Chemo Brain and Prospective Memory in Breast Cancer Patients: A Mixed Methods Study

by

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Some breast cancer patients report memory deficits after undergoing cancer treatment. This deficit has been given the term *chemo brain*. Patients who report such deficits usually complain about attention and concentration problems, such as forgetting to take their medication, or taking it twice, forgetting doctor's appointments, reduced ability to multitask, and difficulties with driving, among others. These difficulties can significantly affect their quality of life. Most of the research to date has focused on examining a global neuropsychological aspect of chemo brain, and in the last decade, attention has been directed to the use of neuroimaging techniques. The major question addressed in this study is whether chemo brain in breast cancer patients specifically a prospective memory deficit, and whether neuropsychological assessment lacks ecological validity to measure chemo brain. It is also suggested that biological factors such as sleep and sleepiness are altered during the course of cancer treatment, and those factors may also be playing a role in the cognitive impairment of cancer patients. The method used to examine these questions included a mixed methods design in which a quantitative study was conducted using a neuropsychological battery and physiological measures as well as a qualitative study, which involved thematic analyses and case studies, aided by semi-structured interviews and questionnaires.

Overall, the results of this study confirmed that breast cancer patients have poorer prospective memory than controls, and that patients' self-reports are inconsistent with results derived from the objective neuropsychological battery. This implies that more

sensitive measures for the assessment of chemo brain should be developed, and that more emphasis needs to be placed on the study of prospective memory and chemo brain to provide patients with the most efficient care and psychological treatment in order to improve their quality of life.

“Now to Him who is able to do exceedingly abundantly above all that we ask or think, according to the power that works in us, to Him be glory in the church by Christ Jesus to all generations, forever and ever. Amen.”

Ephesians 3:20–21

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1.

Tables and figures

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CHAPTER ONE

1 INTRODUCTION

1.1. Explanation of the phenomenon under study

Breast cancer is by far the most common form of cancer in women in the UK, accounting for 31% of all cases. The probability of developing breast cancer in women is one in nine over the course of a lifetime. Most of the women diagnosed with breast cancer are in the 50–69 age group and, while 99% of diagnoses are found in women, breast cancer can also occur in men (less than 1%) (Statistical Information Team, Cancer Research UK, 2009).

In recent years, the application of chemotherapy treatment has increased the rate of cancer-free survival in women with breast cancer. However, this treatment, or combinations of treatments, such as hormonal treatment, chemotherapy and radiation, can lead to a whole host of side effects, among which is mild cognitive impairment (MCI) (27–35%) (Vardy *et al.*, 2008). This can result in a significant and prolonged deterioration of their quality of life, even when they become cancer free. This MCI has been given the term *chemo brain* or *chemo fog*, since patients report a mental cloudiness (Ahles & Saykin, 2001; Vardy *et al.*, 2008; Jansen *et al.*, 2007; Jansen *et al.*, 2008; Shilling & Jenkins, 2007; Stewart *et al.*, 2006; Collins *et al.*, 2009; Tager *et al.*, 2009; Bender *et al.*, 2006; Weis *et al.*, 2009; Wieneke & Dienst, 1995).

The existence of chemo brain has already been very well documented (Ahles & Saykin, 2001; Vardy *et al.,* 2008; Jansen *et al.,* 2007; Jansen *et al.,* 2008; Shilling & Jenkins, 2007). However, methodological issues in some of these studies have been controversial (Raffa, 2011). Some of the controversy arises from issues such as small sample size, lack of baseline assessment, different statistical approaches, different testing measures among studies and lack of ecological validity of the measures, and to date, no causal relationship has been established between chemo brain and chemotherapy.

The exact nature of the memory difficulties women experience as a result of chemotherapy is under-reported in the literature. Anecdotal evidence reports suggest that complaints range from forgetting to pay bills to difficulty retrieving familiar words or an inability to remember names and faces. Furthermore, an inability to multitask is common, which profoundly affects their daily activities. They also present difficulties learning simple things, such as a new version of a computer program they were already familiar with. All these problems have a major impact on patients' lives and self-esteem, making them feel that they are not the same people as before and that they have some sort of handicap. Due to these combinations of symptoms, some cannot perform the same activities they used to prior to their chemotherapy and either lose their jobs or are forced to resign (Mulrooney, 2007; Silverman & Davidson, 2009).

When breast cancer survivors realise that their cognitive deficits are due to an actual brain dysfunction, probably caused by chemotherapy treatment, they feel relieved, since feelings of guilt are also a part of the process, as they feel responsible for the cognitive

failures, thinking that they are doing something wrong or not coping as they are supposed to (Silverman & Davidson, 2009).

These reports suggest that the phenomena associated with chemo brain needs to be examined more closely, particularly to help clinicians and nurses provide adequate information and interventions that will result in a better quality of life for breast cancer survivors.

1.2. Purpose of this study

More frequent than not, clinicians fail to recognise the phenomenon of chemo brain. Patients' anecdotal reports show that when they come to the clinic complaining about memory failures, they are usually ignored by their physician and nurses, attributing such failures to fatigue or other factors, ignoring the challenges patients face in their everyday lives. This research was designed with the purpose to help clinicians understand that it is a reality that some patients experience cognitive failures during or after cancer treatment, and that such failures can seriously affect patients' quality of life.

The author believes that, due to similarities between the cognitive failures reported by chemo brain patients – with literature reporting deficits in memory for planned intentions or prospective memory (PM) – chemo brain is a PM failure. The author decided to assess chemo brain objectively, using a tool for the exclusive assessment of PM. Further, as it is a part of the executive function (EF) system, working memory (WM) was also assessed. Measures of objective and subjective sleep, anxiety and

depression were included to explore the influence of these variables on chemo brain and PM.

Consistent with the literature, the studied sample showed no significant cognitive decline in neuropsychological measures, but participants began to report memory difficulties. Due to the fact that there is no in depth study of PM and chemo brain in the literature, a qualitative study was included in order to assess the phenomenon. The author wanted to explore the discrepancy between neuropsychological assessment and patients' reports from the perspective of PM.

Since very little attention has been placed in the study of chemo brain as a PM deficit, one of the purposes of this study was to explore this relationship by considering quantitative and qualitative tools in order to motivate further investigation by the research community and the development of more reliable tools for the assessment of chemo brain in the future. A possible benefit of this kind of study would be that staff within the healthcare system would be able to provide adequate care and intervention to help patients cope with these problems.

It was proposed that in order to gain a deeper understanding of the cause and effect relationship underlying chemo brain, researchers should begin to dissect and study each and every cognitive domain separately. The aim of this study was to focus on memory, specifically WM and PM, which might be considered a part of the WM model (Baddeley, 2003) and the multiprocess PM theory (McDaniel & Einstein, 2007), particularly the central executive system (Baddeley, 2003). Furthermore, sleep/wake activity patterns and day time sleepiness were analysed to observe their effect on WM

and PM and the possible relationship with cognitive decline in patients reporting chemo brain.

According to Shilling and Jenkins (2007), only a minority of patients reported that these cognitive declines interfere with their everyday life; a vast majority of those patients reported experiencing more problems with attention and memory than those identified by objective cognitive measures. According to these authors, this should not undermine the personal experiences that patients report, which are mostly lapses and slips in their everyday lives.

Patients who experience chemo brain report memory deficits that interfere with everyday living, ranging from minor disturbances to major problems that lead to a decrease in their quality of life, such as losing their jobs and social isolation. Depending on the social support patients have, they also feel misunderstood by people around them, because they attribute the memory declines to faulty thinking or poor performance rather than to chemo brain effects. They feel slow in their cognitive abilities, their self-esteem decreases, their ability to multitask declines and they face difficulty retrieving words (Mulrooney, 2007; Silverman & Davidson, 2009).

According to the literature, one of the most affected cognitive domains in chemo brain patients is WM (Vardy *et al.*, 2008; Jansen *et al.*, 2007; Jansen *et al.*, 2008; Shilling & Jenkins, 2007; Stewart *et al.*, 2006; Collins *et al.*, 2009; Tager *et al.*, 2009; Bender *et al.*, 2006; Weis *et al.*, 2009). For this reason, one of the aims of this study was to focus on Baddeley's WM model (Baddeley, 2003) as well as on the multiprocess prospective

theory proposed by McDaniel and Einstein (2007) as a theoretical framework, to systematically assess the memory deficits experienced by some chemotherapy patients.

The WM model is a multimodal system in which short-term memory (STM) is implicated and considered as an active, rather than a passive, component of memory. WM may be defined as "a limited capacity system, which temporarily maintains and stores information, supports human thought processes by providing an interface between perception, long-term memory and action" (Baddeley, 2003). The components of the system are the central executive, the phonological loop and the visuospatial sketchpad (Baddeley, 2003).

The central executive in the WM model is an attentional control mechanism responsible for coordinating all the activities among the other systems (slave systems). The phonological loop is a slave system made up by the articulatory control process and the phonological store. The articulatory control process controls subvocal rehearsal, and the phonological store is a memory store that can retain speech-based information for a short period of time (about two seconds). The visuospatial sketchpad processes and manipulates visual-spatial information, and the episodic buffer serves as a backup store that supports serial recall and other types of information. This last system is out of the scope of the study, due to the fact that no tests have been developed to assess it. Overall, WM deals with the ability to learn new information and retrieve stored information from LTM (Neath & Surprenant, 2002).

Furthermore, according to Cohen and Conway (2008):

> "planning, prospective memory and carrying out action sequences, depend on the ongoing operation of working memory and the allocation of attention".

The same authors explained that errors in PM are manifested in the form of slips of actions: repetition errors (forgetting that an action has already been performed and repeating it, e.g. placing two cheques in an envelope for the same bill); goal switches (forgetting the goal of a sequence of actions and switching to a different goal, e.g. intending to drive to one place and driving to another); omissions and reversals (omitting or wrongly ordering the component actions of a sequence, e.g. filling the kettle, but failing to switch it on); and confusion/blends (confusing objects involved in one action sequence with those involved in another sequence, e.g. taking a tin-opener instead of scissors into the garden to cut flowers (Cohen & Conway, 2008).

PM is defined as "the ability to remember to perform some intended action at a particular point in the future" (McDaniel *et al.*, 1999). It has been associated with daily and routinely performed activities such as paying bills, taking medications with certain schedules and requisites and remembering to pick up things. PM also involves performing familiar actions in novel contexts or at different times (Cohen & Conway, 2008).

The memory experiences that breast cancer patients report soon after chemotherapy are in accordance with the PM slips of action. As mentioned before, the sorts of complaints found in the literature are as follows: having a hard time remembering appointments, difficulty remembering words and names, problems with organizing their thoughts

together in a coherent sequence in a sentence, not learning new things because they are no longer fast enough to do so, difficulty with concentration, missing the exits while driving, not knowing how to get to familiar places, being unable to focus on work, difficulty following stories, losing train of thought, being unable to multitask or do two things at the same time and difficulty in keeping track of their workload (Mulrooney, 2007; Silverman & Davidson, 2009).

Therefore, it was suggested that chemo brain might be a problem of WM and PM and executive dysfunction. This work was aimed at analysing chemo brain in a mixed-study design to explore all the aspects involved in depth. In order to accomplish this, a series of psychology tests were used to observe whether this battery was sensitive enough to detect cognitive decline in breast cancer patients as a result of cancer treatment (chemotherapy, radiotherapy, adjuvant treatment) and to compare these test results with patients' lived experiences through thematic analysis of online questionnaires and case studies.

Furthermore, one of the most common complaints that chemo brain patients have is the difficulty in retrieving words. The author of this thesis suggests that this difficulty might be related to the tip-of-the-tongue (TOT) phenomenon, which is when a speaker cannot fully retrieve a word from memory that he or she knows will eventually be recalled; one common example is that when the speaker is unable to produce the name of a person from an individual, like the name of a teacher, but the name is "stuck" on the tip of the individual's tongue (Gianico-Reyea *et al.*, 2012). Our thematic analysis led us to believe

that chemo brain patients suffer from a persistent TOT experience, and further analysis should be recommended.

1.3. Mixed methods design

The research approach where we combine both qualitative and quantitative methodologies in the same study is known as "mixed methods". It is suggested that more mixed methods studies are necessary, because in recent years, the UK's health system has shown an increased demand of the investigation of complex health services, which need to be addressed by different methodologies to assess multifaceted interventions (O'Cathain, 2006; Bradley *et al.*, 1999) to better understand the impact of an illness from every perspective.

O'Cathain (2006) and Creswell (2003) explain that "quantitative components include experimental designs such as randomised control trials and surveys, while qualitative components include ethnography, case studies, in-depth interviews, focus groups and observation". There are different mixed methods approaches, those considered within the context of a single study and those within the context of a programme, where different methods are used in separate parts of a programme of research and later integrated in some way (O'Cathain, 2006).

After extensive discussions and analysis, it was decided that this study would take a mixed methods approach in order to combine quantitative and qualitative data and gain a deeper understanding by looking at all aspects of chemo brain, considering quantitative and qualitative reports. Quantitative data collected from neuropsychological assessment provided us with information about the appropriateness of our measures to assess PM within the context of chemo brain in various time points and the significance of our results when compared with the general population. On the other hand, the qualitative studies provided more meaningful and specific information about how patients everyday experience cognitive difficulties in their own environment and to understand in specific detail how these failures relate to PM, with the proposal that in future research, more sensitive objective measures should be developed. This was followed by a deductive reasoning or "top-down" approach in which we analysed chemo brain and PM beginning from a broad spectrum of information, i.e. qualitative results, working down to specific cases.

The use of mixed methods in a study is particularly useful because every method has its own limitations that can be overcome by the use of other methods (Cresswell, 2009). By combining qualitative and quantitative methodologies, each with its own strengths, it was hoped that the overall value of the study would be increased. The use of qualitative studies allowed more flexibility through interaction with the participants with the possibility of obtaining more detailed and in-depth exploration (Balbotin, 2012); it gave us a more comprehensive understanding of chemo brain and PM on breast cancer patients. Our study was strengthened with the use of mixed methodology, because we could explore how patients experience chemo brain difficulties in depth, and we were able to compare their experiences with their own neuropsychological tests, which at

times were inconsistent with patients' reports. This provided useful information regarding the lack of sensitivity of objective tools to detect chemo brain cognitive failures.

The use of quantitative methodologies allowed the testing of hypotheses derived from previous theories. The mixed methods approach enabled the combination of both methodologies in the same study in order to improve the quality and validity of the study.

Balbotin (2012) reported that there are different designs for organising data for mixed methods studies. Parallel or concurrent mixed designs are used when the quantitative and qualitative phases are carried out in parallel either at the same time or with a time lapse in between. For sequential mixed designs, the different phases are carried out in a chronological order, with one component evolving as a consequence of the other (Balbotin, 2012).

In this study, a sequential design was used in which the qualitative phase emerged from the quantitative phase. The qualitative study was designed to explain why the test results were inconsistent with patients' reports and to test the hypothesis that chemo brain is a PM failure and further, to document the research hypotheses in a more comprehensive and reliable manner. Data collection began by testing some participants at two time points and others at four time points during the course of their treatment. After completion of that phase, the qualitative data was collected, beginning with an online

questionnaire to develop a thematic analysis, followed by face-to-face interviews to build case studies that gave rise to emerging theories.

Equal weight was decided to be given to both the phases of the study. It was proposed that each phase depends on the other in order to achieve maximum credibility, validity and reliability. The quantitative approach provided the tools to begin to understand the cognitive decline as a PM deficit after cancer treatment and to better understand the discrepancy between neuropsychological tests and chemo brain complaints. The qualitative study led to gaining deeper knowledge and understanding of how the problem with words is a problem of the TOT associated with LTM. Without this knowledge, it might have been mistakenly believed that when patients reported having problems retrieving words and names, it was a problem similar to aphasia in patients who cannot pronounce words, or a problem of LTM, not related to metamemory, which refers to the feeling of "knowing that we know". By comparing patient's reports with what has been reported in the PM literature, it was also possible to corroborate the hypothesis that chemo brain is a PM problem.

From a methodological standpoint, this study was based on "paradigmatic pluralism" by acknowledging that a variety of paradigms can be used as the underlying philosophy when conducting mixed methods (Balbotin, 2012; Tashakkori *et al.*, 2010). The main objective of this study was to make sense of the data in a comprehensive and coherent manner; it did not adhere to any particular paradigm, rather used the most suitable approaches to help explain and understand the research questions based on the literature surrounding these topics.

1.4. Research design

For our quantitative study, 56 participants took a neuropsychological battery and questionnaire. Twenty-eight participants underwent cancer treatment, and twenty-eight were healthy controls. Statistical analyses were conducted using SPSS V.21 Mixed ANOVA to explore mean scores across, between and within groups. Our qualitative research design combined multiple cases; the first part of the study consisted of three online questionnaires in which participants responded to eight open-ended questions and to PM self-reports. A thematic analysis was conducted, which comprised six different case studies in which quantitative and qualitative data were integrated.

The focus of this work falls within the context of a single study undertaken sequentially, i.e. the qualitative study followed by the quantitative arm and two different methods, which produced two sets of data (Bryman, 1988; O'Cathain, 2006). The integration of qualitative and quantitative data was necessary, because it is not uncommon that a cancer patient's memory decline reports are inconsistent with those shown in neuropsychological tests. In this work, the use of multiple methodologies allows a deeper understanding of such a phenomenon compared with the use of a single methodology alone, in which the study of chemo brain within the context of PM and the TOT phenomenon would be incomplete.

Because of the nature of chemo brain and PM failures, which are associated with everyday memory lapses, we consider the patient's personal reports to be very important. Chemo brain studies that have used neuropsychological batteries have sometimes failed to explain the cause and effect relationship between cancer treatment and cognitive impairment, to the point that some researchers deny the existence of the problem or attribute it to factors such as personality or fatigue. Other studies successfully explain that chemo brain might be the consequence of structural damage in certain regions of the brain, but fail to recognise the meaning of chemo brain on patients' experiences in their daily lives. By using multiple methods, it was possible to gain a deeper understanding of the TOT phenomenon experienced by participants. Problems with words are often reported in the literature, but have not been linked to this phenomenon before. TOT is a phenomenon in which a speaker cannot fully retrieve a word from memory that he or she knows will eventually be recalled; one common example is that when the speaker is unable to produce the name of a person from an individual, like the name of a teacher, but the name is "stuck" on the tip of the individual's tongue (Gianico-Reyea *et al.*, 2012). It is believed that chemo brain patients suffer from a persistent TOT experience, and further analysis should be recommended.

As in every quantitative methodology, this study aimed to test the hypotheses that breast cancer patients would have lower scores than healthy controls; that they would present cognitive impairment after undergoing cancer treatment; and that such impairment is due to PM failure. To accomplish this, a series of neuropsychological tests and questionnaires were used along with a sleep monitor. In contrast, our qualitative arm aimed to generate new theories through an exploratory analysis by combining different methods to gain a deeper understanding and to obtain more consistent results. It is the

opinion of the author that the study was enhanced by the use of mixed methods, because a more complete picture of the phenomenon under study was achieved.

1.5. Philosophical assumptions of mixed methods design

According to O'Cathain (2006), qualitative and quantitative researchers are committed to different epistemological and ontological positions, in that qualitative researchers base their assumptions on constructivists or interpretivist paradigm, and quantitative researchers are inclined to positivism or post-positivist paradigm. The author explains that

> "the paradigms are contrasted on subjectivity-objectivity, induction-deduction, relativism-realism, holism-reductionism…"

and argues that there is controversy amongst researchers, because they consider that the two paradigms represent incompatible assumptions (O'Cathain, 2006). Some authors propose that mixing methods is both unacceptable and impossible (O'Cathain, 2006; Ryman, 1988). Other researchers favour a more "pragmatic" or "instrumental" approach, claiming that the choice of which method to use depends on practical demands and on what would be the best approach to answer the research question. The researcher can then adopt the paradigm or philosophical stance that they consider the most appropriate for mixed methods research (O'Cathain, 2006).

For this study, a pragmatic stance was adopted (O'Cathain, 2006; Tashakkori & Teddlie, 1998) due to the fact that the research question was considered more important than the paradigm underlying the method.

1.6. Rationale of the methodology

Due to the fact that the majority of the existing research on chemo brain and PM is quantitative in nature, with few qualitative studies, it was decided that combining methodologies in a longitudinal study on chemo brain would be the most valuable approach to better understand the phenomenon of chemo brain as a PM failure and to understand how this impacts patients' lives. Furthermore, to the author's knowledge, no previous study has investigated the TOT phenomenon as a problem of chemo brain, although it has been widely recognised that chemo brain patients have trouble with words.

To better understand the reality of patient's experiences after receiving cancer treatment, a patient-focused approach was considered to be particularly useful for explaining the phenomenon in more depth and to explain contradictions in the current literature, such as neuropsychological batteries not showing impairment while patients reporting distressing memory complaints. In particular, the author considered that quantitative and qualitative findings would complement each other to explain the phenomenon in a broader manner through patients' lived experiences as well as how and why there are discrepancies between test results and the patients' self-reports.

1.7. Quantitative methodology

A longitudinal approach was conducted for the quantitative study. Psychological scales and neuropsychological measures along with objective and subjective measures of sleep and sleepiness were administered at two point times to a group of breast cancer patients before and in the middle of patients' treatment and to the healthy volunteers control group. Demographic information was collected at the beginning of the study.

The memory problems reported by cancer patients known as chemo brain might be a problem of WM (ongoing STM) and PM (memory for the intended actions) on breast cancer patients undergoing chemotherapy treatment. Both WM and PM were assessed by scores resulting from neuropsychological batteries and questionnaires.

Neuropsychological battery raw scores were the primary outcome measure.

Neuropsychological Battery:

1. CAMPROMPT (Cambridge Prospective Memory Test)
2. BVRT (Benton Visual retention Test)
3. DIGITS FORWARDS
4. DIGITS BACKWARDS
5. DIGITS SYMBOL
6. COWAT (Controlled Oral Word Association Test)

Other Screening measures:

7. NART (National Adult Reading test)
8. HADS (Hospital Anxiety and depression Scale)
9. Demographic information

Sleep time was also considered, and participants were required to use a sleep monitor over a four-day period.

1.8 Qualitative methodologies

Two different qualitative approaches were considered in this study to gain deeper insight into the lived experiences of chemo brain. The first approach was to conduct a thematic analysis of the data collected through online asynchronous open-ended questionnaires, and the second approach was to build six case studies for the development of new theories explaining chemo brain with PM and the TOT phenomenon. This was accomplished through face-to-face interviews.

1.8.1 Thematic analysis

Cancer patients who took part in the quantitative assessment were invited to take part in an online questionnaire. This method of interviewing participants was selected because it was recognised that at this stage, cancer patients would be feeling tired or would be

still recovering emotionally and physically from their treatments. One of the advantages of the online questionnaire was that participants could respond to the questions at their own pace and had more time to think about their responses. Furthermore, they could ask their family members to help them provide answers, particularly about memory lapses they themselves might not have noticed. However, one major disadvantage was that if they provided an answer that was too short, or the answer was not very clear, there was no way for the author to gain further explanation or clarification. This issue was overcome by conducting additional face-to-face interviews conducted at a later date after they had recovered from their treatment. The questionnaires comprised eight open-ended questions related to their memory difficulties and two PM questionnaires.

To look for a major insight into the phenomenon of chemo brain and to interpret, organise and describe its observations, a thematic analysis was conducted, which was a process of encoding qualitative information through a list of themes that emerge as patterns derived from the information obtained from participants (Boyatzis, 1998). Boyatzis (1998) defined thematic analysis as follows:

> "a translator of those speaking the language of qualitative analysis and those speaking the language of quantitative analysis", which allows the incorporation of operant and open-ended measures of information.

1.8.2 Case studies

Balbontín (2012) explained that a case study is an event taking place in a natural way where the researcher aims to gain deep insight into a phenomenon and to enquire how

and why the phenomenon occurs. Yin (2009) described a case study as an empirical enquiry investigating a phenomenon in depth within its real life context. In this study, case studies were analysed to explore the phenomenon of chemo brain as a whole, considering the patient's perspective, test results and experiences, along with statistical analysis. The aim was to present individual cases with the objective of developing a theory of chemo brain and PM and the TOT phenomenon.

Following the online questionnaire, cancer patients from the sample were invited to participate in individual face-to-face interviews to further analyse their responses and integrate their test results to explore the discrepancies between anecdotal reports and neuropsychological tests results.

1.9 Integration/triangulation

This study focussed on data triangulation described by Patton (2002), in which information of the same phenomenon is collected from multiple sources, i.e. neuropsychological battery, online questionnaires and face-to-face interviews, to build case studies in order to present the information from different perspectives and approaches to explain and make sense of a phenomenon under study.

According to Yin (2009), the strength of case studies relies on the fact that data collection comes from different sources of evidence, which are more likely to be relevant because they allow the researcher to address a broader range of behaviours or observations of the same phenomenon. Yin (2009) emphasized that

"the most important advantage presented by using multiple sources of evidence is the development of converging lines of enquiry, a process of triangulation and corroboration", resulting in more accurate and conclusive findings.

1.10 Thesis outline

Chapter one of this thesis is dedicated to an introduction of the research topic, explaining the phenomenon under study and the rationale of the methodology selected to conduct the study. Chapter two focuses on the explanation of breast cancer and the psychological impact it has on patients since being diagnosed with a potentially life threatening disease. Chapters three and four present a systematic review of the literature on chemo brain (Chapter three) and on PM (Chapter four). The following chapters present the quantitative methods and results (Chapters five and six) and qualitative methods and results (Chapters seven, eight and nine). The final chapter is the focus of the final discussion (Chapter ten).

CHAPTER TWO

2 UNDERSTANDING BREAST CANCER: PSYCHOLOGICAL FACTORS, DIAGNOSIS AND TREATMENT

2.1 Introduction

This section will try to explain the psychological implications and challenges in women's lives when they are diagnosed with breast cancer. It is important to understand the process that they have to go through for a better understanding of the cognitive deficits experienced even before treatment. The author will also explain potential biological markers that affect cancer patients, which may be playing a role in chemo brain, such as sleep and sleepiness.

Breast cancer is the most common cancer in the UK. Of the 55,000 people diagnosed with breast cancer each year, only 350 are men. Eighty percent of women being diagnosed with breast cancer are over the age of 50. Breast cancer patients may be diagnosed with early or primary breast cancer or secondary (metastatic) breast cancer, which is when the cancer has spread to other parts of the body. Primary breast cancer is the cancer that has not spread beyond the breast or the lymph nodes (glands) under the arm. Different types of breast cancer include ductal carcinoma (non-invasive) and invasive breast cancer, which has the potential to spread to other parts of the body (Breast Cancer Care, March 2016, BCC4Ed. 10). All the participants in this study had been diagnosed with primary breast cancer.

Since breast cancer survival rates have increased over the years as a result of more effective treatments, it is important to understand how treatment and illness affect patients' psychological well-being. When a woman is diagnosed with breast cancer, she faces a very traumatic event. Many experience anxiety, depression, sexual problems and sometimes cognitive impairment. Patients' approach to life is changed permanently, and their expectancies of the future have to be revised. Even when they complete treatment successfully, many regard themselves as not fully cured, because of the fear of relapse and therefore experience a permanent feeling of uncertainty (Ray *et al.*, 1985).

Most women being diagnosed with breast cancer have a mastectomy, which is an operation to remove the breast. There are several types of mastectomies. It can be segmental mastectomy in which the tumour and a large area of normal breast tissue around it is removed, and some lymph nodes under the arm may also be removed. In simple or total mastectomy, the whole breast is removed, but not the lymph nodes. In a modified radical mastectomy, the whole breast and surrounding lymph nodes, muscles, fatty tissue and skin are removed. After surgery, most women experience soreness that lasts for two to three days, and many women experience what is called "phantom breast" sensations, which include itching, pain, pins and needles, pressure or throbbing, which may be a result of damage to the nerves. Many women may choose to have a breast reconstruction, and after choosing the appropriate procedure with a plastic surgeon, they must look at factors such as infections, implant movement or contracture. Women may also decide to wear an artificial breast instead of breast reconstruction, for whom a prosthesis is designed (Turkington, 2005).

The impact on women's quality of life after losing a breast is very damaging. It affects their self-esteem, body image, feminine identity and sexual relations, added to the stress of having to decide whether they would have a reconstructive surgery (Eiser, 1985). After being diagnosed, most women are advised to take a combination of therapies that include surgery, radiotherapy, chemotherapy, hormone therapy and targeted therapies, which can be given in different orders. Guided by their oncologist, they have to decide the course of treatment they will receive. Sometimes, they can have the choice as to undergo chemotherapy or local treatments, and this itself is a very difficult decision making time for them, because they need to think about the implications about both the courses of treatment, and how these decisions will impact their lives and their health. As a result, worry, anxiety and low mood are present since the moment of being diagnosed, throughout the treatment, and many times these psychological factors increase even after post treatment because of the fear of the cancer coming back.

When women are diagnosed with breast cancer, they also face the challenge of telling other people and family about it. They usually struggle talking about their diagnosis and how they feel. It is particularly difficult to tell their children or their employers about it. They also may need to take some time off work, but this is not always the case. Some patients feel upset and angry and worry about the side-effects of treatment, such as nausea, fatigue, lymphedema and menopausal symptoms and the changes in their appearance due to hair loss and nail and skin damage.

Breast cancer is graded depending on its rate of growth into grade one or low grade, grade two or moderate or intermediate grade and grade three or high grade. It is also

classified by stages through a staging system called TNM staging, and depending on the tumour size (T), spread to lymph nodes involvement (N) or metastasis (M), the type of treatment is recommended (Macmillan Cancer Support, October 2013. MAC11616, 10th Ed.):

Stage 0: In situ (non-invasive treatment) breast cancer.

Stages I and II are often called early breast cancer.

Stage I: Tumour is less than 2 cm and has not spread to the lymph nodes in the armpit.

Stage II: Tumour is greater than 2 cm, but less than 5 cm; axillary nodal involvement.

Stage II is divided into two stages:

1. **Stage IIA** – The tumour is not bigger than 2 cm and has spread to the lymph nodes in the armpit OR is bigger than 2 cm and has not spread to the lymph nodes OR it can't be found in the breast, but is present in the lymph nodes.
2. **Stage IIB** – The cancer is smaller than 5 cm and has spread to the lymph nodes in the armpit OR is bigger than 5 cm but has not spread to the lymph nodes.
3. Stage III: Tumours greater than 5 cm; axillary nodal involvement; called locally advanced breast cancer.

Stage III is divided into three stages:

1. **Stage IIIA** – The cancer can't be found in the breast OR it is under 5 cm and has spread to the lymph nodes in the armpit (which are clumped together) OR it is bigger than 5 cm and has spread to the lymph nodes.

2. **Stage IIIB** – The cancer has spread to tissue near the breast and may be attached to skin or muscle. There are usually cancer cells in the lymph nodes in the armpit.
3. **Stage IIIC** – The cancer has spread to 10 or more lymph nodes in the armpit or to lymph nodes below the breastbone, near the neck or under the collarbone.

Stage IV: The cancer has spread to other parts of the body, and it is called secondary or metastatic breast cancer.

2.1.1 Understanding adjuvant chemotherapy and its toxic effects

The role of chemotherapy as a cancer treatment is to interfere with the ability of cancer cells to divide and grow. Different chemotherapy treatments work in different ways affecting the cancer cells at different phases of growth. For primary invasive breast cancer, adjuvant chemotherapy (given in addition to other treatment) is recommended usually after surgery and radiotherapy after the chemotherapy treatment is completed.

Primary or early breast cancer patients usually undergo a series of treatment every two to four weeks over a period of four to six months, depending on the stage of the tumour and the combination of drugs. These drugs may include hormone therapy usually prescribed to primary invasive breast cancer patients to reduce the risk of relapse. This therapy usually begins after surgery, but it can also begin post chemotherapy treatment. In some cases, it may even begin before surgery to reduce the size of the tumour, which is known as neoadjuvant treatment (Breast Cancer Care, March 2016, BCC4, 10th Ed.).

Chemotherapy drugs are often administered in combination. Some commonly used combinations include the following:

1. **FEC** – fluorouracil (5FU), epirubicin and cyclophosphamide
2. **FEC-T** – FEC followed by docetaxel (Taxotere®)
3. **AC** or EC – doxorubicin (Adriamycin®) and cyclophosphamide or epirubicin and cyclophosphamide
4. **CMF** – cyclophosphamide, methotrexate and 5FU
5. **E-CMF** – epirubicin and CMF

Adjuvant chemotherapy for breast cancer usually includes an anthracycline drug, such as epirubicin or doxorubicin. If the risk of the cancer coming back is higher, docetaxel is also usually included. The patient's doctor may offer the patient a choice of the chemotherapy treatments.

If the patient has HER2 breast cancer, they may be given trastuzumab (Herceptin) along with chemotherapy.Chemotherapy drugs can cause side effects. Many of these can be controlled well with medicines and are usually overcome post treatment. The patient's doctor or nurse tells the patient more about what to expect.

2.1.1.1 Chemotherapy side effects and necessary precautions

Some of the most common side effects of chemotherapy treatment are listed as follows:

1. Reduction in number of white blood cells: Increased risk of infection due to chemotherapy can reduce the number of white blood cells, which help fight infections (neutropenia).
2. Bruising and bleeding: Chemotherapy can reduce the number of platelets in blood, which aid in blood clotting. This increases the risk of bleeding.
3. Anaemia: It is caused by a low number of red blood cells and can make the patient feel very tired and lethargic. The patient may also become breathless.
4. Feeling sick: Some chemotherapy drugs can make the patient feel sick (nauseated), leading to vomit.
5. Tiredness (fatigue): The patient is likely to become tired and have to take things more slowly.
6. Hair loss: This includes loss in body hair, eyelashes and eyebrows.
7. Loss of appetite.
8. Sore or dry mouth: Patients' may notice small ulcers during treatment.
9. Diarrhoea.
10. Effects on the nerves in the patient's hands or feet: This can cause tingling or numbness, a sensation of pins and needles or muscle weakness (peripheral neuropathy).
11. Early menopause.
12. Infertility.

To better understand chemo brain, it is useful to get an understanding about the neurotoxic agents of chemotherapy, because they may pose as a very significant confounding variable.

At the biological level, chemotherapy drugs affect cellular enzymes that are involved in DNA synthesis and/or function, which takes place during the cell cycle. Chemotherapy drugs interfere with the cell activities during one or more phases. Cell cycle specific (CCS) drugs affect cellular activity during specific phases, and cell cycle nonspecific (CCNS) drugs affect the cell during any phase. Actively diving cells are more sensitive to chemotherapy. Chemotherapy drugs can also be classified according to their functions and structures during cell cycle (Table 2.1).

Drug	**Cell cycle**	**Function**
ALKYLATING AGENTS	CCNS	Damage completed DNA molecule
ANTIMETABOLITES	CCS	Make cellular reproduction impossible
NITROSOUREAS	CCNS	Cross the blood brain barrier
ANTITUMOR ANTIBIOTICS	CCNS	Interfere with cell division and transcription of RNS
MITOTIC INHIBITORS	CCS	Interfere with mitotic spindle formation

Table **Error! No text of specified style in document.**.1. Chemotherapy drugs classification on their function and structure during cell cycle (Preston *et al.*, 1997).

Combining two or more agents has an advantage depending on the composition of malignant cells, which do not have a uniform composition within a given tumour. These combinations can have a greater chance of destroying a larger number of cancer cells, while at the same time increasing the toxicity of healthy cells.

It is also important to understand the way chemotherapy is administered, because dosages can be greatly influenced by the routes of administration. Drugs that can potentially cause cellular damage when they infiltrate the subcutaneous tissue are called vesicants. Even a minute amount can cause damage. Breast cancer can be treated with vesicants (Doxorubicin). The routes are oral, subcutaneous, intramuscular, intravenous, intra-arterial, intrathecal and intracavitary (Preston *et al.*, 1997).

A list of the most common chemotherapeutic agents used for breast cancer and their side effects is presented in Table 2.2. As mentioned before, some of the side effects may alter cognition and have a psychological impact on the patient.

Agent	**Dosage**	**Administration**	**Side effects**
Aminoglutethimide (Cytradren) CCNS	Varies	Oral. Always administered with a steroid (**hydrocortisone** 40–100 mg PO daily in 4 divided doses;	Anorexia, dermatologic reaction (rash with or without fever), **fatigue**, gastrointestinal alterations (nausea, vomiting),

		Florinef 0.1 mg PO every other day)	**hepatic toxicity**, **metabolic alteration**, **neurotoxicity** (ataxia, head ache, nystagmus, somnolence)
Cyclophospahmide (Cytoxan, Neosar) Alkylating Agent CCNS	Varies	IV, PO, intraplenural, or intraperitoneal	Alopecia, anaemia, anorexia, cardiac toxicity, haemorrhagic cystitis, hepatic toxicity, leucopoenia, gastrointestinal alterations (nausea, vomiting), metabolic alterations (hyponatremia), renal toxicity, reproductive dysfunction, thrombocytopenia
Chlorambucil (Leukeran) Alkylatin agent CCNS	Varies	Oral	Anaemia, cystitis, dermatologic reaction, gastrointestinal alteration (nausea, vomiting, diarrhoea), hepatoxicity, leucopoenia, neurotoxicity (seizures,

			peripheral neuropathies), pulmonary toxicities (fibrosis, alveolar dysplasia), renal toxicity (hyperuricemia), reproductive dysfunction (amenorrhea, ologospermia, azoospermia), secondary malignancies (acute myelogenous leukaemia), stomatitis, thrombocytopenia
Agent	**Dosage**	**Administration**	**Side effects**
Doxorubicin (Adriamycin-RDF) Antibiotic CCNS	Varies	IV	Alopecia, anaemia, anorexia, cardio toxicities, diarrhoea, flu-like syndrome, nausea, vomiting, dermatologic reactions, leucopoenia, stomatitis, thrombocytopenia
Fluorouracil/5FU (Adrucil)	Varies	IV, intra-arterial, intra-peritoneal, topical, oral	Alopecia, anaemia, anorexia, cardiotoxicity,

Antimetabolite CCS			dermatological reactions, diarrhoea, nausea, vomiting, increased lacrimation, leukopenia, neurotoxicity (photophobia, cerebral ataxia, stomatitis, thrombocytopenia)
Agent	**Dosage**	**Administration**	**Side effects**
Lomustine/ CCNU (CEENU) Nitrosourea CCNS	Varies	Oral	Alopecia, anorexia, anaemia, nausea, vomiting, hepatotoxicities, leucopoenia, neurotoxicities (disorientation, lethargy, ataxia, dysarthria), pulmonary toxicities, renal toxicities, stomatitis, thrombocytopenia
Megestrol Acetate (Megace, Pallace)	Varies	Oral	Alopecia, breast tenderness, dermatologic reaction, nausea,

Hormone Progestine Appetite Stimulant			vomiting, stomach cramps, hepatic toxicity, neurotoxicity (headache), reproductive dysfunction, venous phlebitis, weight gain
Mechlorethamine/ Nitrogen Mustard/HN2 (Mustargen) Alkylating agent CCNS	Varies	Intracavitary infusion	Alopecia, anaemia, anorexia, burning sensation along vein, dermatologic reaction, fever, diarrhoea, nausea, vomiting, peptic ulcer, leukopenia, neurotoxicities (weakness, headache, drowsiness, vertigo, convulsions, progressive muscle paralysis, paraesthesia, cerebral degeneration, coma), hepatic toxicity, ototoxicity, reproductive toxicity, renal toxicity, thrombocytopenia

Agent	Dosage	Administration	Side effects
Melphalan/L-Phenylalinine Mustard/L-Pam/L-Sarcolysin (Alkeran) Alkylatin agent CCNS	Varies	Oral	Alopecia, anaemia, dermatologic reactions, diarrhoea, nausea, vomiting, leukopenia, pulmonary toxicity, reproductive dysfunction, secondary malignancies, stomatitis, thrombocytopenia
Medroxyprogesterone (Depo-Provera, Provera) Hormone Progestin	Varies	IM, oral	Alopecia, fluid retention, nausea, vomiting, gluteal abscess, hepatoxicity, hypersensivity, metabolic alteration (increased calcium), weight gain
Agent	**Dosage**	**Administration**	**Side effects**
Methotrexate/ A-Methopterin/MTX (Mexate, Folex) Antimetabolite CCS	Varies	PO, IM, IV, intrathecal, or intra-arterial	Alopecia, anaphylaxis, anaemia, dermatologic reactions, abdominal distress, nausea, diarrhoea, vomiting, hepatic toxicities, leukopenia,

			neurotoxicities (dizziness, fatigue, headache), renal toxicity, stomatitis, thrombocytopenia, pulmonary toxicity

Table **Error! No text of specified style in document.**.2. Chemotherapeutic agents to treat breast cancer.

The most common side effects that can cause cognitive impairment are as follows:

1. Hepatic toxicity (impaired mental status, lethargy, confusion, disorientation, altered thought processes)
2. Metabolic alterations (disorientation, confusion, alteration in thought processes)
3. Hyponatremia (change in mental status, lethargy, seizure activity)
4. Neurotoxicity (change in mental status, seizure activity, depression, altered thought processes)

Other potential biological markers affected in breast cancer patients that might be interfering with cognitive decline are fatigue, sleep and sleepiness, which will be examined in the following section. We will also examine the role of breast cancer in health anxiety and depression.

2.1.2 Relationship between cognition and sleep, anxiety and depression

There is a strong relationship between memory processes and sleep. Depressive symptoms, fatigue and poor sleep are frequently reported in breast cancer patients and frequently occur at the same time. They have a negative effect on the quality of life and are presented as a cluster of symptoms, which can be related to disease or treatment and could be mediated by relatively stable individual differences such as anxiety tendency to react when experiencing life threatening situations (trait anxiety). High trait anxiety leads to the development of depressive symptoms when experiencing stress and adverse events. Anxiety has also been identified as a risk factor in developing fatigue and sleep disruptions (Lockefeer *et al.,* 2012). It is due to this cluster of factors that the current study aimed to explore the effects of sleep, sleepiness and affective disorders (anxiety and depression) in the context of PM and chemo brain.

The discovery of rapid eye movement (REM) and non-REM (NREM) sleep has led researchers to gain insight into the hypothesis that sleep and specific sleep stages actively influence memory development. Today, this relationship is known as sleep-dependent memory (Walker & Stickgold, 2006).

According to Ancoli-Israel *et al.* (2001), fatigue is one of the most common complaints in cancer patients, which interferes with their daily lives and affects their quality of life. It is also one of the most common reasons why patients withdraw treatment. It is believed that fatigue can be originated by physical as well as psychological factors. Research has demonstrated that there is a relationship between self-reported fatigue and self-reports of sleep quality (Ancoli-Israel *et al.*, 2001).

Ancoli-Israel et al. (2001) also made the point that breast cancer patients are among those who most often experience fatigue during, and several months after, treatment. Sleep disruption in cancer patients may be caused by multiple factors, such as insomnia or/and hypersomnia, whose causes may be pain, depression or anxiety. Chemotherapy and radiotherapy are also known to cause sleep disturbance.

On the other hand, two major memory systems are identified by Schatcter and Tulving (1994) that consist of five memory systems. The most general of all are procedural and declarative memory. PM is involved in behavioural and cognitive skills related to "knowing how" to do things (how to ride a bicycle, how to type, how to solve puzzles), whereas declarative memory involves "knowing that" (e.g. knowing that 2+2=4). PM includes learning motor skills, simple conditioning, simple associative learning and learning about patterns and regularities in the environment. STM (WM), episodic and semantic memory are encompassed into what is known as declarative memory. Semantic memory processes factual information, and episodic memory includes autobiographical memory, which includes involvement of personal experience (Neath & Suprenant, 2003).

