, 2014). Moreover, standardized neuropsychological measures that are often utilized were originally designed to assess impairment in patients with overt neurological injuries or disease, and thus may lack the nuance associated with cognitive decline in cancer patients (Ahles and Root, 2018). Nevertheless, behavioural performance-based research has furthered our understanding of CRCI in breast cancer. Typically, the specific domains that have been found to be most affected include executive functioning, attention, working memory, processing speed, learning and memory (see Pendergrass, Targum, & Harrison, 2018, for a review). Indeed, in a recent longitudinal study by Janelsins et al., (2017), breast cancers survivors showed worse performance on computerized measures of working memory, recognition memory and processing speed compared to healthy controls up to 6 months post chemotherapy.

The body of neuroimaging studies investigating the neurocognitive mechanisms at play in CRCI is growing, with structural and functional MRI indicating alterations predominantly in the prefrontal cortex. Studies indicate multiple changes including density of grey matter, integrity of white matter, volume of multiple brain regions and decreased activation during cognitive tasks (see Andryszak, Wiłkość, Izdebski, & Żurawski, 2017, for a review). In addition, multiple studies now demonstrate neural compensatory mechanisms at play, with increased recruitment of additional regions

necessary to reach levels of premorbid cognitive effectiveness. For instance, using task-based fMRI, McDonald and colleagues found prefrontal hyperactivation and more distributed activation patterns involved in working memory performance during an n-back task in cancer survivors relative to controls (McDonald et al., 2012). In a more recent study, increased prefrontal activation during a working memory task, coupled with decreased white matter integrity, was found in breast cancer patients relative to controls even prior to the start of adjuvant treatment (Menning et al., 2015). Importantly these neural differences were found in the absence of performance differences between groups, suggesting that more effortful processing is required for breast cancer patients to function effectively – i.e., cancer survivors perform tasks inefficiently, consuming greater processing resources to achieve the same level of performance (cf. Berggren & Derakshan, 2013; Ansari & Derakshan, 2011).

Resting state fMRI designs have also been employed to assess neural activity without the complications of task-related studies that are dependent on task design, difficulty and participant cooperation (Shen et al., 2019). Wang et al., (2016), showed that a reduction in functional connectivity in the dorsolateral prefrontal cortex and inferior frontal gyrus is associated with deficits in executive functioning 1 year post chemotherapy. Further, even 3 years post chemotherapy, Miao et al., (2016) found that executive functioning deficits were related to reduced functional connectivity in the anterior cingulate cortex. Shen and colleagues recently used the mean fractional amplitude of low-frequency fluctuations (mFALFF), which is recognized to be a meaningful measure of spontaneous neural activity at resting state, finding altered brain functional connectivity in the dorsal attention network (DAN) (Shen et al., 2019). Specifically, there was decreased mFALFF in the occipital lobe and increased mFALFF in the frontoparietal lobe. The authors concluded that this was reflective of a compensatory mechanism, mirroring other studies that have indicated that when

functional alterations occur, the brain is able to recruit alternative brain regions to reach premorbid task performance. Finally, Shen et al. (2019) found a positive correlation between psychological distress related to cancer and mFALFF in the frontoparietal lobe, suggesting that the alterations of the DAN may be associated with psychological vulnerability.

Few studies to date have used electroencephalography (EEG) to assess neural alterations in breast cancer survivors. Studies have focused on the amplitude and latency of the P3, an event-related brain potential (ERP) marker of the evaluation/categorization of stimuli held in working memory. One study showed a reduced P3 amplitude during an oddball task in breast cancer patients treated with chemotherapy relative to those not treated with chemotherapy (Kreukels et al., 2008). Similarly, Kam et al., (2016) found reduced P3 amplitude to task relevant stimuli in breast cancer survivors relative to healthy controls in a sustained attention task. P3 latencies to non-targets were longer for breast cancer survivors who also displayed higher alpha power at rest compared to healthy controls. Overall, findings indicate disruptions in neural mechanisms of sustained attention for breast cancer survivors.

6.3 Qualitative Research

The current qualitative research surrounding CRCI predominantly focuses on the lived experience of 'chemobrain' and as such consistently only includes participants who have had chemotherapy as part of their treatment plan. This indicates that qualitative research is yet embrace the evolution of viewing CRCI from a pharmacotoxicology perspective, to a multidimensional model that considers multiple factors. Nevertheless, the qualitative research thus far offers important insights into how women experience CRCIs in the real world.

The overwhelming consensus across qualitative studies investigating 'chemobrain' is that it is a real and persistent phenomenon that results in damaging effects to quality of life for breast cancer survivors. The most comprehensive overview of qualitative research into 'chemobrain' was carried out in an extensive meta-ethnography study by Selamat et al., (2014), in which all studies included in the review outlined chemotherapy in their inclusion criteria. Here, third order synthesis of the main concepts across studies resulted in four key constructs relating to the chemobrain phenomenon namely, 1) *The chemobrain struggle*, 2) *The substantial impact of chemobrain across life domains,* 3) *Struggling to self-manage (without support from health professionals),* 4) *Thankful for life, yet fearful of the future.*

Within '*The chemobrain struggle'* construct the main concepts revolved around the types of cognitive changes, the domains most affected and the awareness and trajectory of cognitive change. For instance one study included in the meta-ethnography pointed to 6 major domains of cognitive impairment: short-term memory, long-term memory, speed of processing, attention and concentration, language and executive functioning (Von Ah, Habermann, et al., 2013). In addition, across studies there appeared to be a clear lack of recognition of the phenomenon from the medical community with a lack of information available to validate their experience. Accordingly, this has led to internal frustration for women experiencing chemobrain. The construct of '*The substantial impact of chemobrain across life domains'* is reflective of the significant impact that chemobrain has on the self, family members, social life, finances and work performance. Women consistently reported decreased self-confidence, changes in their relationships and reductions in work related abilities such as memory and concentration. The *'Struggling to self-manage (without support from health professionals)'* construct reflects the various ways that survivors have adopted in order to cope with CRCI despite the lack of awareness and help available from the medical community. Strategies included

taking nutritional products, complementary and alternative medicines, physical and mental activities as well as the use of practical reminders through writing or technology. The final construct '*Thankful for life, yet fearful of the future'* encompasses the overarching acknowledgment that whilst chemobrain has brought about numerous challenges and frustrations to daily life, this did not cause women to withdraw from chemotherapy treatment, with survivors consistently voicing their appreciation for the treatment and desire for survival. Nevertheless, in some cases this led women to 'downplay' their cognitive problems for fear of appearing ungrateful for their survival. Fear of cancer recurrence and concerns that chemobrain will persist were additionally expressed.

6.4 What is Tamoxifen?

For women with estrogen receptor positive (ER+) breast cancer (approximately 70% of all cases), the use of adjuvant endocrine therapy has indicated a reduced risk of cancer recurrence, including a new cancer developing in the other breast, and mortality (Von Ah et al., 2013). As such, it forms a critical part of survivors' treatment plan. Tamoxifen is the most prescribed selective estrogen-receptor modulator (SERM) and works by competing with estrogen to bind to estrogen receptors in breast cancer cells. By impeding estrogen in the breast necessary for tumour growth, tamoxifen slows the growth and reproduction of breast cancer cells. The effects of Tamoxifen throughout the entire body, however, are complex. Tamoxifen by nature is selective, such that it acts as an estrogen agonist or antagonist based on the target tissue (An, 2016). Whilst tamoxifen has antiestrogenic effects in the breasts, it has estrogenic effects in the uterus and liver. The agonist or antagonist effects of Tamoxifen on the brain and central nervous system, however, remain unclear (Benson, 2002). This is possibly due to the fact that Tamoxifen has different mechanisms of action in different areas of the brain (Janicki & Schupf, 2010)

potentially having both agonistic and antagonistic effects on estrogen activity in the brain depending on the pathway of estrogen action (Eberling, Wu, Tong-Turnbeaugh, & Jagust, 2004).

6.5 Tamoxifen, Cognitive Function, and Breast Cancer

The importance of estrogen in cognitive functioning has been increasingly acknowledged over past decades (Luine, 2014). Research in this area has in part been driven by findings indicating that low levels of estrogen may lead to cognitive decline, and is implicated in the etiology of dementia in women (Paganini-Hill & Henderson, 1994). Indeed there is some evidence to suggest that taking hormone replacement therapy may improve cognitive function for women with menopausal symptoms (LeBlanc, Janowsky, Chan, & Nelson, 2001). Similarly, higher levels of estrogen has been associated with better working memory performance in women of reproductive age (Hampson & Morley, 2013). It follows then that Tamoxifen, which reduces levels of estrogen in the breasts, may affect the brain in a similar way, leading to deficient cognitive functioning.

In terms of the effects of Tamoxifen on CRCI, research is limited. This in part is due to the dominant focus on the neurotoxic effects of chemotherapy. In light of the emerging evidence that suggests that chemotherapy is not the sole cause of CRCIs, interest into other potential risk factors, such as the use of tamoxifen, is growing. That said, the majority of studies investigating the effects of tamoxifen included participants who had also had chemotherapy as part of their treatment plan, thus making inferences about the extent of impairment as a result of tamoxifen difficult. A handful of studies have, however, considered the cognitive effects of tamoxifen in women who did not undergo chemotherapy. Eberling, Wu, Tong-Turnbeaugh, & Jagust (2004), investigated the effects of women taking estrogen for menopausal symptoms, women taking tamoxifen for breast cancer treatment, and women taking neither, on positron emission

tomography (PET) measures of brain glucose metabolism and magnetic resonance imaging (MRI) of hippocampal atrophy in postmenopausal women. Findings indicated that the tamoxifen group showed widespread areas of hypometabolism in the inferior and dorsal lateral frontal lobes as well as significantly lower semantic memory scores relative to the other two groups. In addition the tamoxifen group showed significantly smaller left and right hippocampal volumes compared to the group taking estrogen. Results therefore point to the physiological and anatomical neuroprotective effects of estrogen and to the damaging effects of tamoxifen. Similarly, Boele, Schilder, de Roode, Deijen, & Schagen, (2015) investigated the long-term effects (M = 31 months) of tamoxifen (without chemotherapy) on cognitive functioning in postmenopausal women with breast cancer. Here a surgical operation/radiotherapy group was added in order to control for the mental and physical impact of breast cancer diagnosis and treatment. Findings indicated deficits in verbal memory, fluency and perceived cognitive functioning compared to the surgical groups and healthy controls. Similar effects have been found on verbal memory and executive functioning for women taking tamoxifen in the absence of chemotherapy treatment (Schilder et al., 2010). Other studies have corroborated these findings. In a study investigating the effects of chemotherapy and tamoxifen on neurocognitive functioning in breast cancer, Castellon et al., (2004) found deficits in verbal learning, visuospatial functioning and visual memory compared to breast cancer patients who'd only been treated with surgery. Those who had received both chemotherapy and tamoxifen, rather than chemotherapy alone, showed the greatest compromise.

6.6 Summary and Research Aims

In sum, a growing body of behavioural, neuroscientific and qualitative research indicates that breast cancer diagnosis and treatment is associated with debilitating long-term cognitive deficits. Whilst originally thought to be caused by the neurotoxic effects

of chemotherapy, evidence now points to a multifactorial model which incorporates genetic, sociodemographic, biological, psychological and lifestyle factors. In addition, the detrimental effects of other treatments for breast cancer, such as tamoxifen, are beginning to be acknowledged with research indicating that decreased estrogen levels may result in damaging effects on the brain. Nevertheless, it is clear that due to the complex nature of CRCIs and the ambiguity that remains across the literature, more research is necessary to further our understanding of the impact of cancer diagnosis and treatment on the brain. Through this, targeted interventions may be developed to reduce their impact and improve quality of life for survivors. With this in mind, the final chapters of the current thesis aim to build upon the current literature with two novel studies investigating CRCIs. In light of the limitations associated with traditional neuropsychological measures of CRCIs, experiment 4 of chapter 7 adopts a neuroscientific approach. Here, the aim is to investigate the neural correlates of cognitive-control related error monitoring, a process that is imperative for behavioural adjustment in maintaining task performance and which is yet to be explored in breast cancer survivors. In chapter 8, study 5 aims to extend upon the present qualitative research into CRCIs by investigating the contributive effects of tamoxifen on cognitive decline in breast cancer survivorship.

Chapter 7: Exploring the Neurocognitive Mechanisms and Processing Efficiency in Breast Cancer

7.1 Chapter Overview

Section A of the current thesis presented a series of intervention studies which further emphasized the importance of cognitive processes in emotion regulation. As such, it is critical to understand the impact of breast cancer diagnosis and treatment on cognitive functioning. Through better awareness of the processes affected, targeted interventions for both cognitive and emotional deficits in breast cancer can be further developed. Accordingly, adopting a neuroscientific approach, the current chapter set out to investigate how breast cancer survivors respond to making cognitive errors, a process yet to be explored in this population.

7.2 Experiment 4: Cognitive Efficiency in Breast Cancer Survivorship: An ERP Study

7.2.1 Introduction

Amongst women, breast cancer is the most commonly diagnosed and leading cause of cancer death worldwide with increasing incidence (Bray et al., 2018). Nevertheless, the improvement of medical treatment has meant that significantly more women survive breast cancer. In recent years this has prompted researchers to investigate the long-term side effects of cancer treatment and resulting impact on survivors' quality of life. The acknowledgement of cancer-related cognitive impairments (CRCIs) is now well established across the literature surrounding cancer survivorship. Whilst research indicates that the majority of breast cancer patients are affected by cognitive deficits

during active treatment, longitudinal studies now indicate that a subset of survivors (approximately 20-30%) report problems with cognition for up to 20 years post treatment (Wefel, Saleeba, Buzdar, & Meyers, 2010; Koppelmans et al., 2012). Such deficits have been commonly referred to as 'chemobrain' or 'chemofog' due to the initial view that impairments were the result of neurotoxicity from chemotherapy. However, increasingly this notion is disputed, with increasing evidence pointing to the contributive role of other factors. Indeed, whilst cancer treatment can impact cognition itself, it can also interact with numerous other factors which are both predisposed (genetic, sociodemographic, cancer type) and modifiable (physiological, psychological, allostatic load and lifestyle) (Ahles & Root, 2018). This has led to the view that the etiology of CRCIs is multifactorial.

Nevertheless, whilst research into CRCIs has progressed, there is still a lack of understanding surrounding the extent of CRCIs, which functions are most affected, and how they can be managed. Indeed, there are currently no treatments for CRCIs available to survivors (Denlinger et al., 2014) and the presence of such deficits are often downplayed by the medical community (Selamat et al., 2014). This lack of clarity, in part, is due to the emphasis on neuropsychological testing which is limited by measures that were originally designed to test acute brain injury, and not subtle changes in cognitive functioning as a result of cancer diagnosis and treatment. Thus, whilst many cancer survivors may score within the normal range on standard neurological tests, this is at odds with their experience of cognitive dysfunction in the real world.

Accordingly, it has been suggested that a neuroscientific approach may facilitate the elucidation of the underlying mechanisms involved in CRCIs. Whilst there have been some neuroscientific investigations of CRCIs, predominantly using magnetic resonance imaging (MRI; structural and functional), a much more comprehensive program of investigation is required (Horowitz et al., 2018). Thus far, studies demonstrate structural

and functional changes primarily in the prefrontal cortex, with findings showing alterations in the density of grey matter, integrity of white matter and volume of multiple brain regions (see Andryszak et al., 2017, for a review). Additionally, functional imaging studies have indicated task-specific hypoactivation and hyperactivation of multiple brain regions (Horowitz et al., 2018). These alerations in the pattern of neural activation is thought to reflect compensatory mechanisms. For instance, using fMRI, McDonald et al., (2012) found prefrontal hyperactivation and more distributed activation patterns involved in working memory performance during an n-back task in cancer survivors relative to controls. Similarly, Menning et al., (2015) demonstrated increased prefrontal activation during a working memory task, coupled with decreased white matter integrity, in breast cancer patients relative to controls even prior to the start of adjuvant treatment. Pertinently, neural differences were found in the absence of performance differences between groups, suggesting that tasks were more challenging for survivors and required greater neural processing resources to reach the same level of performance (cf. Berggren & Derakshan, 2013)

Resting state fMRI designs have further been employed to assess neural activity without the complications of task-related studies that are dependent on task design, difficulty and participant cooperation. Findings indicate that a reduction in functional connectivity in the dorsolateral prefrontal cortex and inferior frontal gyrus is associated with deficits in executive functioning 1 year post chemotherapy (Wang et al., 2016). Similarly, Shen et al., (2019) found decreased neural activity in the occipital lobe and increased activity in the frontoparietal lobe, pointing to compensatory mechanisms.

A limited number of studies have used electroencephalography (EEG) to assess cognitive dysfunction in breast cancer survivors. Studies have primarily focused on the amplitude and latency of the P3, an event-related brain potential (ERP) marker of the evaluation or categorization of stimuli held in working memory. Kreukels et al., (2008)

showed a reduced P3 amplitude during an oddball task in breast cancer patients treated with chemotherapy relative to those who were not. Similarly, Kam et al., (2016) found reduced P3 amplitude to task relevant stimuli in breast cancer survivors relative to healthy controls in a sustained attention task. Overall, findings indicate disruptions in neural mechanisms of sustained attention and working memory for breast cancer survivors.

The Current Investigation

Given the lack of ERP research in the area of CRCIs and the ambiguity across the literature in identifying the exact etiology and underlying mechanisms at work, it follows that there is scope to investigate other ERP components to better our understanding of cognitive inefficiency in breast cancer as a means to build more efficacious interventions targeting this vulnerability. Hinging on the aforementioned findings that indicate attentional and working memory dysfunction in breast cancer survivorship, the current study sought to further investigate the neural correlates of cognitive-control related error monitoring, a function that is critical in behavioural adjustment to maintain task performance. Cognitive control relies on engaging top-down mechanisms to regulate attention towards task relevant information and inhibiting task irrelevant information, and as such plays a critical role in monitoring and orienting behavioural response to errors (Miller & Cohen, 2001; Eysenck, Derakshan, Santos, & Calvo, 2007). The mechanisms through which the brain detects and responds to errors, particularly in clinical populations, has become one of the fastest growing research areas in the field of neuroscience (Schroder & Moser, 2014; see Gehring, Liu, Orr, & Carp, 2012, & Gehring, Goss, Coles, Meyer, & Donchin, 2018, for a review). Neuroimaging studies predominantly implicate regions of the anterior cingulate cortex (ACC) and prefrontal cortex (PFC) in error monitoring and regulating necessary behavioural adjustments to

maintain or improve performance on trials following mistakes (Hester, Madeley, Murphy, & Mattingley, 2009).

The most widely measured neural index of error processing is the error related negativity (ERN), a negative ERP which reaches peak amplitude within 50-100ms following an error response in basic reaction-time tasks such as the flanker or go/no-go tasks (Gehring, Goss, Coles, Meyer, & Donchin, 1993). Broadly, the ERN is believed to index cognitive control-related error monitoring involved in signaling the need for implementing cognitive control functions when performance has broken down (Gehring et al., 2012). The ERN is followed by the error positivity (Pe) component, a positive ERP with a centroparietal topography which reaches maximum amplitude between 200 and 400ms after an erroneous response. Whereas the ERN is considered to reflect a more general conflict signal (Hughes & Yeung, 2011), it has been hypothesized that the Pe may either reflect the conscious awareness of an error, the affective response to an error and the adaptation of response strategies following an error, disassociating these two components (Schroder, Moran, Infantolino, & Moser, 2013). To date, a number of studies have investigated the ERN/Pe relationship in psychopathology, specifically in depression, anxiety disorders and substance abuse, with findings indicating abnormal response monitoring for such disorders (see Olvet & Hajcak, 2008 and Pasion & Barbosa, 2019, for reviews).

Whilst promising findings continue to emerge in the fields of psychopathology, the ERN and Pe have yet to be investigated in relation to CRCIs in breast cancer survivors. Having the cognitive capacity to adapt to failures and setbacks seems particularly pertinent to breast cancer survivors, a population with known cognitive and emotional deficits who often struggle with feelings of self-efficacy post treatment, potentially hindering their ability to function effectively at both work and home. To this end, the current study examined the neurocognitive correlates of error processing by investigating

the ERN and Pe components during a flanker task specifically designed to challenge cognitive-control related error monitoring. In addition, behavioural measures of working memory performance were used, as well as measures of emotional vulnerability, perceived cognitive functioning and fatigue in order to explore their relationship with neural processing in each group, and control for potential confounds. In consideration of the aforementioned studies on compensatory mechanisms at work in breast cancer, it was predicted that breast cancer survivors would show a greater ERN and Pe compared to healthy controls in the absence of performance effects, indicating the requirement for more effortful processing in error monitoring.

In light of studies that show both decreased (Wang et al., 2016) and increased (Shen et al., 2019) neural connectivity at resting state in breast cancer survivors, as an exploratory outcome we further measured resting state EEG as an alternative electrophysiological measure of trait attentional control. Neural activity was quantified in different frequency bands (i.e. theta band, 4-7hz for slow oscillations; beta band, 13-30hz for fast oscillations). It is considered that changes in power in these frequency bands are a reflection of increased or decreased attentional control. For instance, fast wave oscillation is related to top down processes involved in the regulation of attentional control, whereas slow wave oscillation is involved in bottom up stimulus driven processes (Knyazev, 2007). Therefore, an increased ratio between these two frequency bands is considered to indicate a decrease in attentional control (Putman, Verkuil, Arias-Garcia, Pantazi, & van Schie, 2014).

7.2.2 Methods

Participants

The study was advertised through the Birkbeck Centre for Building Resilience in Breast Cancer (BRiC) and various breast cancer support networks via social media platforms such as Facebook and Twitter. In total, 62 participants (30 Breast Cancer, 32 Non-Breast Cancer) were recruited for the study. Participants were required to have had a diagnosis of breast cancer and have had chemotherapy as part of their treatment plan. Participants must have finished active treatment to partake in the study. Participants received a fee of £25 upon completion of the study. For participant demographics, clinical characteristics and psychiatric history see Table 7.1.

Table 7.1. Participant demographics, Clinical characteristics and psychiatric history.

	Breast Cancer (n= 30)		Non Breast Cancer (n = 32)		P
Age (Years)[a]	48 (8.47)		44 (8.94)		.07
Age at Diagnosis (Years)	43 (7.54)		-		-
	No. (%)				
Education					.07
GCSE's	5	(16.7)	1	(3.1)	
A-Levels	5	(16.7)	5	(15.6)	
Undergraduate	10	(33.3)	20	(62.5)	
Post Graduate	10	(33.3)	6	(18.8)	
Ethnic Origin					
White	27	(90)	23	(71.9)	.3
Black	-		1	(3.1)	
Asian	1	(3.3)	3	(9.4)	
Mixed Race	1	(3.3)	4	(12.5)	
Other	1	(3.3)	1	(3.1)	
Employment Status					.89
Full Time	13	(43.3)	15	(46.9)	
Part Time	7	(23.3)	8	(25)	
Unemployed	3	(10)	2	(6.3)	
Maternity Leave	1	(3.3)	-	-	
Retired	2	(6.7)	1	(3.1)	
Volunteering	1	(3.3)	-	-	
Student	1	(3.3)	1	(3.1)	
Sick Leave	-	-	1	(3.1)	
Self Employed	1	(3.3)	2	(6.3)	
Other	1	(3.3)	2	(6.3)	
Marital Status [b]					.001*
Married	19	(63.3)	5	(15.6)	
Divorced	2	(6.7)	4	(12.5)	
Single	4	(13.3)	16	(50)	
Separated	-	-	2	(6.3)	
Cohabiting with Partner	5	(16.7)	2	(6.3)	
Other	-	-	2	(6.3)	
Current Psychological Medication					
Yes	5	(16.7)	5	(15.6)	.91
No	25	(83.3)	27	(84.4)	
Previous Psychological Condition					.07
Yes	9	(30)	17	(53.1)	
No	21	(70)	15	(46.9)	
Alcohol Intake					
None	6	(20)	6	(18.8)	.99
1-5 units	13	(43.3)	14	(43.8)	
6-9- units	3	(10)	3	(9.4)	
10-14 units	5	(16.7)	5	(15.6)	
14+ Units	2	(6.7)	3	(9.4)	
Diagnosis					
Primary	30	(100)	-	-	-
Secondary	-	-	-	-	
Grade of Cancer					
Low	2	(6.7)	-	-	-
Moderate	9	(30)	-	-	-
High	19	(63.3)	-	-	-
Chemotherapy					
Yes	30	(100)	-	-	-
Radiotherapy					
Yes	28	(93.3)	-	-	-
Surgery Type					
Mastectomy	9	(30)	-	-	-
Lumpectomy	16	(53.3)	-	-	-
Both	5	(16.7)			
Endocrine Therapy [d]					
Yes	24	(80)	-	-	-

[a] *Values indicate means and standard deviations unless indicated otherwise.*

[b] *One participant did not disclose their marital status.*

[c] *Two participants did not disclose their alcohol intake.*

[d] *One participant did not disclose whether they had taken endocrine therapy.*

Significant between-group difference, P = .05.

Materials and Experimental Tasks

Resting State EEG Task

Resting state neural activity was recorded across 8 one minute blocks of alternating eyes open or eyes closed conditions (based on, Putman, Arias-Garcia, Pantazi & van Schie, 2012). Participants were instructed by an audio cue to alternately open or close their eyes after each minute, and to simultaneously press the space bar on the keyboard. Starting block condition was randomly decided for each participant.

Flanker Task

Participants completed a modified letter version of the Eriksen Flanker task (Eriksen & Eriksen, 1974). Participants were presented with a string of five letters in which the target (the centre letter) was either congruent (e.g. MMMMM or NNNNN) or incongruent (e.g. MMNMM or NNMNN) which included distractor letters. Participants were instructed to respond by clicking the right or left side of the computer mouse based on the instructions they were presented with at the beginning of each block. For example, during the first block, participants were instructed to responded with a left sided mouse click if the target letter was M, and a right click if the target letter was N. Flanking letters were presented 35ms prior to target letter presentation and remained on the screen for a further 100ms (total trial time 135ms). During a variable inter-trial interval (1200-1700ms) between each trial, a fixation cross was presented. Stimuli was presented via the software package E-Prime to control the presentation and timing of stimuli along with determination of response accuracy and measurement of reaction times. The task included 480 trials grouped into 12 blocks of 40 trials. Across the task, 50% of trials were congruent and 50% incongruent. Characters were presented in a standard white font on a black background and subtended 1.38° of the visual angle vertically and 9.28° horizontally. To ensure elicitation of a sufficient number of errors for reliable ERN

analysis, (Olvet & Hajcak, 2009) the letters used for trial stimuli differed across blocks (Block 1 & 2: 'M' and 'N", Block 3 & 4: 'F' and 'E', Block 5 & 6: 'O' and 'Q', Block 7 & 8: 'T' and 'I', Block 9 & 10: 'V' and 'U' Block 11 & 12: 'P' and 'R'). Additionally, mouse button-letter response mappings were reversed within each block pair (e.g. a M target for Block 1 required a left click response, whereas a M target for Block 2 required a right click response). Accuracy and speed were equally emphasised to the participant. No performance feedback was given across the task. The task was designed on E-Prime and was presented on an Asus VG248QE 24 inches LCD Monitor with a resolution of 1920 x 1080 and a refresh rate of 60Hz.

Automated Operation Span

The Automated Ospan task (Unsworth, Heitz, Schrock, & Engle, 2005) which allows completion independently of the experimenter was administered to participants. The task required participants to respond via the mouse for its entirety. Instructions were presented on the computer screen throughout the practice section which was divided into 3 parts. The first part comprised of a simple letter span in which a letter appeared on the screen, and participants were asked to recall the letters in the same order in which they had been presented. At recall a 4 x 3 matrix consisted of letters 'F, H, J, K, L, N, P, Q, R, S, T, and Y' and participants were required to click a box next to the appropriate letters. Recall response was untimed. Letters remained onscreen for 800ms for all experimental conditions. The second part of the task comprised of a math operation (e.g., $(1*2) + 1 = ?$) in which participants were required to solve the operation as quickly as possible and then click the button to advance to the next screen. Here, a digit (e.g., 3) appeared, and participants were asked to respond 'true' or 'false' based on their answer to the equation. Participants were given accuracy feedback after each operation. After the math practice, the program calculated each individual's mean time required to solve the equations. This

time (plus 2.5 SD) was then used as a time limit for the math portion of the experimental session for that individual. In this maths practise session, participants completed 15 math operations. The final practise session comprised of both the letter recall and math tasks together, preparing them for a real block of trials. The maths operation appears first, followed by a letter to be recalled. If the participants took more time to solve the math operations than their average time plus 2.5 SD, the program automatically moved on and counted that trial as an error. This prevented the participants from rehearsing the letters when they should be solving the math operations. Participants completed three practice trials each of set size 2. After completion of the practise session participants proceeded to the experiment which comprised of three sets of each set size, with the set sizes ranging from 3 to 7. This totalled at 75 letters and 75 math problems. The order of set sizes was randomised for each participant. Participants were encouraged to be as accurate as possible.

Change Detection Task (CDT) (see figure 7.1)

The change detection task was modified from Vogel et al., (2005). Trials began with a white fixation cross for 700ms with an arrow above pointing to either the right or the left indicating to the participant which side of the screen to attend to. Subsequently, arrays of either 2 red rectangles (two-item condition), 4 red rectangles (four-item condition) or 2 red rectangles and 2 blue rectangles (distractor condition) were presented for 100ms (3° away from the fixation cross, within a region of 4° x 7.2°; memory array). Participants were instructed to memorize the orientation of the red rectangles on the attended side. After a retention interval of 900 ms, the rectangles reappeared on the right and left side of screen (test array). Participants were asked to indicate whether the orientation of the red rectangles they had memorized had changed or not within a two second interval, as accurately as possible. If they perceived the red rectangles to be in the

same position, they were told to press 0 (no change) on the computer keyboard; if they saw that the orientation of the red shapes differed between the test and memory array they were told to press 1 (change). On 50% of the trials no change in orientation occurred for any of the rectangles; on the other 50% of the trials the orientation of one of the red rectangles changed between the memory array and the test array. There were 4 possible orientations for the rectangles: vertical, horizontal, 45° left and 45° right tilted. In each condition, the rectangles appeared in random positions with a minimum of 2° distance from each other. The task comprised a 98 stimuli set for the four item, 105 stimuli set for the two-item and 101 stimuli set for distractor condition. The same stimuli set was not presented more than once during the task and all possible conditions were randomly distributed within the task. Participants completed a short initial practise session consisting of 12 trials (4 per condition) before the experimental blocks. Participants began the experimental session once they had reached >50% on the practise session. The experiment was split into 4 blocks of 48 trials (64 trials per condition), totalling at 192 trials across the experiment.
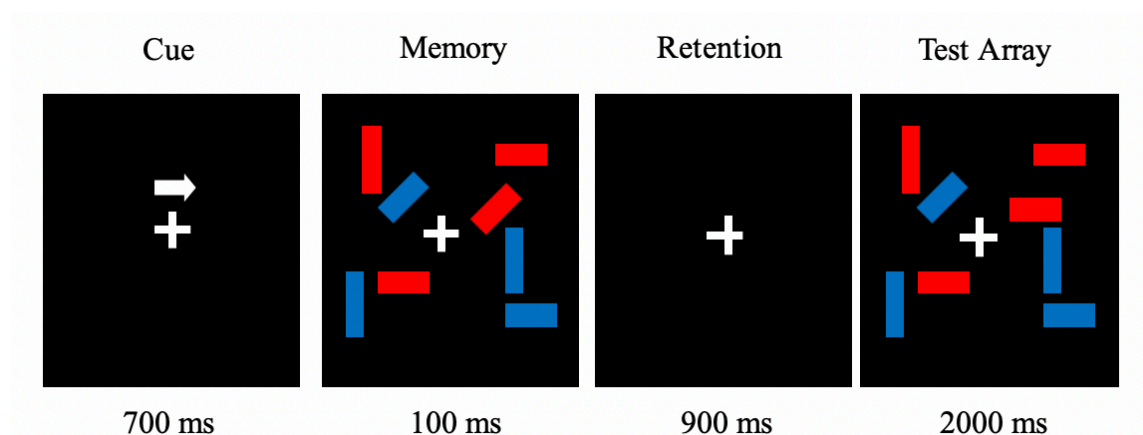
Figure 7.1. An example of the distractor condition in a change detection trail. Participants were instructed to remember the orientations of the red rectangles, ignore the blue rectangles and indicate whether there was a change between the memory and test array by pushing buttons 0 (no change) and 1 (change).

Questionnaires

Participants completed a completed series of self-report questionnaires. All participants completed the following questionnaires: Ruminative Response Scale (Treynor et al., 2003) a 22-item scale with a Likert scale ranging from 1 ("almost never") to 4 ("almost always"), with higher scores indicating higher levels of rumination; a shortened version of the Mood and Anxiety Scale Questionnaire (Watson, Clark, Weber, & Assenheimer, 1995) a 38- item inventory in which frequency of symptoms is indicated on a Likert scale ranging from 1 ("not at all") to 5 ("extremely"), assessing subscales of 'Anxious Arousal', 'Anhedonic Depression', 'Positive Affect' and 'Loss of Interest; Hospital Anxiety and Depressions Scale (HADS), (Zigmond and Snaith, 1983). The HADS is a 14-item inventory assessing anxiety and depression, in which frequency of symptoms are indicated on a Likert scale ranging from 0 ('not at all') to 3 ('most of the time'). Higher scores indicated higher anxiety; Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog, Version 3) (Wagner et al., 2009), a 37-item inventory assessing perceived cognitive abilities and perceived cognitive impairments. Scores are indicated on a Likert scale ranging from 0 ('never") to 4 ("several times a day"). Greater scores indicate better perceived cognitive functioning. The Fatigue Symptom Inventory (Hann et al., 1998) is a 14 item inventory designed to assess the severity, frequency and interference of fatigue. Scores are indicated for 'severity' on an 11 point Likert scale (0 = not at all fatigued; 10 = as fatigued as I could be), 'frequency' on a 7 point Likert scale (0 - 7) indicating the number of days in the past week they felt fatigued, as well as an 11 point scale indicating to what extent each day they felt fatigued (0 = none of the day; 10 = the entire day), and 'perceived interference' on an 11-point scale (0 = no interference; 10 = extreme interference) that assesses the degree to which fatigue in the past week was judged to interfere with general level of activity. Higher scores indicate greater levels of fatigue.