Chemo brain patients often complain about forgetting factual information such as important events, names, appointments, dates, etc., which can be categorised as a problem with their declarative memory. It has also been very well established that breast cancer patients suffer from disturbed sleep patterns, especially in the active phase of chemotherapy (Savard *et al.* 2009). Evidence in literature demonstrates that there is a relationship between memory and sleep, and that declarative memory is enhanced during sleep; therefore, the disruption of sleep patterns may cause a disruption in

declarative memory, which is consistent with chemo brain patient's reports (Rasch & Born, 2008).

According to Rasch and Born (2008), there is evidence that sleep promotes the consolidation of declarative memories for events and facts. It is during sleep that consolidation takes place and memories stabilise against future interference. Neuronal reactivation of recently acquired memories redistributes and integrates these memories into the network of pre-existing memories during sleep consolidation of memories, which takes place during the slow-wave cycle of sleep. According to these authors, sleep specifically enhances declarative aspects of memory.

Circadian rhythms and sleep disruption are becoming an issue of interest among researches. Ancoli-Israel *et al.* (2001) concluded that disruptions in circadian rhythms can affect sleep quality and alterations in rhythms and at the same time, they can disrupt a variety of physiological mechanisms pertaining to fatigue. Other disruptions in circadian rhythms, such as a lack of entrainment to day–night cycle and sleep, can lead to feelings of grogginess akin to those of jet lag (Ancoli-Israel *et al.*, 2001).

Savard *et al.* (2009) analysed how breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. They conducted a study with a sample of 95 women scheduled to receive neo-adjuvant or adjuvant anthracycline-based chemotherapy for a stage I–III breast cancer.

The purpose of their study was to assess longitudinally to what extent circadian rhythm impairments evolve over the course of chemotherapy, as previous research suggested that sleep and circadian rhythms may be altered even prior to the initiation of chemotherapy. Their findings showed that compared to baseline, all circadian rhythm variables were significantly impaired during the first week of both chemotherapy cycles, suggesting that more enduring impairments in sleep-wake activity rhythms worsen with repeated administration of chemotherapy. They also found out that patients with disrupted sleep-wake cycles showed increased fatigue levels and decreased quality of life. Women with breast cancer demonstrated more phase-delayed rhythms, experiencing more daily dysfunctions.

In a study conducted by Kuo *et al.* (2006), the quality of sleep and related factors using actigraphy and sleep subjective and objective assessments of 16 women during chemotherapy in patients with stage I/II breast cancer were analysed. They found that sleep quality was negatively affected during the active phase of chemotherapy. Patients experienced better sleep quality during the recovery phase than during the active phase, meaning that chemotherapy alters sleep/wake activity.

Banks and Dinges (2007) stated that as a consequence of several days of chronic restriction of sleep below <7 hrs per night significantly affects day time cognitive function, similar to the cognitive dysfunction found after severe acute total sleep deprivation. Restricted sleep can cause neurobehavioral deficits on attention, mood, WM, cognition and preservation of thought. These deficits that accumulate after days of partial sleep loss are equivalent to 1–3 nights of total sleep loss. They also suggested

that there is a possibility of a genetic effect with regard to responses to sleep restriction and vulnerability in cognition.

Cognitive function is also associated with sleep disturbance by Meerlo *et al.* (2009). They stated that a short-term sleep restriction interferes with learning processes, and that prolonged sleep loss may endanger hippocampal integrity, leading to cognitive dysfunction and the development of mood disorders.

It is now clear that cognition and sleep loss are inter-related. Davidson *et al.* (2002) suggested that sleepiness in cancer patients is prevalent and causes distress and disturbance in the patient's quality of life. Therefore, its effects on cognition deserve further investigation.

In the current literature, there is a gap in the experimental assessment of memory and its relationship with chemo brain. Most of the studies have focused on neuropsychological assessment and general cognitive performance in those assessments. A specific study on memory and its diverse stages and categories along with their relationship with various sleep stages in cancer patients who experience chemo brain is proposed to help better understand what happens with memory processes in patients' daily lives.

Breast cancer patients undergo a very stressful process from the moment they are diagnosed with cancer. Some authors have suggested that even before treatment, they begin to experience cognitive deficits (Mehlsen *et al.*, 2009). Some of the possible

causes of these cognitive deficits may be fatigue as a consequence of sleep loss triggered by anxiety and treatment.

2.1.2.1 Sleepiness

There is a difference between the definitions of sleepiness and fatigue. For the purpose of this study, it is important to distinguish between them, since both the terms are often used interchangeably. This study does not focus on fatigue because of the lack of objective measures to assess it and to avoid confusion between the overlapping characteristics of both the constructs. Instead, special attention is given to the study of sleep and sleepiness and the related cognitive deficits.

In the literature, several different definitions of sleepiness include a subjective state of sleep need; a physiological drive derived from sleep deprivation; and a strong sleep propensity (Cursio *et al.*, 2001). According to Pigeon *et al.* (2003), sleepiness during the day refers to sleep propensity, dismissed alertness and drowsiness, whereas fatigue should be accounted as exhaustion, worn-out energy and weakness. Shen *et al.* (2006) distinguished sleepiness from fatigue as an impairment of arousal mechanism. These authors also made it clear that sleepiness is a phenomenon that can be a symptom of some psychiatric and sleep disorders and a normal physiological state. In addition, it can be considered as being pathological and abnormal when it occurs at inappropriate times or when desired, as is the case with narcolepsy and insomnia (Shen *et al.*, 2006).

On the other hand, Shen *et al.* (2006) stated that sleep propensity or the act of falling asleep (objective sleepiness) – the transitional state between wakefulness and sleep – should be distinguished from subjective feelings of drowsiness or somnolence (subjective sleepiness) – a greater tendency to fall asleep, with decreased cognitive performance, mood, motivation, autonomic and physiological responses.

Another distinction of sleepiness is the one explained by the four-process model of sleep and wakefulness. In this model, the interaction between sleep and wake drives consists of independent but mutually inhibitory interactions between primary (sleep-wake drives influenced by circadian rhythms) and secondary components (environmental and behavioural factors). Therefore, sleepiness (sleep propensity) results as a function of the interaction between total sleep drive (primary and secondary) and total wake drive (primary and secondary) (Johns 1993, 2002, 2003; Shen *et al.,* 2006).

Sleep propensity has also been considered as a trait (long term, personality related) and as a state (short-term, situational related). Sleepiness is caused by disruptions of sleep/wake mechanisms, which may not be necessarily involved in fatigue (Shen *et al.*, 2006).

A lack of sleep may lead to patients feeling fatigued, but sleepiness is usually underestimated by them. People usually state that they are not sleepy, when in fact they are. For that reason, objective measures are being used to collect physiological measures of sleepiness, such as galvanic skin response and sleep latency, along with a subjective scale. It is hypothesized that deficient sleep patterns lead to sleepiness during the day, which in turn leads to attention deficits and ultimately to problems with PM.

Sleep disturbance in cancer patients was analysed in a cross-sectional study conducted by Davidson *et al.* (2002). They found that sleepiness is one of the most prevalent problems, affecting 28% of cancer patients. A significantly higher prevalence of excessive sleepiness and fatigue was found in those who had undergone recent cancer treatment (37%). Despite the fact that sleepiness is prevalent in cancer patients, the issue has not been widely studied in the cancer population, particularly in the context of chemo brain (Davidson *et al.*, 2001).

It was hypothesized that cancer patients participating in this study would show higher rates of sleepiness and sleep/wake pattern alterations, leading to a decline in PM and WM. Women who are diagnosed with breast cancer experience several challenges ranging from physical challenges imposed by treatment and surgery, and their mental health is also at risk. During and after treatment, they learn to cope with the physical changes that their bodies experience, and patients have to learn to accept their new identity as breast cancer survivors as well as their new body image. This in itself poses a very distressing challenge, and factors such an anxiety and depression are usually present before, during and after treatment, being the most commonly reported psychological problems by breast cancer patients (Burgess, 2005).

The excessive worry or fear about becoming ill or being ill receives the term of health anxiety. This excessive fear or worry is due to a preoccupation with the incorrect belief of being in danger of developing a serious disease or medical condition (Hadjistavropoulos *et al.*, 2012). It has been very well established that women receiving

breast cancer diagnosis develop acute anxiety and depressive disorders (Kissane *et al.*, 2004), and according to Grassi *et al.* (2004), 38% of women diagnosed with breast cancer report elevated health anxiety, with 20% in early breast cancer patients (Wade *et al.*, 2005). Furthermore, even after successfully completing the treatment, anxiety may persist for a long period of time, affecting patients' quality of life (Feng *et al.*, 2014).

CHAPTER THREE

3 CHEMO BRAIN EXPLAINED

3.1 Chapter overview

Despite the fact that cancer treatment significantly improves patients' survival rate, it also has adverse side effects that can be manifested immediately or delayed, depending on the type of treatment received or each individual patient's response. Some of these side effects may be transient, whilst others may last for longer periods of time. The most common and well-known effects are fatigue, alopecia, anaemia, anorexia, cardio toxicity, dermatological reactions, diarrhoea, nausea, vomiting, increased lacrimation, leukopenia, neurotoxicity (photophobia, cerebral ataxia, stomatitis and thrombocytopenia) and hormonal changes.

A lesser known and arguably not so uncommon symptom is MCI. Many patients report difficulties during and after treatment. This impairment has been termed as chemo brain and chemo fog (Raffa *et al.*, 2006; Raffa & Tallarida, 2010). When neuropsychological assessment is conducted, the most affected cognitive domains are attention, concentration, WM, verbal and visual memory and multitasking (Raffa, 2011).

Patients who report cognitive deficits also report having difficulties with multitasking, remembering appointments or planned intentions, problems retrieving words and names, repetition or omissions of actions, problems following instructions and difficulty with learning new information. They also report feeling fuzzy, hence the term chemo

fog. In the literature, it has been very well established that patients experience cognitive failure during and after treatment (Ahles & Saykin, 2001; Vardy *et al.*, 2008). However, establishing a causal relationship between cancer treatment and chemo brain has been questionable.

Most of the research on chemo brain has been conducted using diverse neuropsychological batteries to detect cognitive impairment, and the results are controversial. Some authors found significant impairment (Paquet et al., 2013), while others found non-significant impairment. Some have concluded that the phenomenon does not even exist (Mehlsen, 2007). The problem with this type of research has been the lack of consistency of the use of neuropsychological batteries, the type of sample and control groups, diverse statistical analysis and the lack of qualitative reports.

On the other hand, common difficulties found in the study of chemo brain are several confounding factors such as anxiety, depression, fatigue, hormonal status, education, age and IQ to mention a few. Factors such as anxiety and depression may have an effect on neuropsychological assessment, and it can be argued that cognitive impairment may occur due to such factors, rather than as an effect of chemotherapy treatment (Hodgson *et al.*, 2013; Bender, 2006; Paquet, 2013). However, some authors found no effect on cognition (Ahles, 2007).

In order to establish a causal relationship, the latest research has been focused on neuroimaging techniques, which is shedding some light on which areas of brain get affected after cancer patients undergo chemotherapy treatment, with promising results (Deprez *et al.*, 2011; de Ruiter, 2012).

Below systematic review of the literature will help better understand this little known phenomenon, which emerges after patients have undergone cancer treatment.
The analysis begins with a brief review of the historical background of the study of chemo brain on breast cancer patients, current neuropsychological studies and neuroimaging as well as qualitative reports of patients who have experienced chemo brain as a side effect of their treatment.

3.2 **Historical background of the neuropsychological assessment of chemo brain**

Cognitive changes in patients undergoing chemotherapy was first reported by Silberfarb *et al.* (1980). Patients with different cancer types were included in their study. The authors reported that overall significant worse results were found in cancer patients on various tests of cognition and recall (Alusie *et al.*, 2011). A study by Gregg *et al.* (1991) of 44 pre-bone marrow transplant recipients with a prior history of chemotherapy found that cognitive dysfunction was present in memory, attention, motor and higher processing and that such impairments were associated with previous courses of chemotherapy (Wieneke *et al.*, 1995).

Wieneke and Dienst (1995) conducted the first study that used neuropsychological tests with early breast cancer patients undergoing conventional (not high dose) adjuvant chemotherapy and Tamoxifen treatment (Wieneke *et al.*, 1995). Their findings suggested that breast cancer patients present cognitive dysfunction several months after treatment cessation, which were unrelated to co-morbidity, depression and length of treatment.

An increased interest in the study of cognitive decline after chemotherapy rose after studies by Silberfab (1980), Gregg (1991) and Wieneke *et al.* (1995). Although these preliminary studies lacked baseline assessment, recruited small sample sizes and lacked control groups, they were important, because it became evident that not only does cranial radiation cause cognitive impairment, but also chemotherapy treatment, which does not target the brain.

A study conducted by van Dam *et al.* (1998) examining cognitive impairment in patients undergoing adjuvant chemotherapy for breast cancer was the first to include a control group consisting of 39 breast cancer patients treated with adjuvant chemotherapy and 34 negative breast carcinoma not treated with adjuvant chemotherapy two years after treatment. Their findings suggested that breast cancer patients were at a higher risk of cognitive decline than patients not treated with chemotherapy. They reported that 31% vs. 6% ($p = 0.007$) presented problems with concentration, and 21% vs. 3% exhibited problems with memory.

It was not until the early 2000s that the research community increased interest in the study of chemo brain. Larger samples were recruited, and the first studies were mainly cross-sectional. However, later longitudinal studies emerged, and control groups became more diverse. For example, in a cross-sectional study, Brezden *et al.* (2000) found that cognitive differences were present in breast cancer patients receiving adjuvant chemotherapy when compared with healthy controls. A total of 107 women took part in their study, and it was found that memory and language were significantly different between cancer patients and healthy controls ($p = 0.024$ and $p = 0.33$, respectively).

Pioneers in the study of neural correlates of cognitive impairment and chemotherapy, Meyers *et al.* (2000) reported abnormal results for conventional electroencephalography (EEG) in chemotherapy cancer patients for non-CNS disease, and Schagen *et al.* (2001) conducted a study to gain understanding of the physiological correlates of treatment related to cognitive impairment on breast cancer patients. They found a significant difference between their three groups of breast cancer patients with respect to the asymmetry of the alpha rhythm of 0.5 Hz, which indicates certain cortical or subcortical dysfunction. Their results suggested that there is neuropsychological support for cognitive dysfunction as a complication of high-dose systemic chemotherapy in breast cancer patients.

In the last few years, there has been an increased interest in the study of chemo brain and neural correlates, bringing new insights into the phenomenon.

The existence of chemo brain has been very well documented since the early 1990s (Ahles & Saykin, 2001; Vardy *et al.*, 2008; Jansen *et al.*, 2007; Jansen *et al.*, 2008; Shilling & Jenkins, 2007). However, methodological issues in some of these studies led to the results being considered as controversial (Raffa, 2011). Some of these problems were small sample size, lack of baseline assessment, different statistical approaches, different testing measures between studies and lack of ecological validity of the measures. These methodological problems might be caused as a result of over-reliance on retrospective and cross-sectional designs and a lack of qualitative and mixed methods methodologies, which would provide a wider understanding of the spectrum. However, although subtle, a causal relationship has been established between chemo brain and chemotherapy by some authors, which is discussed further below.

3.3 **Aetiology: The nature of memory impairments in chemo brain**

The fact that some patients who survive cancer present with memory deficits after undergoing chemotherapy has already been established in the literature (Ahles & Saykin, 2001; Vardy *et al.*, 2008; Jansen *et al.*, 2007; Jansen *et al.*, 2008; Shilling, & Jenkins, 2007; Stewart *et al.*, 2006; Collins *et al.*, 2009; Tager *et al.*, 2009; Bender *et al.*, 2006; Weis *et al.*, 2009; Wieneke & Dienst, 1995). However, the aetiology of this phenomenon remains unknown, as does the question as to whether this phenomenon is physiological, psychological or ecological, or a combination of all the three. It is also well known that mood, anxiety, stress, neuro-chemical toxicity and hormone therapies play a role in poor cognitive performance in cancer patients who have undergone chemotherapy treatment and may represent a threat to the validity of the study of chemo brain. For that reason, chemo brain should be considered as a multifactor phenomenon, since no single factor fully accounts for the cause-effect relationship on the memory deficits reported by patients who undergo chemotherapy. All these should be considered as confounding factors for the study of chemo brain.

Objective, reliable and robust neuropsychological measures have shown inconsistencies with patients' self-report indicators, i.e. patients report cognitive declines that are not identified by neuropsychological measures (Mehlsen *et al.*, 2009). The reason for such a discrepancy might be that neuropsychological batteries relate more to laboratory conditions rather than everyday life activities experienced by cancer patients, lacking ecological validity, or that the current neuropsychological batteries are not sensitive

enough to detect the MCIs implicated in chemo brain (Jansen *et al.*, 2007). For that reason, it has become necessary to assess the memory deficits that patients face in their daily living activities with more sensitive measures to further analyse the phenomenon of chemo brain.

When breast cancer survivors realise that their cognitive deficits are due to an actual brain dysfunction probably caused by chemotherapy treatment, they feel relieved, since feelings of guilt are also a part of the process, as they feel responsible for the cognitive failures, thinking that they are doing something wrong or not coping as they are supposed to (Silverman & Davidson, 2009).

On the other hand, most of the literature has been focused on analysing the whole spectrum of what is called the cognitive domain, i.e. memory (short-term, long-term, WM), attention, concentration, information processing speed, EF, visuospatial skills, verbal and visual memory, motor function, language and learning abilities (Vardy *et al.*, 2008; Jansen *et al.*, 2007; Jansen *et al.*, 2008; Shilling & Jenkins, 2007; Stewart *et al.*, 2006; Collins *et al.*, 2009; Tager *et al.*, 2009; Bender *et al.*, 2006).

It is proposed that in order to gain a deeper understanding of the cause-effect relationship underlying chemo brain, researchers should begin to dissect and study each and every domain separately. The aim of this study was to focus on memory, specifically, WM and PM, which might be considered as a part of the WM model (Baddeley, 2003) and the multiprocess PM theory (McDaniel & Einstein, 2007) and in particular, the central executive system (Baddeley, 2003). Furthermore, sleep/wake activity patterns and day time sleepiness were analysed to observe their effect on

working and PM and the possible relationship with cognitive decline in patients reporting chemo brain.

According to Shilling and Jenkins (2007), only a minority of patients report that these cognitive declines interfere with their everyday life, and a vast majority of those patients reported experiencing more problems with attention and memory than those identified by objective cognitive measures. According to these authors, this should not undermine the personal experiences, which patients report are mostly lapses and slips in their everyday lives.

Patients who experience chemo brain-related memory deficits report symptoms ranging from minor disturbances to major problems that lead to a decrease in their quality of life, including losing their jobs and social isolation. Depending on the social support patients have, they also feel misunderstood by people around them, because they attribute the memory declines to faulty thinking or poor performance, rather than to chemo brain effects. They face difficulty retrieving words, feel slow in their cognitive abilities, their self-esteem decreases and their ability to multitask declines (Mulrooney, 2007; Silverman & Davidson, 2009).

To gain further understanding of the underlying mechanisms of chemo brain, some authors have proposed that factors such as chemotherapy-induced menopause, genetics similar to those predisposed to Alzheimer's disease, aging and neurotoxic effect of chemotherapy on brain structures are responsible.

3.4 **Risk factors**

One potential risk factor for cognitive decline is aging (Ahles, 2012). It has been speculated by some researchers that older patients' cognition may be more affected by chemotherapy, and that older patients with lower pre-treatment scores showed poorer performance in post-treatment assessment, particularly processing speed (Ahles, 2010). This theory is confirmed by the analysis of older breast cancer patients in which Tamoxifen had a larger effect on more cognitive domains than in patients younger than 65 years of age (Schilder *et al.*, 2010). However, these conclusions contradict other findings in which women experiencing chemotherapy-induced menopause were the most affected in their cognitive abilities (Tannock *et al.*, 2004; Phillips *et al.*, 2003; Jenkins *et al.*; 2006).

The role of genetics has also been discussed in the literature. Cognitive decline in adults, including Alzheimer's disease, stroke and traumatic brain injury (TBI), has been associated with Apolipoprotein E (APOE), a glycolipoprotein that plays a role in plasticity and neuronal repair. Ahles *et al.* (2003) compared the neuropsychological performance of one group of long-term survivors of breast cancer and lymphoma who carried the E allele 4 (e4) to another group carrying other APOE alleles, both of which had undergone standard dose chemotherapy treatment. After controlling for age, gender, education, diagnosis and IQ, they found that survivors with e4 scored significantly lower in visual memory ($p < 0.03$) and spatial ability ($p < 0.05$). Their findings suggest that the presence of e4 may increase vulnerability to chemotherapy-induced cognitive dysfunction.

The neurotoxic effects of chemotherapy have also been analysed. Although it is believed that chemotherapy does not cross the blood-brain barrier, some neuroimaging studies using positron emission tomography (PET) have shown that some chemotherapy agents were found in the brain after intravenous administration. This might be associated with genetic variability (Ahles, 2007). Furthermore, DNA damage through oxidative stress occurs as a result of exposure to toxins that alter normal cellular metabolism. Chemotherapy agents, such as alkylating agents used for cancer treatment, cause DNA damage in normal cells as well as tumour cells. A link between DNA damage and chemo brain has not been determined, but cognitive changes linked to DNA damage in Alzheimer's patients have been reported (von Zglinicki, 2005). This suggests that studies of the association of cognitive decline with chemotherapy and genetics deserve more attention.

Normal cognitive function depends on cytokines for the regulation of inflammation and the modulation of neuronal and glial cell functioning, normal CNS function in general and regulation of dopamine and serotonin neurotransmitters. Alterations in cytokine activity has been linked with neurotoxicity and Alzheimer's disease, multiple sclerosis and Parkinson's disease (Wilson *et al.*, 2002) as well as with cognitive failure, depression and fatigue (Cleeland *et al.*, 2003).

In a preliminary study that assessed the effects of two different chemotherapy agents on cytokine levels and its implications for cognitive impairment in breast cancer patients, Janelsins *et al.* (2012) examined 54 breast cancer patients undergoing either doxorubicin-based chemotherapy with cyclophosphamide or cyclophosphamide plus fluorouracil (AC/CAF), or cyclophosphamide, methotrexate and fluorouracil (CMF). In their study, they evaluated whether cytokines (IL-6, IL-8, MCP-1) that are markers for

cognitive difficulties in MCI and Alzheimer's disease, which have been associated with inflammation, were differentially expressed depending on chemotherapy regimen. They found that levels of IL-6, IL-8 and MCP-1 increased in the AC/CAF group and decreased in the CMF group, suggesting that AC/CAF chemotherapy is more cytokine inducing than CMF. This result suggests that inflammatory responses following the use of these chemotherapy agents contribute to brain oxidation, which may lead to cognitive impairment.

Hormonal changes can also account for memory loss. Many breast cancer treatments involve hormone therapies, which might have an effect on cognitive function. Collin *et al.* (2009) suggested that further research should be conducted to analyse whether adjuvant hormonal therapy affects cognition in breast cancer patients. According to their findings, subtle cognitive changes occur in breast cancer patients after experiencing chemotherapy, which remain for one year after the treatment, but they advised that their results should be considered tentative, because hormone therapy exerts a negative impact on cognition by itself. They suggested that studies on the effects of these therapies on mood and cognition should also be addressed to better understand their impact on quality of life in patients who have survived breast cancer.

Many cancer patients experience chemotherapy-induced menopause, and research has shown that these hormonal changes are associated to cognitive decline (Jansen, 2005). Links between verbal memory and levels of oestrogen have been established in which high levels of oestrogen are associated with improved verbal memory, while low levels are linked to poorer verbal memory (Anderson-Hanley *et al.*, 2003).

In a study aiming to analyse the effects of oestrogen in cancer patients, Shilling *et al.* (2003) found significant impairment on measures of verbal memory ($p = 0.026$) and processing speed ($p = 0.032$). Similar results were found by Schilder *et al.* (2009) where although no statistically significant differences were found between cancer groups, memory complaints were reported by 28% of Tamoxifen users, 24% of Exemestane and 6% of healthy controls, where both the cancer groups were undergoing chemotherapy. Tamoxifen users reported lower scores in verbal memory, whereas Exemestane users reported slower manual motor speed. Both the cancer groups scored significantly lower than healthy controls for verbal fluency and processing speed.

The role of oestrogens and anti-oestrogens should also be considered when studying the effects of cancer treatment on cognition, because they have been associated with the modulation of cognitive function (Shilling *et al.*, 2001). Since they are widely used in cancer treatment, it would be useful to know whether or not they contribute to chemotherapy-related cognitive decline.

3.5 **Neuroimaging studies: Chemo brain neural correlates**

An alternative proposal to study potential risk factors, which provides a more objective assessment of cognitive failures associated with chemo brain, has been aided by the advancement of neuroimaging techniques. Due to variations as a result of methodological inconsistencies and to better understand the aetiology of chemo brain, new techniques have been implemented in order to obtain more reliable and consistent findings.

Despite the fact that few studies using neuroimaging have been carried out so far, the increased interest in the study of chemo brain using neuroimaging techniques has provided further empirical evidence of the phenomenon (Shagen *et al.*, 2001; Deprez *et al.*, 2013; Koppelmans *et al.*, 2011). Several neuroimaging techniques have been used to find abnormalities in brain structure in cancer patients, which might explain cognitive deficits (Deprez, 2011). Such techniques are conventional EEG, which analyses the timing and organisation of brain processes while performing a task (Mayers *et al.*, 2000), PET, which provides a measure of neural metabolism (Ahles, 2007) and magnetic resonance imaging (MRI), which produces high resolution images of atrophy and visible pathology that allows the researchers to segment or classify structural images, including grey and white matter (Koppelmans *et al.*, 2011). Diffusion weighted MRI (DWI) assists the assessment of changes in grey matter and loss of integrity of white matter (Deprez *et al.*, 2013). Functional magnetic resonance imaging (fMRI) assesses functional activation of cortical and subcortical regions while the patient performs cognitive or sensory motor tasks through blood-oxygen-level contrast (Zunini *et al.*, 2012).

Results from these studies have shown that the regions of the brain that are most affected in breast cancer include the frontal cortex, cerebellum and basal ganglia (Silverman, 2006), white matter (Inagaki *et al.*, 2007; Abraham *et al.*, 2008; Deprez *et al.*, 2011; Ruiter *et al.*, 2012), grey matter reductions (McDonald *et al.*, 2010), prefrontal cortex (PFC) (Kesler, 2009) and bilateral, frontal and hippocampal cerebral regions (McDonald *et al.*, 2010). The cognitive domains most commonly assessed in neuroimaging studies are WM (Cimprich *et al.*, 2010; McDonald *et al.*, 2012; Scherling *et al.*, 2011; Ferguson *et al.*, 2007), response inhibition (Sherling *et al.*, 2012), selective

attention (Cimprich *et al.*, 2010), memory recall (Silverman *et al.*, 2007), declarative memory (Kesler *et al.*, 2009), EF (de Ruiter *et al.*, 2011; Kesler *et al.*, 2011) and episodic memory (de Ruiter *et al.*, 2011). The brain regions implicated in chemo brain are shown in Table 3.1.

Cognitive domain	**Brain region**
Working memory	Bilateral prefrontal and parietal regions
Episodic Memory	Temporal lobes and prefrontal cortex
Verbal Memory	Left hemisphere
Attention/Concentration	Left hemisphere
Reaction time	Frontal subcortical network
Visual-spatial ability	Right parietal and bilateral frontal lobes
Visual memory	Right hemisphere
Motor speed	Bilateral, frontal lobes and pyramidal tracts
Processing speed	Frontal subcortical network
Executive function	Bilateral prefrontal cortex

Table **Error! No text of specified style in document.**.3. Cognitive domain and brain regions implicated in chemo brain (Argyio *et al.*, 2011).

A selection of the seminal studies using neuroimaging techniques are discussed below. Although neuropsychological assessment conclusions from these studies have not been free from the same controversies as in previous studies, imaging results appear to be more promising for understanding chemo brain.

In a cross-sectional study, breast cancer patients (*n* = 16) treated with chemotherapy were recruited 5–10 years after treatment. Participants were required to undergo neuropsychological testing and a PET scan and were compared with control subjects (*n* = 8) who had never received chemotherapy (Silverman *et al.*, 2006). It was found that during a performance of a short-term recall, modulation of cerebral blood flow in specific regions of frontal cortex and cerebellum was significantly altered in the study group. Alterations were mostly found in frontal cortex, cerebellum and basal ganglia activity, particularly in participants using Tamoxifen.

In an attempt to explain the neural circuitry of chemo brain, de Ruiter *et al.* (2011) conducted a fMRI study with a group of breast cancer survivors 10 years after high-dose chemotherapy treatment (*n* = 19) compared to breast cancer survivors who never received chemotherapy (*n* = 15). It was found that during the assessment of EF in the whole brain analyses, a hypo-responsiveness was present in the whole brain in regions of bilateral posterior parietal cortex in the chemotherapy group.

Both the studies confirmed that the differences in brain alteration in cancer patients 5–10 years after treatment indicates a long-term effect after chemotherapy. However, although they provided reliable information, the aetiology of the phenomenon remains unknown because of its cross-sectional nature and small sample size. These studies showed differences in the condition of the brain compared to controls, but no pre-chemotherapy assessment was provided, and the status of the brain structure before or immediately after treatment is unknown.

One of the first longitudinal studies aiming to isolate the effects of chemotherapy treatment was conducted by Deprez *et al.* (2012). Thirty-four premenopausal women

with early breast cancer were tested with a neuropsychological battery together with diffusor tensor imaging (DTI) MRI immediately after surgery, but before commencing chemotherapy, and again at 3–4 months after treatment. Results were compared with 16 patients not exposed to chemotherapy and 19 healthy controls.

The aim was to study white matter integrity before and after chemotherapy treatment. It was found that the chemotherapy-treated group scored significantly lower after treatment ($p < 0.05$) in tests of attention, memory and psychomotor speed, and there was a significant decrease in frontal, parietal and occipital white matter tracks after treatment, suggesting that white matter is compromised by chemotherapy treatment.

In another study of white matter and grey matter alterations, Scherling *et al.* (2012) recruited 23 early stage breast cancer patients who underwent MRI scanning before chemotherapy and after surgery, matched with non-cancer controls. They found significant neuroanatomical differences between patients and controls depending on the type of analysis and covariates used. Their conclusions highlighted the importance of including baseline assessment and rigorous methodological designs in future studies, challenging previous studies, which argue that chemotherapy treatment affects structures of the brain.

Stewart *et al.* (2006) observed that after exposure to chemotherapy and radiation treatments, computerised brain scans and MRI demonstrated brain damage, which affected white matter. It has been suggested that possible mechanisms implicated in cognitive dysfunction generated by adjuvant chemotherapy treatments (supplementary therapy implemented after surgery in which all noticeable illness has been removed, but where there might be a danger of setback due to hidden illness) could be

> "direct or indirect chemical toxicity to neurons or other non-neuronal elements in the central nervous system, oxidative damage, inflammation and destructive autoimmune responses" (Barton & Loprinzi, 2002).

Major organ toxicity and endocrine systems can ultimately have an effect on brain function, as in the case of oestrogens, which play an important role in normal memory function. Other side-effects of chemotherapy treatment such as anaemia and fatigue can also hold back brain function (Stewart *et al.*, 2006).

Studies that focus on the neuroimaging analysis of chemo brain offer a promising perspective on the objective basis of the phenomenon, but caution should be taken in the methodology and attention should be paid when considering the whole of brain rather than specific areas. The fact that chemo brain is a multifactor phenomenon should also be considered, and cognitive changes should not only be attributed to a single factor, but to a combination of factors (Scherling *et al.*, 2012).

3.6 **Systematic review of the literature**

As mentioned above, Silberfarb *et al.* (1980) were the first to report cognitive impairment in cancer patients. Since then, an increased interest has emerged, but there has been a lot of controversy surrounding the topic. Some studies report significant impairment, whereas others even deny the existence of the phenomenon. On the other hand, a great deal of interest has been placed in the aetiology of the phenomenon. Some have associated it with APOE allele 4, menopause status and hormonal treatment, but

the results are inconclusive. In recent years, an increased interest in neuroimaging has emerged to explain the aetiology of chemo brain, which has shown promising results.

One of the main problems in this area of study is that a large number of methodologies are involved, which in turn produce different results and make it difficult to predict the incidence of chemo brain in the cancer population. Most of the publications use different methods of neuropsychological assessment, different statistical analyses, diverse control groups or lack control groups and baseline assessment, which would provide a better understanding of the cognitive status before treatment.

As a result of these inconsistencies, there is a lack of agreement on whether the phenomenon is significantly affecting cancer patients and physicians are failing to provide proper care, because the patients are not given information about this possible side effect, or by not referring patients to adequate psychological therapies for further support, leaving patients feeling helpless and distressed about their memory difficulties.

The review below discusses issues related to chemo brain and current research directions. An explanation of cognitive functioning is followed by a synopsis of the literature. The review is divided in three sections: common neuropsychological assessment, neuroimaging and neuropsychological assessment and qualitative studies. The common neuropsychological assessment analysis is divided into retrospective, cross-sectional and prospective studies and candidate mechanisms for chemo brain.

3.7 **Cognitive functioning**

Cognitive functioning is a process in which the primary sensory areas located in both central hemispheres of the brain (temporal, parietal and occipital lobes) register the sensory input from the external environment. For this process to take place, a degree of alertness, concentration and attention is required. Verbal information is processed in the left hemisphere of the brain and visuospatial information in the right hemisphere. All new information is screened in relation to previous experience already stored in the subject's memory and proceeds to the highest level of central processing, involving reasoning, abstraction, logical analysis and concept formation. Processing implies an appropriate response to the initial stimulus, and thus, impairment at this level affects an individual's ability to function in a logical and meaningful way. The most common factors that affect cognitive function are age, education, intelligence, fatigue, anxiety and depression (Vardy *et al.*, 2007).

The assessment of cognitive function is carried out through neuropsychological tests. Most of the studies include these domains; however, there is wide inconsistency because each study includes different domains with very diverse tools, providing very different results, and making it difficult to make accurate or reliable inferences.

The cognitive domains most studied in chemo brain are WM, episodic memory, verbal memory, visual memory, EF, processing speed, visuospatial ability, attention, concentration, reaction time and motor speed.

3.8 **Studies using neuropsychological assessment**

Some of the most influential works that have used neuropsychological assessment for the study of chemo brain are described below, including a discussion of how the topic has evolved over time, the major findings and assumptions to date. They are divided into cross-sectional and prospective studies.

3.8.1 Cross-sectional studies

The first attempts to investigate the phenomenon of chemo brain were mostly retrospective in nature and relied on neuropsychological assessment and self-reports. The cognitive status of the patients before treatment was unknown.

The first study to include three groups to assess cognitive function and mood in breast cancer patients was by Brezden *et al.* (2000), which also controlled for age, education level and menopausal status, factors that are of high importance to control, as they may represent significant confounding variables. In a cross-sectional study, they assessed if there was a difference between breast cancer patients treated with adjuvant chemotherapy compared with healthy controls. Their three groups consisted of 31 breast cancer patients undergoing adjuvant chemotherapy (A), 40 patients who had completed adjuvant chemotherapy treatment approximately two years earlier (B) and 36 healthy controls (C). A univariate analysis showed statistically significant difference ($p = 0.009$) in overall cognitive function between groups A and C on the High Sensitive Cognitive Screen and the Profile of Mood States (POMS). Both the patient groups showed a

moderate to severe cognitive impairment compared with controls ($p < 0.002$). They did not find significant differences in POMS, suggesting that mood does not influence the results.

To analyse the long-term impact of chemotherapy regimens on cognition, Ahles *et al.* (2002) conducted a cross-sectional retrospective study of breast cancer and lymphoma survivors five years after diagnosis. The two groups were divided into 35 breast cancer survivors plus 36 lymphoma patients not presently receiving treatment and 35 breast cancer plus 22 lymphoma patients treated with local therapy only (radiation or surgery). Some of the patients were receiving Tamoxifen. They completed a series of neuropsychological and psychological tests, controlling for affective measures and fatigue. A significant, but low correlation was found between the number of cycles and test results ($p < 0.02$, $r = -0.31$), indicating that the more the cycles of chemotherapy undertaken, the lower the test results. No significant differences were found between patients taking Tamoxifen and those who were not. These results suggest that systemic chemotherapy can have a detrimental effect on cognition, although not all cancer survivors are prone to experience them. Depression, anxiety and fatigue did not affect the results.

To further assess long-term effects of cancer treatment, Schagen *et al.* (2002) conducted a follow-up from a previous study, in which patients showed elevated risk of cognitive impairment two years after treatment (van Dam *et al.*, 1998). Seventy-six cancer patients treated with chemotherapy and 39 controls consisting of ancillary lymph node-negative breast cancer patients not receiving chemotherapy were re-examined using neuropsychological tests four years after treatment. In this case, the cancer patients showed an improvement in performance. These findings suggest that the detrimental

effects of cancer treatment may improve with time. However, the control group showed a subtle decline, though this might be due to age differences and menopausal status. Patients who performed worse were premenopausal, raising the question of the influence of hormone status on cognition.

One of the first studies to consider the use of anti-oestrogen drug Tamoxifen as a factor influencing cognitive decline in breast cancer patients was by Castellon *et al.* (2004). Tamoxifen is widely used in hormone therapy for breast cancer both during and after treatment. Since some patients begin using Tamoxifen immediately after surgery and before commencing chemotherapy, it would be useful to know its impact on cognition. A sample of 53 cancer survivors were tested 2–5 years after diagnosis, with 19 healthy controls. Along with a comprehensive neuropsychological battery, they measured mood, energy level and self-reported cognitive function.

Among the cancer groups, breast cancer patients who received adjuvant therapy scored significantly lower than those who did not receive adjuvant therapy ($p = 0.01$). Neither group differed significantly from the healthy controls, but their finding suggests that those who received adjuvant treatment and Tamoxifen showed more cognitive decline. The domains most affected by adjuvant therapy were visual memory, visuospatial function and verbal learning. The results from self-reports did not show a relationship between cognitive complaints and objective measures, instead cognitive complaints were associated with anxiety, depression and fatigue.

Another study reporting inconsistent results between self-reports and neuropsychological impairment was conducted by Mehnert *et al.* (2006). In a cross-sectional design, breast cancer survivors were compared five years after chemotherapy.

They were divided into three study groups: 23 standard adjuvant, 24 high-dose and 29 early-stage following radiation therapy. Participants were assessed using a neuropsychological assessment, together with the questionnaire for self-perceived deficits in attention (FEDA), the Multidimensional Fatigue Inventory (MFI-20) and the EORTC-QLQ-C30. Forty-six percent of the patients reported self-perceived cognitive deficits and 82% reported cancer related fatigue. However, there was no significant finding on objective measures. They did not find an association between self-perceived cognitive decline and neuropsychological measures, despite the fact that cognitive impairment was present in 13% of the standard dose patients versus 8% of high-dose, compared to 3% of the comparison group.

In spite of the importance of these publications, one of the major limitations of all these studies is the lack of baseline assessment, meaning the status of cognition before treatment, cognitive function immediately after treatment when cognitive problems begin to develop, and whether cognitive decline is improving or worsening is unknown. All these factors are important because it is not known if participants' cognition is affected by chemotherapy or simply because of being diagnosed with cancer.

In summary, cross-sectional studies help to raise more awareness that some cancer patients experience cognitive difficulties after chemotherapy treatment. However, these are limited to the long-term impact of chemotherapy on cognition, and there is no information on when patients begin to experience symptoms, once treatment has begun. In general, most of the studies assessed cognitive functioning 2–5 years after chemotherapy and although no significant differences were reported, impairment was found in some patients (Mehnert *et al.*, 2006; Ahles *et al.*, 2002), and that the use of hormonal treatment has a major impact on cognition (Castellon *et al.*, 2004), as opposed

to mood and fatigue, which were found to have no influence on test scores (Ahles *et al.*, 2002).

Despite the finding that neuropsychological test results are not influenced by mood and fatigue (Ahles *et al.*, 2002), the opposite was found for patients' self-reports (Mehnert *et al.*, 2006; Castellon *et al.*, 2004), which might be biased by patients presenting higher levels of anxiety, depression and fatigue.

An interesting finding was reported by Schagen *et al.* (2002), where an improvement was found in cancer patients and a decline in healthy controls over time. These findings, along with Castellon *et al.*'s (2004), show the importance of studying hormonal treatment as covariates of chemotherapy-induced cognitive decline.

The use of control groups helped to realise that despite patients reporting memory difficulties, with objective decline present in some, the differences were not statistically significant and fall within normal limits, therefore classifying chemo brain as a MCI phenomenon. To address this issue of normality, authors analysed an index of individual impairment, which helped to provide evidence of cognitive decline.

3.8.2 Longitudinal studies

Because of not being able to compare results with the patients' previous cognitive abilities and the research design drawbacks mentioned above, researchers began to consider longitudinal assessments with a baseline, which included testing before and after treatment, and larger sample sizes were recruited. Initially, most of the studies

considered neuropsychological assessments, self-reports and interviews only. However, controversy surrounding the phenomenon emerged due to the fact that some studies found no significant changes in cognition, which contradicted patients' complaints. To further analyse this phenomenon and to try to explain such controversy, increased attention has been paid to neuroimaging techniques combined with neuropsychological assessment.

One of the first longitudinal studies was conducted by Wefel *et al.* (2004). In their study, they evaluated 18 breast cancer patients before treatment (baseline), three weeks after treatment and six months after baseline. Although the sample size of 18 was relatively small, they found that while 33% of the women presented cognitive impairment at baseline, 61% presented a decline after baseline. Six months after baseline, 50% of participants who showed decline in the previous test exhibited an improvement and the other 50% remained at the same level.

The importance of this publication was that it was the first longitudinal study assessing cognitive decline as a result of chemotherapy treatment. Although their results were not statistically significant, they showed some indication of how cognition can be affected even before treatment, that it can deteriorate after treatment and that some improvement could be seen six months later.

Shillings *et al.* (2005) reported the neuropsychological test results of 50 women with early breast cancer prior to the start of chemotherapy and 43 healthy controls, before and after treatment, using a neuropsychological battery and self-report measures of quality of life and cognitive failures. The testing schedules were conducted at baseline and six months and 18 months after treatment. Their findings suggested that

chemotherapy patients were significantly more likely to show cognitive impairments than the comparison group. At testing session two, participants took part in a semi-structured interview to determine whether they had experienced memory changes. Seventy-eight percent of the patients reported experiencing memory difficulties, although significant cognitive decline was not indicated by the objective measures.

To address cognitive function in older women receiving adjuvant chemotherapy for breast cancer, Hurria *et al.* (2006) conducted a longitudinal pilot study, which included 28 breast cancer patients with Stage I, II or III. Participants were tested prior to treatment and 6 months after treatment. No significant differences were found from baseline to second testing. Fifty percent of the subjects remained stable, 39% showed decline and 11% showed improvement. Limitations of this study are that there was no control group and a lack of statistical power due to the small sample size. However, baseline assessment was included.