Participants in the experimental breast cancer group additionally completed the following questionnaires which related specifically to their diagnosis: Quality of Life in Breast Cancer Patients Scale (Ferrell, 1997), which assesses the physical, psychological, social and spiritual dimensions of breast cancer patients. Scores are indicated on a Likert scale ranging from 0 ('no problem') to 10 ('severe problem'). Higher scores indicate better outcomes; Cancer related thoughts was assessed by the Cancer Impact of Events Scale (IOE), (Weiss, 2007) whereby frequency of symptoms is indicated on a Likert scale ranging from 0 ("not at all") to 4 ("extremely"). Higher scores indicated worse outcomes; Cancer Worry Scale (Custers et al., 2014) is an 8 item inventory which assesses worry associated with cancer recurrence. Score are indicated on a Likert scale ranging from 1 ("not at all or rarely") to 4 ("almost all the time"). Higher scores indicate higher levels of worry; Fear of Cancer Recurrence Scale (Simard & Savard, 2009) is a 42 item inventory which assesses cancer recurrence fears. Fears are scored on a Likert scale ranging from 0 ("never") to 4 ("all the time"). Greater scores indicated higher levels of fear.

EEG recording and data reduction

Flanker Task: Continuous electroencephalographic (EEG) activity was recorded using the BrainVision system (Brain Products, Gilching, Germany). Recordings were taken from 32 Ag-AgCl electrodes placed in accordance with the 10/20 system, which comprised of both left and right mastoids. Electro-oculogram (EOG) activity generated by eye movements and blinks was recorded at FP1 and via additional electrodes placed inferior to the right pupil and on the left and right outer canthi which were all approximately 1 cm from the pupil. During data acquisition, all electrical signals were digitized at 1024 Hz using the BrainVision recording software (Brain Products, Gilching, Germany). Offline analyses were subsequently performed using BrainVision Analyzer 2 (Brain Products, Gilching, Germany). Scalp electrode recordings were referenced to the

numeric mean of the mastoids and band pass filtered with cut-offs of 0.01 and 30 Hz (12 dB/oct roll off). Ocular artefacts were corrected using the procedure developed by Gratton, Coles, and Donchin (1983). Response-locked data were segmented into individual epochs beginning at 200ms prior to response onset and continuing for 800ms post response. Physiological artefacts were identified using a computer-based algorithm build into BrainVision software. To be consistent with behavioural analyses, blocks that were identified as failed switched response mappings (i.e., switch blocks) were removed from the ERP analyses. Trials failing to meet the following criteria were rejected: a voltage step exceeding 50 µV between contiguous sampling points, a voltage difference of more than 200 µV within a trial, or a maximum voltage difference less than 0.5 µV within a trial. This resulted in a loss of an average of 5.26% of trials across participants.

Resting State: Data was prepared based on Putman et al., (2014). A 50 Hz notch filter, a low-pass filter of 100Hz, and a high pass filter of 0.3 Hz were applied. Data was subsequently segmented into 4s with 50% overlap. Ocular artefacts were corrected using the procedure developed by Gratton, Coles, and Donchin (1983). Remaining segments were then averaged for further analysis. Power densities ($µV2$ /Hz) for the three frontal electrodes (F3, Fz, F4) were then estimated via a fast fourier transformation (10% hamming window, using a resolution of 0.5 Hz). Slow wave oscillations were represented by theta (4-7 Hz), whilst fast wave oscillations were captured by beta (13-30 Hz) frequency bands. The ratio of the average three frontal power densities (F3, Fz, F4) of theta divided by beta was calculated in order to obtain frontal theta beta ratio (TBR) as an index for resting state activity. Natural log-normalisation was applied to average frontal TBR due to typical skewed distribution. Higher TBR indicates relatively greater theta compared to beta power, reflecting lower resting state.

Procedure

The experiment was conducted in a single lab based testing session in a sound proofed EEG testing cubicle at Birkbeck, University of London, UK. Participants were tested individually, with each session taking approximately 2.5 hours. Participants firstly gave informed consent, and then continued on to complete the battery of self-report questionnaires. The EEG cap and electrodes were then applied by the experimentor. The partcipants then completed the resting state neural data task followed by the flanker task whilst their EEG activity was recorded. After completion of the flanker task the EEG cap was removed. Participants continued on to complete the OSPAN followed by the CDT task.

Statistical Analyses

ERP and behavioural data were analysed using EPrime, IBM SPSS Statistics, Version 24.0 and BrainVision Analyzer 2 (Brain Products, Gilching, Germany). A series of Independent samples t-tests and chi-square tests were used to compare demographic, self-reported cognitive and emotional vulnerability questionnaires and behavioural performance.

Behavioural Analyses

Flanker Task

Pre-processing of the flanker data ensured that blocks incorporating failed response mapping were discarded; if a participant reached the error threshold ($>= 60\%$ errors) within a block, the appropriate segments were removed from the behavioural and ERP data. Overall congruency reaction time effects were analysed by a 2 (Congruency: Congruent vs. Incongruent) x 2 (Group: BC Survivors vs. Non-BC) mixed ANOVA.

OSPAN

The partial span score which equals the number of items recalled in the correct order on memory trials was calculated. As recommended by Conway et al., (2005), the partial score has greater variance allowing for better discrimination between high and low ability participants compared to the absolute score in which the participant only received credit for trials in which they were 100% accurate within that trial (e.g., if the participant is performing a trial of set size 3 and answers only 2 out of 3 correctly, the partial score would equal 2, whereas the absolute score would equal 0 due to the participant failing to be 100% accurate on that particular trial).

CDT

To assess performance on the CDT task we calculated WMC scores by means of the broadly used formula: $K = S \times (H - F)/(1-F)$ where K (WMC) is calculated as a function of S: the set size of the array, H: the observed hit rate and F: proportion of false alarms (Pashler, 1988). In order to eliminated potential floor or ceiling effects that can occur with the distractor and two-item conditions, we calculated WMC for the 4-item condition, as in keeping with Lee, Cowan, Vogel, Valle-Inclan and Hackley (2010), Owens, et al. (2013) and Sari et al., (2016).

EEG Analyses

Resting State: Group comparisions for mean frontal theta beta ratio's (TBR) were analysed by an independent t-test. A series of bivariate correlations were also conducted to explore relationships between neurophysiological attentional control (TBR), behavioural measures of working memory capacity and demographic variables.

ERN: ERP waveforms were time locked to participant's responses with a 200ms pre-response baseline. The ERN and the CRN (correct related negativity), its correct trial counterpart, were defined on error and correct trials respectively as the average voltage occurring in the 0-100ms post response time window at Cz where the ERN and CRN were maximal. To establish whether the expected ERN effect was present and to observe any group differences, a 2 (Accuracy: Error vs. Correct) x 2 (Group: BC Survivors vs Non-BC) mixed ANOVA was conducted. A difference wave approach was also used to isolate error-related neural activity by subtracting the ERP waveform on correct trials from incorrect trials. Group comparisons of voltage difference scores were analysed with independent t-tests.

Pe: The Pe and its correct trial counterpart were quantified as the average voltage in the 150- to 350-ms (Early Pe) and 350- to 550-ms (Late Pe) post-response time window consistent with prior work (Schroder, Moran, Donnellan, & Moser, 2014). The Pe was quantified at Pz where it was maximal. The Pe was analysed with a 2 (Accuracy: Error vs. Correct) x 2 (Group: BC Survivors vs Non-BC) mixed ANOVA. Group comparisons of voltage difference scores were analysed with independent t-tests.

7.2.3 Results

Demographic Measures

Table 7.1. indicates group characteristics on demographic variables for the sample of 62. Group differences were found for marital status X^2 (5) = 21.31, p = .001. No other group differences were found for any demographic variable, (all p's > .07).

Self-Reported Cognitive and Emotional Functioning

Mean self-reported symptomatology for each group is presented in Table 7.2. Analyses indicated that perceived cognitive functioning was better for the non-breast cancer compared to breast cancer survivors, t (60) = 6.23, p <.001. Groups were matched on measures of anxiety, rumination, depression or fatigue (all t's < .39, all p's > .31).

Table 7.2. Mean self-report symptomatology total scores for each group (Breast Cancer and Non-Breast Cancer).

	Breast Cancer (n= 30)		Non-Breast Cancer (n = 32)		p
Rumination Response Scale	42.67	(13.96)	42.63	(14.94)	.99
Mood and Anxiety Scale Questionnaire					
Anhedonic Depression	56.57	(13.35)	54.47	(18.77)	.61
Anxious Arousal	26.87	(6.55)	25.16	(7.18)	.33
Hospital Anxiety and Depressions Scale	19.1	(7.02)	17.19	(7.88)	.32
Functional Assessment of Cancer Therapy Cognitive Scale	71.7	(16.55)	95.94	(14.05)	<.001*
Fatigue Symptom Inventory	54.37	(22.01)	57.16	(31.12)	.69
Quality of Life in Breast Cancer Patients Scale	222.83	(49.81)	_	_	_
Cancer Impact of Events Scale	20.7	(12.47)	_	_	_
Cancer Worry Scale	16.57	(3.95)	_	_	_
Fear of Cancer Recurrence	78.33	(21.41)	_	_	_

Note. Standard deviations are in parentheses.
Significant between-group difference, P = .05.

Behavioural Performance

Behavioural performance data are displayed in Table 7.3. Analyses showed a main effect of congruency indicating that RT's were faster on congruent trials compared to incongruent trials, $F(1, 60) = 497.74$, $p < .001$, $\eta_p^2 = .89$. Breast Cancer Survivors showed somewhat faster responses overall than the Non-Breast Cancer Group, (BC survivors, Congruent: M = 505.79, SD = 44.85, Incongruent: M = 547.77, SD = 45.57; Non-BC, Congruent: M = 528.81, SD = 56.81, Incongruent: M = 569.91, SD = 49.59), although the main effect of group did not reach significance, $F(1, 60) = 3.28$, $p = .07$, $\eta_p^2 = .05$, nor did the interaction between Group and Congruency, $F < 1$. Similarly analyses indicated that there were no differences between groups in working memory capacity on both the CDT, $t < 1$, ns, and OSPAN tasks, $t(60) = 1.27$, $p = .21$. Thus, overt cognitive performance was matched across groups.

Resting State Neural Activity

Mean theta/beta ratios are displayed in Table 7.3. No group differences were found for frontal theta/beta ratios, $t < 1$, ns.

Table 7.3. Means and standard deviations for measures of working memory capacity, behavioural performance resting state neural activity and ERP's elicited from the flanker task.

	Breast Cancer (n= 30)		Non-Breast Cancer (n = 32)		t	p
CDT K-Score	1.08	(.77)	.92	(.85)	.82	.42
OSPAN Partial Score	55.07	(16.93)	49.94	(14.98)	1.27	.21
Flanker task						
No. errors	19.53	(14.25)	26.66	(37.46)	.98	.33
Accuracy (%)	95.78	(3.05)	94.01	(8.58)	1.07	.29
Error RT (ms)	460.81	(88.77)	478.81	(92.5)	.78	.44
Correct RT (ms)	529.92	(43.48)	550.88	(52.27)	1.71	.09
Congruent RT (ms)	505.81	(44.85)	528.81	(56.81)	1.76	.08
Incongruent RT (ms)	547.57	(45.57)	569.91	(49.61)	1.83	.07
Theta/Beta Ratio	2.83	(2.08)	3.2	(2.01)	.71	.48
ERPs						
Error-related negativity (ERN)	-1.95	(2.84)	-2.10	(2.30)	.24	.81
Correct-response negativity (CRN)	1.28	(2.07)	-.28	(1.75)	3.23	.002*
ΔERN	-3.23	(3.21)	-1.81	(2.18)	2.05	.04*
Early Pe Errors	2.04	(2.78)	1.08	(4.81)	.95	.35
Early Pe Corrects	-2.67	(3.05)	-3.55	(2.65)	1.20	.23
Late Pe Errors	3.20	(4.81)	.85	(4.43)	2.01	.04*
Late Pe Corrects	-2.91	(2.25)	-3.97	(2.71)	1.64	.11
ΔPe	5.41	(4.01)	4.71	(4.51)	.64	.53

Note. Standard deviations are in parentheses.
Significant between-group difference, P = .05.
ERN and CRN means reflect average at sites Cz. Pe means reflect average at sites Pz. Mean early and late Pe scores were used to create the Pe difference score.

ERP's

ERN

Means, standard deviations and independent samples *t* tests are presented in table 7.3.

Figure 7.1 presents response-locked waveforms and scalp distribution maps for the ERN.

At the time of response, errors elicited a larger negativity (i.e. the ERN) than correct

responses, confirmed by a significant main effect of response type, $F(1, 60) = 52.78$, $p <$ .001, $\eta_p^2 = .47$, showing the typical ERN waveform. The main effect of group was marginal, (BC survivors, Errors: M = -1.95, SD = 2.84, Corrects: M = 1.28, SD = 2.07; Non-BC, Errors: M = -2.10, SD = 2.30, Corrects: M = -.28, SD = 1.75), $F(1, 60) = 3.51$, $p = .06$, $\eta_p^2 = .05$). Consistent with predictions, there was a significant interaction between response type and group, $F(1, 60) = 4.21$, $p = .04$, $\eta_p^2 = .07$, such that the voltage difference between the ERN and CRN (i.e., ΔERN) was larger in the breast cancer, compared to the control, group, $t(60) = 2.05$, $p = .04$.

Pe

Figure 7.2 presents response-locked waveforms and scalp distribution maps for the Pe. In the 150- to 350-ms post-response time window, the main effect of Accuracy indicated that error trials were associated with greater positivity compared to correct trials, $F(1, 60) = 76.49$, $p < .001$, $\eta_p^2 = .56$, confirming the presence of an early Pe. The main effect of Group was non-significant, $F(1, 60) = 1.72$, $p = .19$, $\eta_p^2 = .02$, as was the Accuracy x Group interaction, $F < 1$.

In the 350- to 550-ms post-response time window, the main effect of Accuracy was again significant, $F(1, 60) = 84.43$, $p < .001$, $\eta_p^2 = .57$, showing a late Pe. Importantly, the main effect of Group was also significant, $F(1, 60) = 5.55$, $p = .02$, $\eta_p^2 = .09$, indicating that breast cancer survivors had a significantly larger late Pe compared to the non-breast cancer group. The Accuracy x Group interaction was non-significant, however, $F(1, 60) = 1.14$, $p = .29$, $\eta_p^2 = .02$
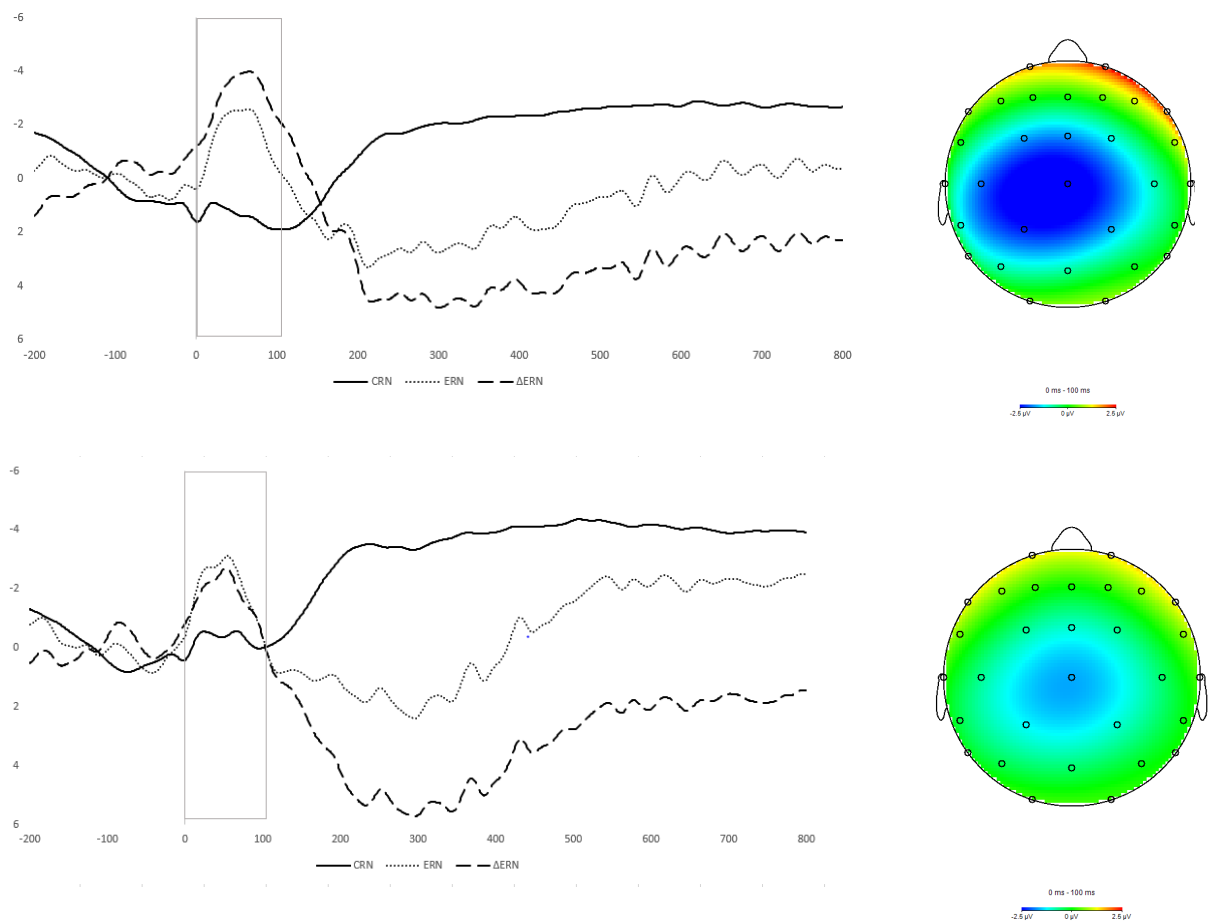
Figure 7.2 Response-locked ERP waveforms recorded from the flanker task at Cz for the breast cancer group (top) and non-breast cancer (bottom) group. On the right are scalp topographies representing the error-related negativity (ERN) derived from the average waveform for error trials.
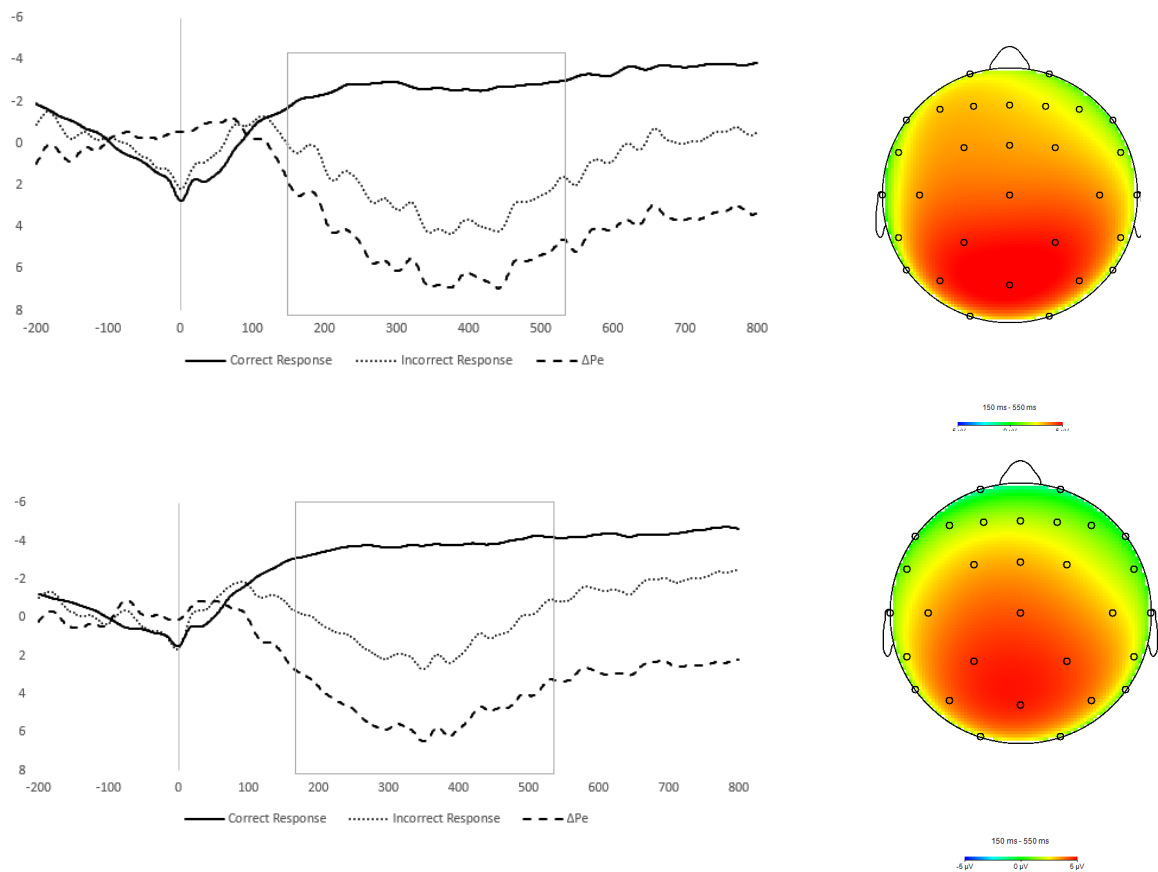
Figure 7.3. Response-locked ERP waveforms recorded from the flanker task at Pz for the breast cancer group (top) and non-breast cancer (bottom) group. On the right are scalp topographies representing the error positivity.

7.2.4 Discussion

The primary aim of this study was to investigate the neurocognitive correlates of error processing in a group of female breast cancer survivors. Whilst numerous fMRI studies have been conducted in the area of CRCIs in breast cancer survivors (Andryszak et al., 2017), investigation into ERP components is lacking, and no previous study has considered the ERN and the Pe in the breast cancer population. During a flanker task designed to challenge cognitive-control related error monitoring, the current study measured the neural activity of both a group of breast cancer survivors and a group of healthy control participants. Emotional and cognitive self-report measures were also used in order to account for previously documented differences between groups in these domains.

Findings firstly indicate that for both groups the typical ERN and Pe waveforms were present, establishing that this pattern is evident in the breast cancer as well as the healthy population. For the ERN, results show that there was a greater ΔERN in breast cancer survivors, illustrating exaggerated early error processing. In line with previous studies indicating neural compensatory mechanisms in breast cancer (McDonald et al., 2012; Menning et al., 2015), the current findings demonstrated neural differences in the absence of performance effects on the flanker task. This suggests that for the breast cancer group, the ability to detect errors and evaluate the need for implementing cognitive control processes at the earliest stage of processing requires greater neural activation compared to healthy controls. Visual inspection of topographical scalp maps further suggests that for the ERN, recruitment of neural areas was more distributed and interestingly skewed centro-parietally to the left for the breast cancer compared to the non-breast cancer group. A number of previous studies indicate that verbal memory is one of the prominent cancer related cognitive deficits in breast cancer (McDougall, Oliver, & Scogin, 2014) which may explain this finding given that the flanker task employed was designed utilising letters; greater recruitment of cortical language regions may be required for breast cancer survivors to reach pre-diagnosis levels of efficiency. Elsewhere it has been shown that the ERN is modulated by verbal worry and left sided brain activity supporting the above interpretation (Lin, Moran, Schroder, & Moser, 2015).

Additionally, findings showed that the breast cancer group had a significantly larger late Pe compared to the non-breast cancer group indicating that exaggerated error monitoring continues through the conscious processing of errors. Considering the theories surrounding the Pe representing the conscious awareness of an error and the allocation of attentional resources necessary for behavioural adjustments and improved performance (Steinhauser & Yeung, 2010; Gehring et al., 2012), these findings have important implications for breast cancer survivors. Again it could be interpreted that as a

compensatory mechanism, greater neural activation is necessary to allocate attention to tasks in order to maintain behavioural performance. Importantly no group differences were found for levels of anxious and depressive symptomatology and therefore findings cannot be attributed to abnormal error processing as a result of emotional disorder as previous studies have found (Olvet & Hajcak, 2008).

Relatedly, the current results indicate that the breast cancer group reported significantly greater perceived cognitive impairments compared to the non-breast cancer group, suggesting that the neural changes observed translates to women's perception of their cognitive functioning. This finding highlights an important point of discussion across the literature on CRCI; whilst behavioural performance may reach equal levels of healthy individuals under controlled conditions in a lab-based environment, behavioural deficits may manifest over time under the pressures of daily life, through the greater fatigue that may result from more effortful and less efficient neural processing. This is further emphasised by the lack of behavioural performance differences on the OSPAN and CDT tasks.

The study indicated no differences for resting state neural measures of attentional control, failing to replicate previous studies indicating neural differences in activation at resting state (Wang et al., 2016; Shen et al., 2019). That said, EEG was used in contrast to the FMRI employed by previous studies and therefore findings are not fully comparable.

Limitations

The current study has a number of limitations. Firstly, participants were recruited via social media platforms and therefore may not be representative of the wider popultaion of breast cancer survivors. Secondly, a comparison group that did not undergo chemotherapy was not included, and therefore it is difficult to asess whether the neural

differences observed are a result of the neurotoxic effects of chemotherapy or other potential contributing factors in the development of cognitive dysfunction such as the biology of the disease istself, or other treatment modalities such as hormone therapy, which many of the participants were taking. Thirdly, baseline measures of neural activity and cognitive performance were not used either pre-treatment or immediately after treatment, and thus it is difficult to conclude whether any neural changes in patterns of activation are a continued deterioration, or representative of partial recovery after active treatment.

Conclusions

The current study was the first of its kind to investigate error monitoring in the breast cancer population. The findings point to compensatory error monitoring in breast cancer survivors. This suggests that greater recruitment of neural processing resources are required as a compensatory mechanism to reach pre-morbid levels of functioning. These findings have important implications for developing cognitive rehabilitation programmes for breast cancer survivors affected by cognitive decline and illuminate error processing as a novel treatment target.

Chapter 8: The Role of Tamoxifen on Cognitive Impairment in Breast Cancer

8.1 Chapter Overview

So far, the current thesis has firstly established that anxious and depressive symptomatology can be targeted through interventions that engage attentional control processes (Section A: chapters 2, 3 and 4), further emphasising an association between levels of cognitive control and emotional vulnerability. In Section B (chapter 7), an investigation into the neurocognitive correlates of error processing aimed to expand on the current understanding of cancer-related cognitive impairments (CRCIs) as a means to advance future interventions for both cognition and emotion moving forward. Findings indicated differential neural processing of errors for breast cancer survivors compared to healthy controls in the absence of performance effects, signposting neural compensatory mechanisms. Whilst a substantial amount of research has now been conducted investigating CRCIs in patients treated with chemotherapy, less is known about CRCIs in the subgroups of patients who did not undergo chemotherapy. Accordingly, my final empirical chapter sought to bridge this gap, by evaluating the lived experience of CRCIs in a subset of women administered with the hormonal therapy Tamoxifen. Here, Interpretative Phenomenological Analysis (IPA) (Smith, Flowers, & Larkin, 2009) is employed in an experiment investigating the impact of Tamoxifen in relation to CRCIs on the lives of a group of women treated for breast cancer in the absence of chemotherapy.

8.2 Study 5: Personal Accounts of Tamoxifen and Cognitive Function: A Qualitative Experiential Study

8.2.1 Introduction

Cancer-related cognitive impairments (CRCIs) are frequently reported by both patients with cancer and those in remission (Pendergrass et al., 2018). Whilst it is well established that chemotherapy can induce cognitive impairment, emerging evidence suggests that several other factors may contribute to observed deficits. Indeed a recent review indicates that up to 30% of patients can experience cognitive deficits even prior to treatment, with 75% of patients experiencing problems during treatment, and up to 35% having persistent impairments in the months and years post treatment (Janelsins, Kesler, Ahles, & Morrow, 2014). Typically, the cognitive domains most affected include memory, attention, executive function, processing speed, visual and verbal memory as well as language (see Ahles & Root, 2018, for a recent review). Ambiguity surrounding the etiology and extent of CRCIs persists across the literature in part because of the wide range of definitions and tests that have been utilised as measures. However measurement has additionally proved complicated due to the complex nature of cancer and the multiple treatment modalities that are used. For instance research now indicates that hormonal therapies such as tamoxifen may contribute to long-term cognitive deficits in breast cancer survivors (Castellon et al., 2004; Schilder et al., 2010). Tamoxifen is prescribed as a preventative method to women with estrogen receptor positive (ER+) breast cancer for up to 10 years post active treatment and operates through impeding estrogen in the breasts necessary for tumour growth. The critical role of estrogen in cognitive functioning is well established (Sherwin, 2012; Luine, 2014). As such, the estrogen depleting nature of tamoxifen may have detrimental effects on cognition. Nevertheless only a small number of studies have examined the effects of tamoxifen on cognition in breast cancer,

with the majority including participants who'd also had chemotherapy, making inferences about the extent of tamoxifen's impact complex. Indeed, qualitative research examining CRCIs has thus far exclusively focused on the effects of 'chemobrain' with studies outlining chemotherapy as part of their inclusion criteria. Findings highlight, however, the real and damaging impact that cognitive impairments can have on long-term quality of life with an extensive meta-ethnography study emphasizing the negative consequences CRCIs can have on functioning at the personal, social and work levels (see Selamat et al., 2014). Nevertheless, the current qualitative research in this field is limited in that it fails to consider the current view of CRCIs as a phenomenon with multiple contributing factors. It follows then that more research investigating the role of other treatments, such as tamoxifen, in the etiology of CRCIs is necessary.

The Current Study

The current study directly examined the lived experience of a group of female breast cancer survivors taking the endocrine therapy tamoxifen in the absence of chemotherapy treatment. The study received ethical approval from the research ethics committee of the Department of Psychological Sciences at Birkbeck University of London. Informed consent was obtained from participants prior to participation.

8.2.2 Methods

A qualitative design using semi-structured interviews and interpretative phenomenological analysis (IPA) (Smith et al., 2009) was used to investigate the impact of tamoxifen on cognitive functioning in breast cancer survivorship. IPA, which is commonly used within health psychology, aims to investigate in detail how an individual makes sense of their life's experiences. Rooted in phenomenological philosophy and hermeneutics, IPA is committed to an ideographic focus which aims to understand how

a particular person makes sense of their experiences in a given context. IPA's in depth and personal interview style was deemed suitable for the current study due to the particularly sensitive nature of the topic and population. Through the rigorous analysis that transcripts are subjected to in IPA, it gives the researcher the opportunity to interpret accounts at a deeper level focusing on both the convergences and divergences within a participant group's experience. The 'double hermeneutic' (Smith et al, 2009), at play in IPA, (i.e. the researcher making sense of the participant making sense of a particular experience), allows for the researcher to both identify with and remain separate from the participant. The researcher is constrained to interpreting the particular experience through a unique person's perspective, however the researcher is also able to draw upon their own experiences and resources as a human in order to make sense of the world.

Participants

Participant demographic information can be viewed in Table 8.1. The study was advertised through the Birkbeck Centre for Building Resilience in Breast Cancer (BRiC) and various breast cancer support networks via social media platforms such as Facebook and Twitter. 7 participants were recruited for the study. Participants were required to be at least 1 year post diagnosis, to be currently taking the hormonal therapy Tamoxifen, and to have not had chemotherapy as part of their treatment plan. The mean age of participants at the time of participation was 51, and the mean age at diagnosis was 48. No participants were taking any psychological medication at the time of participation. All names have been changed to protect confidentiality. Participants received a fee of £25 upon completion of the study.

Table 8.1. Participant demographics and clinical characteristics.

Name (Pseudonyms)	Age	Age at Diagnosis	Ethnic Origin	Marital Status	Employment Status	Diagnosis	Grade of Cancer	Surgery Type	Radiotherapy
Ann	52	49	White British	Married	Part-Time	Primary	Low	Lumpectomy	Yes
Becky	53	51	White British	Married	Full-Time	Primary	Moderate	Mastectomy	No
Carol	53	51	White British	Married	Full-Time	Primary	Moderate	Mastectomy	No
Debbie	32	30	White British	Single	Full-Time	Primary	Low	Lumpectomy	Yes
Elaine	57	53	White British	Married	Part-Time	Primary	Moderate	Lumpectomy	Yes
Felicity	50	49	White European	Married	Full-Time	Primary	Moderate	Lumpectomy & Mastectomy	No
Geraldine	59	56	White British	Widowed	Full-Time	Primary	Low	Lumpectomy	Yes

Procedure

Participants were firstly asked to sign a consent form and complete a short questionnaire relating to demographic and treatment information. This was followed by a face-to face semi-structured interview, lasting between approximately 45-90 minutes. Table 9.2 presents the interview schedule for the current study. Initially participants were specifically asked to describe any general changes they'd experienced since taking tamoxifen to ensure particular responses were not elicited and to establish rapport. Participants were questioned in a flexible and facilitative manner which encouraged speaking about their experiences freely and in their own terms. If participants openly spoke of experiencing cognitive impairment, a gradual line of enquiry centering around this topic proceeded in order to gain a richer account of their experiences. An inductive approach was adopted for the interviews which allowed for the conversation to flow with the particular experiences of the participant. All interviews were audio-recorded with permission from the participants.

Table 8.2. Semi-structured interview schedule.

IPA Semi-Structured Interview Schedule

1. Let's begin with a timeline of your breast cancer. If you could please explain when you were diagnosed, what treatment you had, when your initial treatment started and finished, and when you started to taking Tamoxifen.