Cognitive function, fatigue and menopausal symptoms in women after adjuvant chemotherapy for breast cancer from a follow-up prospective study were assessed by Mar Fan *et al.* (2005). Matched pairs of patients were recruited (n = 104 patients and 102 healthy controls). Baseline assessment took place towards the end of chemotherapy and at least three cycles of chemotherapy were completed. At this stage, participants completed self-reports for fatigue, quality of life and menopausal symptoms. Cognitive performance was measured using a neuropsychological battery. Blood samples were collected for measuring hormone status. Participants were classified as pre-menopausal or post-menopausal. Follow-up assessment was conducted one and two years after baseline. Patients who received chemotherapy showed substantial levels of fatigue compared to controls ($p < 0.0001$) and showed improvement over time. They found a

significant association between menopausal symptoms at follow-up sessions ($p < 0.0001$), but no other significant association was found. Patients undergoing chemotherapy showed more menopausal symptoms due to chemotherapy-induced menopause, but hormonal therapy had no effect on patients' menopausal symptoms. Cognitive function results showed that near the end of chemotherapy, patients showed more cognitive dysfunction than controls ($p = 0.02$). These results improved over time for both the groups. Hormonal treatment did not have an effect on test scores.

One of the strengths of this study was that it included the analysis of biological factors in a longitudinal study, highlighting the importance of comorbidity, and because it shows how symptoms of fatigue and menopause affect cancer patients, which in turn might be one of the underlying factors inducing cognitive impairment. This might be confirmed by the fact that fatigue and menopausal symptoms as well as cognitive impairment improved over time, but this may also be a result of practice effects. Another important aspect of Mar Fan *et al.*'s (2005) study is that it followed a large group of patients over a two-year period. However, a weakness of the study is that it does not provide the cognitive status of patients before chemotherapy treatment, and it is unknown whether cognitive deficits were present.

In a three-year longitudinal study conducted by Jenkins *et al.* (2006), 85 women with early stage breast cancer who were scheduled for chemotherapy were tested. The study was divided into three groups: 83 women were scheduled for chemotherapy and/or radiotherapy, 43 were scheduled for endocrine therapy and/or radiotherapy and 49 were healthy controls. Testing was carried out at baseline or before treatment, post-treatment or six months later and 18 months after baseline. Controls for variables such as menopause status, age and education were used. Their results reported that 20% of

chemotherapy recipients presented cognitive impairment in one or two measures. For the control groups, 26% of cancer patients not receiving chemotherapy showed a decline and 18% of the healthy control group presented a decline. Improvement was observed in 22% of chemotherapy patients, 16% of patients undergoing other cancer treatments and 16% of the healthy controls.

Their findings suggested that only a few women experienced cognitive impairment, those who experienced chemotherapy-induced menopause, although no significant changes were found. Improvement of performance after baseline in test scores was also found in some patients, which was attributed to practice effects. It is interesting to observe that women experiencing chemotherapy-induced menopause are the most affected, which is consistent with the findings of Mar Fan *et al.* (2005). The results of these studies may be interpreted as showing that accelerating menopause in women has a detrimental effect on cognition.

To further evaluate cognitive function prior to chemotherapy treatment and assess changes in cognition over time and the potential relationship between this and anxiety, depression, fatigue, haemoglobin levels, menopause and self-perception of cognitive function, Jansen *et al.* (2008) evaluated 30 women with breast cancer before chemotherapy and after four cycles of treatment. Contrary to previous studies, they found significant changes in some cognitive abilities. They reported a significant decrease in visuospatial skills ($p = 0.001$) and total cognitive scores ($p = 0.001$) following chemotherapy, confirming the hypothesis that chemotherapy may have a negative impact on cognition. However, these results should be treated with care due to the small sample size and the lack of a control group. Of interest for the current study is that the work by Jansen *et al.* (2008) used the Repeatable Battery of Adult

Neuropsychological Screening (RBANS), which includes some aspects of PM (attention and delayed memory). The authors concluded that RBANS is more sensitive than other neuropsychological tests for detecting subtle changes in cognition. However, their results are consistent with other studies with other measures of psychological assessment, in that no significant changes were detected.

In an attempt to address the controversy regarding cancer patients' cognitive status at baseline, Ahles *et al.* (2007) compared test results of breast cancer patients with invasive cancer (n = 110) and non-invasive cancer (n = 22) prior to adjuvant treatment. Participants completed a battery of neuropsychological tests after surgery, prior to commencing chemotherapy, radiation or hormonal therapy. They also included a control group comprising 45 healthy women. Their results showed no statistical significance in abnormal test results, but patients with invasive cancer showed significantly lower scores than healthy controls in the reaction time domain (p = 0.005) and were more likely to be classified as having lower than expected cognitive performance compared with non-invasive counterparts and healthy controls.

The authors concluded that patients with early breast cancer do not exhibit cognitive decline before treatment, whereas invasive carcinoma patients presented some decline, but the differences are minor or non-existent when compared to controls. Factors such as depression, surgery, anaesthesia and biological markers were not associated with lower than expected cognitive performance. This may indicate that the severity of the illness may affect cognition and the more threatening the condition, the more the cognitive abilities might be affected. It is interesting to mention that invasive carcinoma patients' self-reports did not indicate more cognitive impairment than the non-invasive patients, meaning that they are not aware of their deficits.

The studies discussed above show a common characteristic, which is a general agreement that MCI exists in a subsample of cancer patients, despite such results being statistically insignificant, that anxiety and depression are not at the core of these results and that patient's self-reports are inconsistent with the findings, in which patients seem to overstate their cognitive complaints. However, in a study conducted by Mehlsen *et al.* (2009), the findings showed disagreement with previous studies.

Mehlsen *et al.* (2009) conducted a study in which 34 cancer patients receiving chemotherapy were examined and compared with 12 cardiac patients and 12 healthy controls in a 3–4 month interval. The rationale for using a cardiac patients group was to control for the fact that both the groups of patients were facing a life threatening condition, which by itself may cause cognitive problems. They argue that the symptoms reported by patients are merely a subjective experience as a result of the psychological distress caused by the disease and treatment-induced stress and fatigue, because they did not find statistical significance on test results. They supported their rationale by the discrepancy between results of self-reports and validated batteries. Their results showed no differences in cognitive abilities between the three groups, with no significant deterioration in performance exhibited by cancer patients compared to cardiac patients and healthy controls. Twenty-nine percent of cancer patients showed a decline in more than two cognitive measures versus 25% of cardiac patients and 25% of healthy controls. They attributed this to normal variation over time, rather than illness or treatment. The testing intervals were different between the groups. Cancer patients were tested 0–7 days before treatment and 4–6 weeks after the last cycle of chemotherapy. Cardiac patients were tested four days after hospitalization, before being discharged and retested three months later. Healthy controls were tested at 12–16 weeks. The results

should be treated with care, because the control groups had shorter testing intervals, which might have influenced the test results. Similar results were reported by Jenkins *et al.* (2006) and Hermelink *et al.* (2007). It is possible that the observed improvements might be due to practice effects, rather than improvement in cognition over time.

Another study not supporting the hypothesis of cognitive decline after chemotherapy treatment is that of Tager *et al.* (2009) for a group of post-menopausal women. Thirty patients received chemotherapy, while 31 received no chemotherapy and were used as controls. Their testing schedules were post-surgery but before commencing chemotherapy treatment, followed by a second testing session within a month of completing treatment and a third testing session six months after the second testing session. In a sample of 61 post-menopausal women with non-metastatic breast cancer, patients treated with chemotherapy performed worse at baseline than in the following assessment.

However, Stewart *et al.* (2009) found the opposite results in a similar population. They found that post-menopausal breast cancer patients scheduled to receive adjuvant chemotherapy ($n = 61$) showed a subtle negative influence of chemotherapy when compared to breast cancer patients scheduled to receive adjuvant hormonal treatment ($n = 51$). The mean scores for both the groups were within the normal range in both testing sessions, remaining stable from baseline to time two. However, chemotherapy patients were 33% more likely to show cognitive decline than controls.

These findings suggest that there is no causal effect of adjuvant chemotherapy on general cognitive dysfunction, with a poor correlation between subjective and objective measures. These two studies controlled for menopausal changes by including only post-

menopausal participants, but they differed in the neuropsychological batteries applied, statistical analysis, sample size and number of testing sessions.

More recent studies have focused on domain-specific analyses rather than on global cognitive domain. In a study conducted by Ganz (2013), where 189 early-stage post-treatment breast cancer patients were assessed with a neuropsychological battery and self-report questionnaires prior to endocrine therapy, 23.3% showed higher memory complaints and 19.0% higher EF complaints. Regression modelling showed statistically significant association of higher memory complaints with combined chemotherapy and radiation treatments ($p = 0.01$), inferior verbal memory performance ($p = 0.02$) and greater depressive symptoms ($p = 0.001$). For executive functioning complaints, they found a statistically significant relationship with superior visual memory performance ($p = 0.03$) and higher depressive symptoms ($p = 0.001$) using multivariable modelling. On the other hand, combined chemotherapy and radiation treatment showed being statistically significant ($p = 0.05$). These results provide evidence that breast cancer patients present significant levels of memory and EF difficulties associated with domain-specific neuropsychological performance, but it is unclear if breast cancer patients were compared to healthy controls and they were subject to the limitations of cross-sectional studies. However, their sample size was very large, providing confidence in their results.

Collins *et al.* (2013) found a dose-response relationship, which provided "the most compelling clinical evidence to date that cognitive decline is *caused* by chemotherapy exposure". They enrolled 60 women with early breast cancer, matched with a poll of 60 healthy women, who underwent neuropsychological assessment after surgery and prior to chemotherapy treatment and after each cycle.

They included paper-based assessment and a computerised cognitive test that measured attention, WM, EF and visual and episodic memory. To assess change over time and domain-specific cognitive scores, they used multilevel modelling, which accounted for individual or group baseline status depending on the variable under investigation. The model also controlled other variables that may affect change such as age, education and depression.

These results showed that the chemotherapy group showed a significant decline after each testing session compared to controls, although raw data fell within normal ranges. However, they argued that when corrected for practice effects, the magnitude of the decline was large. This argument is worth noting, because it might be that despite the lack of sensitivity of common neuropsychological tools, the selection of statistical analysis makes a big difference to the results and when drawing conclusions (Shilling *et al.*, 2005), and common statistical methods might be becoming obsolete, and therefore, more attention should be paid to newer and more effective statistical analyses.

According to Shilling *et al.* (2005), the extent of impairment found in chemo brain patients is influenced by the type of statistical analysis chosen. To confirm this statement, they analysed data from 92 breast cancer patients at four weeks post-chemotherapy and from 42 healthy controls, using seven different methods previously used in publications related to the topic. They reported that impairment ranged from 12% to 68.5% in the chemotherapy group and from 4.8% to 64.3% in the healthy control group, demonstrating that different methods of analyses yield very different results, obscuring the understanding of chemo brain.

It is due to these contradictions found in the literature that one of the aims of the current study was to include qualitative measures as well as in-depth interviews and domain-specific qualitative analysis. It is evident that some decline is observed in neuropsychological batteries, but results indicate only moderate impairment and no significant difference when compared with controls. Due to statistical methodology bias, it is not possible to rely on quantifying symptoms, because despite all the studies that do not find a link between chemotherapy treatment and cognitive impairment, patients continue to report these problems and the effect they have on their lives.

Neuropsychological studies assessing global cognitive domain have failed to provide standard and sensitive measures to assess chemo brain accurately. Mehlsen *et al.* (2009) suggested that the more cognitive tests that are included, the greater the probability of finding evidence of cognitive decline, whereas in the literature, most studies only include tests from a single session. A greater awareness of what patients are experiencing is needed, and therefore more sensitive and reliable measures should be developed.

3.8.3 Summary of longitudinal studies

To resolve the lack of baseline assessment, researchers began to address the limitations of cross-sectional studies by including baseline assessment before treatment (Wefel *et al.*, 2004; Shillings *et al.*, 2005; Jenkins *et al.*, 2006; Jansen *et al.*, 2008). This has been of paramount importance because since then, emphasis has been placed on having patients' previous mental status.

Another significant advancement in the study of chemo brain was considering other biological factors and covariates such as haemoglobin (Jansen *et al.*, 2008) and blood samples (Mar Fan *et al.*, 2005) in order to consider comorbidity with other biological factors.

Menopause-induced cognitive dysfunction and menopause status have been considered as potential underlying factors of chemo brain in at least two of the studies (Jenkins *et al.*, 2006; Mar Fan *et al.*, 2005). These studies influenced subsequent studies, which began to include hormone treatment as control groups in order to further analyse the effects of hormone therapies on cognition (Stewart *et al.*, 2008; Schilder *et al.*, 2009; Jim *et al.*, 2009; Collins *et al.*, 2009).

Attention was also paid to whether patients' cognitive abilities were affected by chemotherapy alone or as a result of the illness, surgery, anaesthetics or psychological distress due to facing a life-threatening illness. To control for these issues, studies of the potential impact of surgery were undertaken (Ahles *et al.*, 2007); cardiac patients were included in some studies (Mehlsen *et al.*, 2009) and menopausal status began to be considered. Biological factors were also considered by analysing patients' blood samples (Shillings *et al.*, 2005; Jansen *et al.*, 2008).

Studies not supporting the hypothesis of cognitive decline started to emerge where no causal effect of adjuvant chemotherapy on general cognitive dysfunction was found (Tager *et al.*, 2009; Shillings *et al.*, 2006; Mehlsen *et al.*, 2009). Self-reports had been included in the majority of the studies. However, there is poor correlation between them and objective measures of cognition (Tager *et al.*, 2009). Interestingly, while objective measures are not affected in the most part by mood or anxiety (Ahles *et al.*, 2007), self-

reports are influenced by them, according to some authors (Tager *et al.*, 2009). To determine change over time, some researchers started to use the Reliable Control Index (RCI) (Wefel *et al.*, 2004; Shillings, 2005), although this method yields high error rates (Temkin *et al.*, 1999).

Arriving at the conclusion that chemotherapy alters cognition remains controversial, but the majority of studies differ greatly in their designs, tests used, control groups, disease stage, therapy regimens and sample size, which makes the results difficult to interpret (Jansen *et al.*, 2008; Shilling *et al.*, 2005).

3.9 **Prospective memory, attention and chemo brain in the literature**

It is hypothesized that PM, the memory for planned intentions, is implicated in chemo brain. The author suggests that cognitive decline after chemotherapy is associated with memory difficulties presented in day-to-day life and with planned intentions, which are related to attention difficulties and EF impairment.

This new line of research on chemotherapy-related cognitive impairment was pioneered by Paquet *et al.* (2013). Their findings suggest that breast cancer survivors exhibit a PM deficit, with fatigue as a major contributing factor. They examined failures of PM in the everyday lives of breast cancer patients. In a cross-sectional study, they assessed 80 patients diagnosed with early breast cancer within one year of having completed adjuvant chemotherapy, with or without hormonal treatment, and 80 matched healthy controls. The PM assessment was carried out using the Memory for Intention Screening Test (MIST), which includes event-based and time-based activities. It is important that

the activities are relevant for an effective study of PM (McDaniel, 2007). A statistically significant difference ($p = 0.001$) was found between groups on the MIST scores, with post-menopausal patients showing significantly lower scores ($p = 0.05$) than matched controls. These findings suggest that PM might be one of the cognitive domains most affected by chemotherapy treatment. In contrast to Ahles *et al.* (2007), who suggested that factors such as depression and fatigue are not intervening factors in chemo brain, Paquet *et al.* (2013) found that patients had significantly higher levels of fatigue and depression ($p = 0.0001$) than controls. This contradiction might be explained, because MIST is a more reliable measure of daily living. On the other hand, Ahles *et al.* (2007) used a more laboratory-like battery, which may mask the effects of such factors.

However, this finding should be taken with caution due to the fact that the Canadian study (Paquet *et al.,* 2013) was cross-sectional in nature. A baseline assessment of PM should be considered. Nevertheless, the results were promising due to the fact that other domains of cognition have been well studied, using very diverse statistical measures, and very few have found statistically significant difference, although cognitive decline has been found consistently. The study of PM, and evidence from Paquet *et al.* (2013), should start gaining more attention, due to the fact that patients reports widely associated with those of PM failures.

Factors such as selective and divided attention, EF and attentional function have been associated with the study of PM. However, very few studies in these areas have been related to the area of chemo brain.

Weis *et al.* (2009) examined the effect of cognitive impairment in cancer patients in their everyday lives. They evaluated the correlation between subjective self-appraisal

and neuropsychological test results in a population of 90 breast cancer patients, nine months after receiving adjuvant chemotherapy. Participants were assessed on measures of attention, using the Test Battery for Assessment of Attention (TAP), a computer-based test that examines alertness, reaction change, divided attention, sustained attention and WM at three time points: at the start of in-hospital rehabilitation, the end of in-hospital rehabilitation and 6 months later. They also included measures of quality of life, fatigue, anxiety, depression and self-perceived measures of attention.

Participants were divided in three groups: the neuropsychological training group (n = 33), an individual personal computer-supported training group (n = 34) and a no special training group (n = 29). Their findings showed that an improvement in cognition took place after some time had elapsed. Time three parameters were normal, confirming the hypothesis that adjuvant systemic therapy does not play a long-term role in cognition, and only 21% of the study group showed significant clinical impairment. A low correlation between self-perceived deficits and objective measures was obtained, but an association with depressive mood was found, supporting the hypothesis of Shilling *et al.* (2007) that depressive symptoms impair performance.

However, the authors found that 87.5% of patients showed a decline at Time one in at least one of the neurological test results (1.5 SD below the mean of age-adjusted norm data) and 56.2% showed a decline in more than two or three tests and hence were classified as having relevant impairment. Most deficits were found in measures of sustained attention (TAP, omissions, 49%) and semantic memory (delayed reproduction, 34%). Patients who were objectively shown to be severely affected reported their everyday living subjectively as being extremely poor.

The important aspect of this study is that a very different approach was used, focusing on the study of specific aspects of attention. Although there was an improvement over time, this might have been due to their training sessions, which shows promising results to develop patients' interventions after experiencing cognitive decline after chemotherapy. However, this is not the scope of the current study. What is noteworthy is the fact that patients were assessed for the first time nine months after treatment, at which point they exhibited attentional deficits such as omission errors. This is important because this confirms that PM plays a role in chemo brain.

To further assess everyday functioning in chemo brain patients, Adams-Price *et al.* (2009) recruited 38 breast cancer survivors (3–45 months after chemotherapy treatment), who were compared with 55 age-matched healthy controls. They used Useful Field of View (UFOV), a computerised test of visual information processing; this test is used to predict driving performance in older adults and has been associated with information processing speed, ability to divide attention and the ability to ignore distractors or selective attention (Ball *et al.*, 1990). They found significant interactions between treatment and age on processing speed ($p = 0.002$) and marginal significance for selective attention ($p = 0.074$) measures. Older participants performed less well than younger controls on speed of processing, but not in the other measures.

Care should be taken when considering results from this study due to several methodological issues. Although it has a healthy control group, the sample size was relatively small and no baseline was assessed before treatment. Of greater concern is the fact that the differences between the post-chemotherapy groups with respect to end of treatment were very wide and participants were at very different stages. This group

could have been divided into short-term effects and long-term effects to better understand the effects of time on these measures.

3.10 **Qualitative studies**

In the chemo brain literature, very few studies have focused on the study of the phenomenon through qualitative analysis. Although many studies include self-reports and quality of life questionnaires, few have conducted semi-structured interviews, face-to-face interviews and case studies to analyse patients' daily-lived experiences.

Due to contradictory findings in qualitative results and particularly because of the contradiction between patients' reports of daily living and neuropsychological assessment, the author believes it is of greater relevance to pay more attention to the study of the patients' experiences so that better assessment tools can be developed and to focus attention on PM cognitive failures in these areas of study.

In the following section, some of the most relevant qualitative studies of chemo brain are discussed, in order to better appreciate what sufferers of chemo brain report, how they experience their cognitive failures and how this relates to PM complaints.

The first study to analyse self-reported cognitive complaints and report what patients were saying was by Downie *et al.* (2006). They tested 21 breast cancer patients while undergoing chemotherapy using a neuropsychological test, followed by a semi-structured interview. Unsurprisingly, they found no correlation between self-reports and objective assessment, with patients' self-perceptions of cognitive changes greater than

scores in the objective assessment. They suggested that the neuropsychological assessment used in their sample was not sensitive enough to detect MCI, and they attributed this discrepancy to factors such as lifestyle, mood, fatigue and resilience, which may have an impact on the experience of symptoms.

They followed up their assessment with a semi-structured interview, where questions about patients' memory, concentration, attention, spatial orientation, ability to organise, menopausal symptoms and coping strategies were asked. The results indicated that patients suffered from changes in STM, concentration, verbal fluency and word finding abilities, mental fluency, processing speed and, to a lesser extent, planning and visuospatial abilities. They also reported that patients experienced increased forgetfulness of names, words, places and appointments.

These cognitive problems affected all aspects of life (work, home and social), with problems related to reading and concentration, processing information more and mental sharpness decline. Decreased ability to multitask and problems with their ability to drive were also reported.

Limitations of this study are the relatively small sample size, a lack of baseline assessment before chemotherapy and that no comparison group was included, which is understandable because of the qualitative nature of the study, which aims to report what patients were experiencing.

Another study analysing self-reports was conducted by Shilling *et al.* (2007). They reported interview data from a large sample of 142 breast cancer patients receiving adjuvant chemotherapy and the associated cognitive impairment to quality of life and

psychological distress. Baseline assessment was included as well as assessment of six months and 18 months after treatment. They divided their participants into two groups, those scheduled to receive chemotherapy (n = 100) and those receiving radiotherapy and/or endocrine treatment (n = 53). All the participants took part in a semi-structured interview and a neuropsychological battery.

They found that 71% of the participants reported problems with memory and concentration at six months after treatment and 60% after 18 months. As with Downie *et al.* (2006), these reports were unrelated to objective assessment. The majority of failures were associated with everyday slips and lapses and were associated with psychological distress and quality of life. Reports from family and friends were also included, with 53% of the cases reported having noticed memory and concentration problems in the patient.

To capture the experiences and perceptions of cognitive decline, two studies conducted in-depth analysis of the phenomenon. Mitchell *et al.* (2011) explored how this decline is interpreted and made meaningful to the individual, providing a reference of how patients perceive chemo brain. The authors reported that patients and healthcare providers were usually unaware that the phenomenon exists. Memory decline was attributed by the patient to other factors such as fatigue illness, bereavement and in some cases, even dementia. One patient also believed that she was unable to remember words because of her menopause status. The authors argue that the use of neuropsychological batteries merely provides external evidence that is not related to the reality of patients' experiences.

Reports of more in-depth studies indicate that patients perceive chemo brain as the most troublesome side effect of chemotherapy treatment. In one study, patients reported a diminished quality of life and daily functioning, which led them to develop coping strategies to be able to continue with their daily routines and social life (Boykoff *et al.*, 2009). Fitch *et al.* (2008) reported that patients indicated that they would have preferred to be warned about chemo brain as a side effect and its implications on their lives after chemotherapy. This last finding contradicts Schagen *et al.*'s finding (2012), who concluded that patients informed about cognitive changes may induce a stereotype threat, which may contribute to the incidence of cognitive problems.

The suggestion that factors such as personality, stereotyping, mood and fatigue may interfere with the accuracy of self-reports is of concern if reliable results are to be obtained. However, relatives and friends of the patients usually notice these changes and can help to validate the responses. On the other hand, experiences in daily life are also important and for that reason, case studies and interviews were decided to be included in the current research. Things such as misplacing things, missing appointments and not finding words are a fact of life for patients, regardless of their self-perceptions.

Emerging themes from a phenomenological analysis conducted by Player *et al.* (2014) revealed that participants have varying experiences as a result of chemotherapy, with six themes being reported. Among these themes, the majority of patients expressed uncertainty about the origin of chemo brain and attributed their memory difficulties to diverse factors such as mental fatigue and shock of diagnosis. All the participants from their sample reported persistent but inconsistent impacts on cognitive function, and that simple functions turned complex, causing significant frustration and loss of identity. They also reported losing functional independence in family life due to reduced

concentration and motivation, and that they had to learn to depend on strategies to maintain function. Finally, participants reported the need for recognition of the subjective experience of the treatment.

Reports from case studies also allow an understanding of how patients experience memory decline after chemotherapy. In an analysis of two case studies using neuropsychological test results and cognitive self-reports, along with blood samples to assess hormone status, Paraska *et al.* (2003) reported that both the participants experienced cognitive decline during and after treatment. Interestingly, both reported self-perceived cognitive decline before deterioration was detected in their tests scores at baseline testing, which might be due to the shock of the diagnosis, and both experienced chemotherapy-induced menopause.

These studies corroborate the importance of drawing attention to qualitative reports. Although quantitative studies are of great importance and provide information about the general population, in the case of chemo brain, their results cannot be considered in isolation because of the risk if misinterpreting a diagnosis. Factors such as diverse statistical analyses or inconsistent methodologies may lead to a loss in the richness of patients' experiences and a lack of understanding of reality of the phenomenon. Most importantly, patients may miss quality care and proper intervention to help them cope with this debilitating side effect of chemotherapy.

3.11 **Animal research**

The focus of this research is not based on animal models, but it is very important to consider what is being done in the experimental area of psychology and biology with animal models to gain information about potential confounding variables, such as the effects of toxicity on the hippocampus and other brain regions.

Chemo brain can be greatly influenced by chemotherapeutic agents. Studies in animal research have helped to understand factors that might affect brain structures related to memory and cognition, specifically in hippocampal regions. Many animal studies have been conducted to observe the effects of chemotherapy on cognition.

El Beltagy *et al.* (2010) studied the chemotherapeutic agent 5FU. They found that it crosses the blood-brain barrier, having a direct impact on brain function. They also reported that Fluoxetine, an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, can improve cognition and memory.

Within the same line of research, Yang *et al.* (2010) studied the effects of cyclophosphamide (CYP). They suggested that CYP may act as an underlying mechanism for memory impairment after a regimen of chemotherapy by inhibiting adult hippocampal neurogenesis involved in learning and memory processes. Their results showed significant memory deficits in mice trained at 12 hrs after CYP injection. They explained that cognitive impairment following chemotherapy might cause indirect chemical toxicity and oxidative damage, direct injury to neurons and inflammation. These toxic effects reduce cellular resistance to oxidative stress allowing entry of

possibly neurotoxic molecules to the brain as a result of damage to the blood-brain barrier, which probably incurs cognitive changes. The authors suggested that

> "the impairment of memory retention might be associated with the change in neural progenitor/stem cell marker proteins in the hippocampus in adult mice. In addition, this study shows that a single injection of CYP in adult ICR mice can interrupt the functioning of the hippocampus, including learning and memory, possibly through the inhibition of neurogenesis" (Yang *et al.*, 2010).

Animal models of research are needed to better control for potential co-occurring diseases or psychological factors. They have also provided knowledge about the potential locus of action on pharmacological agents, allowing researchers to make predictions, as in the case of the effects of chemotherapy on cognition, and to identify neurobiological effects of different agents. The studies discussed above provide insight into the sense that it has been discovered that chemotherapeutic agents can cross the brain-blood barrier, causing neurotoxicity on hippocampal structure and leading to cognitive deficits (MacLeod *et al.*, 2007).

3.12 **Summary**

It is a fact that patients who have survived cancer present memory and language deficits after undergoing chemotherapy. However, the underlying causes remain unknown. Mood, depression and anxiety might be important factors that could be altering cognitive function due to psychological distress, because there might be a strong

relationship between depression and mood disturbances and cognitive deficits in cancer patients (Burgess *et al.*, 2005).

The most commonly affected domains in chemo brain are WM, processing speed, attention and learning. Despite these declines usually being subtle, patients have reported high incidences of functional loss, such as decreased ability to work, which seem to be associated with a central neurotoxicity.

Hormonal changes can also account for memory loss. Many breast cancer therapies involve hormone treatment, which might be having an effect on cognitive function (Collins *et al.*, 2009). Therefore, the effects on cognition of adjuvant hormonal therapy on breast cancer patients should be studied.

In a meta-analysis study of neuropsychological batteries implemented to test the effects of chemotherapy on cancer survivors, Jansen *et al.* (2007) implied that the adequacy of the test being used for the assessment should be considered more carefully. Factors to consider when selecting a test should be the domain to be measured, reliability and validity, appropriateness of the test, the normative data, availability of parallel forms and the specificity and sensitivity of the test.

3.12.1 Key points

1. Neuropsychological measures have shown inconsistencies with patients' self-report indicators.
2. Mood might be an important factor that could be altering cognitive function, but evidence comes mostly from self-reports.

3. Chemical toxicity to neurons causes oxidative damage, inflammation and destructive autoimmune responses, such as anaemia and fatigue.
4. Despite these declines usually being subtle, patients reported high incidences of functional loss, such as decreased ability to work.
5. Hormonal changes can also account for memory loss.
6. Changes remain for one year after treatment.
7. There is a need to identify more reliable, valid and sensitive tests for short or long-term effects.
8. Subtle cognitive impairment is observed in some breast cancer patients.
9. A vast majority of the research has been focused on global cognitive dysfunction.
10. A more specific and detailed study is necessary to deeply analyse the specific memory processes affected.
11. More sensitive and domain-specific memory measures are required.

CHAPTER FOUR

4 PROSPECTIVE MEMORY THEORETICAL FRAMEWORK

4.1 Chapter overview

This chapter briefly explains the history of the study of memory in order to explain some of the concepts that are essential for the understanding of PM, and how it is associated with daily cognitive function. After a brief explanation of how the study of memory emerged, diverse models of memory, such as the modal model and the WM model are summarised. Since EF has been largely associated with WM (Repovs & Baddeley, 2006) and PM (McDaniel *et al.*, 2007), this is also explained, along with the theory behind PM.

4.1.1 Brief history of the study of memory

Memory function is crucial for daily life for doing any kind of activity. Research has shown that memory is not a single system, but a complex system involving several regions of the brain, and different theories of memory have been developed to explain its complexity (Baddeley, 2009). To gain a better understanding of memory processes, particularly PM and EF, which are included in the scope of this investigation, a brief explanation of memory models and theories is presented.

The study of memory has been the subject of interest dating from Plato (427–347 BCE), who believed that the truth was stored in memory and that learning is the recollection of these truths, and Aristotle (384–322 BCE), who explained that memory was the power of retention and that recall was due to recollection, which is formed by associations (connection of two mental events) (Neath *et al.*, 2003). It was Augustine (354–430 BCE) who was the pioneer in identifying separate kinds of memory: sense and intellectual memory, the first one associated with reproduction of images, sound, odours and touch, and the latter related to knowledge, such as the study of literature, science and philosophy. Augustine's view was that memory was not a passive or a simple process, but a complex series of actions (Neath *et al.*, 2003).

The Spanish humanist Luis Vives (1492–1540) began talking about forgetfulness and suggested writing things down to aid memory. A few years later, Rene Descartes (1596–1650) introduced his ideas of Cartesian Dualism, in which mind and body are separated into two distinct entities, whereby the essence of man was the mind, which can interact with the body, but can also act independently. The experimental approach for the study of the human memory emerged with David Hume (1711–1766), who based his assumptions on Aristotle's ideas of association through similarity and continuity, but with emphasis on the principle of cause and effect (Neath *et al.*, 2003).

One of the first people to study memory under laboratory conditions was Herman Ebbinghaus (1850–1909) in an experiment in which he studied how learning interacted with what was already known. He studied associations between stimuli and responses by using lists of words and non-words (Baddeley, 2009). The importance of his research

was that although he was his only subject of study, the emphasis was placed on creating two conditions to assess his predictions; he conducted an experiment to analyse his hypothesis, thus becoming the first experimental psychologist (Neath *et al.*, 2003).

The modern history of the study of memory began in 1890 when William James distinguished primary memory from secondary memory, dividing memory into multiple stores. Primary memory refers to "the contents of consciousness or the information that is the focus of attention at any one time" (Neath *et al.*, 2003). It has also been termed STM, WM and short-term store, because primary memory specifically holds on to information for a short period of time (Neath *et al.*, 2003). Secondary memory, on the other hand, refers to "a long lasting, unlimited capacity store holding information that is no longer in the focus of consciousness" (Neath *et al.*, 2003) and items that have been absent from consciousness for a period of time, which have to be retrieved (Neath *et al.*, 2003).

The study of human memory has continually increased, and more recent studies on memory explain the different subsystems that have been identified, such as sensory memory (SM), STM, WM and PM, which will be explained later in the following section of this chapter. To expand the study of memory, researchers nowadays also rely on neuroimaging techniques to observe the biological basis of memory, in which participants are required to perform a task while diverse types of brain scans are conducted, so that researchers can identify the structures of the brain involved.

Furthermore, the complexity of memory systems are better understood by comparing them with computer-based theoretical models, which are commonly used to explain

memory processes by comparing memory systems with computer systems. The computer metaphor has become a very useful model to explain memory processes (information processing approach). One example is the use of this metaphor by Baddeley (2009) to explain memory processes as comprising mere storage systems that require the same elements as computer systems, which are as follows:

1. The capacity to encode or enter information into the system
2. The capacity to store it
3. The capacity to retrieve it

4.2 **Theoretical models of memory and executive function**

To better understand PM and EF, it is useful to understand some theoretical models of memory that attempt to explain its role in our daily lives. To date, the question of how many types of memory exist is still controversial, but this study will follow Baddeley's (2000, 2009) assumptions to explain the structures and processes involved in WM and EF processes (Baddeley, 2009) due to the associations found in the literature with these processes and chemo brain.

The discussion begins with an explanation of Atkinson and Shiffrin (1968) modal model, which describes sensory, short-term and LTM systems, divided into separate components in order to explain human memory. The Baddeley WM model (Baddeley, 2000) is also discussed, in which the key components are the central executive system,

the phonological loop, the visuospatial sketchpad and the episodic buffer. EF and PM are discussed later in the chapter.

4.2.1 The modal model

The way information is stored determines what and how it is stored, and how it will be retrieved. Several theories of memory have emerged, with one of the most influential being the modal model presented by Atkinson and Shiffrin (1968). In the model, the general assumption was that sensory input that comes from the environment is first processed by a series of SM systems, to later be passed on a temporary STM system, where information is maintained for a short period of time (Figure 4.1). If this information is rehearsed, it will be encoded or registered in LTM to be retrieved at a later time. If not rehearsed, information will be lost (Baddeley, 2009).

4.2.2 Sensory memory

SM is described as a brief storage of information more related to perception than memory and can be subdivided into iconic (visual) SM and echoic (auditory) SM. These perceptual processes are summed to lead to temporary STM or WM and capable of temporary storage (Sperling, 1960; Neisser, 1967; Jones *et al.*, 2007; Baddeley & Larsen, 2007).

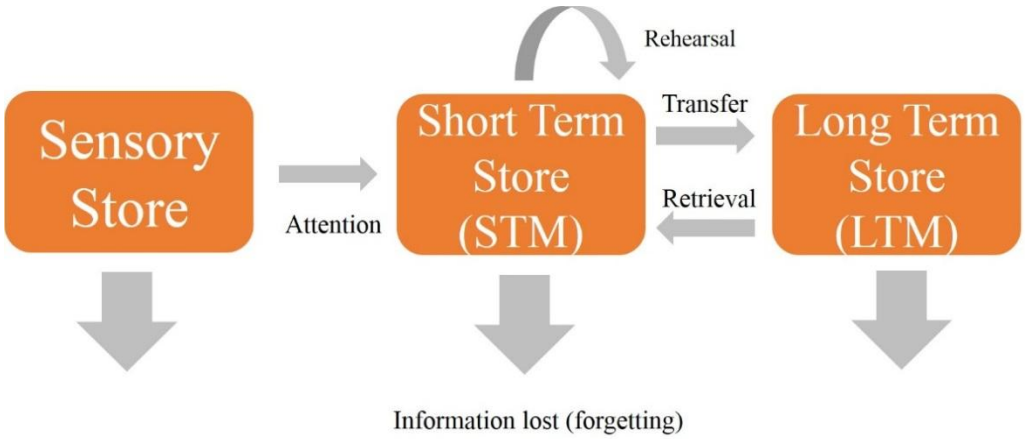

Figure **Error! No text of specified style in document.**.1. The Atkinson and Shiffrin Modal Model (1968).

4.2.3 Short-term memory

STM is a temporary storage of small amounts of material over periods of a few seconds. It is not only limited to verbal material and verbal rehearsal, but also involves visual and spatial information, smell and touch (Baddeley, 2009). Generally speaking, STM refers to remembering things over a brief period of time, but it is best to describe it as the performance of a particular task by retaining small amounts of information, tested either immediately or after a short delay, in contrast to WM, which not only temporarily stores information, but also manipulates it to perform complex activities such as learning, comprehension and reasoning. It serves as a mental workspace.

STM is usually reflected by the digit span test, which is the maximum number of sequentially presented digits that can reliably be called in the correct order. Assessment

of WM span involves more complex tasks and is described as a range of complex memory tasks in which simultaneous storage and processing is required.

The modal model (Atkinson & Shiffrin, 1968) identifies STM as WM, because they have common and similar models. It assumes that information perceived from the environment enters a brief temporary SM system (iconic + echoic), which is then transferred to short-term store, freeing it into LTM and acting as a WM by operating and selecting rehearsal strategies and serving as a global work space (Baddeley, 2009).

4.2.4 Working memory model

Badderley and Hitcht (1974) proposed a more complex model to analyse STM, which they called WM model. The term "working" was used to differentiate from STM, which was more focused on storage, whereas "working" refers more to a functional role, which involves complex cognitive activities that support mental work and coherent thought (Baddeley *et al.*, 1974). WM can be described as a "combination of controlling attentional mechanisms (the central executive) and a number of subsidiary slave systems (phonological loop, and visuospatial sketchpad)" (Neath *et al.*, 2003).

4.2.4.1 Working memory: A multicomponent model

This model comprises three components:

1. Phonological Loop: This component holds sequences of acoustic or speech-based items.
2. Visuospatial Sketchpad: Its main function is to hold visual and/or spatial-encoded items and arrays.
3. Central Executive: This controls the whole system. It is an attention limited system that selects and manipulates material in the subsystems.

According to Baddeley (2000), the central executive, phonological loop, episodic buffer and visuospatial sketchpad are associated with fluid cognitive capacities, such as attention and temporary storage (Figure 4.2). On the other hand, visual semantics, episodic LTM and language are associated with crystallised abilities, such as language and semantic knowledge (Hadjiefthyvoulou, 2011).

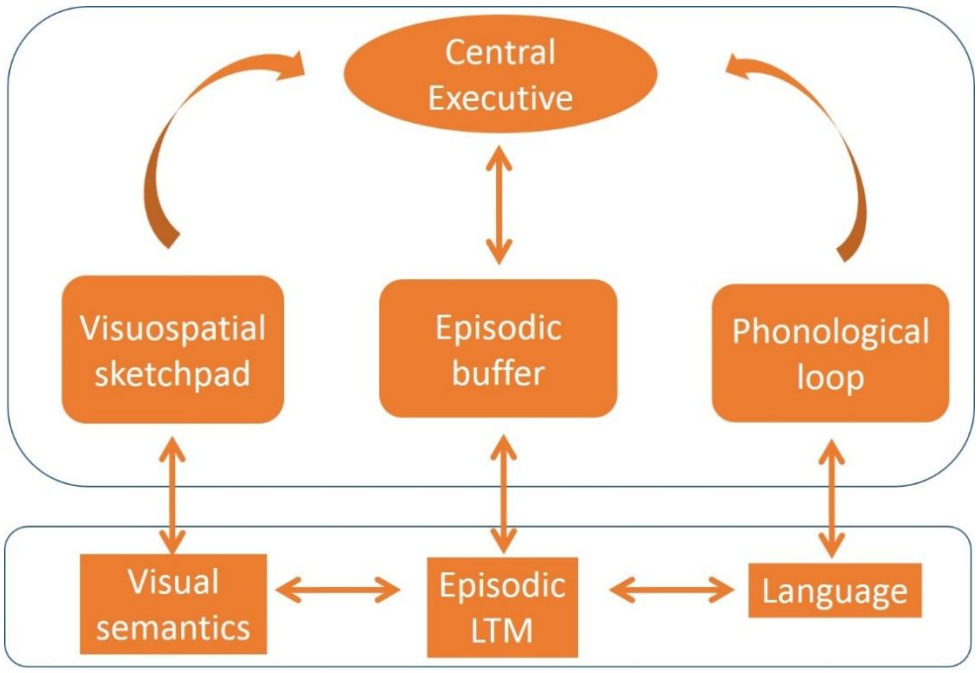

Figure **Error! No text of specified style in document.**.2. Baddeley's Working Memory Model (Baddeley, 2000).

The phonological loop consists of the slave system of the model, which is concerned with verbal STM and assumes a temporary store and a verbal rehearsal process. The loop is responsible for temporary storage of speech-like information. It is assumed to have two subcomponents, a short-term store and an articulatory rehearsal process. The store is of limited capacity and decays within a few seconds, but items can be refreshed by sub vocal rehearsal.

Memory span deals with remembering items and the order in which the items are presented. Two terms usually studied in memory are interference and forgetting, as there is evidence that learning can be disrupted by subsequent activity. Interference

occurs when retrieval of a memory is disrupted by the presence of similar traces in memory.

The visuospatial sketchpad is the second component of Baddeley's model (Baddeley *et al.*, 1974), which is responsible for temporary maintenance of visual and spatial information (to store visuospatial information and to solve problems) (DiVesta *et al.*, 1971; Baddeley *et al.*, 2000; Finke *et al.*; 1988). The episodic buffer, the third component of the slave system, helps to understand how WM links, or interacts with LTM. It is assumed that the buffer is a storage system that can hold chunks of information in a multidimensional code and acts as a link between the various subsystems of WM, connecting them to LTM and forms of perception. Each of these information sources uses a different code, but these can be combined within the multidimensional buffer through what is called binding.

WM is assumed to be directed by the central executive, which is an attention controller rather than a memory system. Norman *et al.* (1986) assumed two modes of functioning of the central executive, one automatic (habitual actions) and the other attention limited. It is possible to describe them with the example of driving a car, which is a skill based on habitual actions that require little attention, but when a novel situation occurs such as a road closed for repairs, the second system is called into action. This second system is known as the supervisor attention system (SAS) and is activated to seek other alternate solutions. This SAS is of major importance for the central executive (Baddeley, 2006).

One of the major functions of the central executive is that of attentional focus, which is the capacity to direct attention to the task in hand and also the capacity of dividing

attention between two or more tasks (Henson *et al.*, 1996; Baddeley *et al.*, 1991a). This assumption is very relevant to this research work, because one of the major areas of the study of PM is focused and divided attention, which are discussed in the following sections of the chapter.

In summary, the four main functions of the central executive according to Baddeley (1996, 2000) are selective attention, which is the ability to attend a piece of information while ignoring irrelevant information; executing two or more activities simultaneously, i.e. the ability to effectively multitask by coordinating the WM resources required for the tasks; switching attention and mental flexibility required to perform habitual behaviours; and retrieving information from LTM (Hadjiefthyvoulou, 2011).

Failures of the central executive result in an inability to multitask, rigid behaviour and failure to identify target events in goal-oriented behaviour (Hadjiefthyvoulou, 2011), which are also relevant for PM performance. Norman and Shallice (1986) also investigated attentional control in patients with frontal lobe damage, usually reflected in perseveration, which is when the person repetitively performs the same action or makes the same mistake repeatedly, or fails to focus attention by simply responding to environmental cues present at that time, leading to bizarre behaviour.

For a better understanding of WM in action, Baddeley (2009) explained how this system operates in a simple and clever way by inviting us to think of our current house and work out how many windows it has. To figure out how many windows there are, we would probably create a visual image of the house which relies on the sketchpad, or we

would probably count the windows verbally by using the phonological loop, and to do so, the central executive would select and run the strategy, and thus, these are the three components of WM in action.

Examples in which SAS fails to operate are slips of action (a lapse of attention producing unforeseen consequences) such as planning to go to the grocery store at the weekend, but finding yourself driving to work or, more tragically, errors that pilots commit that lead to plane crashes (Norman & Shallice, 1986). Additionally, according to Gilbert and colleagues (2008), damage to the supervisory system can cause excessive rigidity, which involves failing to make the right decision or not being able to make alternative choices, and also when experiencing excessive distractibility, there is a reduction in supervisory involvement, failing to pay attention to cues in the environment that would otherwise lead to making the right choice (Gilbert *et al.*, 2008).

To summarise, WM is the temporary maintenance and manipulation of information, which helps in performing a number of complex tasks. It helps to "keep things in mind" when performing complex tasks and "works as a mental work space, providing the basis for thought" (Baddeley, 2009). It is assumed to be linked to attention and EF (Miyake & Shah, 1999, in Baddeley, 2009), which are central cognitive skills for PM and fall within the scope of this study.

Additionally, the author believes that the study of WM is relevant for PM, because the central EFs are essential components of PM. These functions are task switching, divided attention and inhibition (Burgess *et al.*, 2000). Furthermore, according to Cohen and

Conway (2008), “planning, prospective memory, and carrying out actions sequences depend on the ongoing operation of working memory and the allocation of attention”; thus, it is believed that PM is embedded or correlated with WM, as a part of EF system.

4.3 **Executive function (EF)**

4.3.1 Executive function explained

Several definitions exist in the literature that attempt to explain cognitive function. This is mainly due to the overlap among related distinct abilities (Gioia *et al.,* 2004). However, despite the fact that many authors may give many different definitions, most of them agree that cognitive function is a set of separate multiple processes, controlled mainly by the central executive. Since the main scope of this research is PM, attention was focused on definitions that help better understand the overlap of PM with the processes that we consider are interrelated.

Friedman *et al.* (2008) described EF as the collection of control processes that regulate lower level cognitive abilities in order to shape complex performance. These functions are separable, but correlated by the same control processes. Gioia *et al.* (2004) summarised the list of cognitive domains that fall under the umbrella of EFs as a set of interrelated capacities rather than a unitary function. These abilities include the following:

1. Ability to initiate behaviour
2. Inhibition of competing actions or stimuli
3. Selection of relevant task goals
4. Planning and organising means for problem solving
5. Flexible strategies for shifting and problem solving
6. Monitoring and evaluating one's own behaviour
7. WM capacity to hold information actively for problem solving
8. Emotional control

Within this context, EF's role is that of a directive system that exerts regulatory control over basic functions such as language, memory, visuospatial functions and emotions in order to reach a goal by making intentional active decisions. For this reason, EF is a self-regulatory system that organises cognitive abilities and behaviours (Gioia *et al.*, 2004).

According to Friedman *et al.* (2008), EF can be understood as the cognitive control process that regulates thought and action. EFs have also been described as

> "the high level cognitive processes that facilitate new ways of behaving, and optimise one's approach to unfamiliar circumstances" (Gilbert *et al.*, 2008).

Other mental processes can be organised and controlled because of these higher processes. Thanks to these processes, people are capable of living independent lives and are able to make plans for the future, switching from one activity to the other, or inhibiting certain behaviour in the face of temptation. The structures in the brain involved in these processes are those related to the frontal lobes, particularly the PFC (Gilbert *et al.*, 2008).

Although there is disagreement on what are the underlying components of EF, response inhibition **(Inhibiting**), updating WM representations **(Updating**) and set shifting (**Shifting)** have received most attention within EF research. Dual tasking and proactive interference have received less attention, but are also are also considered as functions of EF (Friedman *et al.*, 2008; Della Salla *et al.*, 2004). According to Friedman *et al.* (2008), response inhibition refers to the ability to inhibit either automatic or dominant responses. Updating WM representations can be explained when monitoring takes place while looking for incoming information relevant to the present task and then updating the no longer relevant information by replacing it with the new information. Set shifting is the ability to accurately switch back and forth between tasks (Friedman *et al.*, 2008).

In the literature, EFs are defined as the superior abilities that help with self-regulation and monitoring of the environment as well as to design plans and to anticipate and establish goals (Lezak, 1983). According to Gioia *et al.* (2001), EF is

> "a collection of interrelated processes that are responsible for goal-directed or future-orientated behaviour with the executive system acting as the 'conductor'

that controls, organises and directs cognitive abilities, emotional responses and behaviour" (Hadjiefthyvoulou, 2011).

To better understand EF, it is necessary to understand that schemas (a set of actions or cognitions) become activated by events in the environment, such as a red light triggering the appropriate automatic behaviour when we are driving (use the brakes) (Sahllice *et al.*, 1991; Gilbert *et al.*, 2008). However, for non-automatic behaviours, where inhibition of a well-learned response has to take place, such as in a novel situation, and where environmental prompts are insufficient, a "supervisory system" goes into action, supported by the frontal lobes (Gilbert *et al.*, 2008).

For the purpose of the current study, it was hypothesized that a damage to the supervisory system explains the kind of distractibility reported when there is frontal lobe damage, which corresponds to PM failures and chemo brain cognitive decline. This has been observed in patients who misplace things, become unable to multitask or miss the exit on their way home when they find an unexpected detour.

4.4 **Prospective memory: Theory and terminology**

The following section aims to summarise the most prominent theories and concepts of PM, particularly those that the author of this thesis believed are more related to chemo brain. An examination of the models of PM, including time and event tasks will follow, which are associated with the PM measure selected for our current study.

PM refers to the realization of intended actions at the appropriate time. McDaniel *et al.* (2007) referred to it as "remembering to carry out intended actions at an appropriate point in the future", and the main challenge is remembering to recall. An intended action is the willingness of a person to perform a certain activity or behaviour that has been previously and consciously organised or planned in the future. PM can also be described as the realisation of delayed intentions, which means that an intention is postponed until its execution at the appropriate time or when an appropriate event for its realization occurs (Kvavilashvili & Ellis, 1996). In daily life, people usually depend on prompts in the environment that remind them to perform PM tasks.

To date, most of the literature on memory has focused on retrospective memory (RM), which relates to learning and reproduction. A technique associated with it is known as "cue remembering" (Gonen-Yaacovi *et al.*, 2012), in which the experimenter presents cues to the participant that help them retrieve the information. On the other hand, PM requires a person to remember to perform intentions in the future without obvious cues triggered by the environment. These remembering of intentions has been termed as "self-cued" remembering (Gonen-Yaacovi *et al.*, 2012). This means that to perform an intention, the process of remembering must be self-initiated, using strategies for monitoring for cues that reminds the person what they are supposed to remember. PM remembering differs from RM, in that RM is the memory for events that have occurred in the past, and PM is the memory for the future.

Intended actions or delayed intentions, either in laboratory tasks or in everyday activities, are formed of PM and RM, where remembering to recall an intention is the PM component (go to the grocery store to buy a loaf of bread on our way home) and remembering the content of the intention is the RM component (stop by the grocery shop and remember to buy the bread). An example of an unsuccessful attempt might be to forget to stop by the shop to by the loaf of bread (PM failure) or to stop by the shop and forget to buy it (RM failure). The key difference is that in RM, one needs to remember the content of the intention, whereas in PM, one needs to remember to recall the intentions or plans for the near future. This study focused on the PM component of memory.

Research on PM involves tasks in which participants are usually required to perform an ongoing activity of behaviour that demands attention. They are usually kept busy or distracted by this ongoing activity. Then, at the moment of the target event (namely the event-based PM) or at the termination of a pre-determined time (namely time-based PM), they need to perform an action that is unrelated to the ongoing activity (McDaniel, 2007; Costa *et al.*, 2011). An example of a real life situation of PM paradigm is when a person holds a delayed intention (e.g. post a letter) while performing an ongoing task (e.g. driving to the post office while engaged in a conversation). On encountering the target (the post office), one may make the appropriate PM response (stop by the office to post the letter) or miss the target and continue the ongoing task (drive past the post office).

Since PM is the memory for intentions, goals and plans for the future, it is intimately related to our everyday life activities. Examples of successful PM range from going to the grocery shop to buying some food for today's dinner, or remembering to take our medicines, or attending to a very important appointment with the doctor or a job interview. Daily routines such as driving from home to work, posting a letter or giving a message to a friend also depend on PM. Poor PM leads to failures in meeting such goals and plans, such as forgetting to give a message, missing appointments, failing to take one's pills or taking them twice.

More often than not, when someone refers to their own memory's poor performance, they refer to PM (Baddeley, 1990). Lapses in attention are particularly important in PM. When a person's attention is divided or they are distracted, it is still sometimes possible to successfully carry out the tasks in hand, but if PM is poor, they fail to execute them successfully, forgetting or missing the cues that would lead to the successful execution of the intention.

Furthermore, PM relies on self-initiating retrieval of intentions, which get encoded when the intention is formed; therefore, in order to attend the target event or goal, it is necessary to pay attention or monitor the environment, for cues that prompt the execution of the planned action, i.e. in order to remember to execute the intentions, a person relies on cues in the environment to remind them what they had planned. Missing those cues leads to failure to execute plans successfully. However, in the literature on PM, there is controversy as to whether these processes are automatic (or spontaneous), or if there is a more conscious process that aids in monitoring these cues.

Theoretical models are reviewed later in this chapter. Firstly, the terminology and the parameters of PM are discussed to gain a clearer picture of PM and its function in everyday life, which in turn helps to understand the hypothesis that chemo brain patients experience PM failure when they report having memory difficulties. The PM theory has been related as much as possible to everyday PM failures to give a better picture of what the participants have experienced.

Throughout the literature, diverse approaches or explanations have been found that try to explain cognitive processes involved in PM. For example, Ellis (1996) distinguished five phases for delayed intentions to take place; Einstein *et al.* (1992) analysed PM according to the complexity of the task; Harris (1980) stressed on the importance of analysing the frequency of the tasks; and McDaniel *et al.* (1990) explained how delayed inattentions are executed depending on time-based or event-based retrieval phases, and how delayed intentions are formed, maintained and executed (McDaniel *et al.*, 2007).

These approaches to PM will be the focus of the following section, paying particular attention to time-based and event-based PM, as our main analysis of PM was based on the analysis of such variables on breast cancer patients' PM, as a result of cognitive impairment developed thought their course of cancer treatment. It was hypothesized that chemo brain affects time-based tasks the most, as a result of the tasks being more demanding, which requires more attentional resources. In the literature of chemo brain, findings suggest that problems with attention are found in breast cancer patients (Vardy

et al., 2008; Stewart *et al.,* 2006; Collins *et al.,* 2009; Tager *et al.,* 2009; Bender *et al.,* 2006).

Ellis (1996) explained that the realization of the intended actions or delayed intentions takes place in five phases:

1. **Formation and encoding of intention and action**. This phase is mainly concerned with the content of an action and the form of the retention of an action ("what is what we want to do"), an intent (the decision to do something) and the retrieval context (associated with the conditions of recall). Einstein *et al.* (1990) suggested that this phase corresponds to the retrospective aspect of PM, and that the subsequent phases are the prospective components of PM; readiness and motivation play a role in the execution of the intended action. Factors such as the strength of the intention, personal importance, benefits and consequences are associated with this phase.

2. **Intention retention.** This phase involves the delay between encoding (phase A) and the possible beginning of the performance interval (Phase B), and it is the period prior to the occasion to carry out the action (Gillian *et al.,* 2008), in which the intention is retained in memory at the time the ongoing activity is taking place (Kliegel *et al.*, 2008). This period or interval can vary significantly either in duration or in content. Here, the primary cognitive ability is storage.

3. **Performance interval or intention initiation.** This is the phase when the intended action should be recognised and the intention should be initiated.

4. **Initiation and execution of intended action**. This is the actual execution of the intended plan (Kliegel *et al.*, 2008).

The previous two phases rely on monitoring, cognitive flexibility or inhibition. Retrospective remembering and executive functioning are believed to play a major role during PM performance, i.e. being aware of the appropriate moment to initiate and execute an intended action (the prospective component of PM) strongly depends on EF (Kliegel *et al.*, 2008). Therefore, the retrospective aspect of PM relies mostly on RM abilities.

5. **Evaluation of the outcome.** This phase is necessary to avoid repetition of a successful realization of an intended action.

To better understand how delayed intentions or plans for the future are performed, McDaniel *et al.* (2007) explained that it is necessary to form an intention and maintain the intention in memory for a period of time while performing other activities (ongoing task, execute the plan at the appropriate time and evaluate the outcome). The following parameters have been identified:

1. Execution of the intended action is not immediate. The delayed intention must be performed at some point in the near future.
2. The PM task is embedded in the ongoing activity. In PM, task stimuli or cues appear as a part of another activity or situation, and performance of that activity must be interrupted to carry out the PM task. For example, when we intend to buy a loaf of bread at the store, we must stop driving our car to perform the activity. In everyday life, PM involves interrupting daily routines or activities to perform an intended

activity. During an ongoing activity, we need to remember that there is something else that has to be done.

3. The window of response initiation is constrained. A PM intended action must be performed during a specific window of opportunity. It is because of this window that PM remembering or forgetting is defined. Remembering takes place when we perform the PM task within this window (e.g. it is when 20 minutes have elapsed that we need to take the cookies out of the oven). Failing to perform these activities will be considered as forgetting.

4. The time frame for response execution is limited. Kavavilashvili and Ellis (1996) refer to PM tasks when they have to be executed in no more than a few hours. Reading a book or planning a trip are not PM actions despite the fact that they do arise from intentions and cannot be accomplished immediately, but the time frame required is much longer.

5. There must be an intention. To distinguish PM from other behaviours, a conscious intention or plans must be formed. For instance, we plan to attend an important meeting at work, take our pills, pick up our children from school, buy our groceries, give a message or pay the bills.

4.5 **The role of context in PM**

For successful execution of an intended action, it is important to consider the role of how the environment or the circumstances in which events take place influence the retrieval of an intention. Considering the context in which the intention was encoded,

the context of the ongoing activity and when the target event is going to be executed has received attention in the research community, because it has been shown that context plays an important role in PM.

For instance, Marsh *et al.* (2002) found that changing the context had a negative effect on participants' ability to remember whether they had executed the target event or not, in a study where output monitoring (recalling that a task has already been performed) was under study. In a study conducted by McDaniel *et al.* (1998) using semantic manipulations, changing the context conditions between encoding and retrieval lead to poor PM performance. Other authors have also reported the influence of the context on PM performance (Craik, 1986; Henry *et al.*, 2004). The influence of context familiarity has also been considered, suggesting that familiarity with the context improved planning in PM tasks (Titov & Knight, 2001). Other studies stressing the importance of the contexts on event-based and time-event tasks are those trying to replicate real life PM tasks while ongoing activities take place, keeping the participants busy (Einstein *et al.*, 1990; 1996).

However, the findings of these studies were based on laboratory conditions and should be interpreted differently than naturally occurring events, because naturalistic situations vary greatly from laboratory conditions in the way they prompt automatic retrieval on PM (Henry *et al.*, 2004). This observation is of great importance in this study, because chemo brain has usually been assessed under laboratory conditions, and so there is a need to consider developing more sensitive measures that resemble what patients experience in their everyday lives while they undergo treatment. It is assumed that their mental state, mood and sometimes their physical surroundings (e.g. at home or at hospital, during the time they received treatment) would be very different than at other

times where their lives seem more normal (e.g. between chemotherapy treatments and/or after finishing treatment). Factors such as this should be considered at the time of testing. For that reason, it was decided to include a qualitative analysis to the study, in order to obtain a broader spectrum of memory problems associated with everyday life PM dysfunction in breast cancer patients.

4.6 **Types of PM failures**

In the literature, there are differences of opinion on the difference between PM failure and absent-minded errors (or slip of action). Kvavilashvili *et al.* (1996) distinguished PM failures from absent-minded errors by defining slip of actions as failures occurring during the execution of an intended action and PM failures as consisting of failures to retrieve an intended action completely.

An example of an absent-minded error or slip of action is the substitution error (e.g. taking one thing out of the fridge when the plan was to take another). Another type of absent-minded error that Kvavilashvili *et al.* (1996) deny to be a PM failure is when someone starts carrying out an intended action, but suddenly realises that they no longer remember what they had planned to accomplish (e.g. when someone goes into a room and forgets why they are there). These authors argue that this cannot be a PM problem, but rather a loss of contents of an immediate intention during an ongoing activity (Kvavilashvili *et al.*, 1996). On the other hand, Einstein *et al.* (1996) explained that PM contains components of RM and that in order to execute a PM task successfully, the RM component must also be executed successfully, and that many PM failures occur as a

result of problems with remembering the RM component. For example, in the situation where a person forgets why they went into a room, it is because they have forgotten the RM component of PM.

Slips of action has been classified by Cohen and Conway (2008) as follows:

1. **Repetition errors (commission errors)**. Forgetting that an action has already been performed and repeating it, e.g. placing two checks in an envelope for the same bill. Scullin *et al.* (2012) suggested that commission errors are of great importance in the study of PM. These types of errors occur when an individual fails to suppress executing an intention that has already been performed, when the completed intention is spontaneously retrieved (Scullin *et al.*, 2012).
2. **Goal switches.** Forgetting the goal of a sequence of actions and switching to a different goal, e.g. intending to drive to one place and driving to another.
3. **Omissions and reversals.** Omitting or wrongly ordering the component actions of a sequence, e.g. filling the kettle, but failing to switch it on.
4. **Confusion/blends.** Confusing objects involved in one action sequence with those involved in another sequence, e.g. taking a tin-opener instead of scissors into the garden to cut flowers.

Breast cancer patients usually report things such as forgetting to turn the vacuum cleaner off (goal switches), frequently misplacing things (confusion blends), not remembering if they have already taken the medicine or not, paying bills twice, repeating the same story to the same person over again, reading the same article twice

and not noticing that they had read it before until the very end (commission errors). These common complaints fall into the category of PM lapses; therefore, it was hypothesized by the author of this thesis that poor PM plays an important role in chemo brain.

4.7 **Prospective memory models**

A review of different views on underlying mechanisms of PM is presented in this section. At the core of the debate among the presented models is the question as to whether the successful execution of an intended action is activated by automatic or strategic monitoring or both (two-process model).

The monitoring model is discussed first, because it provides a clear explanation of what monitoring implies for PM and the costs of monitoring too late, followed by the key aspects of the two leading (opposing) models on the theory of PM, i.e. the preparatory attentional and memory processes (PAM) theory and the multiprocess theory of PM, which is the main focus of the current study, because it is the opinion of the author that some cancer patients complaints have to do with some automatic monitoring, such as routine activities like driving back home from hospital, whereas others are more self-initiated and require a more conscious decision, such as beginning a new course of medication and keeping their appointments for treatment.

4.7.1 Monitoring model

A successful PM requires that individuals monitor the environment, which means checking for cues or signals that will lead to the performance of the intended action at the appropriate time, and according to the monitoring model (Harris, 1984), monitoring the environment implies an attentional cost, i.e. attentional resources must be allocated to monitor for the cues in the environment and to check if the response is correct.

This model suggests that people do not necessarily monitor continuously, but periodically, to observe if the conditions are suitable to perform a planned action, and that the cost of monitoring late can be high, which can lead to missing the target event (McDaniel *et al.*, 2007) and subsequently causing problems for individuals, such as when they forget to take their medication, which puts their health at risk. Thus, late responses have been associated with poor monitoring behaviour. On the other hand, frequent monitoring, particularly when the target event approaches, helps to execute PM tasks effectively. However, engagement in the ongoing activity can disturb monitoring by keeping a person distracted and disturbing the maintenance of the intention awareness, which accounts for PM lapses (McDaniel *et al.*, 2007).

Miller *et al.* (1960), in a procedure called Test-Wait-Test-Exit (TWTE), found that people monitor periodically and begin to monitor early because if monitored late, the cost may be too high by forgetting to perform their target event. They found that early monitoring follows a waiting period where attention is maintained, and then another monitoring test takes place and so on, until the appropriate time to perform the target action occurs. Similar results were found by Harris and Wilkins (1982), Einstein, and McDaniel *et al.* (1995). These authors also reported a periodical checking rather than

occurrence of continuous monitoring, with frequency of monitoring increasing as the time to perform the targeted action approached, and that a possible executive system interfered in the participants' decision to initiate the checking behaviour (McDaniel *et al.*, 2007).

4.7.2 The preparatory attentional model (PAM)

Another view for the monitoring approach is the PAM theory, which maintains that monitoring is constant rather than periodical, and that attention is always implicated through a strategic preparatory attentional process that helps to monitor the environment, which should be present at all times for successful PM (Smith & Bayen, 2004). According to PAM, the individual is always conscious of the plan in order to perform an intended action, and the intention is always the focus of attention when the plan is encoded (or formed) and at retrieval (when it is actually performed). Smith (2008) defined an intention as "a decision about an action that consciously references a prior plan" and distinguishes between immediate intentions (performed at the time the intention is formed) and delayed intention (action that is not in the focus of attention during the time interval between encoding and retrieval). The ongoing activity is what receives the focus of attention during that interval. Furthermore, when an event of the environment captures the attention for retrieval of the target event, a preparatory attentional process leads the individual to a conscious recollection of the delayed intention to execute the plan or intention (Smith, 2008).

Nevertheless, McDaniel *et al.* (2007) argued that continuous monitoring for retrieval of a target event would be too costly for the ongoing activity. If PM requires continuous monitoring from the moment the intention is formed and its execution in everyday life, it would be impossible that non-automatic monitoring of the environment would take place, especially because PM execution is sometimes hours or days from the formation of the intention, arguing that cognitive systems rely more on automatic processes. On the other hand, increasing attentional demands should reduce attentional resources available for monitoring.

4.7.3 The multiprocess theory of prospective memory

An opposing view to the PAM theory of conscious and constant monitoring is the multiprocess theory of PM. This theory takes into account that memory processes can be context dependent and that their effectiveness also depends on factors such as the importance of the task, the salience of the target item and the dispositions to remember. The multiprocess theory assumes that PM retrieval involves spontaneous processes triggered by cues in the environment and considers variables such as how busy the individual is during the ongoing activity, the length of the retention interval, the salience of the cue and the importance of the task (McDaniel *et al.*, 2007).

Three main assumptions comprise the multiprocess theory (McDaniel & Einstein, 2000). The first one is that PM is supported by strategic monitoring of the environment and by spontaneous retrieval. The second assumption is that an individual's personality, ongoing tasks demands and uniqueness of the PM tasks play an important role on

effective monitoring and retrieval. The less engagement in monitoring processes anticipates that spontaneous retrieval will be favoured by the context in which the PM retrieval is expected to take place (i.e. a very salient cue that will automatically remind the person of the target event). On the other hand, when it is perceived that spontaneous retrieval will be unlikely, the person tends to rely more on monitoring. The third assumption implies that spontaneous retrieval is more common than constant monitoring because of the cost implicated for the ongoing activities, which may negatively affect their performance during the retention interval, i.e. a few hours or days (McDaniel *et al.*, 2007).

McDaniel *et al.* (2007) claimed that monitoring can be identified as a self-regulatory behaviour with a limited capacity. According to Bargh and Chartrand (1999), this capacity is limited and quickly exhausted. As McDaniel *et al.* (2007) explained, exerting conscious self-regulatory behaviour for a task will affect people's ability to expend conscious effort in a later stage, just as someone who runs a marathon on one day will not be able to run another one the following day, because their physical abilities are depleted. For that reason, it is believed that monitoring is not the preferred strategy, because it represents a cost for ongoing activities and it is difficult to maintain consistently over extended retention intervals (McDaniel *et al.*, 2007).

In the multiprocess theory,

> "the nature and demands of the ongoing task affect the degree of processing of the PM target event and thus determine the type of processes that support PM retrieval and the likelihood of PM success" (McDaniel *et al.*, 2007).

Furthermore, when more effort is allocated to the ongoing task, PM is poorer, because it pulls resources away from processes needed to detect PM targets (McDaniel *et al.*, 2007).

Another postulation essential to the multiprocess theory is that ongoing tasks that promote focal processing of the target event are more likely to lead to spontaneous retrieval. However, when this focal processing is absent, strategic monitoring of the environment for the target event takes place depending on the situation, and some tasks and activities are more demanding than others. Tasks and ongoing activities that are more demanding leave fewer resources available for strategic monitoring, which could be the cause of PM failures. The more someone engages in an ongoing activity, the less they think about PM tasks (McDaniel *et al.*, 2007).

More distinctive or salient target events produce better performance than less distinctive ones and cause spontaneous attention and automatic noticing. Salience of a target item can be the meaning of an activity, physical size of an item, how something is written, a geographic location, etc. Moreover, strong and weak associations between the target cue and the intended action play a role on PM performance. Target actions can be sometimes highly associated with the intended actions and sometimes not. When the association is strong, spontaneous retrieval takes place, and when it is weak, monitoring is the preferred behaviour (McDaniel *et al.*, 2007).

4.7.3.1 Cues

Good PM is necessary for efficient and effective everyday life functioning, such as carrying out social obligations (remembering to attend an engagement with a friend), managing household needs (paying bills) and accomplish work activities (remembering to finish your job) (Parker *et al.*, 2011). It is more likely that PM failures take place when good cues are not available for spontaneous retrieval, and good PM takes place when the intended action depends on resource demanding monitoring processes (Parker *et al.*, 2011; Einstein *et al.*, 2005). According to Parker *et al.* (2011), successful PM retrieval depends on the relation between the ongoing task and the PM cues.

Focal cues relate to those where ongoing task attention is directed to features of the cue or target event proceed at encoding. Presentation of the cue can trigger retrieval, even if monitoring is absent. An automatic spontaneous retrieval process can be initiated with the occurrence of the cue, bringing the intended action into awareness (Parker, 2011; Harrison *et al.*, 2010; Scullin *et al.*, 2010). Nonfocal cues are those in which attention of the ongoing task is directed away from the target. Remembering depends on monitoring processes, assumed by performance on the ongoing task. Monitoring is more likely to happen with nonfocal cues (Einstein *et al.*, 2005; Parker *et al.*, 2011). Nonfocal PM tasks are thought to require a larger effort.

Current studies on PM have been trying to explain controversies between the different models of PM, particularly between those favouring strategic vs. automatic monitoring. Gilbert *et al.* (2012) developed a computational model in which PM reactions emerge from direct environmental triggering, meaning that some PM responses can be made in

the absence of strategic monitoring (Scullin *et al.*, 2010). This view is consistent with the multiprocess framework proposed by McDaniel and Einstein (2000).

On the other hand, more automatic responses can trigger PM cue recognition in the presence of the stimulus and in the absence of preparatory monitoring (Gilbert, 2012). In some circumstances, focal cues can lead to automatic PM, and nonfocal cues require monitoring (Gilbert, 2012; McDaniel & Einstein, 2013). Depending on the nature of the task, monitoring becomes more or less important according to the nature of the PM and ongoing task (Gilbert *et al.*, 2012).

For the propose of the current study, it is suggested that that chemo brain's PM failures fall into the "multiprocess theory of prospective memory", because this model considers the context, salience of the target, individual's personalities, uniqueness of the tasks and spontaneous retrieval, as opposed to constant monitoring. It is important to consider that breast cancer patients face very particular circumstances. Their contexts become extremely transformed, even at the moment of diagnosis. Their physical bodies begin to change after surgery and during treatment. Each patient faces the illness in a very different manner according to their personalities and depending on the amount of their social support, and their focus and attention are directed towards survival, which becomes their main goal. In addition, their physical strengthen might prevent them from constant monitoring of the environment, because more effort has to be put on the ongoing tasks (treatment, survival), which might pull away the resources required for successful PM.

4.7.3.2 Time-based and event-based PM tasks

It has also been suggested that PM is performed within two contexts: time-based and event-based PM. For time-based tasks, a certain period of time must elapse during the ongoing activity to perform the PM task, which relies on self-initiating monitoring behaviour, because no external cues in the environment are available to remind the subject of the intention and an action should be performed; therefore, the subject must self-monitor the environment to perform the intention in the absence of any cue in the environment.

Event-based tasks are when a particular stimulus or event must occur while performing the ongoing activity to carry out the PM task, which relies on cue-dependent responses, depending more on spontaneous retrieval when the target event or intention is prompted by a cue found in the environment. For example, *take the cookies out of the oven after 20 minutes* (time-based) or *stop to buy the milk when you see the grocery shop* (event-based) (see McDaniel, 2007 for further reference).

In the current study, these two last features of PM were analysed based on the CAMPROMPT test. It was hypothesized that time-based tasks would be more affected than event-based tasks as a result of cancer treatment. It was assumed that due to the demands of the cancer treatment itself and anxiety experienced by patients, self-initiating monitoring would be more affected, and the absence of focal cues in the environment for time-based tasks would lead to missing the target events in breast cancer patients

4.7.3.3 Executive function, frontal lobes and PM

Since it is believed that EF and PM are highly correlated (McDaniel *et al.*, 2007; Kliegel *et al.*, 2008), this section explains the role of EF in PM. Although this is only a small section within the chapter, it is important to stress that EF plays an important role in PM, because of the hypothesis that chemo brain is a PM failure, and therefore, it might also be considered as an EF dysfunction. If this hypothesis is correct, it would help with the diagnosis of chemo brain in the future and lead to the development of therapies that could help patients cope with the memory lapses that they might encounter.

Some examples of why it is important to consider patients' day-to-day lived experiences with quantitative research, followed by an explanation of WM and its relationship with PM and chemo brain, the main focus of this thesis, are discussed below.

Memory lapses associated with PM in everyday life involve forgetting to realise an intended goal, plan or activity, such as forgetting to buy the milk on the way home, not passing on a message to a friend when meeting them or not attending an important medical appointment. Furthermore, lapses such as leaving the vacuum cleaner on, frequently misplacing things, forgetting to take medicine or, more dangerously, taking the medicine twice without even realising, losing track of a conversation and forgetting the usual route when driving are considered everyday life failures of PM associated with attention, some of which can have serious consequences for sufferers.

The rationale behind the assumption that EF is a part of PM performance relies on the evidence that the frontal lobes of the brain are involved in PM, particularly the PFC (Martin *et al.*, 2003; Burgess *et al.*, 2008), and that PM tasks depend on executive processes, including monitoring the environment, planning and attentional control (Kliegel *et al.*, 2008).

Some authors have found no association of PM failure and executive control and have attributed the PM impairment to automatic reflexive processes instead (Costa *et al.*, 2011). This discrepancy might be attributed to the fact that PM relies on the frontal lobes, but to various degrees, and depends on the PM task and/or the test being used. For instance, if the retrospective aspect of PM is being assessed, it is not expected to find frontal lobe involvement. Nonetheless, if complex self-initiating tasks are required, such as tasks demanding WM, planning, time tracking, inhibiting ongoing activities and when the environment has to be monitored to search for clues, frontal lobe involvement is required (Glisky, 1996).

To successfully perform a planned intention in the future, multiple cognitive abilities are involved, such as organising how to execute that plan, remembering the plan for a period of time while other activities are taking place, monitoring when and how to execute the plan, followed by execution of the plan and remembering that the plan has already been carried out (van den Berg *et al.*, 2012).

An everyday example of PM in action is when someone is given a medical prescription that requires taking the medication every 12 hrs for the next three months. From the PM

literature point of view, the first thing they do is to organise the intention as to when to take the medication (e.g. every day, first thing in the morning and before going to bed). Every day they need to remember in the morning and at night that they must take the medication, and they must keep monitoring the time and/or cues that remind them to take the pill and inhibit any ongoing activity that may distract them and prevent the realisation of the action. They may look at the clock or look for cues in the environment that help them remember, such as at breakfast and dinner time. During the day, they will delay the intention and hold it in a higher activation state, so that they will not forget to take the pill. When they successfully execute the plan, they must also remember that they have already taken the medication, otherwise, they would be in the danger of taking the medication twice, putting their health and possibly life at risk (van den Berg *et al.*, 2012).

On the other hand, from the EF literature point of view, patients would have to initiate the behaviour. Firstly, by organising how they are going to execute the plan of taking the medication (problem-solving and organisation), they would have to select relevant goals to successfully execute the action (first thing in the morning and before going to bed, paired perhaps with breakfast and supper) and inhibit distractors that may prevent them from taking the medicine, such as leave the house in a hurry to go to the office. They would also have to keep monitoring for cues in the environment in order to remember to take the pills and evaluate their behaviour to remember that they took or have not yet taken the medicine. During the day, they would hold the information in mind, while performing daily activities, so as not to forget to execute the plan (Gioia *et al.*, 2004).

In this simple example, it is possible to observe the active role that EF plays in PM by maintaining the activation level of mental representation of the intended plan. By holding the delayed intentions in a higher attentional state than other mental representations, they would more readily be retrieved for future intention, when the cue occurs (Goschle & Kuhl, 1993; Hadjiefthyvoulou, 2011).

Further evidence that explains the association between PM and EF is that WM and inhibition take place when complex PM tasks are initiated and executed (Kiegel *et al.*, 2000; Hadjiefthyvoulou, 2011), for example, when attention is divided between an ongoing task and monitoring for cues in the environment that may lead to execution of the goal.

Lapses of PM can also therefore be attributed to an EF deficit, and they can also help us understand the role of EF in PM. For instance, Mioni *et al.* (2012) reported that although healthy participants and TBI patients increased their monitoring frequency close to the target time, while performing a time-based PM task, TBI participants monitored more and were less accurate, confirming PM dysfunction. These authors explained that in time-based PM tasks, which are EFs, inhibition and updating are strongly involved (Mioni *et al.*, 2012).

4.7.3.4 Prospective memory in clinical populations

Studies from patients affected by brain injuries have shown that failure to execute intended actions are the most affected areas of cognitive deficits, and it is assumed that this is because TBI often involves PFC and/or medial temporal lobe damage, affecting both the prospective and retrospective components of PM (Kliegel *et al.*, 2008), and although clinical research in the area of PM has been on the rise, it remains under examined. Despite the fact that at the beginning, most of the studies in the area focused on patients suffering from TBI, in recent years, the focus has shifted to other diseases. Additionally, it is essential to mention that this flourishing area of research is of extreme importance due to the fact that PM has been associated with treatment observance (Liu *et al.*, 2004) and with taking medications (Woods *et al.*, 2008; Scullin *et al.*, 2013).

In a study conducted by Costa *et al.* (2011), 24 participants with MCI and 24 healthy controls were recruited and tested with a lexical task and a neuropsychological battery to assess EFs in a 2x2 experimental design. They found that PM is severely impaired when compared to healthy controls; however, their findings suggested that reflexive automatic processes were taking place rather than executive control, and the authors argued that this finding might be because the task in question was a focal task, which is more reliant on reflexive-automatic mechanisms (McDaniel *et al.*, 2004).

Kant *et al.* (2014) investigated PM failure in stroke patients aiming to analyse the underlying processes of time-based or event-based PM within this population. In a study design using an experimental PM paradigm that resembled everyday functioning, a naturalist PM test and neuropsychological test battery that assess EF were used. They found that stroke patients (n = 39) performed significantly lower than their healthy

counterparts (n = 53), and that deficits in PM occurred as often as RM, more regularly than deficits in attention, and that diverse cognitive processes are involved in the different components of PM. They also found that monitoring was positively correlated with time-based PM (r = 0.64) (Kant *et al.*, 2014). The importance of this study is that it was an attempt to systematically study a clinical population, and Kant *et al*. (2014) used a tool that claimed to be sensitive to detect PM failure (the Bourdon-Wiersma test, adapted to study PM) due to its naturalistic nature and deserves careful consideration.

Anxiety has also been related to PM performance. Harris *et al.* (1999) explained that elevated state anxiety also affects PM, leading to a reduced PM performance, but not RM performance. These authors stated that "anxiety may interfere with capacity demanding cognitive tasks because of distracting thoughts (worry) associated with state anxiety competing for limited resources". This suggests that the detrimental effects of anxiety on cognition would be higher in tasks with high demands for WM capacity. Where continuous monitoring is required, such as event-based PM tasks, concurrent WM overload takes place and WM resources are diverted to allow continuous and sustained monitoring. The conclusion of this work was that PM may be sensitive to anxiety. These findings suggest that elevated state anxiety was correlated with poorer performance in PM tasks, but not with RM, and that although anxiety affects PM performance, it is not related to WM capacity (Harris *et al.*, 2003).

Furthermore, PM impairment has also been associated with HIV (Doyle *et al.*, 2013), schizophrenia (Ordermann *et al.*, 2014), depression, Parkinson's disease (Kliegel, 2011), mild dementia (Costa *et al.*, 2011), autism (Henry *et al.*, 2014), hypertension

(Scullin *et al.*, 2013), multiple sclerosis (Thelen *et al.*, 2014), pulmonary diseases (Witkowska, 2011), cardiac disease (Habota *et al.*, 2013) and breast cancer (Paquet *et al.*, 2013).

Another line of research that is receiving increasing attention in this area is sleep, which is relevant to this research because sleep has also been studied within the context of chemo brain. Therefore, a sleep analysis was conducted with the sample in this study to observe if poor sleep has a deleterious effect on breast cancer patients' PM.

4.7.4 Prospective memory in the context of chemo brain

An area of study that has been neglected by PM researchers is related to cognitive impairment in the cancer population. To date, there are only a handful of publications that have directed attention to this subject. Paquet *et al.* (2013) reported that PM deficit and fatigue were seen as the major contributors to increased cognitive decline in breast cancer patients on the MIST when compared with healthy controls. In their study, they found that the breast cancer group showed significantly lower scores on PM than controls t (79) = −3.51, p = 0.001, Cohen d = −0.80, and that 23% of the patients had PM impairment as opposed to 5% in controls. Additionally, Mihuta *et al.* (2012) used a virtual reality assessment to test PM on breast cancer survivors. Their preliminary results showed that the breast cancer group exhibited significantly more cognitive deficits than controls, and that PM experimental tasks correlate with neuropsychological assessments and self-reports of PM. They confirmed that PM deficits were present in breast cancer patients after undergoing chemotherapy.

Cheng *et al.* (2013) have also recently investigated PM in breast cancer patients in a cross-sectional study, in a sample of 40 breast cancer patients and 40 matched controls, using a battery of neuropsychological tests that include assessment of verbal fluency, time-spatial orientation, STM and digit span, paired with event-based (word selection task) and time-based PM (number selection tasks) tasks. Their findings suggest that there are significant memory deficits in event-based PM but not in time-based PM on breast cancer patients who have recently finished treatment compared to controls. A limitation of this study is that it is cross-sectional in nature, and no baseline assessment was provided.

A matter of concern is that studies on chemo brain have shown inconsistent reports with neuropsychological tests, which is evident from PM literature. Burgess (2001) stated that "a clinical mystery in neurology" (Mesulam's frontal lobe mystery) within the context of PM is that some patients who had suffered frontal lobe damage could present no abnormality in behaviour in the clinic or in test performance on neuropsychological measures, yet suffered from some sort of severe disability in everyday life situations (Burgess *et al.*, 2009, referenced in Shallice *et al.*, 1991). Such discrepancies have led researchers to investigate the areas of the brain that are affected when patients suffer from frontal lobe damage while they take PM tasks.

Interestingly, studies in the area of chemo brain have shown similar discrepancies, in which neuropsychological tests do not show impairment on the tests results despite patients reporting significant impairment in their daily routines (Burgess *et al.*, 2009).

These sorts of discrepancies are not surprising. In the famous case of EVR reported by Eslinger and Damasio (1985), they found that despite the fact that EVR had undergone removal of a bilateral frontal meningioma, extensive neuropsychological assessment did not find deficits in cognition. On the contrary, EVR scores were superior or above average. However, his everyday life was completely disrupted, as EVR was unable to make simple decisions and his personality changed in a completely negative way. Elinger *et al.* (1985) identified EVR's problems as failure of PM, because he lost the ability to encode delayed intentions and to act on those intentions at the appropriate time (Burgess *et al.*, 2009). One of the most important findings of Elinger *et al.* (1985) was that they could empirically demonstrate the discrepancies in the everyday behavioural disorganization test, believed to be sensitive to detect deficits in frontal lobe EFs (Burgess, 2009).

Shallice and Burgess (1991) continued with this line of study and reported the case of AP, who had an open head injury in a traffic accident, had the rostral prefrontal cortex (RPC) completely removed and also had a damage to the surrounding regions. However, despite this, AP did not show neuropsychological impairment in measures of intelligence, perception or EF, but performed in the above average range. However, AP did show impairment in experimental measures of PM and multitasking, such as tardiness and disorganisation, and performed below the 5% level compared with IQ matched controls. In real life situations, these results show that people with problems with PM find themselves having to go to the shop more than once to buy items that could have all been bought in one visit, and they also forget to carry out tasks that they needed to or to follow procedures or instructions (Burgess *et al.*, 2009). This kind of

behavioural disorganisation was named by Shallice and Burgess (1991) as "Strategy Application Disorder" (Further examples following this line of research is presented in the qualitative part of this thesis).

Burgess (2009) concluded that "traditional methods of assessing cognitive deficits following frontal lobe damage typically do not measure the full range of deficits that can occur, particularly those involving rostral prefrontal cortex" and that successful performance in well standardised neuropsychological tests cannot always be taken as evidence of unimpaired multitasking abilities, such as those found in PM failure (See Shallice & Burgess, 1991 for further examples).

In this study, it is not suggested that chemo brain patients have the same magnitude of frontal lobe damage as the cases presented above, but it is hypothesized that their cognitive problems are related to those presented in frontal lobe damage or more specifically, of PM, because neuropsychological assessment fails to detect such impairments. It is for this reason that the author wants to emphasize the importance of considering the use of mixed methods studies in which patient's day-to-day life experiences are taken into account, in order to provide suitable care and help while learning coping strategies related to chemo brain.

The Shallice and Burgess (1991) studies presented above might explain why some authors report no cognitive decline in their samples. However, this does not mean that the problem does not exist or that it is driven by patient's expectations or suggestions,

but that neuropsychological assessment measures do not include features that resemble everyday life situations (domestic or work related) (Burgess *et al.*, 2009).

Experimental tests presented to assess PM, such as those used by Shallice and Burgess, have made successful attempts to include situations presented in everyday life, such as doing errands in a shopping mall (Multiple Errands *t*-Test) and time-based situations (Six Element Test) (Shallice *et al.*, 1991). The author believes that the neuropsychological battery CAMPROMPT includes features that make the assessment of PM similar to everyday life situations.

This study aims to analyse if CAMPROMPT is a more sensitive measure of PM and to analyse case studies to compare neuropsychological assessment of EF vs. patients' experiences with chemo brain through PM self-reports and interviews in a mixed design study.