2. Can you describe to me any changes, if any, you have noticed in your day to day functioning and wellbeing since you started taking Tamoxifen? Prompts: *Can you think of an example that demonstrates this? How does this compare to before you started taking Tamoxifen?*

3. Have you noticed any changes in the way you think throughout your day to day life since you started taking Tamoxifen? Prompts: *Do you feel any different in functioning at work, managing home life, or interacting with your friends and family or in conversations? Do you feel as sharp/able to pay attention as easily? (If changes noticed proceed to Q's 4-6); If none noticed go to Q4 and then skip to Q8). Can you now compare this more recent period to before you took Tamoxifen?*

4. To what extent would you say that you've felt able to manage your thoughts and emotions since you started taking Tamoxifen? Prompts: *Does anything make you feel more in control over your emotions and thoughts? What makes you lose control? How does this compare to before you started taking Tamoxifen?*

5) Describe to me which particular aspects of your thinking seem to be most affected.
Prompts: *do thoughts come and go easily, or do you get stuck on some thoughts? Do you feel clear headed or fuzzy headed? Are you able to learn new things easily and quickly? Describe how focused/forgetful you are (people's names etc). How does this compare to before you started taking Tamoxifen?*

6) Describe any particular strategies you use to manage the way you think since you started taking Tamoxifen? Prompts: *To what extent do you have to exert more effort into tasks? How much more time do you need to spend or learning new information? What tools do you use to help?*

7) To what extent do you feel any changes you have described are a direct result of taking Tamoxifen? Prompts: *If so, why is it that you think that? What other factors may be affecting your wellbeing since your diagnosis?*

8) Describe to me your thoughts around continuing to take Tamoxifen moving forward.
Prompts: *Can you describe any time where you've thought about stopping? Can you describe any positive feelings surrounding taking Tamoxifen? To what degree is this a result of its side effects? How do you think your life would be different? What reasons would stop taking it?*

Analytic technique

The current study used IPA (Smith et al., 2009) as an analytic technique to examine transcripts. All interviews were transcribed verbatim by the researcher. Analysis of the transcripts included a number of stages. First the transcript was read several times by the researcher. For anything that appeared significant or of interest, initial thoughts were noted in the left-hand margin of the transcript or highlighted directly. The next stage involved returning to the transcript afresh and, using the right-hand margin, transforming

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initial ideas into more specific themes. Following on, the data is further reduced through establishing connections between preliminary themes and clustering them accordingly. The clusters are then labelled in such a way as to communicate the conceptual nature of the themes (i.e. the higher order superordinate themes). A final table is then produced demonstrating each superordinate theme and the subthemes that comprise it.

8.2.3 Results

The core superordinate themes along with their corresponding subthemes extracted from the data are presented in table 8.3.

Table 8.3. Superordinate themes and sub-themes.

Experiencing Cognitive Dysfunction	The Past, Present and Future Self	Coping with Cognitive Impairment	Consequences of Cognitive Impairment	Uncertainty Surrounding Tamoxifen	Scarcity of Awareness Surrounding Tamoxifen and Cognitive Dysfunction	Conflicted Feelings Towards Tamoxifen
Cognitive Domains of Dysfunction	Nostalgia for Past Self	Memory Aids: Technology, Physical Objects and Mental Repetition	Diminished Functioning at Work	Ambiguous Attribution of Cognitive Failures to Tamoxifen	Lack of Information/Support from Clinicians	Positive Feelings Towards Tamoxifen
Undesirable Feelings towards Cognitive Failures	Adapting to a New Self	Trivialising and Humourizing Cognitive Failures	Concerns for Career progression	Uncertain Trajectory of Cognitive Change	Value of Information and Shared Experience	A Balancing Act
Cognitive, Physical and Emotional Interactions	Ambiguous Future Self	Support/Lack Thereof from Others	Negative Impact on Social Life			
			Concerns surrounding Perception of Others			

Experiencing Cognitive Dysfunction

With relative haste, upon being initially questioned about general changes in functioning and wellbeing since the administration and commencement of Tamoxifen, participants reported experiencing continued cognitive failures across a variety of cognitive domains and life situations. As such, this has led to the development of the first

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superordinate theme being identified as 'Experiencing Cognitive Dysfunction', a core theme that paves the way for the remaining themes which are inextricably linked to the experience of cognitive failures.

Cognitive Domains of Dysfunction

Participants reported problems with a broad set of cognitive domains, including working memory and attentional failures, problems with language processes, decreased speed of processing, impaired learning abilities and problems with multitasking and executive functioning. The domains reported most commonly are described below.

Working Memory, Attentional and Executive Functioning

Problems with working memory, recall and attentional processes were consistently reported for participants across both their work and personal lives. Typically participants would have problems remembering family or social events, forgetting names and problems with constantly losing important items:

> "I left it in the house. I don't know why I did that. So it's just constant constant constant…Where's this?....Where's that?.....Which doesn't sound a big deal but actually it is." (Geraldine)

Here Geraldine describes the perpetual nature of her forgetfulness pointing to an internal struggle that has been ignited by such deficits. This was mirrored by other participants who described their memory problems as occurring 'everyday'.

Some participants described how quick they were to forget important information in a work environment:

"I've really noticed I could go to the boardroom, have a trustee meeting, and literally walking from the boardroom back to my office…if I don't write down the things I need to remember they're just gone. And I look in my brain…..looking trying to find things…...I think my concentration span definitely struggles more." (Felicity)

We really get the sense here of the struggle that Felicity experiences with her memory as she mentally searches for information she's recently been given. She looks for it, but it's gone. Geraldine indicates similar problems at work:

"Well, I have to sit and think, and by that time I've forgotten about what documents I'm trying to open or why I'm trying to open it." (Geraldine)

Elaine aptly encapsulated her experience of attentional failure by describing her thinking pattern as a 'massive spider diagram which is literally going everywhere', unable to concentrate on one topic before 'shifting and flitting from one thing to another'. Likewise Geraldine's reduction in acute attentional focus has affected her ability to multitask at work, commenting that 'I actually need to just do one task', and Debbie describes how in conversations her 'thoughts trail off' and she fails to remember what the other person has said. Participants further described frequent attentional lapses whilst doing an activity such as cooking or driving and walking into rooms only to immediately forget why they are there:

"You go in the larder for the umpteenth time or literally from just one moment in the kitchen to the other… you think, oh, what was it?......it's this sort of mind absence." (Felicity")

"I go around the kitchen and I forget what I was supposed to be doing; I often forget what I'm doing when I'm cooking." (Becky)

Language Processes and Verbal Memory

A number of participants expressed problems with word finding whereby they incorrectly expressed words for items or people, or through which the problem manifested by misnaming objects or people with whom they are familiar with. Geraldine explained how she would misname colleagues she'd worked with for twenty or so years:

> "In the end I just said Claire, I'm going to have to call you Catherine because I just can't get it in my head that you're called Claire - so we called her Catherine for two days….but why am I calling Claire Catherine? I don't know – no idea. I'm looking at her, I know she's Claire but I still say Catherine". (Geraldine)

It's interesting to see Geraldine's metareflection here. Whilst she is fully aware of the error she is making, she seems unable to regulate her responses. In the end, it is easier for her to accept the error and continue making it rather than wrestle for correction.

Felicity outlined similar experiences with objects:

> "Sometimes my head comes out with things which are similar to what I mean to say… and so even sometimes cutlery, if I wanted to say spoon. I'll come out with saying you need a knife…..and it's wrong." (Felicity)

A number of participants further described that they would be able to recall the first or last letters of a word but failed to remember it in its entirety. Carol described how 'even when I was watching the program, I would struggle to remember the name of it. And I know it either begins with a 'Pr' or an 'Er' or an 'Fr'.

Cognitive Lethargy and Brain Fog

Participants commonly described in various ways a decrease in the speed of their mental processing explaining that they often feel 'foggy' and 'slow'. Elaine described how she'd noticed 'a sort of fuzziness appearing if you like, a sort of a sense of not being as sharp and as alert'. Similarly Becky described the experience as 'that sort of jet lag feeling' and Ann commented that she felt that she was 'wading through treacle' in her thoughts. Carol commented that she's '100% just not as quick' and described how she felt a mental lag whilst speaking:

"I still speak as quickly, but my brain doesn't catch up as much as it did before". (Carol)

Felicity describes how her brain is always lagging behind and likens her mental state to that of a camera shutter:

"It feels like, you know how some people run and the legs drag behind, and the body's already somewhere else. Sometimes I feel that my face, everything is, my first thoughts are there, and I know what I need to do, but the brain's like with the camera shutter lag, that is what I feel I have." (Felicity)

Here we get the sense that whilst Felicity is aware of what she needs to do, her brain is unable to keep up and drags behind.

In addition to describing the types of cognitive domains affected, participants went as far as to describe the extent to which they'd felt a mental decline. Carol commented that 'it's a twenty to thirty percent decline in my performance' and continued on to liken her cognitive capabilities to a faded Christmas tree:

"Imagine you've got a Christmas tree lit up and you've got a hundred lights on the tree, I think about 20 – 30 percent mentally of those lights have now faded from there." (Carol)

Undesirable Feelings towards Cognitive Failures

Across participants, it was apparent that cognitive dysfunction, and in particular problems with memory, were a cause for great concern; typically such forgetfulness was frequent across tasks and situations that were previously handled with ease and as such brought about great frustration. A feeling of annoyance and irritability, predominantly directed at themselves, was commonplace:

"The sort of lack of cognitive sharpness I find frustrating and you know irritating." (Elaine)

"I get annoyed at myself…. It drives me nuts." (Ann)

In some instances the frustration brought about by memory failures provoked severe reactions. Geraldine commented that losing her diary had caused her to have 'a complete breakdown' and went on to describe how she would make herself physically unwell from how angry she became at herself over the mistakes:

"I become a person possessed I can't bear it. I actually feel you know physically unwell, as in the stomach aches. Sometimes I think I'm going to give myself a heart attack, I get so angry, so angry….. I don't beat myself up at anything apart from when I lose things and I actually make myself feel physically unwell. Not just lose things, but when in a muddle or whatever…I get so annoyed at myself." (Geraldine)

All of the participants expressed a general sense of vulnerability that the deficits have brought about describing reduced levels of confidence and self-efficacy. Multiple

participants described how they had started to panic over and question whether it was too 'risky' to attempt certain tasks in case they are unable to cope with them:

> "I might look at it now and just think, you know, I'm not even going to understand the instructions so I just might not even go there." (Elaine)

Others described how they had started to feel 'exposed', 'helpless' and even 'stupid' in some cases:

> "You know sometimes I get annoyed because I feel very thick and I'm not thick you know… because I'm just very slow to pick things up." (Ann)

Participants commonly described a sense of shame over their cognitive failures and often felt the need to hide their problems from others. Ann described how she doesn't 'like being laughed at' whilst others repeatedly spoke of how they were 'embarrassed' in front of others.

Cognitive, Physical and Emotional Interactions

As participants described their experiences of cognitive failures, other physical and psychological factors were brought up indicating an additive effect. For instance many described continued feelings of fatigue and physical lethargy. A number of participants also described how their cognitive failures often coincided with a physical side effect of Tamoxifen, such as a hot flush:

> "I was delivering some leadership management training a couple of weeks ago and there was a part when I just thought – I literally cannot remember the bit that's coming up next….I suspect it was also connected with having a hot flush…if I think back to that presentation there was probably a combination of this whole, you know hot flush coming on, being in front of people knowing that (the hot

flush) makes me feel completely out of sorts…. If I look back I can sort of see myself just freezing and thinking, literally what do I do?" (Elaine)

Similarly for some, increased cognitive load seemed to coincide with the onset of a hot flush:

"I do tend to get them (hot flushes) more when I'm driving which is a bit strange. I don't particularly get them when I'm at home, um, but I do quite often get them at work as well." (Debbie)

"When I first started taking Tamoxifen it was shocking… I couldn't remember anything, and then it got better and now it's bad again. It sort of seems to coincide with the fact that the hot flushes are worse." (Becky).

These excerpts suggest an interaction between cognitive, physical and emotional factors that increase the frequency and intensity of the deficits experienced.

The Past, Present and Future Self

The second superordinate theme reflects how experiencing cognitive failures has led to a general shift in identity and sense of self. Participants described a longing for their previous self, the continual struggle of adapting to a new self, and anxieties surrounding who they will become in the future.

Nostalgia for Past Self

Participants frequently expressed a sense of longing for a past self in relation to the cognitive capabilities they previously had. For instance comparison of current memory abilities were made against how they were in the past:

"It's just I doubt myself more inside now, so I will have two or three thoughts about something before I'll say something, or I just take longer to recall information. It's like getting a book from a library shelf – before I would have got

it straight away. Now, it will take me two or three minutes to bring down that book. And just the recalling information is not as quick and silly little things. And I used to have quite a lot of trivia memory about stupid things like the name of that program, which I still can't remember… and I wouldn't have forgotten those before. And it kind of eats you up a little bit inside slightly, and then you beat yourself and then I just start beating myself up about it and it just gets a little bit worse…it's a confidence issue and I'm trying to maintain….what's the word….I used to be very good with words as well…. No yeah it's confidence…. is the biggest thing." (Carol)

Here Carol is quite clearly anguished by the loss of her memory abilities, repeatedly highlighting how capable she was previously. Indeed elsewhere in her interview she commented that 'I just want to be like I was before'. Pertinently the explanation she gave about her struggles was demonstrated throughout the interview; on numerous occasions Carol had difficulty with memory, recall and word finding when trying to describe her experiences, leading her to get flustered and frustrated with herself at times when speaking. In addition she underscores the domino effect of her memory deficits – the distress of struggling with her memory leads to a worsening of the problem and a loss of confidence. Geraldine further affirmed the theme of nostalgia for her past self, commenting that she remembers 'the old me', and by describing how people used to interact with her at work:

"Before it would just be you know it was go and ask Geraldine, and it's great – loved it. Because I was in the company from when it was a tiny company, so I've always just been there… it's a bit hard really…just to…I still want to do that you know, that's what I love." (Geraldine)

Here Geraldine shows a love of her past identity in which her work colleagues would rely on and go to her for information due to her expertise. The sense of pain that she feels from the loss of her former self is unequivocal. Such sentiments were further emphasised

by Felicity who commented that she doesn't 'work on a level' that she has done previously. Other participants placed emphasis on an emotional shift they have felt since starting tamoxifen. Elaine highlighted a stark contrast between her former confident self and her present self in which she feels more hesitant about the world:

> "I just don't want to be out here, I would rather be safely tucked away at home, and again, that is such a change for me. I'm quite a sociable person, I quite liked to be with people, I was happy to be busy and working, to be travelling a lot prior to that. And you know those sort of changes in your life stop certain things." (Elaine)

We really get the impression here of Elaine's loss for her former outgoing and confident self through the vulnerability she now feels when interacting with the outside world. For her, it would be easier to stay home where she feels comfortable than to face 'that big wide world'. She goes on to attribute her feelings to 'being on this type of medication, this sort of hormone therapy' indicating that it can change 'perceptions in terms of whether you can cope out there'.

Adapting to a New Self

Participants described how the process of adapting to their new and current self is ongoing and predominantly challenging. For example Felicity expressed how in the past she identified as the 'fixer' in situations of conflict both at work and at home. However as her new self she has struggled to play this role:

> "I will always try and smooth things over and that, I like doing that, but if all of a sudden if you think you can't always cope with what you have to deal with…" (Felicity).

In relation to her new problems with memory and organisational skills she comments that 'for a German OCD person that is really unheard of' indicating that she feels she's not

the same person that she once was and how she wants 'to go back to normal, you want that back'. We gather here her sense of frustration adapting to these changes; she doesn't feel that she is 'normal' any longer, but a different, more difficult self. Others expressed concern over the perception of others in relation to their 'new' self:

> "I don't want pity or anything but I suppose when you're saying it you're always asking for a little bit of extra levity…or what the word is…or you're asking not for an excuse, but I do want to let people know I guess that it's not really me, and this is not the real me." (Carol)

Here Carol shows her difficulty in adapting to her current self and indicates a lack of acceptance for her current state asserting that it's not the true version of herself. The desire to declare this to her colleagues is indicative of the internal struggles Carol faces in adjusting to the changes she is experiencing.

Ambiguous Future Self

A common theme amongst participants related to ambiguity about who they will develop into as a person in the future, however there was both commonalities and differences amongst participants in how this was portrayed. For instance, some participants expressed hope and expectations that they will return to their former selves and regain the capabilities they feel they have lost:

> "I look forward very much to a time when I'm not taking it. And I...my perception of that time in terms of not taking it is that I, part of me that I've lost I will regain once I stop taking it and that some of those things will come back." (Elaine)

> "I'd get some memory back, that would be very nice." (Debbie)

On the other hand, a number of participants expressed fears that their cognitive deficits will continue to get worse, with some fearful that such problems are an early sign of a neurodegenerative disease:

"Well I'm worried about dementia and hope it's not dementia." (Ann)

"Scared in terms of is it going to get any worse." (Carol)

"And I suppose you…everybody worries about getting Alzheimer's don't they…so there is always that in the back… is this Tamoxifen or am I just going completely crazy." (Geraldine)

It is remarkably evident here how worrisome participants find their cognitive difficulties in that they have become fearful of neurocognitive disease in the future.

Coping with Cognitive Impairment

Participants described various coping mechanisms that they had developed in order to compensate for their deficits and continue functioning at pre-morbid levels of performance:

Memory Aids: Technology, Physical Objects and Mental Repetition

The most common coping strategy reported by participants related to memory aids used on a daily basis. Participants emphasised the importance of writing things down using sticky notes, calendars, notebooks and lists as mental reminders. The need for writing things down immediately, especially in work-related situations was emphasised due to the difficulties experienced with short term memory:

"I wrote myself a post-it note last night to make sure I put it out this morning because it wasn't out, so I put it out. So just little reminders. If I have a sudden appointment, I put everything on the calendar…..on what I call our family

planner.. but if something comes up that's quite sudden I will write myself a post-it note and put it either in the study or in the hallway." (Ann)

The frequent use of technology was consistently reported as a memory tool. Participants described how they would send emails to themselves, take photos of important information and write lists on their phone. Some participants had invested in new pieces of technology such as a watch that comes up with message alerts from their calendar as reminders. Debbie went as far as to comment that 'my phone is my life' indicating that she views technology as a lifeline in helping her cope. In addition participants described how they would use mental strategies to remember day-to-day items or events. For instance, Carrol described how she would use mental repetition in order to remember to take her lunch to work:

> "I will say right 'soup soup soup' and I'll make it into a little song or something." (Carol)

All participants commented that the strategies now employed in order to cope were in contrast to how they previously would function without the need for memory aids.

Trivialising and Humourizing Cognitive Failures

Making light of and humourizing cognitive failures as a means to cope was an emergent theme across transcripts. It appeared that this strategy has been adopted by both participants and their family members alike. Carol commented that she would only forget 'silly little things' none of which were 'vitally important'. Here we get the sense that she is trying to downplay the importance of the information that she forgets in order to minimise their impact. Similarly Elaine described how she'd 'learned to sort of make a joke of it' and Geraldine commented that 'you make light of the because you have to'. It seems that the participants use humour as a line of defence in coping with their deficits as they feel there is no alternative option. Participants also noted that their family

members trivialised their memory problems. Ann described how 'in terms of forgetfulness basically the family laugh at me' and similarly Felicity remarked that her family 'laugh because they think it's funny'. We get the impression here that participants feel a lack of understanding from their family members and actually feel somewhat hurt by their family diminishing the problems with their memory. Ann, in fact, found this the cause of great distress explaining how she doesn't 'like being laughed at for forgetting things'. We gather that Ann feels a sense of humiliation and indignity from her memory deficits which is exacerbated by her family's need to devalue their importance, which is perhaps reflective of their own way of coping with such changes.

The Need to be Organised

In light of the persistent memory failures experienced by participants, a common strategy that arose as a coping mechanism was the need to be extra organised. Participants spoke of needing to keep their possessions in 'a certain place' to avoid losing them and the necessity to keep an exceptionally tidy environment:

> "Yeah I have a really tidy house. Really really tidy house and I really try and keep on top of everything. So whether it be bits of paperwork that needs to be sorted or just literally putting dishes away or putting things away so I have less opportunity to lose things." (Geraldine)

In the same way participants felt a pressing need to structure and plan their lives to aid coping:

> "I've never been, I'm a doer not a list writer. My husband's more of a list writer, he makes lists for everything. Even shopping lists I don't, because I've got it all in my head. But now I need to really have a plan of what I'm doing…. Now I've got like books, notebooks where I write everything down." (Felicity)

We see here how Felicity used to function without the need for lists or memory aids, however now it is critical for her to be organised and well-structured in order to manage.

Support/Lack Thereof from Others

The importance of support and understanding from others was apparent across interviews, however participant's experiences of this were divergent. On the one hand some participants described how their close family members were a great source of assistance to them and had adapted their own behaviour in order to offer support:

> "He's been well aware (the husband) of the side effects of the various medications and treatments that I've been on and I think that we've kind of accepted it as a status quo that actually, that loss of sharp thinking is how it is. And he would easily talk to me about it, I would easily talk to him about it because I would share my frustration about it with him and I think he's probably adapted slightly the way that he might give me some information." (Elaine)

> "But I would think okay I'll wait until Ben is about and then we'll have a look at it together. So I think what you're kind of doing is trying to mentally replace that cognitive function by perhaps borrowing someone else's." (Elaine)

We can conclude here that for Elaine, the support and understanding offered by her husband is invaluable. Not only does he offer comfort by listening and talking through the problems with her, but at times Elaine feels she can utilise his cognitive functions as a substitute for her own. In contrast, for others, it appears that their family have shown little understanding for the cognitive impairments experienced:

> "I definitely noticed it within a few weeks because my husband kept complaining and I wanted to send him an email saying read this article about what Tamoxifen does to your memory….. it's still in my drafts box." (Ann)

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We sense Ann's frustration here at her husbands' complaints regarding her memory failures; she does not even feel comfortable enough to send him information explaining the potential side effects of tamoxifen on cognition. Similarly Geraldine described how her daughter was having difficulty accepting her mother's changes explaining that 'she doesn't want to see her Mum being a twit'. Nevertheless, whilst her daughter is clearly struggling to come to terms with such changes, Geraldine described how her daughter had now adopted the parent role in certain situations demonstrating support:

> "She's more of the grown up now I think possibly in the relationship when we're together. Because we were on holiday, you know, we go in a little holiday every year and she is the one now that would you know be looking after the passports, making sure we've got the reservations for dinner, all that kind of stuff. So she's taking the lead there. So yeah, it's not easy for her." (Geraldine)

For Felicity, whilst she felt that her family was understanding of her problems, she felt that her workplace had little tolerance for her difficulties with coping, commenting that there's 'no slack at work'. Upon asking her boss for reduced hours or help with her role, her boss refused and showed little empathy for her struggles to function efficiently. This lack of understanding in the workplace was corroborated by Debbie's experiences:

> "I think a lot of people because I'm younger, don't quite understand that younger girls can be forced through the menopause as well. Um, so they might potentially be you know, in their 40s but they've not started the menopause, and I don't think they understand the symptoms of it… like with your memory." (Debbie)

We see here the social expectation that because Debbie is still in her early 30s, she should be high functioning. Her colleagues appear to have little knowledge or understanding about the cognitive side effects of breast cancer or the menopause, as highlighted.

Consequences of Cognitive Impairment

The consequences of cognitive impairments for participants largely related to the workplace, social lives and concerns surrounding how their 'new self' appears to others.

Diminished Functioning at Work

Participants commonly described how their cognitive impairments have resulted in damaging consequences at work. Participants expressed an inability to function at premorbid levels and as such, have struggled to cope. Here Elaine describes giving a presentation to her colleagues:

> "I was delivering some leadership management training a couple of weeks ago and there was a part when I just thought I literally cannot remember the bit that's coming up next. And again I don't think that's the kind of age-related thing necessarily, it was literally my brain had actually emptied if you like at that particular point………….If I look back now, I can sort of see myself just freezing at that particular point and thinking, you know, literally, what do I do? What do I do now?" (Elaine)

Here Elaine gives an apt example of mind blanking in a work scenario indicating how detrimental the deficits can be to her career. We sense the feeling of panic she clearly felt under the pressure of delivering training whilst knowing that her cognitive capabilities are not as they once were. Correspondingly, Geraldine expressed a new sense of feeling overwhelmed in the workplace:

> "I'm a sales manager, I've got a big team so the door is always open, so people are constantly firing, so they might just come to the door for me to say yes or no to something. Can we do this? Yes or no. And then someone comes in and says could you just tell us you know, what do you think about this? Can you just proofread this for me? So, but it's constant. So then I'd put that down, and they'd

be something else on my desk. And that's what I used to love it's like, you know, suddenly the phone rings and this this this this, but now I actually just want to scream, will you all just shut up and let me finish one thing and then come up with the next thing. So I find that multitasking at work very difficult." (Geraldine)

Here Geraldine shows how the fast-paced office environment that she used to relish in and enjoy has now become a source of stress as she feels less capable to keep up with the demands of her role. We sense a feeling of disappointment in herself; it is clear that she has always excelled at her job and thus has found the shift in her capabilities arduous.

Concerns for career progression

Many participants expressed anxieties surrounding the future of their careers. Debbie, for instance, who works as an accountant is required to do continued professional development as part of her job. She expressed having difficulty retaining information in training sessions and as a consequence felt unable to take exams:

"If I was asked to take an exam I'd say no because I just wouldn't be able to retain anything." (Debbie)

Here we can clearly see Debbie's diminished self-efficacy and apprehension in progression in career related tasks. For others, direct threats regarding potential changes to their current roles generated great distress for those whose identities are evidently tied to their working role:

"When you get the threat at work where somebody says to you oh, we'll just have to take you out of HR and you'll just do something else, that's very, that means a lot. You know, it's very hurtful for me because I think my vocation, you know how some people want to be a nurse or want to be a doctor or want to be a policeman, my vocation is to help people, make sure that everybody is you know

happy and that you always come to a conclusion which works together for the company and the employee." (Felicity)

Felicity seems tormented here by the disposable mentality of her superiors at work. For them, it would seem, she is just an operational part in the mechanics of a corporate company, however for Felicity, her role in HR is entangled with who she feels she is as a person. Accordingly their dismissive attitude appears to her as an attack on her identity.

Concerns surrounding the perception of others

The perception of others surrounding their cognitive decline appeared to be a great cause of concern for many participants and they frequently reported the desire to hide their deficits from others:

"So I would raise it before anyone else has got the chance to raise it…. If they don't say it and if it's not acknowledged then it's not real, do you get what I mean. Yeah I'll step in first and say oh God it's my tamoxifen or my chemobrain whatever first.. and a lot of it is in my head and in my thinking which isn't…..obviously I don't think out loud so they wouldn't notice that I was making mistakes, or they wouldn't notice that I'm not recalling as much as I used to. So I can hide a lot of it probably. But I'm just conscious if it gets worse then it's not so easy to hide. And I just don't want to be that person that someone has to say oh Carol you've forgotten this or you've done that." (Carol)

"I choose to work but that's really important to me for something to do. I think you're just worried that once they see a decline you'll be treated differently. And then I think that has a sort of knock-on effect that you then will have a lesser thought of yourself…..I probably do go to some degrees to hide it." (Carol)

In these two excerpts Carol indicates that, for the most part, she tries to hide her cognitive deficits from her work colleagues and is quick to acknowledge any errors herself, in an attempt to minimise their impact in front of others. Carol highlights how important

working is for her and fears that if people notice her decline, people will view and treat her differently. Carol's self-esteem appears to be rooted in her ability to function well at work, and therefore the thought of this outcome is exceptionally painful. Geraldine has similar concerns about her work colleagues noticing her cognitive failures:

> "People do notice, my colleagues notice. My right-hand lady, in days gone by she'd be called a PA, but she's certainly not she's way more than that. I was doing a presentation to the international group and she said, I booked the meeting room for an hour and a half beforehand. I said, have you why? She says I think you should go down and practise your presentation, which is really sweet…looking out for me, but I'm thinking oh, but God you've noticed then haven't you….but she said, also some of the team know that you forget stuff…..well they'll use it to their advantage because they'll say, now I'm sure Geraldine said that I could do that… knowing you'll go… did I? And that's very frustrating, very frustrating especially if you're a control freak. So yeah." (Geraldine)

Here we see that Geraldine's work colleagues have not only noticed her memory failures, but it is reported that they have started to exploit them, using it to their own advantage within work situations. This is a cause of great frustration for Geraldine who is used to being proficient at her job.

Negative Impact on Social Life

Participants described a shift in their social lives indicating that they often would forget important events such as birthdays entirely. For instance Debbie expressed a strong sense of guilt for recently forgetting to buy her Aunt a birthday card, however she explained that 'I can't think of other things… think about others. I'm a lot more selfish. Unintentionally, but I just don't have the brain capacity to think about others as much'. Here we gather that Debbie has inadvertently become less sociable simply because she

doesn't feel capable. In addition, participants expressed a loss of enjoyment in activities they used to take pleasure in:

> "I mentor a little girl with a befriending project, these are socially isolated children, and I used to really love, used to really love it. And now after work I'm thinking…ooooh I've got to take the child out and that's such a shame because it should be a joyful experience for her and me and it's just like I don't have the energy…….it's a shame because I used to love things like that and it just really really upsets me that I don't get the joy from that anymore." (Geraldine)

> "I never had a telly until recently…..and now I'm thinking oooooh I don't really want to go to that sixties night. I think I'll just stay in and that is so alien to me. I was the girl that was out dancing really out dancing on a Friday and Saturday despite my age. Me and my friend would clear the dance floor and we would just go to gigs and things but now it's just easier to stay in." (Geraldine)

In these two excepts Geraldine indicates how different her social life has become. It seems she feels a real sense of loss for the enjoyment she used to experience through her volunteering work and has feelings of guilt towards the girl she mentors, indicating that she now perceives it as somewhat of a chore. In the same way, whereas she used to enjoy going out and socialising with friends, it now feels far too effortful.

Uncertainty Surrounding Tamoxifen

Ambiguous Attribution of Cognitive Failures to Tamoxifen

Participants generally attributed their cognitive changes to tamoxifen, however to varying degrees. Whilst some participants felt with certainty the changes were as a result of the medication, others felt confused over whether other factors such as age, the menopause and other side effects such as fatigue were contributing to their mental decline. Ann comments that 'whether it's the tamoxifen, the menopause, or both, I don't know – they all intersect' and later, 'because of my age I don't know what's causing

what'. Similarly Geraldine rhetorically questions 'how much of that is tamoxifen and much of that is getting older?'. On the other hand both Felicity and Carol feel certain such changes are due to tamoxifen:

> "I think a hundred percent……I don't think there's a problem in my brain with regards to my brain matter. I think that's all hunky-dory up there. But I just think the tablets do something, a reaction, where you have a delay. I'm still all there because otherwise I wouldn't be able to function. It just costs me a lot more focus, a lot more determination." (Felicity).

> "They all are a direct result (of taking Tamoxifen). Because I don't see, and they've all happened so quickly, and they can't naturally……. But 100% all of it, there's no way this would have happened just effectively overnight." (Carol)

Both Felicity and Carol here show total attribution of their cognitive failures to tamoxifen.

Whilst for some participants the exact etiology of their deficits remained ambiguous, many participants expressed hope that they were related to tamoxifen. Ann commented that 'I think, and I hope that a percentage of the memory is down to tamoxifen for sure' which is mirrored by Felicity's hopes:

> "I think in these studies, when they look at a lot of people, maybe it crystallizes out of that, the effects are not age related, but it's more related to tamoxifen. That would be great because I think that will help everybody to sort of then be able to say it's not your age, you know, it's not you going doolally, or you not being able to power on a hundred and ten percent all the time. You need to sit back, or you need to be mindful of that, you don't have the energy anymore. I think that would be comforting". (Felicity)

Here we gather that Felicity is hopeful that more research into the effects of tamoxifen will result in a greater awareness of the cognitive side effects of the drug. For her, she

believes that women would find this information soothing and help reduce the uncertainty surrounding the cause of their cognitive failures.

Uncertain Trajectory of Cognitive Change

Participants expressed uncertainty and discrepancies surrounding the trajectory of their cognitive change. For some participants, they felt that whilst they felt an acute onset of cognitive failures when initially starting tamoxifen, they'd felt that they had reduced over time, indicating partial recovery:

> "I found myself getting slower. I definitely forgot words for things…..That's all settled down a bit now." (Becky)

On the contrary, other participants felt that their cognitive failures have got worse over time:

> "It seemed to get worse about a year after I started taking Tamoxifen. It's probably been there and probably been building up, but I really really noticed it about a year or so into taking the tablets." (Debbie)

> "It has been sort of what's the word, accumulating, so it's almost like the effects get worse. So I was thinking, oh no it will settle down, settle down in six months, but I'd say two years on I am more puddled." (Geraldine)

Scarcity of Awareness Surrounding Tamoxifen and Cognitive Dysfunction

Lack of Information/Support from Clinicians

None of the participants were given any warning about the possible cognitive side effects of tamoxifen by their healthcare providers:

"I mean all I was told is that it's going to give you menopausal symptoms. But you know, you don't know what those are…. I didn't know about the brain fog and forgetting words and your train of thought and I mean I just thought it was hot flushes." (Becky)

Here Becky shows that she felt left in the dark about the potential side effects of tamoxifen and goes on to comment that 'I wish I'd known that, but I found out quick enough'. Felicity mirrored this sentiment pondering about 'why the doctors don't tell you all these things'. This feeling was further reiterated by other participants:

"I think if you look on the patient information leaflet, it's much more about the physical things……you know, where do you go for your information? Is it talking to other women, is it talking to a Macmillan nurse, is it talking to your oncologist?" (Geraldine)

"I think it's probably there if you are able to search for it and access information and perhaps whatever kind of practical support that you might need. I don't think it's forthcoming and I don't think it's offered straight away as a, you probably are going to need this………so it's (tamoxifen) kind of presented to you as a sort of, you know, after you've crossed the line you finish that race, so you've crossed the line and then we're just going to give you… we're going to dish out these sort of you know aspirins to you. So you don't feel the weight of what's coming." (Elaine)

Both Geraldine and Elaine express the scarcity of the information available to them and indicate inadequate support from the medical community. Geraldine goes so far as to suggest that health professionals downplay the potential impact of tamoxifen by likening them to a box of aspirin. She even goes on to say that she felt 'almost quite confused and quite duped if you like'. It is clear that both participants felt unprepared for the cognitive changes they have experienced which is exacerbated by a lack of validation from clinicians. It seems that participants, after experiencing cognitive failure, were pushed to

research such side effects on their own terms, with whatever resources they had available to them. Even then, it seems, participants struggled to always find necessary reassurance:

> "I researched further about tamoxifen and about how potent a drug it is, and the different effects people were having. I didn't in the early days make the connection between the fuzzy thinking and the sort of slight anxiety. I didn't make the connection with tamoxifen because the information out there is very much about chemobrain and people who you know who've had chemotherapy talking all the time about them feeling foggy and you know, kind of blurry, and all those sorts of things. And not having had chemotherapy, I didn't make that connection and it may sound an odd thing to say but I didn't feel I had the right to make that connection because when you don't have chemotherapy you're eternally grateful that you haven't had to have chemotherapy. But in some ways, I don't exactly know how to describe it to you but in some ways it feels to me that I haven't done it properly that I've got away with something that I've managed to, cheat the system almost." (Elaine)

We see here the struggle felt by Elaine whilst trying to make sense of her own cognitive failures. Whilst there appears to be a lot of information readily available regarding the effects of chemotherapy, information regarding the impact of tamoxifen on cognitive function is limited. Moreover, Elaine expresses a sense of guilt in even acknowledging her deficits since she did not undergo chemotherapy. She further explains that she'd 'be very hesitant to talk to a lot of people about it' because she feels 'fraudulent' and thinks that her 'feelings are not valid'. She therefore questions whether she should be 'moaning' about it. We can really feel how critical Elaine is of herself here. She believes that her struggles do not deserve attention because she has not had chemotherapy treatment and thus feels that her experiences are not justified.