Considering the failure of neuropsychological tests to detect EF deficits in patients who have suffered extensive frontal lobe damage, even though they present severe PM impairment in everyday life situations, it is not surprising that the literature on the study of chemo brain has not always validated the deficits reported by patients. For this reason, the problem has sometimes failed to be recognised as such, leaving patients frustrated and with no confirmation of their impairment (Scherling *et al.*, 2013). As a result, patients do not receive enough information and support when they receive cancer treatment and start reporting cognitive deficits.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), diagnostic criteria, patients are diagnosed with mild neurocognitive disorder (MND) when there is evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains, including EF, learning and memory, based on a concern of the individual, a knowledgeable informant or the clinician that there is a mild decline in cognitive function. A modest impairment in cognitive performance either by standardised tests or quantified clinical assessment; the cognitive deficits do not interfere with independence on daily activities, although there may be subtle interference with function or report that tasks require more effort or take more time than previously.

Anecdotal reports from breast cancer patients show that few patients stop driving or quit their jobs as a result of the cognitive decline experienced after chemotherapy, and a lot more effort has to be put in tasks that were very easy to accomplish before treatment (Silverman *et al.*, 2009), and despite some inconsistencies in the literature, there is scientific evidence that this mild neurocognitive impairment exists and that it is significantly affecting patient's quality of life (Deprez *et al.*, 2012; Sherling *et al.*, 2013; Koppelmans *et al.*, 2011).

4.7.5 Neuropsychological assessments of PM

There are only a handful of tests that can be used to measure PM within clinical populations that have been specifically designed to assess PM or that include a PM aspect in them. Such tests are the Rivermead Behavioural Test (RBMT) (Wilson *et al.*, 1985), which includes two items of PM and has been used with MCI patients, "patients involved in substance abuse and neuropsychologically impaired patients. The drawback of this test is that it does not provide a standardised score and only offers a score of the overall memory impairment (Thone-Otto *et al.*, 2008).

Another measure designed for the specific assessment of PM is the MIST. This test consists of eight PM tasks divided into four time-based and four event-based tasks. However, the tasks are not evenly distributed in the type of responses and, consequently, there are three time-based tasks requiring a verbal response and only one requiring an action response.

The other measure that has been developed to measure PM is the CAMPROMPT. This was the first standardised test that is ecologically valid, specifically designed to measure PM (Wilson *et al.*, 2005). The CAMPROMPT will be discussed further later in this work, because it was the measure of choice for this research.

Other tests that include a PM aspect are Test Everyday Attention (TEA) (Robertson *et al.*, 1994) and the Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson, 1996). Currently, an experimental paradigm is under way to assess everyday living PM, which has been used in clinical population, such as in breast cancer patients (Green *et al.*, 2011).

4.7.6 The CAMPROMPT test battery

According to Gioia *et al.* (2004), there is no single measure for the assessment of EF, and the assessment has largely relied on laboratory or clinical conditions, which, lacking ecological validity, do not reflect real life situations. The term ecologically valid refers to the ability to generalise results of controlled laboratory conditions to naturally occurring events in real life situations. Therefore, an ecologically valid measure is one that reflects situations similar to naturally occurring events and behaviours and are valid for predicting everyday behaviour.

In the selection of tools for the assessment of PM in this study, the CAMPROMPT test was chosen because it attempts to overcome problems of ecological validity and contains a balance between time-based and event-based PM assessment that are in line with the theoretical model proposed by McDaniel *et al.* (2002). The authors of the test designed testing conditions that resemble demands in everyday life, such as giving a message when a certain event happens and remembering to give a set of keys to the researcher at a certain time, while they are working on distractor tasks. Another reason for deciding to use CAMPROMPT and a neuropsychological battery was because it was believed that it would be more convenient to use them with a clinical population, particularly with recently diagnosed breast cancer patients. Furthermore, although there is evidence of the validity of many PM paradigms, such tasks take too long and are too complicated to administer, and an important aspect of this work was to disturb patients as little as possible using less demanding tasks. The most viable possibilities for NHS

ethics approval were also taken into consideration, and therefore, a neuropsychological battery was considered more likely to receive approval. When making these decisions, the least intrusive strategy was chosen, particularly because it was difficult to reach the population and because of the difficult circumstances the patients were experiencing at that moment in their lives.

To better understand what is happening with PM processes in chemo brain patients' daily lives, the hypothesis was that CAMPROMPT was a more sensitive as well as a more valid measure to detect the MCI reported by some cancer patients. Therefore, it was expected that cognitive decline in attention would be detected using this battery and that the healthy controls would perform better than the cancer group, due to the fact that they were not under the influence of cancer treatment. A decline in attention was expected in patients receiving cancer treatment, but not in healthy participants.

The CAMPROMPT was developed by Wilson and Watson (2005) as a result of an increased interest in PM (Shimamura *et al.*, 1991; McDaniel, 1996) and from the realisation that there was very little transfer to the clinical setting; therefore, no clinical benefit was being obtained from experimental studies that studied PM (Wilson *et al.*, 2005). Wilson and Watson concluded that in the area of neuropsychology, no formal assessment measure existed for PM.; although the RBMT included three PM items, it only included event tasks, failing to provide a comprehensive assessment of PM (Wilson *et al.*, 1985).

PM failure can occur due to several reasons such as attentional difficulties, EF deficits, such as planning and organisational problems (Wilson *et al.*, 1996), which lead people to have problems with organising and initiating the appropriate behaviour at the appropriate time. The lack of standardised test led this team to develop a tool for the assessment of PM to suit the clinical need to identify PM failures.

They defined PM deficits as a "failure to do things at the right time, or within a certain interval or when a particular event occurs" and tried to make the test items comparable to everyday life experiences (Wilson *et al.*, 2005).

4.7.7 Description of the test

In this test, examinees were asked to work on several distractor tasks (paper and pencil). These tasks consisted of answering quizzes and puzzles during a period of 25 minutes. While they were working on the tasks, they were instructed to remember to do other tasks, such as reminding the examiner of something, or for them to remember to do something, either during or after the session.

Examinees were required to perform three event-based tasks and three time-based tasks. The time interval between instructions and actions is balanced across conditions. There were two parallel versions of the test (A and B) with different materials for each version. A minimum of six weeks passed between each testing session.

4.7.7.1 Time-based tasks

These three tasks were cued by a kitchen timer and a clock. One time-based task consisted of giving the instruction to remind the tester to ring the garage/reception. The task should be carried out 20 minutes after the instruction was given, at the end of the distractor period. The cue came from a clock. Another time-based task was to remind the examiner not to forget the keys/cup, with a time interval of 13 minutes. The last task consisted of changing the task/pen with a time interval of seven minutes.

4.7.7.2 Event-based tasks

One event-based task was to remind the tester about five objects that were hidden at the start of the session. The time interval was cued by the beeper going off and by a prompt, with 20 minutes between the instruction and the cue "we have finished this test". The other event-based task consisted of giving a book/map to the examiner when they come to a quiz question about EastEnders/Coronation Street. The time interval was seven minutes. The last event-based interval was to give the tester a message in an envelope at an interval of 13 minutes. The cue was when the tester said "there are five minutes left".

Depending on whether the examinee performed the right action, the tester responded as follows:

1. If the response occurred at the right time, the examiner informed the examinee that it was the correct response and timing. If it was the wrong action, the tester prompted the examinee that she had to do something, and if there is no correct

response, the tester informed the examinee that it was not the right action and reminded her which one was correct.

2. When there was no response at the expected time, the tester waited for one minute following the question or for 15 seconds depending on the task, and then prompted the examinee by reminding her that she was going to do something when the specified time/event cue took place, followed by prompts or assurance, depending on the response.
3. When there was no response at the correct time even after the prompts, the tester prompted again and said "good" if the correct action was performed or "don't worry" if no correct action was performed.

4.7.7.3 Classification

The CAMPROMPT test classifies test score results into six categories: impaired, poor, borderline, good, above average and very good. In this study, the categories impaired, poor and borderline were classified as being Below Average, with good, above average and very good classified as Above Average.

The distractor tasks or ongoing activities consisted of various quizzes and puzzles. They ranged from very difficult to easy, verbal and non-verbal. They involved puzzles, word search, shapes, scrambled words, word squares, general knowledge, famous people, sentence checking, spot the difference, mazes and join the dots. Participants were

advised to change to another task if they had difficulty with a particular task or if they were not enjoying it. These tasks were designed to keep participants distracted for 20 minutes. Quiz questions were handed out on separate sheets 13 minutes into the testing session.

The interrater reliability of the CAMPROMPT according to Wilson (2005) is $r = 0.998$ (correlation coefficient). The test-retest reliability is 0.64 (Kendall's Tau-b) between performances of the test (Wilson *et al.*, 2005). Validity and reliability of the test have also been reported by Kliegel *et al.* (2008).

The CAMPROMPT test has previously been used in studies related to substance and tobacco abuse (Hadjiefthyvoulou *et al.*, 2011; Heffernan & O'Neill, 2012). None of these studies used the test more than once, but their findings confirm that it is a valid measure for PM.

CHAPTER FIVE

5 QUANTITATIVE METHODS

5.1 Aims and objectives

The literature on chemo brain has demonstrated that there is subtle cognitive impairment in some breast cancer patients subjected to chemotherapy. It remains unknown which are the mechanisms underlying this phenomenon. More sensitive memory measures are needed to better understand the MCI as a by-product of chemotherapy, known as chemo brain.

In this study, we aimed to identify whether PM and WM along with quality of sleep and sleepiness during the day are underlying factors of the so-called chemo brain experience reported by cancer survivors who received chemotherapy treatment and completed it successfully. It is hypothesized that cognitive deficits on breast cancer patients are due to PM and WM impairment, and PM being an attentional process, we hypothesized that chemo brain is an attentional deficit.

To date, most of the studies have focused on neuropsychological assessment and in general, on cognitive performance in those assessments. A specific study on memory, particularly on PM and WM in cancer patients who experience chemo brain, is proposed in this study, in order to better understand what is happening with memory processes in the daily lives of patients.

For this purpose, MCI, decline in attention, impairment in retrieval of words, memory and visual memory, sleepiness and sleep efficiency were measured using the following criteria and hypotheses:

1. A decline in attention on these two interrelated aspects of memory was expected in patients receiving cancer treatment and no decline in healthy participants. PM and WM were tested by using the CAMPROMPT, Digit Span (Forward and Backwards) tests (Wechsler, 1997, 2008) and digit symbol tests (Wechsler, 1997). It was hypothesized that CAMPROMPT (Wilson *et al.*, 2005) was a more sensitive as well as a more valid measure to detect the MCI reported by some cancer patients.

2. Anecdotal accounts showed that one of the most common complaints chemotherapy patients report is that they have difficulty retrieving common words; therefore, it was hypothesized that participants would show a decline in their test results from COWAT, which assesses verbal communication deficits and evaluates spontaneous production of words compared to a baseline, with more decline in the cancer group and no decline in the healthy group.

3. The BVRT was used to analyse memory and visual memory. It was hypothesized that the chemotherapy group would have shown more decline in this test results than the non-chemotherapy group, and no decline was expected for the healthy group (Benton, 1996).

4. A possible cause of the cognitive deficits may be sleepiness, which alters attentional process as a consequence of sleep loss triggered by anxiety and treatment; therefore, we hypothesized that alteration of sleep patterns during the course of cancer treatment caused sleepiness, impairing PM and WM. Sleepiness was evaluated by the subjective measurement Epworth Sleepiness Scale (ESS) (Johns, 1991). It was hypothesized that participants undergoing cancer treatment would report more daytime sleepiness than the other group.

5. Factors such as anxiety, depression, chemical toxicity, hormonal treatments for cancer and menopausal status of the patients represent confounding variables of the study, and it was aimed to control them by matching participants with the healthy groups. It was hypothesized that the chemotherapy group would show the highest rates of impairment on these measures than the healthy group.

Sleep efficiency was observed to further analyse sleep impairment using a SenseWear® Armband (SWA) multi-sensor activity monitor. It was hypothesized that more impairment on sleep efficiency would be found on the chemotherapy group as a consequence of altered sleep patterns and no significant impairment in the healthy group. It was expected that self-reports from the Pittsburgh Sleep Quality Index (PSQI) (Buysse *et al.*, 1989) would show a correlation with results obtained from the SWA in the two groups, with no sleep disturbances for the healthy group and more sleep disturbances for the cancer group.

To summarise, it was hypothesized that breast cancer patients would develop prospective and WM impairment as a consequence of sleepiness and attentional decline caused by altered sleep patterns. This impairment may last for many years after completing their treatment. For the healthy control group, a significant difference between PM and WM cognitive impairment was not expected. However, some decline would be found due to menopausal status or hormonal, non-chemotherapeutic treatment. To control for this potential risk factor, we would be matching patients according to their age and menopausal status.

It is important to highlight that although this study observed sleep and sleepiness, it was not the aim of the researcher to make comprehensive analyses of such biological factors, but merely observe if changes in such factors may or may not have had an effect on memory process, specifically, WM and PM during and after the course of cancer treatment; therefore, only raw data obtained from those measures were considered for analysis in this study.

In summary, the aims of this part of the project were to

1. Analyse only one aspect of the cognitive domain (as opposed to the general cognitive domain), by analysing EF, including PM and WM. This would be achieved by using a neuropsychological battery targeted specifically to assess WM according to the Baddeley (2000) WM model and a specific battery that assessed PM. By doing so, it was hoped to be able to identify whether the CAMPROMPT was more sensitive to the mild cognitive changes presented in chemo brain patients.

2. Control for potential confounding variables (i.e. depression, anxiety, hormonal changes, variety of chemotherapy treatments, demographic information), by recruiting and matching a group of cancer patients not receiving chemotherapy and a group of healthy participants.

3. Identify if changes that occur as a consequence of cancer treatment on biological factors such as sleep and sleepiness had an effect on memory processes, causing impairments in WM and PM. These were analysed by assessing sleep activity (SWA and sleep quality scale) and sleepiness during the day (ESS sleepiness scale).

4. Control for practice effects that could happen as a consequence of taking the same tests several times. This was controlled by using alternate forms of the tests and the healthy group.

5.2 **Recruitment**

After receiving ethics approval from NHS REC Ethics Committee Southampton A (IRAS) and from research and development (R&D) from each NHS trust where recruitment and testing took place and from Bournemouth University ethics committee, an invitation to participate in the project was provided to patients and healthy controls who met the inclusion criteria. Cancer patients were identified by clinicians, oncology

support nurses, breast cancer care nurses and at oncology team meetings at Bournemouth and Poole hospitals and Dorset County and Weymouth Hospitals.

5.2.1 Cancer patients (PT)

As required by NHS ethics procedures, members of the staff at the hospital extended letters of invitation to patients to participate in a study to test their memory during cancer treatment. If patients were interested in the study, they were invited to talk to the principal investigator (PI) to receive further explanation about the project. They were provided with an Information Sheet for Participants, which expanded on the implications of the study. If they agreed to participate, PI took consent and provided the self-report questionnaires.

Most of the cancer participants were tested the day of their pre-treatment assessment to avoid an extra visits to the hospital, and healthy controls were either tested at the hospital or at the university.

Ninety-three patients were invited and 62 agreed to take part in the study. Two cancer participants cancelled on the day of testing and another six cancer participants withdrew after measuring the baseline and were excluded from the study. Most of the 28 cancer participants underwent both chemotherapy and radiotherapy (n = 19), while the others only received radiotherapy treatment (n = 9).

All cancer participants underwent surgery before chemotherapy or radiotherapy and received additional adjuvant hormonal treatment before and during testing. They were tested before commencing chemotherapy or radiotherapy (baseline). All chemotherapy participants received the standard treatment of six cycles over a period of four months. One of those participants discontinued her treatment in the middle of the cycles, but decided to continue with our testing sessions. Radiotherapy-only participants received three-week radiotherapy treatment.

The patient group consisted of 19 participants undergoing chemotherapy and adjuvant treatment (n = 19) and nine participants undergoing radiotherapy and adjuvant treatment.

5.2.2 Healthy control group (HC)

A convenience sample of 28 women from Bournemouth University and from Bournemouth and Poole hospitals as well as from Dorset County NHS trusts was recruited to be a part of the healthy control (HC) group. The study was advertised around the hospitals and at the university.

5.2.3 Inclusion criteria

For cancer patients: being recently diagnosed with early breast cancer, scheduled to begin cancer treatment and no previous history of cancer treatment.

For the healthy controls: no previous history of cancer treatment. Due to the nature of the tests, English language proficiency was required for all the participants.

5.2.4 Exclusion criteria

Patients with previous history of cancer and/or chemotherapy could not be invited to take part in the study. Patients who had been previously diagnosed with some sort of cognitive impairment, mental problem, dementia, brain injury and mood or anxiety disorders were also excluded.

Participants were 98% British, with one cancer patient from Portugal and one healthy control each from Slovakia and Peru. All participants were proficient in the English language and well-educated (98% went to secondary school or above). The Intelligence Coefficient (IQ) mean FIQ (Full IQ) scores on the NART test for PT group was 118 and 113 for HC. Eighty two percent of participants were in employment, while 64% were menopausal. Since alcohol or substance abuse affect cognition, participants were asked if they drank alcohol. None of the participants said they were heavy drinkers.

5.2.5 Amendments to the recruitment process

During this study, seven amendments had to be made to change recruitment strategies such as adding a research site, change typo errors in invitation letters and participant information sheet details, changes in advertisement strategies to improve recruitment,

add collaborators, change questions to background information and make changes in the protocol, such as requesting authorization for a qualitative study. Each process of amendment took between 35 and 60 days to complete and involved liaising with R&D departments from each NHS trust and with the National Research Ethics service (NRES) in the UK. Although necessary and efficient, the processes required by the ethics committee within the NHS represented a major drawback to the study, particularly because they are extremely time consuming and affected recruitment and testing schedules.

5.2.6 Testing schedule

Of the cancer group, 28 participants (100%) were tested two times:

1. Baseline (start of treatment) (Test one).
2. Eight weeks after baseline (before fourth cycle of chemotherapy), in the middle of their treatment (mid-treatment) (Test two).

Twenty six patients were tested for the third time after their treatment was completed: during their post-chemo assessment (approximately three weeks after finishing their treatment (post-treatment) (Test three). Thirteen patients were tested six months after treatment for the fourth time (Test four). Test results for stage 3 and 4 were used for qualitative analyses.

The cancer patients who did not undergo chemotherapy treatment as well as the healthy controls were tested for the second time, six weeks after baseline.

5.3 **Procedure**

All the participants were screened for a history of any mental illness that may be altering cognition and may affect test results. The HADS was used at baseline and before every testing session. None of them showed abnormal levels of anxiety or depression, and no other significant history of mental illness was reported.

Participants who agreed to participate and met the inclusion criteria were scheduled for testing sessions and were provided with the sleep monitor SWA multi-sensor activity monitor, the HADS questionnaire and subjective measures of sleep (PSQI and ESS) to complete at their convenience one week before the testing session. Testing sessions for cancer patients were often conducted the same day before their chemotherapy treatment, in order to avoid extra visits to the hospital. For the healthy controls, testing sessions were conducted at the hospital or at the university at their convenience.

For each testing session, participants were asked about any change in their medical condition.

The researcher was not provided a particular room to test participants, and therefore the testing rooms were usually different from session to session, and this study could not

account for controlling the environment at testing sessions, although all sessions were conducted in a quiet room specifically reserved for that purpose.

5.4 **Measures**

The order of the test was the same for each participant across conditions. The battery was composed of six standardised neuropsychological tests and three self-reports. Self-reports to assess sleep, anxiety and depression were conducted at home, and the neuropsychological tests took place at the hospitals and at the university. The duration was about 45–50 minutes. Additionally, a SWA monitor was delivered to record measured sleep for four days and nights.

To control for practice effects, different versions of the tests were used that provided alternate versions. For CAMPROMPT, versions A and B were used for the first and second time, respectively, only for a subset of participants to take part in the qualitative aspect of this study. For the Digit Span tests, Wechsler versions III and IV were used. For the BVRT, versions D, C and E were used, with version D repeated for the fourth test. The Digit Symbol and COWAT tests do not provide alternate versions; hence, the same version was used every time.

CAMPROMPT Scoring

Each response was recorded according to the values given in the record form. The responses were categorised using letters A to H and they translated into marks of 6, 4, 2, 1 or 0 and were assigned to time tasks (CAMPROMPT TIME) or to event tasks

(CAMPROMPT EVENT). The sum of the scores gave the CAMPROMPT total score. The developers of the test classify tests takers into five categories according to their total score compared to a normative sample into Poor, Borderline, Average, Above Average and Very Good. In the current study, in order to simplify our analysis, we subcategorised Poor and Borderline as Below Average (BA), and Above Average and Very Good as Above Average (AA), using a cross tabulation analysis.

The distractor tasks consisted of various quizzes and puzzles. They ranged from very difficult to easy, verbal and non-verbal. And they involved puzzles, word search, shapes, scrambled words, word squares, general knowledge, famous people, sentences checking, spot differences, maze, and join the dots. Participants were advised to change the task if they were finding it difficult or if they were not enjoying it. These tasks should have kept participants distracted for 20 minutes. Quiz questions were handed out on separate sheets, 13 minutes into the testing session.

Version A and B of the tests presented equivalent but different distractor tasks, and the commands given by the instructions were slightly different for each version. For example, on version A of the tests, participants were instructed to give the researcher a book or a mug, depending on the test version, or give a response when they found a question about East Enders or Coronation Street.

The interrater reliability of the CAMPROMPT according to the authors is 0.998 (correlation coefficient). The test-retest reliability was 0.64 (Kendall's Tau-b) between performances of the test (Wilson *et al.*, 2005).

5.5.2 Digit symbol test

This test is a subtest of the Wechsler test (WAIS-III), which consists of four rows containing 100 small pair of squares, one containing a number from 1 to 9 and the other one blank (Wechsler, 1997). Above these rows, there is a key that matches each number with a symbol. After a practice trial, the individuals are instructed to fill in the blank spaces with the symbol that corresponds to the number above the blank space as quickly as they can, without making any mistakes and without skipping any space. They are given 120 seconds to do this task. The score is the number of squares filled correctly (Lezak, 1983).

The Digit Symbol test intends to determine which skills are deficient if the performance is poor; it assesses the ability to learn unfamiliar tasks, it involves speed and accuracy of visual motor coordination, speed of mental operation (processing speed), attentional skills, visual acuity, visual scanning and tracking, STM for new learning, cognitive flexibility (in shifting rapidly from one pair to another), handwriting speed and possibly motivation. This test is sensitive to visuo-perceptual difficulties (Sattler, 2001).

The test also measures the ability to learn combinations of numbers and symbols and the ability to make associations quickly and accurately. Speed and accuracy are a measure of intellectual ability; therefore, this test is an information processing task. This involves discrimination and memorisation of visual pattern symbols. It is a reliable subtest (*rxx* = 0.84) with reliability above 0.81 at all age groups.

It is useful for evaluating the attention of individuals, when attentional difficulties are suspected. If the examinee has an adequate speed and visual acuity, poor scores indicate attention deficits and not visual perceptive problems. A slow and deliberate approach may indicate depression. The distortion of forms may indicate perceptual difficulties.

Low scores may indicate visual-motor coordination difficulties, distractibility, anxiety, visual defects, poor pencil control, poor motivation, excessive concern for detail, lethargy, boredom, impulsivity (Sattler, 2001).

We consider that this test was relevant for the study of chemo brain, because it reports qualitatively the inability to learn new tasks (Silverman, 2009). Some other patients complain about visual problems, and PM may be related to missing cues in the environment, which may lead to attentional PM problem.

5.5.3 Digit span test

The Digit Span test is a measure of short-term sequential auditory memory and attention. This is a subtest of the WAIS–IV (Wechsler, 2008) test, and it is divided into two parts, digits forwards and digits backwards. To obtain the digit span score, the sum total of the points in each test is calculated.

The Digits Forward subtest is formed of a series of numbers from two to nine digits and digits backwards from two to eight digits. The examinee listens to a series of digits

given orally by the tester and then repeats the digits. There are two sets of digits of each length. The test is discontinued after the examinee gets a score of 0 in the same set. Each series counts one point, and each set has two series.

Each of the tests involves different mental activities, which are affected differently by brain damage. Both the tests consist of seven pairs of number sequences, and the examiner reads aloud at the rate of one digit per second. Both the tests involve auditory attention.

This test is relevant for this study, since digits forwards is involved with planning ability, related to PM and WM, and it is a measure of attention affecting PM. It assesses the ability to retain several elements, which have no logical relationship with one another and sequencing skills. It can be negatively affected by anxiety. It involves rote learning and memory (Sattler, 2001).

The digits backwards test involves transformation of the stimulus previous to responding, i.e. the sequence is mentally manipulated before restating it. High scores may indicate flexibility, good tolerance for stress and excellent concentration. It requires more complex processing than digits forwards and involves planning ability and sequential processing, providing some insight for WM, which was one of the areas of study of this research. It may involve abilities to make mental images and scan internal visual display formed from an auditory stimulus (Sattler, 2001).

According to Lezak (1983), the simplest of mental tracking is digit span, which tests how many bits of information a person can attend to at once and repeat in order. The role of visual scanning in conceptual tracking demonstrates the scanning eye movements presented while performing conceptual tracking tasks, such as digits backwards (Weinberg *et al.*, 1972). Tracking tasks require to track two or more stimuli or associated ideas simultaneously, called double or multiple tracking behaviour (Lezak, 1983). This is important because this multiple tracking most likely to fail when there is brain damage. Furthermore, Lezak (1983) explained that

> "the disturbance appears as difficulty in keeping two or more lines of thought in a cocktail party conversation, in solving two or three number addition or problem, or multiplication problems mentally, or in remembering one thing while doing another."

The reliability of the test is *rxx* = 0.90 with reliability coefficients at or above 0.84 for all age groups. Low scores on digits backwards may indicate anxiety, inattention, distractibility, a possible learning deficit, difficulty in auditory sequential processing, poor short-term auditory memory, boredom, difficulty in shifting, impaired hearing and negativism.

5.5.4 Controlled oral word association test (COWAT)

Lezak (1983) stated that following brain injury, changes in speed and verbal production may be experienced, which does not necessarily mean the presence of aphasia. This verbal impairment fluency is also associated with frontal lobe damage, particularly the left frontal lobe anterior to Broca's area. This fluency problem can be seen in speech, reading and writing (Lezak, 1983).

This test is relevant to this study, since patients experiencing chemo brain complain of having difficulty in retrieving words; although they preserve the mental image of what they want to say, they do not have the word for what they want to describe or the name of the person they want to mention, similar to the TOT phenomenon. They also complain about not being able to follow or articulate sentences in a conversation or when reading a book.

The COWAT (Benton, 1983) consists of three word naming trails (FAS), which were selected on the basis of the frequency of an English word beginning with these letters. The examiner instructs the subject to say as many words as she can think for one minute with a given letter of the alphabet, excluding proper names, numbers and the same word with different endings. A practice trail was provided in this study using the letter "C" to make sure the participant understood the instructions. The score is the sum of all the acceptable words and is adjusted by age, gender and education, which then are converted to percentiles. Word frequency has proven to be a good indicator of brain dysfunction. Frontal lesions tend to "depress" frequency scores (Lezak, 1983).

5.5.5 New adult reading test (NART)

This is the best indicator of premorbid intellectual ability and comprises 50 phonetically irregular words (Nelson *et al.*, 1978). It was used in this study to match participants for IQ level and as a necessity for CAMPROMPT assessment. Participants were required to read the list of words and the number of errors was scored and adjusted later and then converted to WAIS-R VI (Wechsler Adult Intelligence Scale-Revised) , PIQ (Performance IQ) and FSIQ (Lezak, 1983). Accuracy of pronunciation is used to predict IQ.

The NART test reliability estimates are above 0.90, and an alpha coefficient of 0.94 is correlated with years of education.

5.5.6 Benton visual retention test (BVRT)

This test is used to assess visual perception and visual memory (Benton, 1996). The test has shown to be a good measure to identify difficulties in memory, spatial orientation and motor behaviour as well as attentional difficulties. For that reason, it was selected in this study.

The BVRT test consisted of a series of 10 images, which were shown for 10 seconds. After that time, the image was covered and the participants had to draw the image from memory on a sheet of paper. The tests provided three equivalent forms (C, D and E) of the task and four alternative methods of administration (A, B, C and D). In this study, method A was selected, which consisted of a 10 seconds presentation of the image,

because it was the most frequently used, and normative data for this test was most commonly based on administration A (Benton, 1996).

To score the test, each of the images drawn by each participant were compared with those in the scoring manual with examples of correct and incorrect responses. Two scores were used to describe the performance of participants, which were number Correct Score and number Incorrect Score. The number Correct Score was based on all-or-none basis. If the image had no errors, one point was awarded, but if it had any errors, 0 points were received. The range of the possible scores is 0–10. The number Correct Score was used for this analysis.

5.6 Testing sessions

All testing sessions were conducted by the PI in a quiet room, where only the PI and participant were present. Comprehensive neuropsychological assessment of 28 cancer patients and 28 healthy controls was conducted. The duration of each testing session was 45 minutes. The order of the tests was presented as follows for all participants: CAMPROMPT, Digits Symbol (Digits Backwards, Digits Forwards), COWAT, BENTON (second testing session was presented in the same order, but using alternate forms of the tests). All participants were tested for IQ using NART only at baseline.

CHAPTER SIX

6 QUANTITATIVE RESULTS

6.1 Data preparation for analysis

After missing values and data accuracy were examined, assumptions for mixed multifactorial ANOVA were addressed. Participants who did not complete the testing session were excluded to account for the missing values.

6.2 Statistical considerations

The primary form of statistical analysis was mixed between and within ANOVA models, with Group (cancer/healthy controls) as a between-subjects factor and Time of Testing (stage 1, stage 2) as within-subjects factor, with the WM and PM measures as dependent variables.

Questionnaires and other screening measures that produced interval data were analyzed using mixed ANOVA. If the main effects or interactions proved significant, marginal means were analyzed, which examined these effects in more detail and explored which measures contributed to significance in the Group and/or Time of Testing effects.

Participants were for the most part British, except from one cancer patient who

was from Portugal. All the participants were proficient in the English language, well educated (98% went to upper school or above), 64% were menopausal and 75% admitted to having memory problems as a result of chemo treatment.

6.3 **Results**

A summary of independent variables used for these analyses along with mean differences and groups under consideration are presented in Tables 1 and 2. Shapiro-Wilk or Kolmogorov tests were considered to assess normality (according to sample size). Where normality was violated, Z-scores were used to identify outliers; however, no significant violations were found. Homogeneity of variance was addressed using Leven's tabulation for between-groups comparisons.

Table 6.1 Patient and healthy controls means

	Patient Group				Healthy Control Group			
N (28)	**Stage 1**		**Stage 2**		**Time 1**		**Time 2**	
TEST	**Mean**	**Std. Error**	**Mean**	**Std. Error**	**Mean**	**Std. Error**	**Mean**	**Std. Error**
Camprompt Time	12.04	0.65	13.46	0.89	13.79	0.80	16.39	0.43
Camprompt Event	12.96	0.76	13.93	0.59	13.96	0.60	14.54	0.46
Camprompt Total	25.00	1.07	27.39	1.27	27.71	1.13	30.93	0.67
Digit Symbols	68.14	3.11	72.54	2.89	73.64	2.84	78.14	3.18
Digit Span Forward	9.53	0.37	10.28	0.44	10.17	0.37	10.67	0.44
Digit Span Backwards	7.32	0.38	8.53	0.41	7.03	0.38	9.32	0.41
Digit Span Total	16.86	0.57	18.86	0.76	16.82	0.77	20.00	0.76
COWAT	43.18	2.06	44.25	2.16	39.39	2.06	39.5	2.14
BENTON Correct	7.46	0.33	7.64	0.37	8.25	0.22	8.07	0.30
Measured Sleep(4 days and nights)	29.07	0.71	29.38	0.66	26.82	0.66	26.83	0.59
PSQI	7.11	0.69	7.54	0.58	3.82	0.42	4.14	0.41
ESS	4.96	0.75	5.79	0.70	6.39	0.87	6.68	0.81
Anxiety	6.64	0.70	5.54	0.69	4.57	0.42	4.75	0.47
Depression	2.21	0.42	4.04	0.55	1.68	0.40	1.82	0.42

6.3.1 Mixed ANOVA

Table 6.2 Mixed ANOVA simple effects and interactions

	Between Subjects Simple Effect (*n* = 54)		**Within Subjects Simple Effect (*n* = 54)**		**Interactions**	
TEST	F	P	F	P	F	P
CAMPROMPT						
Time	7.959	**.007**	11.845	**.001**	1.010	.319
Event	1.347	.251	.135	.715	.135	.715
Total	5.905	**.018**	12.978	**.001**	.279	.600
Executive function						
Digit Symbol	1.824	.182	15.979	**.001**	.002	.962
Digit Span Forwards	.982	.326	5.899	.019	.236	.629
Backwards	.240	.626	51.328	**.001**	4.810	**.033**
Digits total	.351	.556	36.327	**.001**	1.882	.176
COWAT	2.255	.139	.403	.528	.206	.652
BENTON	2.271	.138	.001	.000	.943	.336
HADS						
Anxiety	3.413	.070	2.305	.135	4.419	**.040**
Depression	5.880	**.019**	10.587	.002	7.731	**.007**
SLEEP						
ME	7.768	**.007**	0.192	.663	.166	.685
PSQI	23.459	**.001**	1.233	.272	.025	.875
ESS	1.171	.284	3.070	.085	.719	.400

6.3.2 CAMPROMPT

When mixed 2x2 ANOVA analyses were conducted, a significant simple effect for between-groups (patient, healthy controls) difference was found for CAMPROMPT

Time-based tasks $F(1,54) = 7.959$, $p = 0.007$, $\eta^2 = .128$, and for CAMPROMPT total score $F(1,54) = 5.905$, $p = 0.018$, $\eta^2 = .099$, but not for CAMPROMPT Event $F(1,54) = 1.347$, $p = 0.251$.

Within groups, simple effects (stage 1, stage 2) were significant for CAMPROMPT Time-based tasks for stage(Time points) $F(1,54) = 11.845$, $p = 0.001$, $\eta^2 = .180$ and for CAMPROMPT Total score $F(1,54) = 12.978$, $p = 0.001$, $\eta^2 = .194$.

6.3 CAMPROMPT marginal means table

	PATIENT	HEALTHY	MARGINAL MEANS
CAMPROMPT TIME			
STAGE 1	12.03	13.78	12.91
STAGE 2	13.46	16.39	14.92
MARGINAL MEANS	12.75	15.08	13.92
CAMPROMPT EVENT			
STAGE 1	12.96	13.96	13.46
STAGE 2	13.92	14.53	14.23
MARGINAL MEANS	13.44	14.25	13.84
CAMPROMPT TOTAL			
STAGE 1	25.00	27.71	26.16
STAGE 2	27.39	30.92	29.16
MARGINAL MEANS	26.19	29.32	27.75

6.3.3 CAMPROMPT Time (CTIME)

Estimated marginal means for time points (stage 1 and 2) indicated a trend for higher scores for the healthy control group. The marginal means for CTIME between-groups for patients' scores were 12.75(SE = .087) and 15.08 (SE = .586) for healthy controls, a statistically significant mean difference of 2.339, 95% CI [.677, 4.002], $p = .007$. Additionally, marginal means for CTIME within-groups effects scores were 12.91 (SE

= .516) for stage 1 and 14.92 (SE = .499) for stage 2, a statistically mean difference of 2.018, 95% CI [.842, 3.193], p = .001, indicating improvement over time for both the groups.

6.3.4 CAMPROMPT Total (CTOTAL)

Estimated marginal means for CTOTAL between-groups for patients' group scores were 26.19 (SE = .909) and for healthy controls were 29.32 (SE = .909), a statistically significant mean difference of 3.125, 95% CI [.547, 5.703], p = .018, which indicates a trend for higher scores for the healthy control group. Within-groups simple effect marginal means for stage 1 were 26.35 (SE = .780) and 29.16 (SE = .722) for stage 2, statistically significant mean difference 2.804, 95% CI [1.243, 4.364], p = .001, indicating improvement over time for both the groups.

Overall, our results confirmed the hypothesis that breast cancer patients have poorer PM, particularly on time-based tasks, than healthy controls, and that the effects are stronger in the middle of the treatment. The hypothesis that PM would be poorer for the patient group for the second time, in the middle of treatment, was not confirmed by these tests. This might be due to familiarity effects with the tests.

6.3.5 Executive function measures

6.3.5.1 Digits Symbol

6.4 Digits symbol marginal means table

	PATIENT	HEALTHY	MARGINAL MEANS
	DIGITS SYMBOL		
STAGE 1	68.14	73.64	70.89
STAGE 2	72.53	78.14	75.33
MARGINAL MEANS	70.33	75.89	73.11

The hypothesis that patients will obtain lower scores on Digit Symbol test was not confirmed; however, no statistically significant higher rates of improvement were observed to confirm the hypothesis that healthy controls will show better performance than patients.

Significant within-groups simple effects were found for Digit Symbol $F\ (1,54) = 15.979$, $p = .001$, $\eta^2 = .228$. Estimated marginal means for between-groups for patient group were 70.33 (SE = 2.907) and 75.89 (SE = 2.907), and for healthy controls, a non-statistically significant mean difference was found, 5.554, 95% CI [−2.690, 13.797], $p = .182$; however, a statistically significant mean difference was found for the within-group comparisons, which indicated an improvement over time for both the groups 4.446, 95% CI [2.216, 6.677], $p = .001$. Marginal means were stage 1 70.89 (SE = 2.109) and stage 2 75.33 (SE = 2.150), indicating improvement over time for both the groups, with a higher increment for the healthy control group, confirming the hypothesis that healthy controls will show better performance than patients.

6.3.5.1.2 Digit Span

6.5 Digit Span marginal means table

	PATIENT	HEALTHY	MARGINAL MEANS
DIGIT SPAN			
	DIGIT FORWARDS		
STAGE 1	9.53	10.17	9.85
STAGE 2	10.28	10.67	10.48
MARGINAL MEANS	9.91	10.42	10.16
	DIGIT BACKWARDS		
STAGE 1	7.32	7.03	7.17
STAGE 2	8.53	9.32	8.92
MARGINAL MEANS	7.92	8.17	8.05
	DIGIT SPAN TOTAL		
STAGE 1	16.85	16.82	16.83
STAGE 2	18.85	20.00	19.42
MARGINAL MEANS	17.85	18.41	18.13

Generally, our results indicate that our hypothesis that the patients group would experience *cognitive decline after cancer treatment has not been confirmed; however, mean results* confirm the hypothesis that the healthy group would perform better than the cancer group.

Significant within-groups simple effects were found for Digits Span Forward $F(1,54) = 5.899$, $p = .019$, $\eta^2 = .098$, Digits Backwards $F(1,54) = 4.810$, $p = .033$ $\eta^2 = .487$, and Digit Span Total $F(1,54) = 36.327$, $p = .001$, $\eta^2 = .402$. Marginal means for digits forwards indicated a statistically significant mean difference for within groups .625, 95% CI [.109, 1.141], $p = .019$. Stage 1 mean was 9.85 (SE = .267), and stage 2 mean was 10.48 (SE = .314), indicating improvement over time for both the groups. Digits backwards for stage 1 and stage 2 indicated a significant mean difference 1.750, 95%

CI [1.260, 2.240], p = .001; stage 1 mean scores were 7.179 (SE = .272) and for stage 2 were 8.929 (SE = .294). Digit Span total within-subjects marginal means for stage 1 16.839 (SE = .484), stage 2 19.42 (SE = .542) showed a statistically significant mean difference 2.589, 95% CI [1.728, 3.451, p = .001. A significant interaction was found for Digits Backwards test $F\ (1, 54) = 4.810, p = .033, \eta^2 = .082$. Related t-tests showed significant improvement on cancer patients t (27) = −4.320, p = 0.001, d = 0.816 and on healthy controls t (27) = −4.391, p = 0.001, d = 0.830 with a greater improvement for the healthy control group.

Together, these results indicate that there was an improvement over time in the above measures, and that although the patient group scores improve overtime, there was greater improvement within healthy controls scores. Our hypothesis that scores after chemotherapy treatment would decline was rejected; however, the hypothesis that healthy controls will show a better performance was met.

6.3.6 Sleep

On measures of sleep, no interaction and within-subjects simple effect was found; however, measured sleep (ME) $F\ (1, 54) = 7.768, p = .007, \eta^2 = .126$ and PSQI $F\ (1, 54) = 23.459, p = .001, \eta^2 = .303$ showed significant between-subjects simple effects.

6.6 Sleep marginal means table

	PATIENT	HEALTHY	MARGINAL MEANS
	MEASURED SLEEP		
STAGE 1	29.07	26.82	27.94
STAGE 2	29.38	26.83	28.11
MARGINAL MEANS	29.22	26.83	28.02
	PSQI		
STAGE 1	7.10	3.82	5.46
STAGE 2	7.53	4.14	5.83
MARGINAL MEANS	7.32	3.98	5.65

Measured sleep (ME)-4 days–24/7

Between-groups simple effect marginal means for patient group 29.22 (SE = .607) and healthy control group 26.83 (SE = .607) showed a statistically significant mean difference of 2.393, 95% CI [.672, 4.144], p = .007, indicating that the patient group significantly slept for more hours than the healthy control group. Furthermore, independent t-tests were examined, and the results confirmed that the patient group slept significantly for more hours at both times when compared with healthy controls, stage 1 $t(54) = 2.305$, $p = 0.0125$, stage 2 $t(54) = 2.847$, $p = 0.003$.

On the other hand, self-reports data analysis from PSQI showed that the patient group reported significantly higher scores on measures associated with poor sleep. PSQI marginal means for between-groups for patient group were 7.32 (SE = .488) and for healthy controls 3.98 (SE = .488), a significantly mean difference of 3.339, 95% CI [1.957, 4.722], p = .001, indicating that the patient group reported more sleep disturbances. Independent t-test reports revealed significantly poorer scores for the patient group than for the healthy control group for both time points stage 1 $t(54) = 4.045$, $p = 0.001$; stage 2 $t(54) = 4.709$, $p = 0.001$.

The hypothesis that the patient group would show poorer sleep patterns, which in turn would affect PM, was not confirmed by measured sleep; however, PSQI results confirmed the hypothesis; the patient group showed impaired levels of sleep (>5 on PSQI scoring) when compared to controls.

6.3.7 Anxiety and Depression

6.7 HADS marginal means table

	PATIENT	HEALTHY	MARGINAL MEANS
HADS		**ANXIETY**	
STAGE 1	6.64	4.57	5.60
STAGE 2	5.53	4.75	5.14
MARGINAL MEANS	6.08	4.66	5.37
		DEPRESSION	
STAGE 1	2.21	1.67	1.94
STAGE 2	4.03	1.82	2.92
MARGINAL MEANS	3.12	1.75	2.43

Increased levels of anxiety were revealed on the patient group at stage 1, but decreased for stage 2. The healthy controls revealed lower levels of anxiety when compared with the patient group at stage 1 and remained almost the same for stage 2.

Estimated marginal means for depression for between-groups for the patient group mean 3.12 (SE = .401) and healthy control group 1.75 (SE = .401) showed a statistically significant mean difference of 1.375, 95% CI [.238, 2.512], p = .019, indicating higher levels of depression for the patient group. Within-groups marginal means indicated that depression scores were higher for the second testing session, where stage 1 mean scores were 1.94 (SE = .294) and for stage 2 2.92 (SE = .347),

with a statistically significant mean difference of .982, 95% CI [.377, 1.587], $p = .002$. Independent t-test revealed a significant difference on stage 2 t (54) = 3.195, p = 0.001, but not at stage 1 t (54) = 0.912, p = 0.183.

On measures of anxiety and depression, and interaction was found for anxiety F *(1, 54) = 4.419, p = .040,* η^2 = .076, and for depression *F (1, 54) = 7.731, p = .007* η^2 = .125. Depression results showed significant between-groups *F (1, 54) = 5.880, p = .019* and within-groups *F (1, 54) = 10.587, p = .002* main effects, but not for anxiety. Paired samples t-test exposed a statistically significant difference for the patient group in both, anxiety $t(27) = 2.480$, $p = 0.01$, and depression $t(27) = -3.445$, $p = 0.001$, but no significant difference for the healthy controls for anxiety $t(27) = -0.427$, $p = 0.462$ and depression $t(27) = -0.486$, $p = 0.31$.

CHAPTER SEVEN

7 QUALITATIVE METHODOLOGIES: THEMATIC ANALYSIS AND CASE STUDIES

7.1 Thematic analysis

7.1.1 Thematic qualitative analysis research question

The aim of this part of the research was to analyse to what extent PM self-reports and interviews relate to the actual chemo brain experiences and PM lapses of patients, based on previous research conducted on chemo brain and PM.

The approach taken was a "theoretical thematic analysis" (Boyatis (1998) which was analyst driven due to the fact that we were looking for a specific themes in order to answer the research question. The approach implied looking for patterns in questionnaires interviews and self-reports in order to identify emerging themes.

The research question was that chemo brain is a PM deficit, since common complaints range from forgetting to pay bills to facing difficulty in retrieving familiar words or being unable to remember words and names. The inability to multitask is also common, which could profoundly affect daily activities. Patients also present difficulties learning new, but simple things, such as a new version of a computer program they were familiar with earlier. All these problems have a major impact on the lives and self-esteem of

patients, making them feel that they are not the same people as before and that they have some sort of handicap. Due to these combinations of symptoms, some patients cannot perform the same activities as well as they used to prior to chemotherapy and may even lose, or resign from, their jobs (Mulrooney, 2007; Silverman & Davidson, 2009).

Errors in PM, referred to as PM deficits, are manifested in the form of slips of actions: repetition errors—forgetting that an action has already been performed and repeating it (e.g. placing two cheques in an envelope for the same bill)—goal switches—forgetting the goal of a sequence of actions and switch to a different goal (e.g. intending to drive to one place and driving to another)—omissions and reversals—omitting or wrongly ordering the component actions of a sequence (e.g. filling the kettle, but failing to switch it on) and confusion/blends—confusing objects involved in one action sequence with those involved in another sequence (e.g. taking a tin-opener instead of scissors into the garden to cut flowers) (Cohen & Conway, 2008).

Furthermore, PM failures have been associated with daily and routinely performed activities such as paying bills, taking medications with certain schedules and requisites and remembering to pick up things. It also involves performing familiar actions in novel contexts or at different times (Cohen & Conway, 2008).

Based on these assumptions, the method of analysis of this study was based on the research findings in both areas of study. We aimed to identify the relationship between

both areas through the comparison of qualitative and quantitative data obtained from a population of breast cancer patients.

The research question for the qualitative study was how the lived experience of chemo brain relates to PM failures. In order to understand the extent of this relationship, PM self-reports, descriptions from participants of their memory complaints and neuropsychological test results were analysed. Sample results were also compared with what other patients have reported on Internet blogs and in previous research.

7.1.2 Advantages and disadvantages of conducting online research

There are many advantages of collecting data through the Internet. According to Mann *et al.* (2000), researchers "can capitalise on the ability of the World Wide Web to cross barriers of time and space". It is now possible to gather information from people who are geographically distant or otherwise difficult to reach because they are ill, busy, working or disabled (Mann *et al.*, 2000). Internet data collection also solves issues related to cost and time. From the participants' point of view, it is cheaper to respond to an Internet survey than attending a specific venue. They save on transportation, petrol, parking and time. From the point of view of the PI, costs are reduced, as no venue is to be rented, no transportation costs and no printing costs. Attrition can also be reduced, because participants do not have to cancel interviews because of illness or work/family commitments. The Internet gives participants the opportunity to take part in scientific research from the comfort of their home or at work. Once data has been gathered, there

is no need to transcribe the information, because the script is immediately available for analysis (Mann *et al.*, 2000, Das, 2012, Bampton *et al.*, 2002).

Another advantage is the "online disinhibition effect" (Suler, 2004) which explains that sometimes people are shy, and they might feel more comfortable answering sensitive questions in private. If the participant feels at ease, they may give more honest and complete responses. Suler, J. (2004). The online disinhibition effect. *Cyberpsychology & Behavior, 7(3),* 321-6.

On the other hand, some people might not be good at expressing their thoughts in writing, and this might present as a problem, particularly when looking for an in-depth exploration of the phenomenon. In this study, to overcome this issue, the online questionnaires were followed by face-to-face interviews.

Misreading the questions or misunderstanding responses are also potential problems, because if the interview is asynchronous, immediate feedback cannot be received. A qualitative researcher relies on non-verbal communication to find out if the interviewee has understood the questions, which gives them the opportunity to clarify. To overcome potential problems, questions related to the experiences of patients were developed with the intention to be clear and simple to understand.

By the time the qualitative part of the study began, cancer patients were already under treatment (chemotherapy and/or radiotherapy) and had already taken part in the

quantitative tests. They would have been exhausted, both physically and emotionally. Although they had shown a constant willingness to participate in the study, it was decided that the qualitative study would begin using the advantages that the Internet has to offer, and therefore, we would not be intrusive at such a highly sensitive time in the lives of the participants. This approach helped us get a good number of participants taking part in the online questionnaires and self-reports.

These types of questionnaires allowed participants to respond at their own pace and carefully think what they wanted to express; it also allowed the PI to get a preliminary sense of what the participants were experiencing. Connections between the data for all participants through neuropsychological tests, PM self-reports, online questionnaires and face-to-face interviews over a period of time allowed the researcher to gain a sense of temporality. Participants had time to reflect on their experience with chemotherapy and how it affected their memory throughout the testing and interview sessions (Mitchell, 2011).

Although the Internet is a relatively new phenomenon, it has helped social science researchers to develop a new combination of methods. The use of the Internet has allowed combining of approaches resulting from different methodological traditions, where qualitative and quantitative methods are used together with data collected from online and offline environments (Hine, 2015).

There are several techniques that can be used when we use the Internet as a tool to do research. The most commonly used in mixed methods research design are presented

below. These techniques help researchers to interpret qualitative data, presenting most of the time a great advantage with regard to recruitment and cost-effective possibilities.

Some of the Internet research methods are as follows:

Online qualitative questionnaires. The use of questionnaires as a data collection tool in qualitative research is a useful way for gathering information about participants, such as attitudes, behaviour, opinions, attributes, beliefs and social interactions. There are a couple of techniques that can be used to gather data from online questionnaires. One could be "real time" using chats or messaging services (synchronous) and the other one is "off line" or asynchronous, using emails or other sources that allow the participants to respond at their own time. This gives the researcher time to analyse at a later time. Interview questions may be very structured or flexible and the data collected is recorded through the exchange of communication between researcher and participants. This method allows the researcher to exchange, in a private manner, sensitive information with participants and to focus on areas of specific concern. However, this technique limits the understanding of the offline, real lives of the participants, leaving little probability of validating participants' responses (Hine, 2015, McGuirk *et al.*, 2005). To overcome this limitation, the author of this thesis conducted face-to-face interviews as well as all the quantitative data collection processes, allowing greater interaction with the participants and avoiding a mere artificial communication that could undermine the richness of interviews' results.

When researchers develop qualitative questionnaires, they must take into consideration that the target population understand the questions and that participants are familiar with

the topic. There are two types of questions when we develop questionnaires: Closed and open questions. Closed questions may be looking for quantitative information, such as years in education, how many times a behaviour occurs, and may require participants to select categories, rank items, etc. In this type of questions, responses are easily coded and analysed. On the other hand, open questions help participants to provide greater in-depth responses making these responses more meaningful. These type of questions are less structured and give the opportunity to participants to express understanding, and to explain experiences and opinions in their own terms (McGuirk *et al.*, 2005).

The focus of our study was to conduct online questionnaires (closed and open), to understand breast cancer patients' PM difficulties and to obtain as much information as possible from participant's live experiences and to help the researcher to guide the face-to-face interviews.

Online surveys. Data collection is conducted by asking structured questions presented on a website, such as Survey Monkey. These kinds of surveys allow the researcher to explore participants' experiences that leads to quantitative analysis. If the population of the survey is unknown as a result of recruiting through online invitations or social media, there may be a problem of generalization which would limit online surveys, thereby complicating the analysis of response bias and how artificial the responses might be. (Hine 2015). However, for this study, our population was well known to the researcher from the beginning of the study.

Studies that have used online research methods are on the rise. They range from being large-scale and small-scale or a combination of both. They can depend on online or offline interactions and usually should complement each other with more traditional methods to gain deeper understanding and provide a more valid and reliable explanatory power, such as quantitative data and/or face-to-face interviews (Procter et al. 2013; De Mayer 2013, Hine, 2015). Due to the nature of the Internet and its role in the everyday lives of people, researchers tend to include it as a tool and use it by mixing both the Internet and qualitative and quantitative methods, in order to gain a deeper perspective of a phenomenon (Hine, 2015).

As we can see, nowadays researchers who design mixed methods studies are beginning to incorporate the Internet more and more as a research tool. This is done through the vast range of communication technology, such as web and videoconferencing, social media, email and mapping tools, which can be conducted globally or at their own communities (Salmons, 2015).

Examples where researchers use the advent of new communication technology are found in literature. Dowling (2012) studied breastfeeding support groups through face-to-face interviews, but his study was complemented with the use of email-based online interviews when the women could not attend the face-to-face meetings. Dowling (2012) carefully designed her online questions based on clear expectations and a steady communication with the participants. In her study, she found that some participants understood the in-depth nature of the open-ended responses and wrote detailed accounts in log emails, but others responded as if they were responding to more structured

questions providing short responses. However, she found that online interviewees responded at their own pace when they could avoid distractions, as opposed to face-to-face interviewees who were usually with their children and/or around other distracting factors during the interview (Salmons, 2015).

Other forms of online tools is found on Castanos and Percy (2010). In a study conducted to analyse a model course content for family therapists, to better understand how relationships differ in consulting and in therapy, the authors created a Wiki community (a virtual space created for data collection that promotes interactions with other participants through the internet), formed with the purpose of creating a research setting. The researchers collected data from online questionnaires, telephone interviews and online observations. Their data collection process began with semi-structured interviews to identify different perspectives, followed by online questionnaires in the form of Linkert-scales and narrative explanations in order to produce more in-depth details of the emerging themes from the initial interview (Castanos, 2010).The advantages of using the wiki community is that wikis are inexpensive, easy to use, and allows participants to exchange ideas, allowing the researcher to identify emergent ideas. However, some limitations occurred because wikis use specific browsers. On the other hand, reliability was also compromised because other participants can edit another person's responses.

In summary, the previous studies collected and triangulated their data derived from their multimethod, multistage qualitative approach, where data is obtained from different sources (QUAL+ QUAL+QUAL) (Salmon, 2015). Other studies focus on mixing quantitative and qualitative data, the same as our current study that obtained data from test scores, online interviews and face-to-face interviews (QUANT- QUAL+QUAL).

To explore the uses and influences of video content on political campaigns, Hussain (2012) designed a mixed methods study in which the qualitative stage comprised observations from blogs and videos that lead to formation of categories with codes that were later analysed through descriptive statistics (QUAL- QUAN) (Salmons 2015). Arsel and Bean (2013) conducted a study using a Quan-QUAL-QUAL approach to observe taste regimens and market-mediated practices, obtaining data from user-posted content and interviews and observation in person and online. McDermott and Roen (2012) also used online observations and user-posted content, online surveys and online interviews for a QUAL-quan-QUAL paradigm (Salmons, 2015).

In our study data was collected and triangulated obtained from neurological assessment test scores, online questionnaires related to PM and chemo brain experiences, and face-to-face interviews where participants provided more in-depth accounts of their memory difficulties after experiencing cancer treatment. (QUANT- QUAL+QUAL).

On the other hand, the E-Interview Research Framework (Salmons 2012, 2015) suggests that studies that include data collected from online interviews or observations should address the following key points to ensure that the choice of methodology is appropriate and our research questions are well-served by our choices of methods of data collection:

Aligning purpose and design: Are research purpose, theories and epistemologies, methodologies and methods clearly aligned? Does the researcher offer a compelling rationale for using the designated methods to achieve the research purpose? Do the qualitative and quantitative aspects of the study fit in a complementary way?

Choosing online or technology-enabled data collection: Are online or technology-enabled methods chosen in order to investigate real-world phenomena or are online methods chosen in order to investigate online phenomena?

Selecting the ICT and milieu: Does the study use text-based audio and/or visual communication data?

Determining the research approach and collecting the data: How does the researcher ensure that the choices made with regard to technology are appropriate to the particular study? How does the researcher align ICT (Information and Communication Technologies) functions, features and/or limitations with the selected methods for collecting and analysing data? (Salmons 2015, Oxford. P. 539).

In our current study the researcher intend aligning the different methodologies used within the theoretical frameworks of chemo brain research and PM, and by triangulating data obtained from qualitative measures with qualitative data collection from questionnaires and interviews, to develop case studies. The use of online data collection

was chosen in order to investigate a real-world phenomenon using online open-ended questionnaires and surveys, in order to facilitate breast cancer patients' participation.

Salmons (2015) concluded that the choice of ICTs influences the entire research design, sampling and mode of data collection, such as what data to collect from and how to collect it, would it be synchronous or asynchronous and if it fits the purpose of our research.

In our study, following the online questionnaires, a conversational-style face-to-face interview was conducted to obtain further insight into the experience of patients and to clarify information that was ambiguous or incomplete in the online interview. The interviews were recorded and transcribed verbatim. To check for accuracy, the interview recordings were compared with the interview transcripts.

Continuity between participants was achieved since the beginning of the study. Prior to the interviews, all the participants met with the PI at least two times for a neuropsychological assessment. These sessions were useful to establish rapport and trustworthiness (Denzi & Lincoln, 2003; Mitchell, 2011).

The time between the interviews and neuropsychological testing was eight months, due to the time it took to receive the approval of ethics committees, and because after analysing the online interview, it was decided that more in-depth information would be useful from some participants. Those interviews allowed us to assess whether their memories had improved or worsened after finishing the treatment.

Both, questionnaires and the interviews were read several times by the PI to find patterns and to provide categories and descriptions in order to help identify themes. The responses of participants to the face-to-face interviews were also used to validate themes.

7.1.3 Recruitment criteria

Only cancer patients who took part in the quantitative study were invited to take part in the qualitative part of the study. This sample bias was unavoidable, since healthy controls did not report memory difficulties and were not suffering from the effects of any treatment.

After obtaining ethical approval from the NHS ethics committee and from Bournemouth University, 27 participants were invited to take part in the online questionnaires. Twelve participants agreed to take the online questionnaires. A convenience subsample of six participants who completed the online questionnaires was selected for the face-to-face interview. In order to explore the implications of PM failure in cancer patients, participants were chosen with a wide range of memory problems (mild-medium-severe).

7.1.4 Methods and tools for data collection

The tools for data collection for qualitative research range from interviewing and observation to document analysis (Mann *et al.*, 2000). Interviewing is the most widely used method for data collection. Interviews can be either standardised (structured) or non-standardised (unstructured) and can be classified as one-to-one (individual) or group interviews (focus groups).

In structured interviews, participants are asked to respond to questions with a limited set of response categories. These are called surveys or self-completion (self-report) questionnaires. These surveys are usually analysed statistically, and the researcher controls the interview by providing standardised questions and constraining responses.

Non-standardised interviews look for the meaning and interpretations of responses, rather than the pre-formulated ideas of the researcher (Mann *et al.*, 2000). In this type of interview, participants are allowed to respond to questions in their own terms, and the choice of interview questions depend on the research question itself (May, 1993; Mann *et al.*, 2000).

According to Mann *et al.* (2000), a semi-structured interview is based on an interview protocol that is structured around specific thematic areas, which follows a conversational manner. Supplementary questions called probes are usually added into the conversation for further clarification and elaboration. In order to gain an in-depth,

subjective understanding of the experiences of patients, unstructured or in-depth interviews are usually chosen (Mann *et al.*, 2000).

The data collection to conduct the qualitative line of enquiry consisted of an online semi-structured, open-ended interview, aided by two validated structured PM self-report questionnaires, followed by a face-to-face interview. This method was chosen because the aim of the PI was to develop questions related to common cognitive problems in cancer patients with PM failure, in order to compare the two approaches with each other and with the neuropsychological test results of patients.

In order to avoid potential researcher bias, reference was made to the chemo brain and PM literature when designing the open-ended, semi-structured questions (Kidd, 2007). Although the interviews allowed for a certain flexibility, the aim of the PI was to accurately interpret the data based on previous research, not her own assumptions, so that the findings would give a clear interpretation of the experiences of patients, relevant and transferable to other sufferers of the phenomenon (Kidd, 2007).

Ethics approval was sought to conduct both the interviews. Invitation letters and information sheets were posted to the participants. They also were contacted by phone and email to confirm participation and to give them access to the online questionnaires. All information remained confidential and only the PI and her supervisory team had access to the interviews. Consent was sought for the interviews before commencing data collection.

For the online questionnaires, participants received an identification code to gain access to the PM questionnaires and the open-ended questions. They were allowed to leave the interview at any time and come back to it later, without losing previously input information. The identification code was unique to each participant, giving access only to their interview.

Once participants accessed the questionnaires, they read a welcome letter and an explanation of the implications of the study and were requested to give their consent. They were instructed to provide demographic information and received specific directions on how to use the web page. The instructions were simple and consisted of clicking boxes to complete the self-reports and typing their responses in the box provided for the open-ended questions. Participants were informed that they could save and close the survey and come back at a later time, allowing them to work at their own pace. The instructions also explained that members of their family were allowed to help them remember their memory anecdotes. No problems with this online system were reported.

The face-to-face interviews were conducted at Bournemouth University at the time that was most convenient for the participants. This interview helped gain further clarification of their experience in order to validate the information from the online questionnaires and gave them an opportunity to expand with examples and to confirm if their memory had improved or worsened. It also allowed the PI to gain more insight into the themes identified in the online questionnaires.

Semi-structured interviews were conducted on two occasions. The first time, participants were asked a series of online open-ended questions related to their memory difficulties and the impact on their social, family and work life. Before responding to the online questionnaires, they were requested to complete PM self-reports to help understand if their cognitive complaints were related to PM, which was the main concern of this mixed methods study. The questionnaires asked questions related to memory problems, such as misplacing things, forgetting appointments, missing the exit on their way home, etc. The second time they were invited to a face-to-face interview, and they were asked to elaborate on how they thought cancer treatment had affected their cognitive abilities and how that made them feel. They were also asked questions on the way they were coping, how people around them reacted to their memory complaints and if they could remember when they had started noticing their memory deficits (Refer to Appendix III).

7.1.5 Prospective memory self-reports

To determine if the participants were suffering from PM failure, two validated self-reports were used: the Prospective and Retrospective Memory Questionnaire (PRMQ) (Smith *et al.*, 2000) and the Comprehensive Assessment of Prospective Memory (CAPM) (Roche *et al.*, 2007).

The PRMQ is "a set of questions about minor memory mistakes that everyone makes from time to time" (Crawford *et al.*, 2003). The participants were asked to rate the frequency of the type of memory failures on a 5-point scale (very often, quite often, sometimes, rarely, never).

The CAPM is a measure that assesses PM lapses using 39 items, with 10 items focusing on basic activities of daily living (e.g. “forgetting to eat a meal”) and 23 items focusing on instrumental activities of daily living (e.g. “not remembering to pay bills”). Participants were required to rate the frequency of memory lapses as never, rarely, occasionally, often and very often. A “not applicable” response was also possible.

All online questionnaires were conducted approximately one year after treatment, followed by the face-to-face interview, which took place two years after treatment. They were recorded and transcribed verbatim by the researcher.

The advantage of conducting this research from before the treatment, until a few years after, was that the patients could discuss the whole experience with the PI, which gave a more complete picture of the effects of their treatment.

Our sample also included cancer patients who did not receive chemotherapy, but received radiotherapy and adjuvant treatment. They were also invited to take part in the qualitative part of the study, but none of them reported memory difficulties. Therefore, the qualitative study is solely based on breast cancer patients who underwent chemotherapy.

7.1.6 Thematic analysis

All the participants in this study took part in the quantitative part of this research and agreed to participate in the second one to analyse their cognitive deficits in depth.

Recruitment of this convenience sample took place at Bournemouth, Poole, Weymouth and Dorset County hospitals. The sample comprised 14 women who were treated with chemotherapy and reported having memory difficulties, despite the fact that the neuropsychological tests showed no impairment. Despite the fact that no impairment was found in the quantitative study for the cancer group, significant differences were found in performance when compared with the healthy control group.

After taking part in the neuropsychological assessment and receiving ethics approval, participants were invited to an online asynchronous questionnaire, which consisted of answering two PM self-reports for screening and eight open-ended questions (see Questionnaires Appendix). The responses of each participant were paraphrased, patterns were categorised and coded, and six emerging themes were identified.

Chemo brain has been defined as follows:

> "A term used by cancer survivors to describe a change in cognitive function, particularly in the domains of memory, concentration/attention, verbal abilities and multitasking that occurs after chemotherapy. The presence and intensity of chemo brain can be impacted by demographics, disease, specific and individual characteristics. Chemo brain has been reported to occur with other symptoms such as depression, anaemia or fatigue and these symptoms may identify the experience. Both objective evidence and subjective perception are important components of chemo brain. Consequences can include a change in functional status and psychological well-being. This in turn can affect work and

educational goals, quality of life, role function and self-esteem" (Mulrooney, 2007).

7.2 Thematic analysis procedure

To look for a major insight into the phenomenon of chemo brain, a thematic analysis was conducted. This implies a process of encoding qualitative information through a list of themes that emerge as patterns derived from the information obtained from participants. This helps to interpret, organise and describe observations of the phenomenon (Boyatzis, 1998). Themes were generated deductively based on previous research findings on the topic. A code book was created, which included the compilation of codes that emerged from the identified themes.

Participants were asked to complete an open-ended, asynchronous online questionnaire after having participated in a series of neuropsychological tests for the quantitative analysis. The interview questions were related to their experience of cancer treatment, specifically how their treatment affected their memory and how this in turn impacted their social life, work and relationships. After completing the online questionnaire, six participants were invited to attend a face-to-face interview to gain a deeper understanding of their experience.

Following thematic analysis procedures, the interviews were paraphrased twice for later building the responses of the participants into a paragraph, which was paraphrased

again. This analysis drew on previous research in the areas of chemo brain and PM, but focused on the question of whether the memory complaints of participants were associated with PM problems.

7.2.1 Methodology

There were three stages in the analysis of interviews, following the recommendations on conducting thematic analysis by Boyatis (1998):

3. Recruitment
4. Development of themes and codes
5. Code validation

7.2.2 Recruitment (Stage one)

Participants who had previously participated in the quantitative study were invited to take part in the online questionnaires and complete PM self-reports. Only those participants who reported memory decline in the online questionnaires were invited to participate in the face-to-face interviews.

7.2.3 Development of themes and codes (Stage two)

Thematic analysis was conducted following Boyatzis's (1999) suggestions for analysis. Boyatzis (1998) defined thematic analysis as "a translator of those speaking the language of qualitative analysis and those speaking the language of quantitative analysis".

Categories and themes development was conducted as follow:

Raw data from participants' responses was analysed. Key words were identified according to frequency of usage, and a colour code was assigned to similar words or phrases. After the key words were identified, participants' responses were paraphrased twice with the objective to create a summary from each participant's responses to later develop a paragraph that makes sense to the researcher. Each paragraph was compared with other participants' paragraphs to identify emergent themes (see Appendix IV for an example).

Participants' responses were analysed using Survey Monkey's word analysis as an initial stage to identify the percentage of usage of similar words (see Appendix IV for an example). This step was followed in order to identify the frequency of usage of keywords, such as "memory loss", "forgetfulness" etc., which contributed to create the study categories. A colour code for each question's category was assigned to identify the key words to aid the development of clusters that comprise similar keywords.

The method of clustering was used in order to identify clusters on the basis of similar characteristics between underlying constructs. For example, key words involving words, names or any other semantic difficulty were identified in the metamemory construct and coded as the Tip-of-the Tongue (TOT) theme.

Each paragraph was then compared with other participants' paragraph to identify the emerging themes.

In order to identify themes and codes, the following steps for thematic analysis were taken:

6. Identify categories from raw data (responses of participants).
7. Paraphrase. Create a summary and a paragraph.
8. Re-read and re-write.
9. Identify key words and cluster them into similar topics for data reduction. Go back to survey to redefine categories and have more accurate categories in order to develop a code.
10. Identify themes. Compare summaries, determine similarities and find patterns.
11. Compare themes. Reduce into small packets.
12. Create a code (simplified themes).
13. Create paragraphs with the responses of participants and make sense of the themes (see Appendix IV for an example of steps followed).

7.2.4 Code validation (Stage three)

For code and themes validation, a face-to-face interview was conducted to corroborate if the identified themes accurately described the experience of participants. The percentage of the codes reoccurrence within the sample was recorded. The themes identified in this study were compared with those in the literature related to chemo brain and PM.

7.3 Data management and analysis

Data were analysed according to the guidelines provided by Boyatzis (1998) for transforming qualitative information. Each participant was assigned an ID, and no data about their identity was recorded. The online questionnaires and recordings helped the PI to better understand the answers to the interviews. Categorization was carefully selected derived from observed patterns; descriptions were assigned for each category, and emerging themes were identified.

7.3.1 Online questionnaires and face-to-face interviews

Qualitative researchers have adopted the Internet and email communication as a research tool for open-ended semi-structured interviews, diary recordings and virtual

focus groups, in areas such as education (Salmon, 2000), sociology (Mann, 1998), health (Stewart *et al.*, 2005) and psychology (Williams *et al.*, 2011). For this study, it was decided to design an asynchronous, open-ended, semi-structured online questionnaire and to include two PM self-reports.

The use of computers for communication has become widely accepted and is accessible to people from all backgrounds. The Internet has been described as a "worldwide interconnected academic, business, military and scientific communication network" and is becoming a very powerful method of communication between individuals (Mann and Stuart, 2000). Qualitative researchers can take advantage of the possibilities that this communication medium has to offer (Mann *et al.*, 2000).

Based on the demographic information of participants, it was assumed that most of them would have access to the Internet, but it was also suggested that they could use their community library if they did not have access to computer or Internet at home. The assumption that the majority of participants were computer literate and had access to Internet was confirmed when the researcher contacted the participants and found out that all of them could provide an email address.

This type of questionnaire allowed participants to respond at their own pace and carefully think what they wanted to express; it also allowed the PI to get a preliminary sense of what participants were experiencing. Connections between the data for all participants through neuropsychological tests, PM self-report, online questionnaires and face-to-face interviews over time allowed the researcher to gain a sense of temporality

(Mitchell, 2011). Participants had time to reflect on their experience with chemotherapy and how this affected their memory through the testing and interview sessions.

Following the online questionnaires, a conversational-style face-to-face interview was conducted to obtain further insight into the experience of patients and to clarify information that was ambiguous or incomplete in the online questionnaires. The interviews were recorded and transcribed verbatim. To check for accuracy, the interview recordings were compared with the interview transcripts.

Continuity between participants was achieved from the beginning of the study. All the participants met with the PI at least twice for neuropsychological assessment before the interviews. This was useful to establish a rapport and trust (Denzi & Lincoln, 2003; Mitchell, 2011).

The time between the first and second interviews was eight months. This was due to several factors, including the time it took to receive ethics approval, and because after analysing the online interview, it was decided that more in-depth information from some participants would be useful. This had the advantage that it provided an opportunity to establish whether their memories had improved or worsened with time after finishing the treatment.

Both the interviews were read several times by the PI to find accurate patterns in order to provide categories and descriptions and to help identify themes. In addition, the PI

asked the participants if the themes were accurate in order to validate the themes after the face-to-face interviews were completed. It was expected that both the interview responses will correlate with each other.

Participants were all British, except for one cancer patient who was from Portugal.

All the participants were proficient in the English language and well educated (98% went to secondary school or above). Sixty-four percent of the participants were menopausal. The mean age was 20.27 for HC and 36.73 for the PT group.

Since alcohol or substance abuse affect cognition, participants were asked about their alcohol intake. All the participants said that they only drank alcohol occasionally. Seventy-five percent of the participants said that they had memory problems, which they attributed to their chemotherapy treatment. When asked to explain how they noticed their memory changes and if it had continued changing after treatment, 50% of participants could not recall exactly when their memory problems started, while 40% said it was during treatment and 10% after the treatment finished. When asked to rate their memory before treatment, 67% said their memories were good, 25% said it was the same and 8% said it was poor. Seventy percent of the participants felt anxious about their memory difficulties, while 55% reported an acceptance attitude.

7.4 Case studies research methodology

According to Balbontín (2012), a case study is an event taking place in a natural way where the researcher aims to gain deep insight into a phenomenon and to inquire how and why the phenomenon occurs. Yin (2009) describes a case study as an empirical enquiry investigating a phenomenon in depth within its real life context.

7.4.1 Aims

The aims of the case studies were

14. to explore the relationship or similarities among PM lapses and chemo brain, and
15. to compare test results of participants with their self-reports and interviews to explore the discrepancies between them, since quantitative test results showed no memory impairment, whereas interviews showed that participants experienced memory difficulties in everyday life related to PM and the TOT phenomenon (LTM).

Due to the nature of the study, participant bias could not be avoided. For the case studies, breast cancer patients who reported memory difficulties were selected from the sample, covering the full spectrum of impairment, ranging from the least affected to the most affected. This selection was based on self-reports and interviews. The overall impact of memory impairment on their everyday life considering their social relations, work and daily activities was examined.

According to Yin (1994), generalizing from case studies to theory multiple case studies can lead to theory development, rather than individual cases. Multiple cases are to be considered as multiple experiments, and the methods of generalization are called "analytic generalization", in which previous theories are used as a template to compare empirical results of the case study (Ying, 1994). The author of this thesis suggests that a complete research design requires the development of a theoretical framework irrespective of whether it is explanatory, descriptive or exploratory, because the use of a theory when we analyse case studies becomes the main vehicle for generalising results. If two or more cases support the same theory, replication may be claimed.

For case studies, as in all other types of research, factors such as construct validity, internal and external validity and reliability are of extreme importance. Construct validity is achieved by using multiple sources of evidence to establish appropriate operational measures to explain the concepts under analysis. In our sample, we used neuropsychological tests, self-reports and interviews to establish a chain of evidence related to PM and chemo brain based in the literature of both the areas.

External validity has to do with how our findings generalise beyond the case studies by relying on "analytical generalization", rather than on "statistical generalization", in order to generalise a particular set of results to a broader theory. In our case, we aimed to analytically generalise to PM and chemo brain theories.

Replication was achieved in our sample by analysing six case studies. Internal validity was used to explain in detail the causal relationship between chemo brain and PM, by trying to identify neural correlates between both the aspects of the study. A brief explanation of these neural correlates can be found in the Prospective Memory chapter of this thesis.

The aim of reliability was to produce the same results following exactly the same procedures to minimise error bias. All efforts were made to establish guidelines, so that the current study could be easily replicated, following the themes that emerged from the thematic analysis. In the current sample, six case studies where presented; all of them reported PM failures as well as problems with words and names.

7.4.2 Case study design

To address the research questions of this study, we used a multiple case study design by presenting evidence from tests and interviews of six participants who also took part in our quantitative study, with the aim to add robustness to it (Herriot & Firestone, 1983; Yin, 1994). We based our assumptions of reliability on the replication logic used in multiple experiments (Hersen & Barlow, 1976; Yin, 1994). That is, we had access to six cases to analyse the effects of cancer treatment on the PM of breast cancer patients.

We analysed the six cases by using tests and data from interviews. We found that the six cases reported PM difficulties that had also been associated with chemo brain; therefore, replication was achieved.

Each case was carefully selected to explore the relation between chemo brain and PM failure, with the logic of literal replication and in order to develop a theoretical framework for generalization. We chose participants ranging from those who reported not having been severely affected to those who admitted being profoundly affected.

We aimed to explain that the phenomenon of chemo brain exists despite neuropsychological tests results, that there is a relationship between chemo brain and PM failures, and that the TOT phenomenon is also a problem, if not the most common problem in this population.

To follow the replication approach suggested by Yin (1994), our initial step consisted of the theory development of chemo brain as a PM failure and the association of the TOT phenomenon in chemo brain. After the theory development was established, six cases where selected from our sample to present data obtained from each participant. Each individual case consisted of a whole study, and convergent evidence was sought. The conclusions of each case were considered for replication by other individual cases, and the summary report was composed of both, individual and multiple case results (Yin, 1994).

Efforts were made to indicate why and how a particular position was demonstrated, i.e. we tried to explain why we believe chemo brain is a PM failure by associating examples and theoretical accounts from each area, reporting on how participants describe their experiences, and how test results differ from participants' reports. We also tried to explain why we believe the TOT phenomenon is involved by presenting reports of patients and looking at how it was manifested. We also presented the contrasting results from neuropsychological tests.

This approach was relevant because by investigating how the experiences of patients with chemo brain relate to PM lapses and attentional difficulties (such as how patients struggle with words and names and fail to remember certain places they have visited), it was possible to observe how neuropsychological batteries might lack sensitivity to detect MCI, which despite being considered mild may have an impact on everyday life that is far from mild.

Despite the fact that neuropsychological tests are extremely useful tools for diagnostic and research purposes, they may misrepresent everyday situations. On the other hand, the use of surveys and self-reports alone to investigate memory deficits are very limited because of the subjective nature of self-reporting. In order to conduct a further in-depth analysis of chemo brain, the research team decided to investigate the contemporary phenomenon within its real context by using interviews for the thematic analysis as well as analysing case studies. Moreover, as the relationship between neuropsychological measures and chemo brain has previously shown inconsistent findings, up to the point

that some authors have concluded that the problem does not exist, the research team decided to present this contradiction within the sample.

The case studies were used to further explore the research question that chemo brain is a PM problem based on the current literature in both the areas of research, by combining qualitative and quantitative data. The advantage of using case studies for this research was seen as the ability to explore the phenomenon of chemo brain within the context of PM from the point of view of patients (adding to the analysis of test results those of self-reports and interviews). It also helped to observe the paradoxical situation where the information provided by the quantitative tests did not reflect the problems reported by patients in their everyday lives.

The questions used in the case studies were related to how cancer treatment had had an impact on the memories of patients, and why it had been suggested as a PM problem. They were designed to explore the difference between what the quantitative test results had shown and what the interviews and self-reports suggested.

Case studies of this sample were drawn from individuals who reported memory deficits as a result of cancer treatment and who had previously participated in the quantitative and qualitative studies.

The approach used to present the case studies was "pattern matching" (Yin, 1994), in which several pieces of information from the same case may be related to the same phenomenon and theoretical findings. Two opposing arguments were presented, e.g. test

results indicating no significant memory problem vs. anecdotal accounts of memory difficulties in everyday life as well as how PM matches with chemo brain complaints. The data on PM deficits and the TOT phenomenon were also presented.

Before each interview, the surveys were carefully analysed to choose the questions for the interview that were relevant to PM and TOT phenomena. This was important because sometimes interviewees deviated from the topic by talking about their physical symptoms and other side effects of chemotherapy, which were not related to memory and were out of the scope of this study.

Data collection was performed using focused interviews (Merton *et al.*, 1990; Yin, 1994). Each patient in the sample was interviewed for about 40 minutes using semi-structured, open-ended questions conducted in a conversational manner (allowing for the possibility to adapt the questions as the conversation progressed), following on from the PM questionnaires and online interviews. The aim of the interview was to corroborate our research question and to validate responses from online interviews as well as to validate themes that emerged from the thematic analysis.

7.5 Case study analysis

As indicated by Yin (1994), in order to conduct this analysis, it was necessary to rely on theoretical proposals for chemo brain, PM and TOT phenomenon to develop the research questions, direct the literature reviews and develop new theories.

According to Yin (1994), there are four analytical techniques that should be used to report case studies: pattern matching, explanation building, time-series analysis and program logic models. Pattern matching was chosen for this study.

The case studies investigated the experiences of patients who had undergone cancer treatment and experienced memory difficulties, regardless of their neuropsychological test results, with PM as one of cognitive domains affected and the TOT phenomenon, associated with LTM, also present.

This statement presents the basis for the theory that chemo brain is a PM deficit. It also gives insight to explore a new theory in the context of chemo brain, the TOT phenomenon, which has not been addressed as such in the chemo brain literature.

7.5.1 Pattern matching

To achieve internal validity in case studies, Trochim (1989) explained that the logic of pattern matching is to compare an empirically based pattern with a predicted one (Yin, 1994). When PM failures were compared with cognitive decline after chemotherapy, both the patterns coincided. The participants reported problems in accordance to PM failures despite the fact that the psychological measures failed to report this, confirming Mesulam's frontal lobe mystery around neuropsychological batteries (Burgess *et al.*,

2009). The TOT phenomenon was also observed through reports of participants having problems with words and names.

Although case studies cannot be generalised to the entire population, this study is relevant because of the emphasis placed on PM. From these studies, we could infer how chemo brain was in accordance to PM lapses and attentional difficulties, and we could clearly observe how neuropsychological batteries lacked sensitivity to detect MCI, which despite being considered mild, could have an impact on everyday life which might have been far from mild.

7.5.1.1 Explanation building

The aim of explanation building, as the name suggests, is to build an explanation about the case (Yin, 1994). The theories behind the current study's research question together with data collected from neuropsychological tests and surveys served as elements of explanation to observe the casual links between the theory and the results and to explain the rival assumptions behind the current study (Yin, 1994). That is, this exploratory study aimed to explain why test results reflect opposite results to the interviews, and why such a discrepancy exists. Another aim was to explore the relationship between PM decline and chemo brain.

7.5.1.2 Time-series analysis

A third analytical approach for case studies is when data is collected over time (time-series analysis). The neuropsychological tests were administered at two, three and four time points: at baseline, mid-treatment, end of treatment and six months later. The qualitative interviews took place one year and two years after the treatment. The design was based on the research question that PM performance would decrease during and after the treatment.

7.5.1.3 Program logic models

The fourth strategy for analysis suggested by Yin (1994) is a complex chain of events which combines pattern-matching and time-series analysis.

7.6 Research questions for case studies

The questions to be analysed for each case study were how cancer treatment had impacted the memories of participants and why the problems could be suggested as a PM problem. The differences between the quantitative test results and what the responses to the interviews and self-reports implied were explored.

7.7 Triangulation

When data collection is based on multiple sources of evidence, the principle of data collection called triangulation takes place, which gives the researchers an opportunity to explore the issue under observation in a much more complete and broader manner, increasing the accuracy of the research (Yin, 2009). This study was based on data triangulation, i.e. multiple sources of information were used for the exploration of the phenomenon of chemo brain. One of the advantages of triangulation is that construct validity can be established, because evidence of multiple measures of the same phenomenon can be provided (Yin, 2009).

Another principle of data collection when conducting case studies is to create a database (Yin, 2009). The database for the current study consisted of the demographic information of the participants, interpretation of data collected from neuropsychological test at various time points and the narratives of six case studies derived from online and face-to-face interviews.

7.8 Significance of the case studies

Among the strengths of the current study were the use of multiple sources of data collection by examining test results, questionnaires and interviews as well as analysing the literature in several areas of study (PM, chemo brain, TOT, sleep), which allowed to study chemo brain in a broader manner by presenting objective and subjective evidence.

Data triangulation was achieved by using multiple sources, helping to corroborate firstly that PM failures and chemo brain present the same cognitive disadvantages to sufferers, that chemo brain patients show the TOT phenomenon and that neuropsychological tests might not be sensitive enough to detect MCI (Patton, 1987; Yin, 1994; Burgess *et al.*, 2004). Issues regarding construct validity were also addressed with data triangulation, because the multiple sources of evidence provided multiple measures of the same phenomenon, enhancing the quality of the case studies presentation (Yin, 2004).

CHAPTER EIGHT

8 THEMATIC ANALYSIS: RESULTS AND DISCUSSION

This study explored the memory difficulties experienced by breast cancer patients after receiving chemotherapy treatment. All the participants in this study had taken part in the quantitative part of this research and agreed to participate in the second one to analyse their cognitive deficits in depth. Recruitment of this convenience sample took place in Bournemouth, Poole, Weymouth and Dorset County hospitals and comprised 14 women who were treated with chemotherapy and reported having memory difficulties, despite the fact that the neuropsychological tests showed no impairment.

After taking part in the neuropsychological assessment, participants were invited to an online asynchronous questionnaire, which consisted of completing two PM self-reports and answering eight open-ended questions (see Questionnaires Appendix). Each participant's response was paraphrased and patterns were categorised and coded from which six themes emerged.

To better understand chemo brain experience in the context of PM, six women who received treatment for breast cancer responded to an invitation to a face-to-face interview. All the participants in this sample also took part in the neuropsychological assessment and online questionnaires. The objective of the case studies was to discuss the potential role of PM in chemo brain patients and to further analyse the discrepancy

between neuropsychological assessment and the experiences lived by patients, following on from the quantitative study and the thematic analysis.

Sleep was assessed by measuring the number of hours (ME) of sleep during a period of four days wearing the SWA. In each table, percentile ranks are included to understand overall percentile rank of each individual patient within the sample and to observe how scores fall within the normal range.

8.1 Research question

Based on previous research conducted on chemo brain and PM, the author wanted to analyse to what extent PM self-reports and interviews relate to participant's chemo brain experiences and PM lapses. The theoretical thematic analysis approach selected to conduct our analysis was analyst driven, because we aimed to look for a quite specific research question. We will look for patterns on interviews and self-reports to later identify emerging themes.

The method of analysis of this study was based on the research findings in both the areas of study. The aim was to identify the relationship between chemo brain and PM through the comparison of qualitative and quantitative data obtained from a population of breast cancer patients.

The research question for this study is essentially how the symptoms of chemo brain experienced by cancer patients relate to PM failures. In order to understand the extent of

this relationship, PM self-reports, descriptions from participants of their memory complaints and neuropsychological test results were analysed. Sample results were also compared with what other patients have reported and accounts on Internet blogs as well as the results of previous research.

8.2 Online questionnaire results

Three themes related to EF emerged from data analyses: words and names, attention and multitasking. The titles of the themes came from the patterns found in the responses of patients and are explained below. Three additional themes were identified related to patients' mood and the ability to cope; more emphasis was given to those related to EF, which is the scope of this research, with those related to emotions analysed later.

Participants were for the most part British, except from one cancer patient who was from Portugal. All participants were proficient in the English language and well educated (98% went to upper school or above), 64% were menopausal and 75% admitted to having memory problems as a result of chemo treatment.

When we asked them to explain how they had noticed their memory changes, and if they had continued changing after the treatment, 50% could not recall when exactly they started, 40% thought that it was during treatment and 10% thought they had started after the treatment was completed. Sixty-seven percent said their memories were good before treatment, 25% said they were the same and 8% said they were poor. Seventy percent

felt anxious about their memory difficulties, while 55% reported an attitude of acceptance.