Value of Information and Shared Experience

When participants did come across information relating to the cognitive impact of tamoxifen, they commonly found it reassuring, and helped to relieve some of their anxieties:

"And I just think it's an information-gathering, sometimes just a relief thinking, oh I haven't got that, you know." (Carol)

Moreover, participants found great comfort in interacting with other individuals who'd experienced cognitive deficits since beginning tamoxifen:

"It's nice to have something in your pocket where you can just write something down and someone could be in exactly the same boat as you and it just makes you feel normal…… invaluable, really invaluable." (Debbie)

"It's just interesting to see other people's experience of it, coping mechanisms, any new symptoms that they've identified that you think might be coming, so some of those are sometimes quite reassuring as I said, that it's more likely to be the drug rather than anything else nasty." (Carol)

"But I know I wanted to try and find out a little bit more about well, you know, is this happening to other people, is this a common occurrence because in a way that's a safe space, isn't it? If you're not the only one, then you kind of think okay fair, in a way fair enough, this is one of those things that's happening to other people, it doesn't make it necessarily any more straightforward for you to manage but you at least know that you know, you're not on your own." (Elaine)

These three excerpts show the value of reciprocity with others experiencing cognitive side effects from tamoxifen. We sense the reassurance that each participant feels through knowing that they are not alone in their experience, and the relief they gain from finding out that they are not 'abnormal'. We gather that through speaking with others in the same position, participants are able to gradually make sense of their experiences of cognitive impairment.

Conflicted Feelings Towards Tamoxifen

We gather that participants have conflicted emotions towards tamoxifen. On the one hand, participants are enormously grateful that they are able to take a medication that may reduce their risk of cancer recurrence. On the other hand, participants resent the daily struggle they now face in adapting to their current state of being.

Positive Feelings Towards Tamoxifen

In spite of all the complaints expressed about the side effects of tamoxifen, overall, many participants expressed an overarching attitude of positivity towards the medication:

> "So it's like I think perhaps psychologically I consider it as my life raft….. to me it's sort of a positive factor keeping the cancer at bay." (Ann)

> "My general feeling is it's a good thing. It's positive because it stops estrogen and my cancer is estrogen fed, therefore it will stop the cancer coming back. So for that I think it's an amazingly positive thing." (Becky)

> "It's probably what I'd call an insurance policy….. it's almost like I feel, it's the feeling of eating an apple or eating a salad. I feel good about taking it." (Carol)

> "It is a, you know, it is a wonder drug." (Elaine)

Here we really gain a sense of thankfulness towards tamoxifen as participants reflect on their survivorship. Many acknowledged that for other types of cancers preventative medication is not available, and with this in mind, they felt fortunate. We gather the impression that in fact participants view the medication as their lifeline which is illustrated by metaphorically labelling tamoxifen as an insurance policy. For some participants the hope attached to the drug appeared extreme:

"It's almost like it's my only little hope to really make sure it gives you another chance….I just see it as a positive and a lot of people might laugh about that and say yeah, but it does do a lot of things which are not ideal……but to me, it's more this, I have this want of being alive….With my shoulder where they said, you need to have an operation to correct something, I'm terrified of the anaesthetic. I'm terrified of being off tamoxifen for two weeks because I'm thinking, because to me it's everything….If the doctor was to say to me you need to take a happy pill, I'd say no because I do not want anything in my, I want to have a virgin body if that makes sense with regards to medication so that I feel that tamoxifen can work best if it's not affected by anything else that I take……I did an eyesight test and you know, from the prescription from two years previously it had worsened – maybe that was from the tamoxifen, I don't know. I haven't mentioned it to the doctor because I don't want them to say you can't take tamoxifen anymore. Because I want to take it…. You start handling life where you think okay, even if I was to go blind at least I hopefully would be still here." (Felicity)

The desperation Felicity expresses here is palpable. Her desire to stay alive has led to an obsessive attitude towards taking tamoxifen indicating that she views it as her whole world. This feeling is so extreme that even when she has experienced other health issues that may be linked to tamoxifen, such as a degenerative eye condition, she refuses to disclose this information to her doctor for fear of being taken off the drug. Felicity sees tamoxifen only as a positive as for her, it is her only hope of staying alive.

A Balancing Act

Participants indicated a constant battle with themselves continually weighing up both the positive and negative sides of tamoxifen:

"It's the balancing this and the daily sort of little embarrassments…….I guess I could stop it, but do I want to live with the consequence of the fear of it coming back, and so it's a trade-off basically." (Carol)

"I mean I was so grateful for it, I have to say, but also there's that kind of double edged thing, on the one hand you're really grateful for it, the other hand, you know, it's not making me feel great….. so I got away lightly which I'm really grateful for, but it's kind of still there niggling away every day niggling away." (Geraldine)

Here participants express their conflicted emotions towards tamoxifen. Whilst they are extremely grateful for the drug, taking it comes with a cost which affects their quality of life on a daily basis. Becky even expressed doubts about taking the medication for the recommended 10 years:

"I don't know if I want to take it for 10 years. I think five years might do me. We'll see. I'll see how I feel in three years' time." (Becky)

8.2.4 Discussion

The current study investigated the lived experience of a group of female breast cancer survivors taking the endocrine therapy tamoxifen in the absence of chemotherapy treatment. First and foremost, the study demonstrates that cancer-related cognitive impairment (CRCI) is a real and problematic phenomenon for this subgroup. This finding is critical in that it extends upon the current qualitative research in this field (which solely concentrates on the experience of 'chemobrain'), by emphasizing the perspective that CRCIs should be considered as a multidimensional condition which has many facets to its etiology (Ahles & Root, 2018).

In line with, and extending upon other recent qualitative studies investigating chemobrain (Selamat et al., 2014; Henderson, Cross, & Baraniak, 2019), our findings can be considered within the framework of Leventhal's Illness Representation Theory, which has more recently evolved to Leventhal's Common Sense Model of Illness Representation (Leventhal et al., 1997; Leventhal, Phillips, & Burns, 2016). Illness representation refers to patients' beliefs and expectations about a specific illness or

symptoms. Using Leventhal's framework we are able to gain an overarching view of the burden that cognitive deficits can have for breast cancer survivors treated with tamoxifen allowing for further interpretation of participant's experiences. Whist the analytic approach utilising IPA was inductive, the use of a theoretical framework relating to illness representation facilitates the recognition of CRCIs as a genuine condition that requires recognition from the research and medical community alike.

In line with Selamat et al., 2014, the dimensions of the illness representation considered in the discussion include *identity, timeline, consequences, causes, controllability, illness coherence and emotional representations*.

The dimension of *identity* refers to the manifestiation of symptoms or illness and as such can be demontrated by the identified superordinate theme 'Experiencing Cognitive Dysfunction'. Analysis indicated that all participants experienced CRCIs predominantely with functions of working memory, attention, executive functioning, language and verbal memory as well as cognitive lethary and brain fog. Within the subthemes indentified, participants described how cognitive failures were compounded by other factors such as cognitive load and other physiological side effects such as fatigue and hot flushes.

The *timeline* of cognitive impairment remains ambiguous for participants, as demonstrated by the subtheme "Uncertain Trajectory of Cognitive Change' under the superordinate theme 'Uncertainty Surrounding Tamoxifen'. Participants had difficulty in pinpointing exactly when their cognitive dysfunction began, with many reporting that they only noticed them months after their intial diagnosis. That said, participants suspected that their awareness of the problem was blinded by their emotional reaction to the cancer diagnosis itself. Dispcrepencies regarding the progression of CRCIs were apparent. Whilst some participants found that their initial dysfunction had eased, others felt that their impairments had got progressively worse over time. Accordingly, this led

to ambiguity surrounding potential recovery from cognitive dysfunction in the future. Whilst some believe that the impairment is a transient state that will exist only whilst they are taking tamoxifen, others have fear that symptoms will persist post-tamoxifen.

A significant number of *consequences* were identified as a result of cognitive impairment, as demonstrated by the superordinate theme 'Consequences of Cognitive Impairment'. Participants strongly emphasized the negative impact that their cognitive impairment had on their functioning at work. Participants commonly reported struggles with their memory, attention and mulitasking skills in a work setting, leading them to feel overwhelmed and less able to cope with their roles. Consequentially, this led participants to develop anxieties surrounding the progression of their careers. In addition, participants described heightened awareness and anxieties surrounding the perceptions of others, which was particularly amplified at work. Participants were so concerened that they would be viewed negatively as a result of their cognitive impairment, that they felt the need to hide their deficits from colleagues. Further consequences extended to a negative impact on social interactions. Participants described a lack of motivation for social activities they previously enjoyed and a reduced capacity to remember others. Moreover CRCIs resulted in alterations in how participants viewed themselves, as exhibited by the superordinate theme 'The Past, Present and Future Self'. Participants pined for their former, more capable selves repeatedly voicing that they just wanted to return to how they used to be. Accordingly, they felt the process of adapting to their new self difficult, pointing to a lack of acceptance. Anxiety surrounding participants' future selves was also common, though beliefs were disparate. Whilst some expected to somewhat return to their former selves, others feared further decline and the development of neurodegenerative disease. This adaptation in sense of self is documented elsewhere in health psychology literature. For instance, in a study exploring the lived experience of chronic pain, participants illustrated how their condition had resulted in the deterioration

of their self-concept and a struggle to accept their new unwanted self, compared to their previous self, the favoured 'real me' (Smith & Osborn, 2007). Like the current study, a major theme that emerged focused around the perception of others leading them to withdraw from social situations or over-compensate depending on the context. This is reflected in the current study by participant's concerns over the perceptions of their work colleagues, and the sense that they need to work harder to compensate for their cognitive failures so that they go unnoticed. Given that the acceptance of illness in chronic disorders is an indicator of functioning and predictor for quality of life (Mazurek & Lurbiecki, 2014), this finding is particularly pertinent.

The *cause* of CRCIs was attributed to tamoxifen to varying degrees as outlined in the subtheme 'Uncertain Attribution of Cognitive Failure to Tamoxifen' within the 'Uncertinaty surrounding Tamoxifen' subtheme. Whilst many participants believed that their deficits were caused entirely by tamoxifen, others showed confusion surrounding the impact of other factors such as age and the menopause.

The *controllability* of participants' cognitive defictis involved a number of coping strategies that were self developed as decribed in the superordinate theme 'Coping with Cognitive Impairment'. For instance, participants highlighted their increased need for memory aids in the form of writing, technology and mental memory techniques. Participants further emphasized how invaluable they found social support, when it was offered. In addition, participants frequently reported that they were only able to maintain their level of functioning through increased effort and concentration. It seems probable, however, that this will lead to increased fatigue for participants, and thus may not continue to be a sustainable coping mechanism.

In terms of *illness coherence*, participants indicated an uncertain understanding of their cognitive impairments, as demonstrated by the superordinate theme 'Uncertainty Surrounding Tamoxifen'. Participants appreared to be in a perpetual struggle with

themselves questionining why they were experiencing cognitive failures and attempting to make sense of them. This is coupled witht the fact that they were given no information or support surrounding potential cognitive dysfunction from medical practitioners, as outlined in the superordinate theme 'Scarcity of Awareness Surrounding Tamoxifen'. Indeed, healthcare providers appeared to downplay the impact of tamoxifen leaving participants unprepared and ill-equiped for the potential impairments to cognition. It is unsurpring then, with little validation from the medical community, that partcipants struggled to comprehend their experiences. After connecting with other breast cancer survivors who had shared similar experiences of cognitive failure since taking tamoxifen, participants felt great comfort and were able to somewhat normalise their impairments, and feel less isolated. This finding builds upon other research surrounding the distress associated with ambiguous health conditions. For instance, a recent study investigated depression symptomatology and perceived distress in women with chronic fatigue syndrome (CFS) and fibromyalgia, compared to those with an autoimmune disorder, (McInnis, Matheson, & Anisman, 2014). Whereas CFS and fibromyalgia are disabling chronic conditions without objective disgnositic tests, clear-cut treatments or established etiologies, chronic autoimmune disorders are medically accepted. Findings indicated that women with CFS and fibromyalgia reported higher depression scores, greater perceived distress and more frequent unsupportive relationships than healthy women, whereas those with an autoimmune disorder showed intermmediate scores. In addition, high problem-focused coping was associated with low levels of depression and perceived distress in those with an autoimmune condition, but not for those with CFS and fibromyalgia. The authors concluded that because the veracity of ambiguous illness is often doubted, this may potentiate distress in those suffering from such conditions and may render typical coping strategies ineffective. Taken together with the current study, findings point to the

importance of appropriate education for health-care providers and the general public in spite of a condition's ambiguous status.

Finally, the dimension *emotional representations* is captured by the many and complex emotions described by partcipants. Participants express an immense amount of frustration towards their cognitive failures. Such anger is predominitely directed at themselves for making such errors which in some cases led to participants making themselves ill through stress. Participants further expressed a number of anxieties surrounding the perception of others, fears for the progression of their impairments and concerns surrounding future employment. In spite of these negative emotions experienced, participants expressed an overall sense of gratefulness towards tamoxifen as they reflected on their survivorship.

Clinical Implications

In line with perspectives from other qualitative research investigating cognitive impairment in breast cancer survivors, (Von Ah et al., 2013; Selamat et al., 2014; Henderson et al., 2019), it appears critical to move towards the acknowledgement of cancer-related cognitive impairment within the medical community. Based on the current findings, it is suggested that the recognition of cognitive impairments should extend to patients who have been treated primarily with tamoxifen in the absence of chemotherapy. The lack of information and support available to survivors treated with tamoxifen appears only to exacerbate psychological distress and anxieties surrounding the progression of impairments, with many expressing concern for neurodegenerative disease. An active approach from the medical community in addressing cognitive impairments may lessen their impact and thus improve quality of life for survivors. Whilst it may be argued that the medical community minimize information regarding the impact of tamoxifen for fear of lack of adherence to the medication, our findings suggest that in spite of the debilitating

side effects, survivors wanted to continue taking tamoxifen. Participants felt, however, that they would have been better equipped to cope with cognitive impairment had they been informed early.

Limitations and Future Directions

The current study was limited in that the sample size was relatively small, and lacked cultural variation. Thus inferences beyond this specific population are restricted. However, the similarities observed across participants appeared consistent, indicating that findings may be more widely applicable. Given that the current study investigating the lived experience of tamoxifen on cognitive function is novel in its approach, further research is neccesary to corroborate findings. In addition, longitudinal research examing the trajectory of cognitive impairment is necessary to gain a better understanding of the phenomenon, with an aim to develop inteventions they may assist in cancer survivorship.

Conclusions

Overall, this study provides evidence for the presence of cognitive impairment in breast cancer survivors treated with tamoxifen in the absense of chemotherapy. In addition, it points to the broad impact that cognitive impairment can have on self-perception, functioning and quality of life for survivors. Moreover, findings suggest a critical need for educational tools to be developed in order to inform health care providers and patients alike. Further research is necessary to understand the longer-term impact of tamoxifen on cognition.