8.2.1 Words and names: Tip-of-the-tongue phenomenon (Theme one)

Phrases such as *difficulty following conversations and completing sentences* and *problems with words and names* were clustered in the category "problems following conversations and remembering names". This theme incorporates how participants had difficulty remembering the names of people, even if they had known them for years, even the names of their children. Another problem within this theme was that chemo brain patients struggled with following conversations. They could not follow their train of thought or simply could not remember the word they wanted to use, and instead, they tried to describe the word that they intended to say. This made patients feel stupid and embarrassed; they felt frustrated and did not like to offend the people whose name they had forgotten. Some patients felt like a "lesser person" than they were before, because their verbal abilities had diminished and they had to use simpler words or needed to ask other people for helping them remember the word they were trying to say.

Cancer patients usually reported that they had difficulty retrieving names, normally very familiar words, even when they could remember the face and the other information about the person. They may have felt confident that they knew the person well, but at that precise moment, they could not recall the name. Pires *et al.* (2012) suggested that

> "forgetting names of family members or friends plays an important role in subjective memory complaints in the clinical setting. This symptom is possibly perceived as particularly worrisome and likely drives people to seek for clinical help."

Unfortunately, the vast majority of chemo brain patients complained about forgetting names and words, as can be seen from the anecdotal reports in this work. Many of the participants in this study expressed their feelings of frustration as a result of not remembering words and names:

> "I still have difficulty remembering words, and I have to describe the meaning so that someone reminds me the word… Although it is frustrating, I am coping perfectly well. It has been a matter of making adjustments". Participant 8

> "I feel frustrated and confused at times, especially because I can't remember simple words, but I am getting on with it. It is my only choice". Participant 8

8.2.1.1 Examples

> "It was very apparent that my memory problems began during treatment. Making sentences became a very difficult thing to do, as well as remembering names." Participant 1.

> "My memory before treatment was average, but better than it is after treatment. I used to remember processes more easily. I had better recall of words,

particularly difficult ones. My memory was good for remembering appointments and names." Participant 8

"I frequently forgot where I put things down, and I even forget my children's names. During a conversation, I had to stop in the middle of it because I forgot what I wanted to say, or I cannot find the word to complete my sentence. As a driving instructor, I feel worried about causing an accident, because I need to be quick giving verbal instructions, but sometimes I can't remember what I have to say. I feel frustrated and confused at times, especially because I can't remember simple words, but I am getting on with it. It is my only choice." Participant 9

"After treatment commenced I have problems remembering people's names. I noticed the forgetfulness after the first cycle when I started having problems with names, and although it has not gotten any worse, it has not improved either. Before treatment, I did not have memory difficulties. I was very good at remembering people and tasks." Participant 10

"My memory has been affected by treatment, but I have not seen significant deterioration, other than confusing words." Participant 13

"I cannot recall when my memory start changing, but it was during treatment that I noticed lack of concentration and forgetting people's names. I feel stupid and that I insult people by calling them with a different name." Participant 14

8.2.2 Attention (Theme two)

Words and phrases such as *forgetfulness, lack of attention, unable to concentrate* were clustered in the category "problems with attention, concentration and forgetfulness".

Some cancer patients complained about attention difficulties. They also mentioned that they found it harder to read, because they could not focus their attention on what they were reading. The same thing happened when they could not follow conversations and lost their train of thought through a lack of attention or forgetfulness, because they did not pay attention to cues in the environment which later could serve as reminders. They may also have frequently misplaced things, forgotten to take medication and missed appointments with doctors or social engagements.

Attention is the ability to focus or concentrate on specific stimuli and comprises selective (focusing on relevant information and filtering out irrelevant information), sustained (maintaining attention on a task over a prolonged period of time), divided (focusing on multiple tasks at the same time) and alternating attention (switching attention between two or more sources of information), which play an important role in WM and PM (Neath *et al.*, 2002; Rich *et al.*, 2007). This section of our study is focused on divided attention, which is the type of attention the author believed affects chemo brain patients and that is most involved in PM.

PM permeates daily life activities such as remembering to take medication, passing on a message, remembering to pay the bills, remembering to attend appointments, etc. People are particularly prone to forgetting to carry out these tasks when they are busy, because increasing the attentional demands of an ongoing task interferes with PM. For example, patients might forget to pick up their children if they are thinking about their next chemotherapy treatment or forget to attend their appointment when they are engaged in a conversation with a friend (McDaniel *et al.*, 2007; Harrison *et al.*, 2013).

Monitoring processes are needed to accomplish PM tasks, and people spend attentional resources on searching the environment for PM cues or to maintain the intention activated at the same time the ongoing activities take place (Harrison *et al.*, 2013; Burgess *et al.*, 2001; Smith, 2003). According to Harrison *et al.* (2013), monitoring must take place before the occurrence of the target event is to be recognised as a signal for an action to occur. Vigilance tasks can be impaired as a result of divided attention. Driving a car provides a good example of this, because a driver might pay attention to the travelling signs while searching for an upcoming turn. To do these monitoring processes, it is necessary to allocate WM and attentional resources, but attentionally demanding divided attention tasks may interfere with monitoring (Harrison *et al.*, 2013; Burgess *et al.*, 2001). This example is relevant to this study because participants complained about having trouble with driving and paying attention and giving instructions while driving. The author's research question is that such troubles are due to the divided attention that might be interfering with monitoring.

Harrison *et al.* (2013) suggested that when a person's attention is divided, superficial analyses of the environment are conducted, leading to poor processing, which in turn prevents retrieval of the intention, and that PM intention enters conscious awareness, as one of the participants explained:

> "I have been unable to concentrate for a long time. This lack of attention does not allow that my memory register things, therefore I cannot remember later." Participant 3

8.2.2.1 Examples

> "My memory has been affected by treatment, but I have not seen significant deterioration, other than confusing words and keep forgetting things, misplacing things, etc." Participant 13

> "After treatment, I have been unable to concentrate for a long time. This lack of attention does not allow that my memory register things, therefore I cannot remember later." Participant 3

> "At work, I have to write everything down, so I do not forget what I have to do. Before treatment I was able to follow map directions by seeing the map once, now I have to refer to the map constantly to get to my destination." Participant 3

> "My life at work became difficult because I couldn't remember what I had previously done the day before, or had difficulty following procedures that I was familiar with, and were easy to follow before. My memory before treatment was

average, but better than it is after treatment. I used to remember processes more easily. I had better recall of words, particularly difficult ones. My memory was good for remembering appointments and people. When talking to my friends, I feel embarrassed because I am unable to remember stories they had told me, and I keep asking questions about things they have already told me about." Participant 8

"I began having really bad and noticeable memory problems during and since treatment. I frequently forgot where I put things down, and I even forget my children's names. During a conversation, I had to stop in the middle of it because I forgot what I wanted to say, or I cannot find the word to complete my sentence." Participant 9

"After treatment commenced I have problems remembering people's names and what household jobs I am doing. I have trouble remembering names, and if I deviate my attention from a task I am working on, I completely forget to finish it, until I see it again later (e.g. putting the washing away)." Participant 10

"Now my mind is having complete blank lapses, and I do not have recollection of certain things at all, for example, when we discuss a holiday or places I have been, I simply cannot remember. I used to have good memory about these sort of things, and at work I had good memory as well. I have always been bad remembering actors/actresses names, and now that is impossible. Once I forgot to turn up for a class (I am the teacher), something that has never happened

before, but I did not attribute this to my current condition. With all these, I feel anxious, but now I avoid making plans in advance as I used to do, because I fear I will forget and I do not want to disappoint people, because that makes me feel very bad. I need to ask them to remind me about our appointments." Participant 7

"I need to write everything down and then remember to look at it. Recently I forgot when we need to leave the hotel and I was checking out a day earlier and moving to a different town a day before." Participant 11

"I have never had a great memory, but since treatment I feel that I cannot remember certain things from the past. The most noticeable thing is the lack of concentration and feeling of fuzziness. I have poor concentration and it is difficult for me to prepare a lesson for work. Also I avoid to work too far away, because I have trouble driving because of the lack of concentration. The lack of concentration has prevented me to drive and I feel very limited because of that." Participant 14

8.2.3 Multitasking (Theme three)

Phrases like *inability to multitask, more difficult to do my job, harder to do my job, slowness*, were clustered in the category "inability to multitask". Examples include, "It

now takes more effort to do simple tasks than before treatment" and "It is more difficult to follow familiar procedures and instructions."

Cancer patients experiencing memory difficulties frequently complained about losing their multitasking abilities. They usually explained that they were unable to do several things at a time as they used to do before treatment. They also complained about being slower or struggled to follow instructions or procedures, even those they were familiar with and used to master before treatment. They often reported being unable to complete a shopping list, or that they very often had to go to the grocery shop several times, because they could only buy one thing at a time.

Performing two or more things concurrently is referred to as the ability to multitask. In real life situations, we face the extra challenge to remember to carry out our intentions at a later time while we are multitasking. This ability to multitask and to remember to do other things requires an effective distribution and coordination of attentional resources, but it can become impaired (Deprez *et al.*, 2013). Cancer patients usually complain about impaired multitasking abilities, despite performing well in the neuropsychological tests. This might be due to increased WM demands and divided attention (Deprez *et al.*, 2013; Santangelo *et al.*, 2013).

Volle *et al.* (2011) reported that multitasking involves RPC and that patients with lesions in this area frequently present problems with multitasking. These authors also stated that an essential component to multitasking is PM, and that patients with rostral prefrontal lesions present difficulties when there are several ways to behave, when the

behaviour is not fully guided by the environment and when two or more task are required to be performed concurrently. Examples of these situations in everyday life are preparing a meal, shopping, completing a job assignment, etc. (Volle *et al.*, 2011). In an experiment with 60 rostral patients, Burgess *et al.* (2000) concluded that these patients showed impairment in the intentional component of multitasking (Volle *et al.*, 2011). Other necessary components of PM are the ability to remember multiple instructions and the ability to switch between them (Volle *et al.*, 2011). Therefore, the inability to follow instructions and slowness at work because of this deficiency are in the same category of multitasking.

8.2.3.1 Examples

> "Since my memory problems began, after chemo, it takes me longer to work. I had to remind myself about procedures and took me more time to follow instructions, but that is improving now. I still struggle following instructions, but I compensate by keeping instructions I can follow." Participant 8

> "During chemo I began noticing bad memory problems. I became unable to multitask and could only manage one thing at a time when I went shopping. I had to go back to the shop to buy another item when I got home. Before treatment, I was able to do a full shop list before chemo, post letters, get the stamps, and go to the recycling centre, all in one go, but I cannot do that anymore. Now I also have trouble remembering names, and that is unusual for me. I used to be a multitasking person, and now I only can deal with one thing at a time." Participant 11

> "Also I avoid to work too far away, because I have trouble driving because of the lack of concentration, and that makes me feel limited and has had a big impact on my social life and work. My work has also been affected because I struggle with emails and planning, and I feel it is falling behind." Participant 14

> "Before treatment I was able to follow map direction by seeing the map once, now I have to refer to the map constantly to get to my destination." Participant 3

Participants were also asked about how their memory difficulties made them feel and how they were coping with these. With regard to mood, two general categories were identified: positive mood and negative mood.

8.2.4 Negative mood, frustration and anxiety (Theme four)

Words like *frustration, cross, stupid, bewildered, worried* were clustered into the category "feeling frustrated and anxious".

This theme explains the associated symptoms of the chemo brain phenomenon. Anxiety is very common during cancer treatment and can be associated with lack of attention and concentration. Patients are usually worried about the outcome of their treatment and how they would cope with all the demands that their treatment required, such as keeping up with appointments, handling the treatment's side effects, surgery, relapse and all the

daily activities not related to their treatment, such as taking care of children, work, etc. To sum this up, they would need to cope with these new memory lapses, and they would worry about not being normal again, offend people around them or to cause harm as a result of their lack of attention. This new situation would sometimes make them feel frustrated, angry, stupid, or that they were not themselves anymore.

8.2.4.1 Examples

> "I was quite concerned, but I realised that I had to accept that I was affected by the chemo, and now I am hoping that the memory will improve with time." Participant 6

> "My family and friends noticed that I had memory problems because I said stupid things." Participant 1

> "All these memory changes make me feel frustrated and angry." Participant 1

> "Sometimes these changes make me feel irritated." Participant 3

> "I feel embarrassed because I am unable to remember stories they had told me, and I keep asking questions about things they have already told me about. I feel frustrated, but I am getting used to these memory changes." Participant 8

> "I feel frustrated and confused at times." Participant 9

"My husband thinks I am not making a good effort to look after the household and family and gets cross when I do stupid things. I feel very stupid at times." Participant 10

"I avoid making plans in advance as I used to do, because I fear I will forget and I do not want to disappoint people, because that make me feel very bad. I need to ask them to remind me about our appointments." Participant 11

"I feel stupid and that I insult people by calling them with a different name."

"I have obsessive thoughts about the diagnosis and treatment, and its consequences." Participant 14

"In a way I feel less than I was before treatment. When talking to my friends, I feel embarrassed because I am unable to remember stories they had told me, and I keep asking questions about things they have already told me about. I feel frustrated, but I am getting used to these memory changes." Participant 8

8.2.5 Positive mood, acceptance, humour and resilience (Theme five)

Words like *laugh, accept, not let me bother, open about my forgetfulness* were clustered in "acceptance and positive attitude".

Some cancer patients showed that they were resilient in the face of adversity, even when they were facing life-threatening conditions. Sense of humour is a quality that could be observed in these patients who instead of letting themselves fall into a depressive state, laughed at those problems and accepted the fact that they were facing cancer. They also seemed to feel better by learning to cope instead of getting depressed about their cancer, thereby improving their quality of life.

8.2.5.1 Examples

> "I was quite concerned, but I realised that I had to accept that I was affected by the chemo, and now I am hoping that the memory will improve with time." Participant 6

> "I like to be a realist person, I think the human brain has imperfections, and I accept that. It is not possible to remember everything anyway." Participant 7

> "The memory changes make me laugh rather than bother me." Participant 13

> "My family and friends simply laugh about my memory lapses, but when I am trying to communicate with my teenage children about their social activities, it sometimes causes problems." Participant 3

"My family laugh about these lapses, but still I get frustrated sometimes when I misplace things, although I do not let these things to bother me." Participant 9

8.2.6 Reminders dependency (Theme six)

Participants were asked about how they were coping with their memory difficulties. The vast majority was relying on reminders of different sorts, such as asking people to remind them of their appointments, using dictionaries and by keeping diaries and lists. Only one participant mentioned about completely avoiding to drive because of her lack of attention, meaning that she was using avoidance as a coping strategy.

8.2.6.1 Examples

"All these memory changes make me feel frustrated and angry, but I am coping fine and I take my time to say things." Participant 1

"…but I am coping well by carrying a notepad with me to make list of the things I have to do." Participant 3

"I still have difficulty remembering words, and I have to describe the meaning so that someone reminds me the word. I still struggle following instructions, but I compensate by keep instructions I can follow. But I am getting used to these memory changes, and I use aids that help me cope, such as calendars and to do lists, and I use simpler words to describe things. Although it is frustrating, I am coping perfectly well. It has been a matter of making adjustments." Participant 8

"I am coping by making lists all the time as my reminders to do things." Participant 10

"I feel fine that I can do my job without any trouble, but I need to be more careful, and write things down so I can remember to do things." Participant 11

"My work has not been affected as much as I thought. I use aids to help me with my problems with words. I am coping fine, but I need to use reminders. I need to write everything down and then remember to look at it." Participant 11

Another coping strategy employed by participants was to work harder or take longer time to do or say things. Those who reported trouble following instructions or procedures tried to adhere to the procedures they were familiar with and used reminders or simply avoided new instructions. Some also avoided making plans in advance to circumvent embarrassment or situations they felt unable to cope with:

"All these memory changes make me feel frustrated and angry, but I am coping fine and I take my time to say things." Participant 1

"At work, I have to write everything down, so I do not forget what I have to do. Before treatment I was able to follow map directions by seeing the map once, now I have to refer to the map constantly to get to my destination." Participant 3

> "My life at work became difficult because I couldn't remember what I had previously done the day before, or it stated having difficulty following procedures that I was familiar with, and were easy to follow before… Since my memory problems began, after chemo, it takes me longer to work. I had to remind myself about procedures and took me more time to follow instructions, but that is improving now. I still struggle finding instructions, but I compensate by keeping instructions I can follow." Participant 8

> "With all these, I feel anxious, but now I avoid making plans in advance as I used to do, because I fear I will forget and I do not want to disappoint people, because that makes me feel very bad. I need to ask them to remind me about our appointments." Participant 11

Not all participants in this study reported significant memory difficulties as a result of cancer treatment. Some reported that their memory was the same after treatment as before treatment. However, they did acknowledge memory difficulties, but attributed them to aging or menopause:

> "I cannot say for sure that my memory lapses are due to chemotherapy. Perhaps it is just due to aging. My family and friends do not notice anything, but they would think it is an age thing anyway. I like to be a realist person, I think the human brain has imperfections, and I accept that. It is not possible to remember everything anyway." Participant 7

"I have always had memory problems, since childhood. Only my husband and children have noticed my memory problems during treatment, but they are not too significant, because my memory is the same than before treatment…"
Participant 2

"After treatment I have slight occasional memory loss, but my family and friends have not noticed them. I have occasional forgetfulness, but I cannot recall a cycle in particular when I noticed the forgetfulness. My memory now is the same as before treatment, and it has not affected my social activities."
Participant 5

"…and think it's an age thing anyway. Who remembers everything anyway? I like to think I'm a realist about the human brain and accept its imperfections. I assumed it is an age issue as has happened gradually since menopause."
Participant 7

8.3 Summary of findings

8.3.1 Emerging themes

16. **Words and names**. The vast majority of participants in our sample reported having trouble remembering names of familiar people and with retrieving familiar words in conversations.

17. **Attention**. Patients reported changes in attention and inability to concentrate, leading to forgetfulness, affecting everyday tasks such as reading and attending appointments.

18. **Multitasking**. Participants reported losing their ability to do several things at a time at work or at home. They felt they became slower and that some tasks became harder.

19. **Negative mood, frustration, anxiety**. Chemo brain symptoms experienced by patients made them feel frustrated and anxious. They had the tendency to "feel less than before" and that created anxiety, affecting their social life, work and family life.

20. **Positive mood, acceptance, humour, resilience**. Despite the frustration caused by chemo brain, some participants reported taking their forgetfulness with humour and becoming resilient, learning coping strategies to survive a life threatening illness.

21. **Use of reminders**. The most common coping strategy used by participants was to become dependent on reminders to be able to remember their plans for the immediate future.

CHAPTER NINE

9 CASE STUDIES: RESULTS AND DISCUSSION

9.1 Case studies

9.1.1 Case study one

Participant one was agreeable, interested and compliant throughout the testing sessions. She communicated at ease with the researcher, and rapport was easily achieved. This participant had consistently reported cognitive decline since the beginning of the treatment and that her life had been affected significantly by these changes. Nevertheless, the support of her family and her own resilience had helped her to cope with the situation. Although her test results showed no significant impairment, her daily life was affected, and she clearly showed PM failure. In her report, she noted that her memory had not improved more than one year after the treatment and according to her partner, it had probably worsened. She worked as a driving instructor, but she reports that her work and social life had not been affected by her memory decline.

9.1.1.1 Background information

Participant one was a 44-year-old, Caucasian, British woman. She lived with her family and received strong family support from her two daughters and partner. She completed her secondary studies in the UK and was self-employed.

She underwent breast cancer surgery in September 2011, one month after being diagnosed. She began chemotherapy treatment one month after surgery and also received radiotherapy and hormonal treatment. She experienced chemotherapy-induced menopause. Her Full Scale IQ was 111 (30^{th} percentile) on the NART. Her overall performance fell within the normal range and was equal to or higher than 30% of the women in this sample. The test was administered four times.

EF scaled test scores for Participant one (Table 9.1) showed that her cognitive abilities fell within the normal range within the normal distribution when compared to women in this sample, showing a consistent pattern in responses over time. Her overall raw scores placed her on the 75^{th} percentile on the Digit Symbol tests (where processing speed and intellectual abilities are measured), indicating that she could learn new tasks and had no problem making associations. The same was true for her attentional abilities, which showed not to be affected at the baseline measurement, even if her performance was poorer more than six months after treatment. Her Digit Span and Benton scores confirmed that her attention was unaffected and did not show any sign of memory problems. Her scores fell within the normal range and were fairly consistent throughout the sessions, falling into the 80^{th} percentile rank.

Executive Function	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
Digit Symbol	73	85	88	80	75
Digit Span Total	18	20	20	19	80
COWAT	34	36	39	45	50
BENTON Correct	10	9	10	10	90

Table **Error! No text of specified style in document.**.1. Test scores for Participant one.

Despite these results, Participant one reported having attentional and concentration problems throughout the testing sessions, and the problems had persisted for several months after the treatment, with no sign of improvement.

Her COWAT test scores indicated that she did not present difficulty retrieving words, but her anecdotal reports indicated the opposite. Despite the fact that she improved her test scores in the last session, six months after treatment, word retrieval was the most evident complication in her daily life, because as a driving instructor, her job depended on giving instructions and remembering what to say.

For the PM measures, Participant one performed worse in the first test, before treatment, but after surgery, however, at post-treatment she performed worse than any of the

previous tests (Table 9.2). This suggested that her PM was more affected, possibly due to the anxiety experienced before commencing the treatment. Her performance was better for focal tasks than for nonfocal tasks, meaning that her self-initiating monitoring was affected even before treatment. Interestingly, her PM scores improved significantly during mid-treatment and immediately after treatment. The improved performance in the second test might have been due to familiarity with the test; however, the most significant improvement was for time-based tasks, which showed that there was a more conscious self-monitoring behaviour. Nevertheless, her performance declined in the third and fourth tests. Six months after treatment, her performance continued to deteriorate. These results are consistent with the findings that cognitive decline after chemotherapy is manifested in some patients several months after treatment. Her overall performance between time-based and event-based prompts demonstrated that her self-monitoring behaviour was better than cue-dependent monitoring.

CAMPROMPT	**Test 1**	**Test 2**	**Test 3**	**Test 4**
Time	12	18	16	16
Event	14	16	16	12
Total	26	34	32	28
Classification	B	AA	A	P

B=Borderline P=Poor A=Average AA=Above Average VG=Very Good

Table **Error! No text of specified style in document.**.2. CAMPROMPT scores for Participant one.

9.1.1.2 Sleep

On measures of sleep, Participant one reported poor sleep patterns and that she felt sleepy during day time. The number of hours she slept were inconsistent with her self-reports, which showed that she slept for more than 8 hrs a day, but she felt that she did not sleep enough and felt somewhat sleepy during the day (Table 9.3). This inconsistency might be because despite the fact that the SWA showed that she slept for more than the average hours of sleep, her sleep time was not efficient. There is evidence that hypersomnia affects sleep efficiency and may also interfere with PM. These sleep patterns might have been contributing to some of her memory difficulties and might have been caused by medication or anxiety.

Sleep	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
PSQI	15	14	16	11	95
ESS	7	5	4	5	50
Sleep (hours)	32.23	22.11	32.23	27.03	50

Table **Error! No text of specified style in document.**.3. Measures of sleep Participant one.

9.1.1.3 Online questionnaires and face-to-face interviews

In the online questionnaires, Participant one reported that her memory became very bad during and after treatment. It was her family who first realised that she was having memory changes, and her partner said that it was worse at over 12 months after the treatment began. She reported that her work had been affected because she was a driving instructor and needed to give many verbal instructions to her students, but sometimes forgot what she needed to say. However, her social life had not been affected, as opposed to some patients who became isolated to avoid embarrassment with their friends. She reported feeling frustrated at times and bewildered as to why she could not remember simple words, but her family support had helped her to face the situation with humour, rather than with complaining:

> "During and since chemotherapy my memory has gotten really bad. I put things down and forget where I've put them. I forget my children's name. I will start talking and stop mid-sentence because I either can't remember what I wanted to say or I have forgotten the next word."

> "Oh, got bad! It hasn't gotten any better either. Umm… I can start a sentence and get half way through and I forget totally what I wanted to say. Umm…I put things…away, umm…and then can't remember where I put them."

9.1.1.4 Prospective memory common failures

PM self-reports were administered for screening and to observe if participants had an actual PM problem. In the PMQ and PRMQ, Participant one reported that quite often if she decided to do something in a few minutes' time, she would then forget to do it. She would also forget things that she had been told a few minutes before.

Participant one reported some of the most common PM deficits: She often found herself repeating the same story to someone on different occasions, but she did not realise until they told her that she had already told the story a few minutes before:

> "…Yeah, Andy will say, "you've told me this already", I'll go, "no I haven't"… "yes, you have."… And he'll go, "but I just told you half an hour ago, I've just told you."…and I say, "Really?"

She also reported that she would quite often forget to buy something that she had planned to buy, even when she saw the shop. She frequently went to do her shopping and found herself inside the grocery shop, because she planned to buy something there, but would then not remember why she was there. Once she got home, she would remember what she wanted to buy and planned to do it the next day, but then the next day, the same thing would happen again:

> "…the other day in the high street I was like… 'I know I wanted to go to Waitrose…what did I want to go to Waitrose for? Hmm…I can't remember,'

> and I get home and then later in the evening I remember and I go, 'Okay tomorrow I'll walk into Winton and go to Waitrose,' get there…can't remember, I still haven't got the stuff (laughs) cause every time I walk into the high street I forget what I want…I've got to write it down so that I remember what I want to get."

She reported that she often failed to recall things that had happened to her in the previous days, but she did not have problems with her LTM. She sometimes got confused about the things she had done, which she did not have recollection of doing.

> "Umm…but yeah, my memory is shot to pieces, but it's not my long term memory really it is…more short term, on an everyday basis."
>
> "umm but events…no…it's more you know, umm…I don't know I mean sometimes I think I'm just getting confused, umm…and my other half will say to me, 'no, no, no, yes you…you did this,' and I'm 'no I didn't… I didn't do that,' he's like 'yes…we did do that.'"

When asked how often she mislaid things, she said that it was quite often, and that very often she would walk into a room and forgot why she went there. She also reported that very often, she would forget to take her medication. She mentioned that to be able to remember an appointment with the doctor, she had to use a reminder, otherwise she would forget it. She would also forget to mention a point during a conversation and would fail to complete a sentence without realising.

> "…and I'll stop and Andy will say…'what you saying? Finish the sentence.' I don't know what I'm saying, I can't remember. A lot of the times I don't realise, I don't realise that I've stopped… talking. Umm…I just stop and carry on doing something different and he'll go, 'what's the rest of the conversation?' 'Oh…umm, oh I can't remember,' but…my memory is shot (laughs)."

9.1.1.5 Words and names: Tip-of-the-tongue phenomenon

Consistent with chemo brain difficulties, Participant one reported having trouble with names, particularly her children's and fiancé's names. She had the tendency to mix their names and call her fiancé by the name of her ex-husband.

> "My children's names, I...get them muddled up and there's nine years between them (inaudible) so they're not even close in age. One is 21 and one, you know 12 nearly, and…can never remember which one is which. Umm…even to the point I'm getting married this year and my other half, I keep going to call him by my children's fathers' name, and…Yeah it's, it's…I think once I have called him it… umm, and the other times I've stopped myself and I've gone "no, that's not right."

At work, she also struggled finding the right words when teaching her students. She worried about this situation because she was a driving instructor, and sometimes she

would know that she had to give the student an instruction, but was unable to remember the instruction or a particular word she needed to use.

9.1.1.6 Attention

Although Participant one reported that she rarely forgot to do her housework, it would often take her several hours because she would find herself doing several things at once, but not finishing any of them. She would start doing a task and would suddenly remember that she had to do something else, so she would stop what she was doing and would start on the second task. While she was doing the second task, she would remember a third one, she would switch, without finishing the second one, and so on. It seemed that she had lost the ability to focus her attention on one thing at a time:

> "…but when I'm doing the house work, I don't seem to be able to concentrate on just doing one thing, let's say the hoovering, start the hovering then finish it then go on to something else. I start and then go, 'Oh! Okay, I'll go and do this,' I get very distracted very quickly. …then about an hour later I go, 'oh! I haven't finished the hoovering,' so I go back… and It'll take me, it took me three and a half hours the other week to do all my house work, and I don't have a big house…I get distracted and do… other bits of housework, not that I go off and watch television or… you know, go and do… I… I just think of other things that I need to do in the house work, or I need to change that bed or I need to do this, and I need to do that. Umm… and then I forgot what I was doing before and then I realised… 'Oh! I didn't actually finish doing that,' and sometimes I've made half a bed, gone off and done something else… and hour and a half later

realised that I didn't actually finish what I had first started… uhh (laughs)… The hoover, I can leave that on… and not noticed that I've left it on, literary it'll still be sucking air and I've gone downstairs and I've come back up half an hour later and go, 'What's that noise? Oh! The hoover is on.' Yeah, that's when I remember I haven't finished hoovering."

Another PM failure that was present in Participant one was that when she was cooking, she would forget things heating on the hob, or she would be unable to remember some of the ingredients of a recipe that she had been cooking for years. Before treatment, she did not have these problems, but subsequently, she could not manage without following the recipe, otherwise she would forget ingredients adding and miss out parts of the recipe. A more serious consequence was that she frequently forgot to switch off the gas after cooking:

"…but something as simple as…umm, Yorkshire pudding, every Sunday I have to get the recipe out to have a look, and every Sunday it's the same recipe! But I can't remember all parts of it, I can remember some of it but not all parts of it, and what order to put everything in, and it's like… really frustrating, uhh…"

"Umm… the one I do the most… is… and it happened the other day, is the stove, and leave the stove on… the hob, and I… it could be when I'm doing rice and stuff so it's down really low but I forget it's on and then I either burn the rice or… the other day umm… my older walked through the kitchen and she went, 'oh god it stinks of gas in here!' and I went, 'why?' and I hadn't switched off the gas, I turned it down so it had gone out… but it hadn't switched off…"

She also commented that when she would be cooking and remembered that she needed an ingredient from the fridge, by the time she approached the fridge, she would completely forget why she had opened it.

Her attention span had also changed since treatment, in that she had found herself reading a book, and it was only near the end of the book that she would remember that she had already read it. The same thing happened with films or TV shows. Every night before going to bed, she struggled to remember the book she was reading. It would take her a few minutes of reading to remember the plot and characters of the book:

> "…most evenings when I go to bed, it takes me a good fifteen, twenty minutes before… I realise what book I'm reading. So like last night when I picked it up I was like, 'I can't remember any of these characters, who are they? And what are they doing? What is this book about?' and then about fifteen twenty minutes later I go, 'Ah okay, now I know what's going on'… I couldn't even tell you the name of the book. I can't even tell you the characters names…"

She also reported that she had trouble following maps and that she needed directions to go to even very familiar places. She had to rely on her Sat Nav to be able to go to the house of her best friend, which was located in another city, even when she had travelled there many times before:

> "…I have to have a Sat Nav tell me… because… I wouldn't be able to just look at a map and remember I have to, even like going to my best mates, she lives in Swindon way, and we go up there quite often but I still have to put the Sat Nav on otherwise I'll not get there and it's one straight road from Salisbury, it's not like having to turn down all different roads and it's all signposted but I still need the Sat Nav on… and when I get there I go, 'I didn't really need the Sat Nav,' but if I tried to do without the Sat Nav I would not get there."

She would usually forget her purse with all her money and credit cards in it; however, she would not realise that she had left the purse until someone else reminded her or found it.

9.1.1.7 Multitasking

The ability of Participant one to multitask was also affected. She was used to handling several things at a time, such as having a conversation on the phone while she was doing some housework or other things. After the treatment, she was unable to pay attention to a phone conversation if she was trying to focus on something else:

> "….I'm not as good at multitasking as I used to be, I can't concentrate… I can't do two things at one time…"

9.1.1.8 Dependency on reminders

As with many of chemo brain patients, Participant one had become dependent on reminders in order to execute her plans. She used her phone to remind her of appointments and had to write notes with to-do lists. Nevertheless, she would usually forget her reminders. For example, she would forget her phone or iPad at home and would not remember where she had left them:

> "…I have to write notes to remind me to do things… even like for today I had to put that in to remind us so this morning my phone came up to remind me…this morning I had to go to the doctor to have my implant in my stomach put in, and that's every four weeks I go for that, and it's the same time every four weeks, same day… I have to program it, so it tells me 15 minutes before I need to be at the doctor's, that I need to be leaving to go to the doctor's."

9.1.1.9 Negative mood, frustration and anxiety

Participant one reported feeling frustrated and bewildered. She showed moderate levels of anxiety, particularly at testing session 4, and she was within the 75% percentile rank in scores of anxiety and depression (Table 9.4). This is consistent with many cancer patients who report being more anxious once they have finished the treatment due to the fact that they are no longer under the care of the medical team. However, EFs were not

significantly affected by this increased anxiety, except for PM and processing speed. Although only a slight increase, it could not be ruled out that this might explain why her PM had been more affected after finishing the treatment.

HADS	Test 1	Test 2	Test 3	Test 4	Overall %rank
Anxiety	7	7	6	9	75
Depression	1	3	2	1	75

Table **Error! No text of specified style in document.**.4. Anxiety and depression scores for Participant one.

9.1.1.10 Positive mood acceptance, humour and resilience

Despite facing an illness such as cancer, Participant one has learned how to cope with her memory difficulties as well as possible. She reported feeling frustrated at times, but she and her family learnt to laugh about her memory changes and did not allow these things to bother her. Her depression scores confirmed this may be true, since they show that there are no signs of concern.

9.1.1.11 Summary of findings for Participant one

The findings for Participant one are summarised in Table 9.5

Parameter	**Comment**
Neuropsychological tests	Overall, neuropsychological tests showed that cognitive abilities were not affected by cancer treatment.
Executive function	Normal
CAMPROMPT	Average, above average
Interviews and self-reports	
PM Failures	Misplacing things, problems with attention and concentration Problems with multitasking Needed to use reminders Forgot appointments, forgot to take medication Forgot to switch things off
Other difficulties associated with chemo brain	Problem with words and names
Anxiety	Mild
Depression	Low
Sleep	Poor

Table 9.5. Summary of findings for Participant one.

9.1.2 Case study two

Participant two showed a positive and interested attitude throughout the testing sessions. She communicated at ease with the researcher, and rapport was easily achieved. Her cognitive tests showed no sign of decline; however, she reported having significant memory difficulties on a daily basis, and these had not improved after more than one year of treatment. She used to be a person who would multitask, but now she thinks she had lost this ability since the beginning of the treatment. She had strong social support and worked full time, despite her illness.

9.1.2.1 Background information

Participant two was a 45-year-old, Caucasian, British woman. She had college level studies and worked full time. She underwent breast cancer surgery and began chemotherapy treatment one month after her second surgery, which was three months after being diagnosed. She also received radiotherapy and hormonal treatment. Her menopausal status was not affected by the treatment, because she had a full hysterectomy two years before being diagnosed with breast cancer.Her Full Scale IQ of 121 (75^{th} percentile rank) was on the NART. The test was administered four times.

The EF abilities of Participant two were in the normal range compared with women in the same age group (Table 9.6). Her ability to learn unfamiliar tasks and process information on the Digit Symbol test showed an improvement during and immediately

after treatment, even though she had reported having trouble learning new tasks and following instructions. Assessment of anxiety, distractibility and sequencing problems on Digits Span measures also showed an improvement in sessions two and three; however, a slight decline was seen six months after treatment. Her visual memory and spatial orientation remained constant during sessions one and two, but a decline was observed in subsequent sessions. This might explain her failures in PM because of a lack of attention to visual cues in the environment that might prompt her to perform an intended action. Her verbal production abilities showed an improvement over time in the COWAT tests scores, but she struggled to retrieve words in her daily life.

Executive Function	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
Digit Symbol	66	81	82	80	75
Digit Span Total	16	18	22	21	80
COWAT	28	39	38	43	50
BENTON Correct	9	9	8	7	50

Table **Error! No text of specified style in document.**.6. Test scores for Participant two.

In the CAMPROMPT test, Participant two showed that her PM was between average and very good range throughout the test sessions when compared with women in her age range (Table 9.7). On her first test, her scores were lower than in the following tests,

performing better in self-monitoring tasks than cue-dependent tasks. Her best performance was precisely in the middle of chemotherapy treatment and immediately after treatment. However, six months later, her performance deteriorated. The fact that she performed better in the second test might have been due to familiarity with the test, but her performance declined in the third and fourth tests; therefore, familiarity could be ruled out. Her performance in event tasks indicated that she had poorer PM for cues that were prompted in the environment than for time-based cues, and that her self-initiating PM was better.

CAMPROMPT	**Test 1**	**Test 2**	**Test 3**	**Test 4**
TIME	18	18	18	18
EVENT	12	18	16	14
TOTAL	30	36	34	32
Classification	A	VG	AA	A

B=Borderline P=Poor A=Average AA=Above Average VG=Very Good

Table **Error! No text of specified style in document.**.7. CAMPROMPT scores for Participant two.

9.1.2.2 Sleep

Sleep self-reports for Participant two showed that her sleep habits were not severely affected, but she presented some degree of sleepiness during day time (Table 9.8).

However, her objective measure of sleep reported that she was sleeping for more than the average number of hours per day, which might explain her feeling of sleepiness (hypersomnia and PM).

Sleep	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
PSQI	6	9	4	6	75
ESS	7	5	5	8	75
Sleep (hours)	33.21	35.24	31.31	34.37	90

Table **Error! No text of specified style in document.**.8. Sleep scores for Participant two.

The anxiety self-report showed that her anxiety levels were in the low range for the first three tests. However, six months after treatment, she showed an increase in anxiety levels (Table 9.9). She did not present significant signs of depression.

HADS	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
Anxiety	3	4	2	7	25
Depression	2	3	1	3	50

Table **Error! No text of specified style in document.**.9. Anxiety and depression scores for Participant two.

9.1.2.3 Online questionnaires and face-to-face interviews

Despite the fact that the PM test results of Participant two showed that her PM was very good and had not been affected by cancer treatment, self-reports and interviews reflected the opposite.

Participant two reported that her memory difficulties became obvious during chemotherapy, and that she struggled at work as she could not always remember what she had done the previous day, or follow procedures that she was familiar with before treatment. She started noticing a difference in her memory after the second treatment when she found it difficult to do some of her work as easily as before. She reported that more than a year later, she still found it hard to remember appointments, so she had to rely heavily on reminders, such as her diary and to-do-lists.

Participant two reported that she did not have memory problems before treatment, and that she could remember processes at work, appointments and people more easily. She used to have a better recall of words, especially more descriptive and difficult words. For these reasons, her work had been negatively impacted, but she had learned how to

cope. On the other hand, in her social life, she sometimes felt embarrassed with her friends, when she asked questions about things that she has been told before.

These memory changes made her feel frustrated, because she enjoyed using complicated language, but now she needed to use simple words and struggled to find the right words to describe things. However, she had learned to cope by using aids and by adjusting to the situation.

9.1.2.4 Attention

Participant two's attention had suffered since she started treatment. Her attention before treatment was fine and she was able to focus on her job and duties quite well. Since treatment, she started to lose attention to things at work and found herself misplacing things in different drawers and files. She also struggled following instructions or procedures she was previously familiar with:

> "I usually misplace files at work. I put them in a different drawer, or the same drawer but in a different file. I also struggle following procedures and instructions, but I try to keep things simple. For example, filling a form can become difficult, so I try to fill forms always in the same way."

She also reported that her attention at work had been affected and that she often repeated actions, such as sending the same email twice. However, she had learnt to cope

with this situation by keeping a reminder or records of the activities she had already performed:

> "At work I have to be very careful with my emails and make notes that I have sent the email, so I do not send it twice…"

When asked about finding herself repeating the same story to the same person on different occasions, she responded that she sometimes had been in that situation and felt embarrassed with her friends or colleagues, and that she sometimes forgot something she was told just a few minutes before:

> "I usually have to ask people if I have told a story before, because I cannot remember if I have told them, or if in a group of people I have said that story before"
>
> "When I drive to a new place, before treatment I just had to refer to a map once, but now I need to constantly look at like, sort of like, one step at a time, and not the complete sequence."

Her attention had also been affected at home, and she got easily distracted, especially after arriving home from shopping:

> "I very often leave the iron on, and when my groceries arrive home, it's a problem because I start unpacking and leave the groceries for a minute to go to another room, I get distracted and begin doing another thing, and then I stop doing that, to begin another thing, and I completely forget about the groceries, until I come back to the kitchen later. The problem is with the frozen food that needs to be kept in the freezer."
>
> "I force myself to keep my attention on one thing until I finish it."

She also complained about having trouble with her concentration, especially when she tried to read a book or a magazine, and could not focus for long periods of time:

> "My concentration is not as good. When I read, I just can read like little chunks, and then I have to move to another thing, but I do not find myself reading and reading the same page several times."

Other abilities that showed poor PM were that she had problems remembering new places that she had visited (with her boyfriend having to remind her that they had already been in some place that she did not remember). When driving to a new place, she needed to constantly refer to a map, going one step at a time rather than in a complete sequence:

> "Now I forgot about places and events I have attended, such as concerts, and I only know I have been there because my boyfriend tells me we went, but I am completely blank about it."

9.1.2.5 Multitasking

Participant two also reported that her attention at work had been affected, and that she had lost her ability to multitask. Before treatment, she used to be able to handle several work-related activities at once, but now she could only cope with one or two tasks at the same time:

> "Also, I was able to do several things at a time, like checking emails, answering the phone, and filing stuff, but now I can only manage one or two things at a time."

9.1.2.6 Dependency on reminders

Participant two reported that she had to rely heavily on reminders, otherwise it would be impossible to remember plans, and that she very often forgot appointments if they were not prompted by a reminder. She had opted for writing things on her hand to remind her not to forget her notes or diary, but she would forget to look at her hand. She would also miss appointments with her doctor:

> "I always have to keep a diary and write up everything I have panned ahead. It has become impossible to remember what I have to do next week, or even tomorrow, or in a few hours without looking at my diary."

> "The other day someone called me to ask if I have noticed that I had forgotten my appointment, and I said, no, because even at that moment I couldn't remember."

She reported that she sometimes forgot to buy something that she had planned to before going to the shops, unless she had written it down, but then she would forget to look at the reminder:

> "When I go shopping I must write everything down on a list or in my hand to remember what I need to buy, but the trouble is that I forget to look at my hand, so I come back home without what I was supposed to buy."

> "I think it would be impossible for me to remember to do things if I do not keep a dairy or use reminders."

Overall, neuropsychological tests showed that her cognitive abilities were not affected and that depression and anxiety as well as reported sleep and objective sleep measures were not abnormal. However, the qualitative analysis showed that her PM and other cognitive abilities associated with PM, such as attention and concentration, and her ability to multitask had been affected by the treatment.

9.1.2.7 Words and names: Tip-of-the-tongue phenomenon

One of the things that made Participant two feel more frustrated was that she struggled to find the right word to say when constructing a sentence. She explained that she had been used to using complicated words, but after treatment, she could not even remember simple things. She felt like she had the word in the back of her mind, but she simply could not retrieve it, so she ended up describing what she was trying to say. She also had problems with names and she kept mixing up the names of people she had known for a long time, particularly at work:

> "I was very good with words, and like to use complicated words, but now I need to use simple words. I feel frustrated, but I am learning to get used to it. The feeling is that I know that I know the word, but I simply cannot recall it. I mix names of people, and I do realise that I have done it."