Chapter 9: General Discussion

9.1 General Overview of Section B

Medical advancements in the diagnosis and treatment of cancer have greatly improved survival rates. Accordingly, the longer-term consequences of cancer have gained increasing attention across the literature in recent years, with quality of life for survivors being a central focus. Whilst reports of cancer-related cognitive impairment (CRCI) are long standing, claims have only been substantiated through experiential research over the past few decades. Most commonly referred to as 'chemobrain' or 'chemofog' the phenomenon was initially considered to be caused by the neurotoxic effects of chemotherapy, however evidence now points to the implication of other factors. For instance, both radiation therapy and adjuvant hormonal treatments have also shown deleterious effects, and the presence of cognitive impairment even prior to treatment has been identified, suggesting the damaging nature of cancer itself. A recent model by Ahles & Root (2018) further considers other fatcors that can interact with cancer treatment (Predisposed factors: genetic, sociodemographic, cancer type; Modifiable factors: physiological, psychological, allostatic load and lifestyle), in the etiology and progression of CRCI. Studies indicate that the cognitive functions most affected predominantly include executive functioning, attention, working memory, processing speed, learning and memory (see Pendergrass, Targum, & Harrison, 2018, for a review), however there remains ambiguity over the extent of such deficits, with prevalence estimates ranging from 17% to 75%. This, in part, is due to the lack of agreed upon definitions of CRCIs and a reliance on a neuropsychological approach which faces both conceptual and empirical problems, limiting our understanding (Horowitz et al., 2018). Whilst clinical neuropsychological measures can detect general deficits in cognition, tests were originally developed to localize severe brain pathology brought about by focal lesions or stroke. Whilst multiple studies describe CRCIs to be subtle, this does not necessarily

translate to the impact on functioning and quality of life for survivors. Indeed, subjective and objective measurements of cognitive impairments are not well correlated (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Costa & Fardell, 2019) and the detrimental impact of CRCIs from chemotherapy is well documented (Selamat et al., 2014). Overall, it follows that we begin to take a different approach to understanding the underlying mechanisms involved in CRCIs and take a broader view of its etiology.

The aim of Section B of the current thesis was to further investigate CRCIs in breast cancer. It has been suggested that further progression in the understanding and countering of CRCI requires applying a neuroscientific approach (Ahles & Hurria, 2018; Horowitz et al., 2018). A convergent approach combining methods of behavioural, electrophysiological and imagining techniques will aid understanding of the nature, prevalence and severity of CRCIs and facilitate the development of new measures of cognitive function specific to the impairment faced by cancer patients. Accordingly, the first experiment of Section B (experiment 4, chapter 7) set out to investigate the neural correlates of cognitive-control related error monitoring, an area which is yet to be explored in the breast cancer population. In light of the detrimental impact that cognitive impairments can have on feelings of self-efficacy and confidence in survivors, investigating processes that facilitate behavioural adjustments in task performance is particularly pertinent.

In recent years the contributive role that qualitative research map play in the investigation of health and illness has been gaining acknowledgement. A qualitative approach allows for the in-depth and unrestrained exploration of psychological problems, gaining rich personal accounts of individual experience. As such, they should not be set against quantitative methods of research, but should be utilized as a complementary approach (Lyons, 2011). Indeed, an integrative approach, with a greater number of researchers gaining familiarity with both approaches would greatly advance the field

(Smith, 2011). This would allow for the flexible employment of appropriate methodologies to assess different research questions in the most relevant way. Adopting this philosophy, the second investigation of Section B (study 5) used interpretative phenomenological analysis (IPA) (Smith et al., 2009) to explore the impact of tamoxifen on cognitive functioning and quality of life in breast cancer survivorship. Whilst previous qualitative studies have researched the impact of 'chemobrain', investigation into the longer term real- life consequences of endocrine therapy is sparse.

9.2 Summary and Discussion of the Main Findings

9.2.1 Neural Mechanisms in Breast Cancer Survivorship: The ERN, Pe and Performance Monitoring

The aim of experiment 4 (chapter 7) was to investigate the neurocognitive correlates of error processing in breast cancer survivorship. Firstly, findings showed that for both the experimental and control groups, the typical ERN and Pe waveforms were present confirming that this pattern is present for breast cancer survivors as well as healthy individuals. Secondly, results indicated a greater ΔERN in breast cancer survivors, illustrating exaggerated early error processing. This builds upon other neural research in breast cancer which show neural differences in the absence of performance effects, pointing to compensatory mechanisms (McDonald et al., 2012; Menning et al., 2015). That is, at the earliest stage of processing, the detection of errors and assessment of the need to implement cognitive control processes requires greater neural activation for the breast cancer compared to healthy controls. This reflects reports by cancer survivors who frequently report that they are more susceptible to distraction during cognitive tasks which require much greater effort (Von Ah, Habermann, et al., 2013). Moreover, it emphasises the problematic nature of solely measuring cognitive function through

behavioural measures in which tests are administered in an environment designed to minimise distraction and maximise performance (Ahles & Hurria, 2018). Further visual inspection of topographical scalp maps suggest that for the ERN, recruitment of neural areas was more distributed and skewed centro-parietally to the left for the breast cancer compared to the non-breast cancer group. Accounting for research that shows verbal memory deficits are evident in cancer patients (McDougall et al., 2014), this may reflect greater recruitment of cortical language regions necessary for the letter-based flaker task used in the current study.

Thirdly, results demonstrated a significantly larger late Pe for the breast cancer compared to the control group, indicating that exaggerated error monitoring continues through the conscious processing of errors. Proposed theories suggest that the Pe is representative of the conscious awareness of an error and the allocation of attentional resources necessary for behavioural adjustments and improved performance (Steinhauser & Yeung, 2010; Gehring et al., 2012). As such, the current findings corroborate the interpretation of compensatory mechanisms at play in the neural processing of breast cancer survivors.

Lastly, findings showed that greater perceived cognitive impairment for the breast cancer compared to the control group, suggesting that the neural changes observed translates to women's perception of their cognitive functioning in the real world.

9.2.2 Personal Accounts of Tamoxifen and Cognitive Function: A Qualitative Experiential Study

Using qualitative methods, the aim of study 5 (chapter 8) was to explore the impact of tamoxifen on cognitive function in breast cancer survivorship. Results indicated seven superordinate overarching themes, namely, Experiencing Cognitive Dysfunction, The Past, Present and Future Self, Coping with Cognitive Impairment, Consequences of

Cognitive Impairment, Uncertainty Surrounding Tamoxifen, Scarcity of Awareness Surrounding Tamoxifen and Cognitive Dysfunction, and Conflicted Feelings Towards Tamoxifen.

Extending upon other qualitative research that has investigated the effects of chemotherapy on cognitive function, findings of the current study are considered within Leventhal's Illness Representation Theory (Leventhal et al., 1997; Leventhal, Phillips, & Burns, 2016), allowing for a comprehensive view of the burden that cognitive dysfunction can have on survivors' lives. Within the *identity* dimension, analysis indicated that all participants experienced persistent cognitive failures in the form of attentional lapses and problems with working memory, executive functioning, language and verbal memory. Participants further reported cognitive lethary and brain fog. Cognitive dysfunction was found to be exacerbated by other factors such as physiological side effects and cognitive load. The *timeline* of cognitive dysfunction remained ambiguous for participants. Participants were unsure when their cognitive dysfunction had begun and reported differential experiences of progression. Whilst for some women impairments had eased, others reported further deterioration across time. Additionally, whilst some women believed their cognitive function would return to pre-diagnosis levels post-tamoxifen, others feared dysfunction would persist for the remaining lifespan. A number of *consequences* were identified as a result of cognitive impairment. Participants particularly emphasized the negative impact on their functioning at work leading to anxieties surrounding employment and career progression. In addition, participants experienced negative alterations in their self-perception and suffered concerns surrounding the perception of others. The *cause* of cognitive failures was attributed to tamoxifen to varying degrees. Whilst many participants believed tamoxifen to be the sole cause of their problems, others were confused about the impact of other factors such as age and the menopause. The *controllability* of cognitive deficits consisted of a number of coping

strategies self developed by participants. These mostly consisted of cognitive aids in the form of writing, technology and mental memory techniques such as repetition. Participants also relied upon social support to help with their failures, when it was available. The need for increased mental effort and concentration was also highlighted. Considering particpants' *illness coherence,* ambuiguity was present. Participants expressed uncertainty reagrding their cognitive failures which was exacerbated by a lack of medical guidance. Lastly, the dimension of *emotional representations* within Leventhal's framework is captured by the overwhelming and complex emotions expressed by particpants. Whilst immense frustration towards their cognitive dysfunction was emphasized repeatedly, participants simultaneously expressed a sense of gratitude towards tamoxifen as they considered their survival after cancer.

9.3 Limitations

The investigations in Section B were subject to limitations. As per the experiments in Section A, participants were recruited via social media platforms and therefore may not be representative of the wider population of breast cancer survivors. As such, results may not be generalizable and may typically include those who are more likely to seek outside support.

Secondly, results are only applicable to the particular subgroups that were tested. For instance for the neural experiment investigating cognitive control related error monitoring (experiment 4, chapter 7) the study specifically only included participants with primary breast cancer who'd had chemotherapy as part of their treatment. Therefore findings cannot extend to those who've not undergone chemotherapy. Conversely, for the qualitative study investigating the impact of tamoxifen on cognitive function (study 5, chapter 8), findings cannot extend to those treated with chemotherapy. Additionally, for both studies, findings cannot apply to women with metastatic breast cancer. The current

studies further lacked cultural variation with a predominantly Caucasian population, and as such cannot fully extend past the particular demographic who took part.

Thirdly, for both studies we lack pre-diagnosis neural, behavioural and qualitative measurement of cognitive function as well as measurement of functioning immediately after initial treatment (surgery, radiotherapy or chemotherapy). We are therefore unable to infer whether cognitive changes reflect continued deterioration or partial recovery from acute impairment. Further, we cannot assess to what extent cognitive decline is associated with the biology of cancer itself.

9.4 General Implications of Findings and Future Directions

There are a number of implications from the findings of Section B of the current thesis, which presented two novel studies in the field of breast cancer survivorship. Firstly, experiment 4 (chapter 7) has given us greater insight into the underlying neural mechanisms at play in CRCIs. Results demostrate that survivors ability to process cognitive errors is compromised, requiring greater cognitive effort. This is particularly pertinent for the breast cancer population, who as a result of the cognitive and emotional deficits associated with diagnosis and treatment, require the capacity to adapt to setbacks and failures. Findings corroborate and extend upon other research which points to compensatory mechanisms as a means to maintain pre-diagnosis behavioural performance levels (McDonald et al., 2012; Menning et al., 2015). This has important implications for breast cancer survivors who may fatigue quicker as a result of the greater neural engagement required to complete tasks. Whilst behvioural deficits may not be observable in controlled lab-based environments optimised to maximise performance, deficits may manifest over time impacting survivors' lives. Indeed, such findings mirror the subjective cognitive complaints frequently reported.

Findings from study 5 (chapter 8) further emphasize the multifactorial nature of CRCIs, extending upon previous qualitative research on cognitive impairment in breast cancer, which has only considered individuals treated with chemotherapy. Findings demonstrate that the endocrine therapy tamoxifen can have deleterious effects on cognition, impairing quality of life for survivors. Given that tamoxifen is administered for up to 10 years post diagnosis, this finding is critical. Whilst participants were grateful to have such a medication that can improve their chances of survival, it is clear that they were ill-informed to cope with the consequences of such deficits, indicating a lack of guidance from the medical community. This reaffirms the need for the medical community to recognise, validate and address cognitive complaints from suvivors (Von Ah, Storey, Jansen, & Allen, 2013).

It is clear that cognitive impairment in cancer is a complex research area which requires further attention. Given the limitations of traditional neuropsychological tests, embracing the theories and methods of neuroscience is a promising approach (Ahles & Root, 2018). For instance, Horowitz et al., (2018) suggest that a core priority should be to develop models of how hypothesized causal pathways for CRCI would propogate to the level of brain systems and cognitive functioning. In addition, new measures of cognitive function specific to the impairments faced by cancer patients should be developed in order to properly assess patients. A collaborative approach with the cooperation of neuroscientists and clinical researchers would facilitate this aim. What's more, the value that qualitative research can add should be further recognised and taken forward. In-depth personal accounts of the particular cognitive deficits that breast cancer survivors face can help further our understanding of this phenomenon, as demonstrated by the current findings.

A critical challenge in the investigation of CRCI relates to the theory that cognitive deficits are determined by a complex interaction of cancer treatment, innate

(e.g. genetic) and accumulated risk factors, and aging, making the elucidation of the exact mechanisms at play difficult. Ahles & Root, (2018) advocate utilising the concept of tipping points in complex systems, in which early warning signs are detected before abrupt changes occur from one state to another. Further investigation of cognitive decline across the cancer trajectory is necessary to identify potential tipping points in order to predict which individuals may be most vulnerable to cognitive impairment.

A broader aim from the current research extends to developing appropriate interventions for CRCIs in order to improve quality of life for survivors. There are no current treatments available to address CRCIs, and whilst preliminary studies have identified some promising avenues, research is limited (Von Ah et al., 2013; Denlinger et al., 2014). That said, as outlined in Section A of the current thesis, cognitive training paradigms show some promise for cognitive rehabilitation for functions of processing speed, verbal memory (Von Ah et al., 2012) and executive functioning (Kesler et al., 2013) in breast cancer survivors. Nevertheless, interpretation of findings are limited by the use of waitlist control groups, and therefore more research using active control tasks is necessary. In addition, Ahles & Root, (2018) propose the potential neuroplastic benefits of combining cognitive training with transcranial direct current stimulation (tDCS), which sends minimal electrical current through electrodes on the scalp, in cortical areas implemented in specific cognitive tasks (e.g. those requiring attentional control). Overall, it is clear that more research is required in order to develop interventions optimised for cognitive impairment in cancer survivors.

Concluding Comments

The current thesis set out to further investigate cognitive and emotional vulnerability in breast cancer survivorship. Hinging on attentional control theory, (Eysenck et al., 2007), Section A outlined three intervention studies aimed at reducing emotional vulnerability in a female group of breast cancer survivors. The first study (experiment 1, chapter 2) indicated that a course of adaptive working memory training can translate to reductions in anxious and ruminative symptomatology which are sustained for up to 18 months post-intervention, compared to an active control task. Experiment 2 (chapter 3) demonstrated an association between the use of words thought to reflect cognitive reappraisal, as well as affectively negative words, with improvements in perceived cognitive function, emotional vulnerability and quality of life. That said, refinement of expressive writing paradigms is required to optimise transfer outcomes. Experiment 3 (chapter 4) indicated that both mindfulness meditation training, adaptive working memory training, and a combined course of both, can result in reductions in anxious symptomatology compared to an active control condition.

Section B presented two novel studies investigating the phenomenon of cognitive impairment in cancer. Experiment 4 (chapter 7) demonstrated that cognitive-control related error monitoring processes require greater neural activation for the breast cancer compared to healthy control group, pointing to compensatory mechanisms. Finally, Study 5 (chapter 8) gave further insight into how tamoxifen can impact cognitive functioning, pointing to the detrimental effects on quality of life in survivorship.

Whilst for the purposes of the current thesis the investigations were divided to focus on emotional vulnerability (Section A) and cognitive vulnerability (Section B), it is important to reiterate that the two are intrinsically linked. Indeed the fundamental premise adopted for the intervention studies of Section A relates to the possible causal influence that cognition may have on regulating emotion (Dolcos et al., 2019). As such,

a greater understanding of cancer related cognitive impairments should not only facilitate the development of interventions for cognitive impairment, but should further aid in the optimisation of emotion-targeted treatments. By the same token, better comprehension of the specific emotional vulnerabilities experienced by breast cancer survivors may advance our knowledge on the particular cognition-emotion interactions at play in women affected by breast cancer, further promoting this aim. An integrative, mixed methods approach, drawing upon behavioural, biological, neuroscientific and qualitative research may assist in this overarching goal.

More broadly, it is clear that cognitive and emotional vulnerability in breast cancer survivorship has been somewhat overlooked in the face of improving medical treatment for the disease (Pitman et al., 2018; Ahles & Root, 2018). In particular, research into the cognitive and emotional vulnerabilities of women with metastatic breast cancer is sparse, despite its increasing prevalence (Park et al., 2018). Indeed, the majority of the extant literature on emotional distress in breast cancer focuses on early stage diagnoses or for individuals in survivorship. However, the cognitive and emotional experiences of women with an early-stage diagnosis may not compare to those with a life-limiting prognosis who may endure greater symptom burden and treatment toxicity. In addition, much of the current research concentrates on early survivorship and fails to consider the potential delayed onset of cognitive and emotional vulnerabilities at later stages along the cancer continuum. Therefore it is critical that the late effects of breast cancer are considered in long-term survivorship and that early interventions are administered for at-risk patients in order to protect against escalating effects and the possible impact on mortality.

Overall, as medicine advances and cancer survival rates continue to grow, it is imperative that a better understanding of cognitive and emotional vulnerability in breast cancer is further developed. Whilst academia now recognises that the breast cancer

population is at risk for both emotional disorder and cognitive impairment, specific targeted treatments and preventative methods need to be further investigated. Moreover, a better dialogue between researchers and clinicians should be cultivated. It is essential that there is a continued movement towards improved awareness of patients' vulnerabilities and increased expectation that cancer care service providers will assess and provide the support required (Tuffaha, El-Saifi, Chambers, & Scuffham, 2019). As demonstrated by the current thesis, the translation of basic scientific research to clinical application should facilitate this aim and improve longer-term quality of life for breast cancer survivors.

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