9.1.2.8 Positive mood acceptance, humour and resilience

Participant two reported coping with these troubles perfectly well and although it was frustrating, she had learnt to adjust to the situation by using calendars, reminders and by being very open about her forgetfulness with her friends and colleagues. However, she also reported that she felt as if she was "less" than she was before.

9.1.2.9 Summary of findings for Participant two

The findings for Participant two are summarised in Table 9.10.

Parameter	**Comment**
Neuropsychological tests	
Executive function	Normal
CAMPROMPT	Average, above average
Interviews and self-reports	
PM Failures	Misplaced things Problems with attention and concentration Problems with multitasking Needed to use reminders Forgot important appointments Forgot to switch things off
Other difficulties associated with chemo brain	Problem with words and names
Anxiety	Mild
Depression	Low
Sleep	Good

Table.10. Summary of findings for Participant two.

9.1.3 Case study three

Participant three was agreeable, interested and compliant throughout the testing sessions. She communicated at ease with the researcher, and rapport was easily achieved. She reported having memory difficulties as a consequence of chemotherapy, but more than one year after treatment, her memory had improved. Participant three was in the middle range of the spectrum of chemo brain and PM for this study, meaning that her memory was not badly affected and she had slowly recovered her cognitive abilities. This particular case was interesting because although she presented very common attention and PM failures, she had the tendency to attribute them to other factors such as age, lack of confidence or miscommunication.

9.1.3.1 Background information

Participant three was a 49-year-old, Caucasian, British woman. She worked full time before treatment and received strong family support. She completed her college education in the UK and worked part time during treatment. She lived with her family and received strong social support.

She underwent breast cancer surgery and began treatment one month after being diagnosed. She also received radiotherapy and hormonal treatment. Before treatment, she was pre-menopausal, but chemotherapy induced her menopause. Her Full Scale IQ

of 121 (75^{th} percentile rank) was on the NART when compared with other women in the sample. The test was administered four times.

In EF abilities, Participant three was in the normal range compared to women in her same age group, meaning that her cognitive performance had not been affected by treatment (Table 9.11). However, a decline was observed during session four for attention span, distractibility on the Digits Span test and on the Digit Symbol test, through which intellectual abilities are assessed. Improvement from baseline in subsequent sessions might have been due to practice effects.

Executive Function	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
Digit Symbol	58	66	82	68	50
Digit Span Total	14	19	22	18	50
COWAT	29	26	38	34	25
BENTON Correct	9	9	4	9	50

Table **Error! No text of specified style in document.**.11. Test scores for Participant three.

In the CAMPROMPT test, Participant three performed better in the first test than the following two tests and improved again in the last test (Table 9.12). This suggested that her PM remained in a very good condition, although a slight decline was present during

treatment, particularly in event-based tasks. Overall, she showed better performance on self-initiating monitoring than on cue-dependent monitoring.

CAMPROMPT	Test 1	Test 2	Test 3	Test 4
TIME	18	18	18	18
EVENT	18	16	16	18
TOTAL	36	34	34	36
Classification	VG	AA	AA	VG

B=Borderline P=Poor A=Average AA=Above Average VG=Very Good

Table **Error! No text of specified style in document.**.12. CAMPROMPT scores for Participant three.

9.1.3.2 Sleep

Sleep self-reports for Participant three showed that her sleep time during treatment was better than both before and after treatment (Table 9.13). In spite of this, objective measures showed that she was oversleeping and that she felt sleepy during the day. Her sleep self-reports showed that she felt her sleep quality was poor and she slept for slightly more hours than the average sleeping hours.

Sleep	Test 1	Test 2	Test 3	Test 4	Overall %rank

PSQI	12	7	4	10	75
ESS	6	6	5	5	50
Sleep (hours)	38.58	32.13	34.00	32.48	90

Table **Error! No text of specified style in document.**.4. Sleep scores for participant three.

9.1.3.3 Online questionnaires and face-to-face interviews

Although Participant three obtained very good PM scores on the CAMPROMPT, she reported that her memory was affected by treatment on a daily basis. In the online questionnaires, she said that she was unable to concentrate for a long time, so she could not register things and therefore, could not remember them later. She reported that her memory before treatment was usually good and that she could not recall exactly when her memory problems began after starting treatment:

> "I think my memory is better now than what it was during treatment. But probably not as good as it was before treatment."

9.1.3.4 Dependency on reminders

Participant three became very dependent on reminders, so that she could remember what she had planned to do. She set reminders on her phone and carried a calendar, but she would often forget them at home:

> "Yeah, I always remember those, but I do use…. I'm quite heavily reliant on my phone to remind me... I... I put all my appointments on my phone and I have a calendar as well, so I do use that. I have to write lists now for shopping… but I forget my phone all the time, my girls are telling me off all the time I have forgotten my phone… but generally I do remember things umm… but as I say it's unimportant things that I don't tend to remember."

9.1.3.5 Attention

Before treatment, Participant three was attending a college course and she reported that she was able to study for several hours; however, during treatment, she lost that ability and could not concentrate, so she could not remember the content of the lectures or her reading, and her studies were affected. By the end of this study, she had not returned to college, so she did not know if she had regained her ability to concentrate:

> "I could sit and study for two hours before…but during treatment there was no way I could have done it."
>
> "…and I couldn't remember what I had learnt… and to sit and study for two hours just…I just couldn't do it…"

When driving to a new place, she needed to refer constantly to maps, but she thought that it was more of a confidence problem rather than attention or memory:

> "...I think that's a confidence thing... umm… I… I could always pick up a map, see where I was, see where I needed to go, and work out the way. Whereas now, more or less at every junction I look… to make sure I'm going to right way."

She reported that sometimes she forgot to do something that she was going to do a few minutes later, and that she quite often forgot to buy things that she had planned to even when she saw the shop. She also reported that she would sometimes find herself repeating the same story to someone on different occasions and that she mislaid things and forgot to pass on messages.

She often forgot something she had been told a few times before, but she attributed it to a communication failure rather than to memory problems, and that this probably happened to her once or twice a week:

> "...and then they say to me, 'oh you promised to take me here!' and I was like, 'I don't remember telling you that?'"
>
> "…somebody might have said…'I'm going to Poole tomorrow,' and then the next day I would say to them, 'what did you do today?' 'Well I told you I was going to Poole', you know I'd forget things like that but they weren't really important to me."

Her lack of attention and a tendency to lose concentration was usually related to TV shows or unimportant things. She had trouble following the sequence of a programme, but she explained that her lack of attention was intentional, and that her failures were due to her lack of interest in unimportant details:

> "…television programs for example… I tend to get bored very quickly… and if there is, say a thriller or something like that, I'm not interested in, I just want to know who's done it, I'm not interested in all… in all the bits in between… I tend to lose concentration and… very often I have to say to one of my daughters, 'what happened there? I missed that, what happened there?'"
>
> "It's usually when I'm not interested (laughs)… I think it's rude actually... I know, I know I do it, but I can't help myself… My husband... my ex-husband often used to say to me, 'you've gone blank again, I've lost you'… but that's because I wasn't interested in what he was talking about."

Despite the fact that her work had not been affected, she admitted that on occasions, she had forgotten to do something, but it did not cause much of a problem at work, and her omissions were related to unimportant issues:

> "...I don't think I ever forgot anything that was major that would have caused a problem at work... umm… I did forget a few things that actually didn't matter if they were done or not, but my boss thought they were important but actually at

the end of the day, you know, in the big scheme of things it didn't matter at all. So I think subconsciously I was filtering out…. to try and prioritise and to try and fit everything in."

9.1.3.6 Words and names: Tip-of-the-tongue phenomenon

Participant three also reported having trouble with words and names and that she felt frustrated because she was supposed to know the word. She mentioned she usually coped well with this, because she would quickly find another word:

"…sometimes I do, even now have trouble thinking of the right word…I consider that I've got quite a good vocabulary.… but sometimes , I'm having a conversation and a word just won't come to me. Even now, normally names. I could usually look at somebody and remember their names straight away, but not now…and this happens very often."

9.1.3.7 Positive mood acceptance, humour and resilience

Participant three had coped well with her memory difficulties and had tried to keep up good spirits throughout. However, even if she did have PM deficits, she did not acknowledge those deficits as important or significant in her life. She preferred to focus her attention on more important things in life rather than to worry about minor problems.

9.1.3.8 Negative mood, frustration and anxiety

Participant three experienced a moderate level of anxiety, particularly before and after treatment. She suffered from a very mild depression, which increased six months after treatment (Table 9.14). She reported a feeling of frustration when she could not find the correct word, but it did not affect her daily life, and she believed that her problems with following maps or driving to new places were due to a lack of confidence and a fear of getting lost.

HADS	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
Anxiety	9	6	2	7	60
Depression	2	2	1	5	75

Table **Error! No text of specified style in document.**.14. Anxiety and depression scores for Participant three.

9.1.3.9 Summary of findings for Participant three

A summary of findings for Participant three are presented in Table 9.15.

Parameter	Comment
Neuropsychological tests	Overall, test scores showed no sign of impairment, and her self-reports were also normal. However, according to her reports, she might be attributing PM failures to factors other than memory, but that would not mean that she had a PM problem. Her reports were consistent with those of PM failures.
Executive function	Normal
CAMPROMPT	Average, above average
Interviews and self-reports	
PM Failures	Misplaced things, problems with attention and concentration. Needed to use reminders Forgot appointments, forgot to take medication, forgot to switch things off
Other difficulties associated with chemo brain	Problem with words and names
Anxiety	Mild
Depression	Low
Sleep	Good

Table 9.15. Summary of findings for Participant three.

9.1.4 Case study four

Participant four was agreeable, interested and compliant throughout the testing sessions. She communicated at ease with the researcher, and rapport was easily achieved. This participant suffered from mild PM impairment during chemotherapy treatment, but her memory had improved over time. Although her test results showed no significant impairment, her daily life was somewhat affected, and she clearly showed mild PM failure. Her social, family and work life had not been affected. She received strong family support throughout her treatment.

9.1.4.1 Background information

Participant four was a 52-year-old, Caucasian, British woman. She completed her secondary education in the UK and worked part time. She underwent breast cancer surgery and began chemotherapy treatment one week after being diagnosed. She also received radiotherapy and hormonal treatment. Her Full Scale IQ of 108 (25^{th} percentile rank) was on the NART. Her overall performance was classified within the normal range and was equal to or higher than 25% of women in this sample. The test was administered four times.

Measures of EF abilities for Participant four were in the normal range compared with other women in this sample (Table 9.16). Processing speed and intellectual abilities

obtained from Digit Symbol were unaffected by treatment. An improvement was observed after baseline, and no decline was observed in any of the tests after six months. For attention span, fairly consistent results were observed during sessions one, two and three, but a slight decline was observed immediately after treatment. Her word naming abilities showed a consistent improvement in sessions one, three and four, but in daily life situations, she reported having trouble retrieving words. A slight decline was observed in session two. Visual memory scores showed a very slight decline during sessions two and three, but improved in session four.

Executive Function	**Test 1**	**Test two**	**Test 3**	**Test 4**	**Overall %rank**
Digit Symbol	70	78	72	82	50
Digit Span Total	17	18	11	17	50
COWAT	37	35	38	39	40
BENTON Correct	8	7	7	8	30

Table **Error! No text of specified style in document.**.16. Test scores for Participant four.

PM test scores showed that Participant four performed better in the first test than in the second (during treatment), but improved in the subsequent tests, particularly six months after treatment (Table 9.17). This suggests that the practice effect did not take place and that chemotherapy treatment might have been affecting her PM. A significant decline was observed for event-based task scores in sessions one and two, and time-based

scores declined from session two to session three. The observed improvement over time might have been due to practice effects, but since the fourth test took place six months later, there was only a very small chance that practice effects were playing a role, and it was more likely that her memory improved once she had finished treatment.

CAMPROMPT	**Test 1**	**Test 2**	**Test 3**	**Test 4**
TIME	11	16	13	16
EVENT	18	8	18	16
TOTAL	29	24	31	32
Classification	A	P	A	AA

B=Borderline P=Poor A=Average AA=Above Average VG=Very Good

Table **Error! No text of specified style in document.**.17. CAMPROMPT scores for Participant four.

9.1.4.2 Sleep

Sleep self-reports indicated that her sleep time was normal, but she felt sleepy during the day, particularly during sessions two and four (Table 9.18). Despite the fact that her sleep time increased over time, her self-reports showed worse perceived sleep efficiency.

Sleep	Test 1	Test 2	Test 3	Test 4	Overall %rank
PSQI	6	7	8	9	75
ESS	5	10	6	12	75
Sleep (hours)	28.31	25.20	31.30	31.28	75

Table **Error! No text of specified style in document.**.18. Sleep scores for Participant four.

9.1.4.3 Online questionnaires and face-to-face interviews

In the online questionnaires, Participant four reported that her memory problems began while she was undergoing chemotherapy treatment. She reported problems remembering words and making sentences, keeping up with conversations and remembering the names of the people she had known for years. Her memory difficulties were evident to her family, but her memory improved after finishing the treatment. She reported that she had not been able to go back to her normal job due to problems with her shoulder and not as a consequence of her memory decline. The memory difficulties made her feel frustrated and angry.

She reported that she very often forgot to do something a few minutes after she had decided to do it. She also reported that she would forget something that she had been told just a few minutes before. She also misplaced things, forgot appointments, forgot to pass on messages and to buy items while shopping. She occasionally forgot to take her medicine and why she had gone in to a particular room:

> "Sometimes I struggle to remember what I was doing half an hour ago…(laughs)…"

9.1.4.4 Dependency on reminders

Participant four reported that she had become reliant on reminders to help her remember her plans. She needed to carry a diary to remind her of appointments and to-do lists. She would refer to the diary first thing in the morning. This was a new habit for her, because before treatment, she did not need reminders. She also used her phone to set reminders:

> "Now I carry a little diary down with me to not forget things such as appointments and things to do and, I never used to do that… I would probably forget. It is not about the things this week, but things about two or three weeks' time, I wouldn't remember the day or the time…"

9.1.4.5 Words and names: Tip-of-the-tongue phenomenon

As with many chemo brain patients, she also struggled with names and words. This caused her difficulties in a conversation when trying to construct a sentence; it would take a lot of time to find the words for what she wanted to say:

> "…I couldn't remember the word for windshield, or windbreaker and I was telling something about down the beach, and I said, you know those things that you put in the sand and stop the wind, and he said, a wind breaker, and I went oh yeah! But it took me ages to describe it, so he knew what I was talking about…"

She also mentioned how sometimes she could not follow conversations, especially when she was in a group of people:

> "…but I still struggle with conversations, I suppose if there is lots of people talking, I tend just to drift off sometimes, because I can't follow it…"

She also described frustration with spelling. She said she used to be a very good speller, but after treatment, her spelling had become very bad, even with simple, common English words:

> "For example if I want to spell WHERE, you know, I want to write WERE and I spell WEAR and I look at it and think, oh no, that's the wrong one…and even then, I say, that doesn't look right, what have I done wrong?"

This made her feel frustrated because she knew that she was familiar with the word, but she could not remember it. She also experienced the same feeling with the names of the people she knew. She was often unable to associate the name of a person whose face she recognised:

> "…It is just frustrating because it is on the back of your head, and you want to say it, but you just can't remember it or can't find the right word to say it. With names of people, I am useless, absolutely usless…I really, really struggle, especially if they are unusual names, I do struggle, there are loads of people at work, I couldn't tell you their names, and it still happens…I can't associate the name with someone…"

9.1.4.6 Attention

When referring to attention, she said it had improved with time, but had been affected by treatment. She was unable to concentrate on anything, and reading was hard work. During treatment, she would sit just staring out of the window for hours just watching what was going on. She found noise irritating, and she could not concentrate on the

television. She reported her brain "feeling fuzzy" and could not concentrate on anything:

> "Trying to read a book is hard work…my son gave me some of his books to read, oh, I ended reading the same page three or four times because couldn't take in what they were saying. I am reading, and I am thinking I haven't got that, so I have to start back at the thing again, and I think oh, I've read this page three times, why hasn't sank it?"
>
> "…your brain feels very fuzzy…that is the only way to describe it, your brain…my husband was trying to explain something, and I just said, don't bother, I just cannot concentrate, and can't take what you are saying…"

She also explained how she struggled following instructions, such as how to use her new phone, and had to wait several months until she felt able to go back again to try and understand:

> "You struggle reading instructions, you would really struggle…I got a new phone in December and I just couldn't work it. I couldn't read the instructions and follow what they were saying to do on the phone, so I just put the phone away for a couple of months, and my son came down and set it all up for me."

She reported that during treatment, she had visited places, but that she did not have any recollection of ever being at those places. She only knew she had been there because her husband confirmed that they had visited the place together.

> "When someone is describing things that happened either last year or maybe the year before, while I was going through the treatment, we've been somewhere, or done something, and he would be explaining it to me…I have just complete blanks, that is the only way to describe it, you know as you've been describing stuff and I say I honestly could say I wasn't there, but you are telling me I was, my husband a couple of times, he sort of describes stuff and I say I really can't remember that, but he is the only one I told him that."

She mentioned that she used to forget appointments, not realising until she received a call from the hospital to remind her. She also found herself repeating the same story to someone several times:

> "…and he'd say you've already told me about, and I say, 'have I?' and couldn't remember that I've already told you. That happens quite a lot recently…sometimes I say have I told you? And he says yes! And I say Ok, or if he says no, I say Ok I'll tell you now…(laughs)…"

She often forgot to eat meals or why she had entered a room. She reported that when she was doing her housework, she got very easily distracted, changing from one chore to another without finishing any of them:

"(laughs)…Before treatment I use to do it occasionally, but I suppose I tend to do it a lot more now…and I say what the hell I am doing here, I can't remember but I go back and do something else. …I flip a lot, I can be in the middle of hovering, and then something distracts me, I don't know, say my telly is dusty, so I go and get a duster, I do that, and then I go do something else, and the hover is still in the middle of the floor because I've forgotten I was in the middle…(laughs)…that is quite common…"

When she cooked, she always realised that she had forgotten to put one of the main ingredients in the dish, as she found it later in the fridge or cupboard:

"(laughs)…I quite often forgot using an ingredient…(laughs)…say I am doing a new recipe or something, I read it and I put all of the ingredients there, but may be one is left in the fridge and I…(laughs)…and then when we get to eat the dinner…(laughs)…the ingredient is still in the fridge. It's quiet often…it has happened before treatment, but not as often…I am well known for doing that."

9.1.4.7 Positive mood acceptance, humour and resilience

Participant four reported coping well, but she needed to take more time to figure out what she was going to say and even if she felt frustrated and angry at times, she faced her failures with humour and laughed about the situation.

9.1.4.8 Negative mood, frustration and anxiety

Participant four initially reported mild levels of anxiety, but by the time her treatment ended, she showed higher levels of anxiety (Table 9.19). Her depression levels were mild throughout the sessions.

HADS	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
Anxiety	5	4	8	5	50
Depression	0	5	3	5	60

Table **Error! No text of specified style in document.**.19. Anxiety and depression scores for Participant four.

Overall, Participant four showed no signs of serious memory impairment, but she did report very common PM decline during her treatment. Her memory improved over time, but a very mild impairment was still present at the end of this study.

9.1.4.9 Summary of findings for Participant four

A summary of findings for Participant four are presented in Table 9.20.

Neuropsychological tests	
Executive functions	Normal

CAMPROMPT	Average, above average
Interviews and self-reports	
PM Failures	Misplaced things Problems with attention and concentration She did not mention problems with multitasking Needed to use reminders Forgot appointments Difficulty following instructions
Other difficulties associated with chemo brain	Problem with words and names
Anxiety	Mild
Depression	Mild
Sleep	Good

Table 9.20. Summary of findings for Participant four.

9.1.5 Case study five

Participant five was agreeable, interested and compliant throughout the testing sessions. She communicated at ease with the researcher, and rapport was easily achieved. This participant reported not having noticed significant memory changes as a consequence of

cancer treatment. She reported that her memory had always been poor. However, her social and work life was severely affected by a lack of concentration and fuzziness. This was because she could not concentrate well while driving, which created social and work limitations. She received strong family and social support and continued working although her inability to drive and lack of concentration had limited her working hours.

9.1.5.1 Background information

Participant five was a 54-year-old, Caucasian, British woman. She underwent breast cancer surgery and began chemotherapy treatment a week after being diagnosed. She also received radiotherapy and hormonal treatment. She was married and completed her postgraduate studies in the UK and worked part time. She experienced chemotherapy-induced menopause. Her Full Scale IQ of 117 (50^{th} percentile rank) was on the NART. Her overall performance was classified as being within the normal range and was equal to or higher than 50% of women in her age group. The test was administered four times.

The EF abilities of Participant five were in the normal range compared with the other women in this sample (Table 9.21). Her ability to learn new things and processing speed showed a decline from baseline to session two, but improved in the last two sessions. She improved on measures of attention span and distractibility from sessions one to two, declining in session three and improving again in session four. On word-producing abilities, she showed a decline in the second session, but improved over time. Her scores on visual abilities were excellent, which might have been because she was a graphic artist. Her visuo-spatial abilities were highly developed, but in situations such as

driving, she felt disoriented and could not cope well with driving since beginning the treatment.

Executive Function	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
Digit Symbol	70	66	69	76	50
Digit Span Total	22	29	24	30	95
COWAT	47	41	51	56	75
BENTON Correct	10	10	10	10	90

Table **Error! No text of specified style in document.**.21. Test scores for Participant five.

In the CAMPROMPT test, Participant five showed that her PM was average in the first two sessions and improved to above average in her last two tests (Table 9.22). Her self-monitoring abilities were poorer at baseline, before experiencing chemotherapy treatment, but significantly improved in the following sessions. These results might be due to familiarity of the tests, but an alternative explanation can be that poor sleep and anxiety at baseline might be interfering with her performance. However, for the second testing session, during mid-treatment, her cue-dependent performance was more affected, and self-initiating monitoring was improved. This can be explained as a more conscious effort of monitoring her time-checking behaviour. Her third and fourth tests scores showed that her performance on self-initiating monitoring remained unaffected,

and that she had poorer cue-dependent PM. Overall, her time-based scores showed a slightly better performance than event-based scores. Her overall PM was very good.

CAMPROMPT	**Test 1**	**Test 2**	**Test 3**	**Test 4**
TIME	12	18	18	18
EVENT	14	12	16	16
TOTAL	26	30	34	34
Classification	A	A	AA	AA

B=Borderline P=Poor A=Average AA=Above Average VG=Very Good

Table **Error! No text of specified style in document.**.22. CAMPROMPT scores for Participant five.

Sleep self-reports for Participant five indicated that she slept well at night, but she felt very sleepy during the day (Table 9.23). Objective measures indicated that she had a tendency to sleep less than the average number of hours, particularly at baseline, which could be associated with her feeling of fuzziness during the day and poorer PM scores.

Sleep	**Test 1**	**Test two**	**Test 3**	**Test 4**	**Overall %rank**
PSQI	6	4	4	4	25

ESS	13	10	13	17	95
Sleep (hours)	21.32	27.27	20.40	26.48	10

Table **Error! No text of specified style in document.**.23. Sleep scores for Participant five.

The levels of anxiety of Participant five were higher before treatment and six months after treatment (Table 9.24). During the course of treatment and immediately after treatment, she experienced mild levels of anxiety. She did not experience abnormal levels of depression, but reported that she was unable to cope with stressful situations or stories.

HADS	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Overall %rank**
Anxiety	12	7	6	10	80
Depression	2	2	6	3	75

Table **Error! No text of specified style in document.**.24. Anxiety and depression scores for Participant five.

9.1.5.2 Online questionnaires and face-to-face interviews

In the online questionnaires, Participant five reported that her memory had always been a bit of a problem, but what she had noticed more than anything else was fuzziness and lack of concentration. Since her memory had always been poor, she was used to relying on reminders and copying strategies all the time. Therefore, she could not tell whether memory problems were a consequence of her cancer treatment:

> "…I do feel like I've got a kind of gap in my memories. From about…probably when… it all started off whether it was the treatment or whether it was before that was just the shock of it. There is a gap somewhere there…which lasted for quite some time. There are things that people mention and I think I didn't know about that... and there's a lot of things that I've sort of…that seem to have dropped out. But…I also found my memory, my concentration… has been awful. Now…I'm not saying I was brilliant to start with, but my concentration has been so bad that I've really, really struggled, umm…to get my life back together."

9.1.5.3 Attention

Participant five reported that when she decided to do something, she very often forgot to do it minutes later; she failed to recognise places she had been to before; she forgot things she had just been told; she forgot appointments; she forgot what she had planned to buy at the shop, even when she saw it; and she could not remember things that had happened to her in the previous few days.

She also said that she misplaced things, failed to pass on messages and that very often went into a room and would forget why she was there. She also reported that on occasions, she accidentally repeated tasks by mistake.

She acknowledged that her lack of concentration had affected her driving capabilities, which affected her ability to work. She could not drive for more than 10 minutes without feeling confused and anxious. Therefore, she had to reject jobs outside her close surroundings. This had also affected her social life, and she found it very restricting:

> "…it's like when you were trying to do something when you're asleep if you see what I mean…and… my driving, now my driving was never…my best thing, I mean…I realised that…I should never drive for too long because it takes a lot of concentration…"

> "…I couldn't cope with the focusing, so basically I was trying to restrict my driving to... night time and ten minutes"

She also reported that very often she found herself repeating a story to the same person on different occasions:

> "Probably not the same day, I mean you know it's…So I see…Mike one week and I see him another week and I tell him the same story and he very politely doesn't say anything … but I would say I would've done that anyway…"

Despite having been a good reader, she started to prefer books for children, since she was not able to follow a more complex story. She also reported problems following a conversation:

> "Well… I started to get back on the adult books which was a great relief cause I've been reading children's books all this time…I need something that would grab me quickly…I've found I couldn't cope with reading a book that could distress me because… I will find it…hard to follow… If somebody is talking and I'm not joining in. At some extent I would've been like that anyway, but at the moment I've gotten worse. Yeah… umm…yeah."

> "I was more able to cope with… all that sort of thing. So where that… I mean it's not memory but it's something. Concentration maybe? Because I know that I would not have that concentration that I need to do it for very long."

9.1.5.4 Words and names: Tip-of-the-tongue phenomenon

Participant five also reported that she had trouble with names and words. She mixed up the names of family members, often forgetting the names of her brothers. She struggled with common words (such as marmite) and although she knew the word she wanted to use, she could not bring it to her mind to complete a sentence:

> "…I mean I've got a weird thing with names at the moment… I find myself mixing up the names of people I know very well, which could get me in quite a

lot of trouble you know. To call my daughter by the name of my sister, You know it's... it is… really not a good thing to do… umm… to call my friends by each other names… that's not a good thing to do."

"…this is just in the last couple of years…it's words that I should know. They're not difficult and I would be having a conversation and… that word is not there, it's an easy word if you see what I mean, and it might come back to me eventually but it might take while some time (laughs). Well you got to say it… and (sigh)…(sigh)…it's just going to come out and it just… doesn't so… I know that I know the word. That's it."

9.1.5.5 Dependency on reminders

Participant five stated that she had always been very dependent on reminders to remember the things she planned to do.

"I am very dependent on reminders…such as phones and a calendar that gives me reminders, which is on the computer now. I have…an alarm that would go off and just to say… 'Have you had your walk?' and sometimes it would go off with things like 'You need to be leaving here in an hour,' and it's always done that."

Her social life had been affected because she could not go to places, and she was anxious about not being able to concentrate and follow a conversation:

"…being able to talk to people and actually feel that I don't know how my conversations came across to you before whether you noticed any difference. It's about being able to feel and make sense in a conversation. …umm…I've been a bit more inclined to say yes, a bit more inclined to go somewhere slightly new, a bit less afraid that it's all going to fall apart, and that isn't a confidence thing that is about… the concentration and the stress and all the sort of thing."

"I don't cope with stress, I know people don't cope with stress, but I have found that that's been a big problem for me. Umm…so… stress, anxiety and concentration are first things have tired me very, very quickly."

9.1.5.6 Summary of findings for Participant five

A summary of the findings for Participant five is presented in Table 9.25.

Parameter	**Comment**
Neuropsychological tests	
Executive functions	Normal
CAMPROMPT	Average, above average
Interviews and self-reports	
PM Failures	Misplaced things Problems with attention and concentration

	No evident problems with multitasking Needed to use reminders Forgot appointments Forgot to take medication
Other difficulties associated with chemo brain	Problem with words and names
Anxiety	Mild
Depression	Low
Sleep	Poor

Table 9. 25. Summary of findings for Participant five.

9.1.6 Case study six

Participant six was agreeable, interested and compliant throughout the testing sessions. She communicated at ease with the researcher, and rapport was easily achieved. At her first testing session, she showed very high levels of anxiety, whereas in the following sessions, she was calmer. This participant was at the low end of the chemo brain and PM memory decline spectrum, meaning that she did not report significant memory changes after cancer treatment. She reported that her memory difficulties had disappeared at the time of the interview, and that she was more able to cope with her family and work life than during and immediately after treatment. Due to a lack of time, this participant only underwent three testing sessions, i.e. baseline, mid-treatment and

two months after treatment. However, she was able to complete the online questionnaires and face-to-face interviews 14 months after treatment.

9.1.6.1 Background information

Participant six was a 58-year-old, Caucasian, British woman. She was married and completed a bachelor's degree in the UK and worked full time. She underwent breast cancer surgery one month after being diagnosed. She began chemotherapy treatment one month after surgery. She also received radiotherapy and hormonal treatments. She was postmenopausal at the beginning of her treatment. Her Full Scale IQ of 113 (40^{th} percentile rank) was on the NART.

The EF abilities for Participant six were within the normal range compared with other women in the sample (Table 9.26). Her processing speed abilities on the Digit Symbol tests improved slightly in the second test session, but declined on session three. On the other hand, her attention span and word-retrieving abilities were better at baseline and significantly declined in the middle of her treatment.

Executive Function	**Test 1**	**Test 2**	**Test 3**	**Overall %rank**
Digit Symbol	49	50	42	10
Digit Span Total	21	18	18	50

COWAT	41	28	35	25
BENTON Correct	8	8	7	50

Table **Error! No text of specified style in document.**.26. Test scores for Participant six.

The PM of Participant six ranged from average to above average (Table 9.27). She performed worst at baseline in time-based tasks and showed an improvement in her last two tests. This might have been due to practice effects or because her anxiety levels were higher before commencing treatment, affecting her ability to self-initiate when completing an action.

She expressed her nervousness before her first chemotherapy treatment. Her performance on time-based tasks was poorer than event-based tasks in session one, meaning that she was more reliant on cues in the environment than self-reminders. However, in the following sessions, her scores showed a balanced improvement and remained constant in the last test session.

CAMPROMPT	**Test 1**	**Test 2**	**Test 3**
TIME	9	18	18
EVENT	16	16	16
TOTAL	25	34	34

Classification	A	AA	AA

B=Borderline P=Poor A=Average AA=Above Average VG=Very Good

Table **Error! No text of specified style in document.**.27. CAMPROMPT scores for Participant six.

Sleep self-reports for Participant six showed that her self-perceived sleep was not affected significantly by the treatment, and that she slept for the average number of hours a day (Table 9.28). She did not report feeling sleepy during the day.

Sleep	**Test 1**	**Test 2**	**Test 3**	**Overall %rank**
PSQI	2	6	6	50
ESS	0	2	2	10
Sleep (hours)	27.32	28.06	28.10	50

Table **Error! No text of specified style in document.**.28. Sleep scores for Participant six.

9.1.6.2 Online questionnaires and face-to-face interviews

At the time of screening for PM failure, Participant six reported that she sometimes forgot to do something that she had decided to do a few minutes before. She also reported that she often failed to do things such as taking tablets or turn off the kettle

even when they were in front of her. She also reported that she quite often forgot her appointments if she was not prompted by a reminder. She sometimes forgot to pass on messages or would find herself in a room, but not remember why she was there. She also misplaced things. However, she reported not having extreme progression of memory difficulties, but sometimes struggled with words. The results showed some PM failures, which improved over time:

> "It is hard to remember how my memory was during treatment, but definitely a lot more vague!"
>
> "…I was doing funny things like starting the tap and walking away, and not coming back, or forgetting…I was doing things like that, yeah, leaving something and then going off, or forgetting what I was doing…"

9.1.6.3 Words and names: Tip-of-the-tongue phenomenon

A new thing that emerged a few months after treatment was that she started to have problems finishing her sentences during a conversation:

> "…I am saying something and I completely forgotten, completely forgotten rather than just hesitating, completely forgotten what I was on about, and then thinking oh well, I just cannot remember it again, there been certain things where I come, oh… I do not even know what I was going to say!…wow! I can't even think what I was going to say!"

However, she did not associate this problem with words to problems with finishing sentences:

> "…slightly different from forgetting what I was going to say…but I do not think I have that now. It was as if I was going to say something to you and then I cannot quiet think the word to describe it may be, or the word I was going to use to explain so, I could not explain what I was going to say, but it is cleared now…I said things in a different way to say things to cope."

9.1.6.4 Dependency on reminders

Participant six also became dependent on reminders to plan ahead, otherwise she would forget what she wanted to do:

> "I do remember my plans…I do write things down, and have to remember to look at it…I do try to remember…luckily I suppose, we have our diary at work so we are every day going in looking. I have habit for work…I think if I do not write it down, I probably would forget to do things…"

9.1.6.5 Attention

Participant six reported she had not had problems with attention, but she was not able to concentrate during treatment:

> "I am very attentive, not so vague. My concentration is much better. During treatment I think I could not concentrate on things…"

9.1.6.6 Multitasking

Participant six described having more difficulties in her work life. During treatment, she found that tasks that were once easy were more difficult to accomplish. She also found that she could not manage to carry out several tasks at the same time:

> "I did find it very difficult at first, it is not that work is difficult but…something I have done for many years…I did find it more difficult… to know what I was doing…even making appointment with people, I was frail and could not know how to do it, and they are very simple things to do."

> "Now I just can get on with things… I have just noticed now that I can cope with all these things, the family and all those things…and the transition was quite difficult… from when treatment stopped…and then you think ok I am fine...simple things seemed difficult…and that took a while to get to this stage…it is like you are learning to do things again…"

9.1.6.7 Negative mood, frustration and anxiety

For her first screening, Participant six had very high (near to abnormal) anxiety levels, which might explain her poor performance on CAMPROMPT at baseline (Table 9.29). However, in the following sessions, anxiety decreased significantly. She showed more signs of depression during her second screening, but this declined in her third screening.

HADS	**Test 1**	**Test 2**	**Test 3**
Anxiety	13	7	7
Depression	2	9	4

Table **Error! No text of specified style in document.**.29. Anxiety and depression scores for Participant six.

Overall, Participant six showed mild PM impairment during and after treatment, but also reported that her daily life was not impacted significantly by memory difficulties despite the fact that some decline was present in her reports. By the end of this study, they had improved.

9.1.6.8 Summary of findings for Participant six

A summary of findings for Participant six is shown in Table 9.30.

Parameter	Comment
Neuropsychological tests	
Executive functions	Normal
CAMPROMPT	Average, above average
Interviews and self-reports	
PM Failures	During treatment only: Misplaced things Problems with attention and concentration Problems with multitasking Needed to use reminders Forgot appointments, forgot to take medication, forgot to switch things off
Other difficulties associated with chemo brain	Problem with words and names
Anxiety	Mild
Depression	Low
Sleep	Good

Table 9.30. Summary of findings for Participant six.

CHAPTER TEN

10 GENERAL DISCUSSION

10.1 Overview of key findings

The primary aim of this thesis was to examine PM within the context of chemo brain using qualitative and quantitative methodologies as well as objective and subjective measures of memory and sleep. The need for this type of research emerged firstly from the fact that until recently, in the literature, very little emphasis had been placed on PM as a cognitive deficit in patients experiencing chemo brain. Nevertheless, evidence exists that chemo brain patients present PM deficits (Paquet *et al.*, 2013; Cheng *et al.*, 2013). On the other hand, evidence that neuropsychological assessment has failed to adequately measure cognitive deficits in breast cancer patients, to the point that some authors even deny the existence of the phenomenon (Mehlsen, 2007), led this study to qualitatively investigate the everyday cognitive deficit experiences that patients report as a result of cancer treatment, and how these failures relate to PM decline.

The need to measure sleep and sleepiness emerged from studies confirming the relationship between sleep, memory decline and breast cancer (Lockerfeer *et al.*, 2012; Savard *et al.*, 2009; Meerlo *et al.*, 2009), in order to analyse its effects within the context of chemo brain and PM decline.

To date, the majority of studies in the area of chemo brain have failed to use measures with reliable ecological validity (Schagen *et al.*, 1998); therefore, a vast majority of

studies found inconsistencies between patients' anecdotal reports and neuropsychological tests (Ahles, 2007); they used a wide variety of measures and statistical analyses, contributing to contradictory results that led to disagreement about whether there is significant impairment on cognition after experiencing chemotherapy treatment (Shilling *et al.*, 2005); they used actigraphy to measure sleep objectively, rather than the SWA (Ancoli-Israel *et al.*, 2001; Savard *et al.*, 2009; Kuo *et al.*, 2006); they assessed cognitive domain in general, leading to more inconsistencies (Mehelsen *et al.*, 2009; Ganz, 2013), with only a handful having focused on a single aspect of cognition, such as PM (Paquet *et al.*, 2013; Cheng *et al.*, 2013) and attention (Weis *et al.*, 2009; Adams-Price *et al.*, 2009; Ball *et al.*, 1990) in particular; and they focused on the neuropsychological assessment of chemo brain, neglecting the qualitative aspect of chemo brain as a PM deficit, with only a handful of studies considering the importance of patients' interviews and case studies (Downie *et al.*, 2006; Shilling *et al.*, 2007; Mitchell *et al.*, 2011). To our knowledge, none of the studies included a comprehensive analysis that includes neuropsychological assessment along with in-depth qualitative analysis and case studies interviews with the inclusion of biological markers to observe comorbidity among symptoms.

To our knowledge, this study is the first one to use CAMPROMPT to investigate if this is a more sensitive tool for the assessment of PM in breast cancer patients, and the first one to combine mixed methodologies, including statistical analyses, thematic analysis and case studies in the same study for the investigation of PM within the context of chemo brain as well as including measures of sleep.

10.1 Key Findings

10.1.1 Neuropsychological assessment

Consistent with previous research, our results did not show significant impairment on neuropsychological measures, but the study added to the limited literature analysing PM in the context of chemo brain, finding that breast cancer patients showed significantly lower scores than healthy controls in measures of PM time-based tasks during treatment on the CAMPROMPT test (Time-based tasks $F(1,54)=7.959$, $p=0.007$, and for CAMPROMPT total score $F(1,54)=5.905$, $p=0.018$).

The hypothesis that PM would be poorer for the PT group for the second time in the middle of the treatment was not confirmed by these tests. The results indicated that CAMPROMPT might be a sensitive measure of PM, reflecting situations presented in real life situations; however, using this measure for retesting is controversial, because of practice effects. Alternate versions A and B of the battery should be revised by the authors.

In the current sample, both the groups showed improvement in most of the tests. Healthy controls performed better in the tests than cancer patients, but cancer patients showed no indication of memory decline as previously predicted. However, this might be due to practice effects. Poorer performance in the tests of the patients when means

were compared with the healthy controls' (patient mean 13.46, healthy controls 16.39) suggest that self-initiating monitoring was better for the healthy controls at both the testing sessions.

Overall, our results confirmed the hypothesis that breast cancer patients have poorer PM, particularly in time-based tasks, than healthy controls, and that the effects are stronger in the middle of treatment. The hypothesis that PM will be poorer for the patient group for the second time in the middle of treatment was not confirmed by these tests. However, the fact that the improvement was greater for the healthy controls might suggest that despite the influence of practice effects in both the groups, the healthy control group has increased cognitive abilities to develop better strategies when PM is tested. Despite the fact that patients did not show a decline in PM performance, the hypothesis that healthy controls will perform better in PM test was confirmed.

One criticism of the last time-based task of CAMPROMPT the author of this thesis has is that in version A, participants are required to stop what they are doing and switch to another task, e.g. while participants are working on the quiz questions, they are asked to change the task and continue with the puzzles. It was found that the participant often finished the quiz questions exactly at the end of the seven minute interval, and it was difficult for the tester to know whether they were changing the task because the participant had remembered the instruction or merely because they had just finished that section. In this case, the examiner had to make a judgement as to whether it was actual remembering or coincidence, which might have had a negative effect on scoring.

Furthermore, results from Heffernan *et al.* (2012) were consistent with these results in which significant differences were found for the time-based tasks, but not for the event-based tasks, and this could be explained by the fact that self-initiating monitoring is more difficult or more demanding than cue-dependent tasks.

Although this test was a good attempt to assess PM—because it includes time-based and event-based tasks and resembles real life situations (having to remember to do things at a certain time or when reminded by a particular cue in the environment)—it could not be recommended for re-testing due to a high familiarity effect. Although the test–re-test reliability was 0.98 (Wilson *et al.*, 2005), it was suspected that in this sample, familiarity for both the groups was very high for the second assessment, although the effect was lower for the PT group, which might suggest that cancer treatment was having a detrimental effect on the PM of breast cancer patients.

Processing speed and intellectual abilities were not affected by treatments, and despite the fact that both the groups showed better performance at testing time 2 in abilities to learn more information and accuracy of visual-motor coordination and attentional skills assessed by this test, the healthy control group showed significantly better rates of performance. These results could suggest that breast cancer patients' attention skills, although not technically considered impaired, are not as good as those in healthy controls. This could mean that cancer treatment or illness affect the attention, learning, motivation and intellectual abilities of patients.

Our results for executive control measures indicate that the scores of Digits Span tests for the cancer patient group were not affected by their treatments. However, attention span, anxiety, distractibility and rote memory (skills assessed by these tests) were less affected by the control group.

BVRT test results assess attentional difficulties, visual perception and visual memory. Our results indicate that patients' group performed poorer than the healthy controls in these abilities, although both the groups showed improved performance from baseline to testing session 1.

COWAT test results indicate that the patient group showed a better performance in both testing sessions when compared to healthy controls in word naming tests. Interestingly enough, word retrieval is one of the most common complaint in chemo brain patients (Mitchell *et al.* 201; Downie *et al.*, 2006; Mulrooney, 2007; Silverman & Davidson, 2009), and our qualitative analysis also confirmed this fact. However, these results might be associated with a lack of motivation in our healthy control group and the fact that IQ scores were higher in the patient group.

Even when practice effects might have taken place, strategies developed by healthy controls led them to perform better, meaning that perhaps the effects of treatment were influencing results in cancer patients.

The hypothesis that the cancer group was expected to perform worse than the healthy group was met, but an improvement was seen in most of the tests in both

the groups. According to Lezak (1983), it is not uncommon that cognitively impaired patients show improved performance on neuropsychological measures, even in robust tests, due to practice effects, and this can be seen even when the tests increase in difficulty.

These results are consistent with previous studies in this area of research, in which cancer patients show improvement on neuropsychological tests (Shagen *et al.*, 2002; Jenkins *et al.*, 2006; Hermelink *et al.*, 2007). However, these results should not imply that there is no cognitive impairment on cancer patients after experiencing chemotherapy. As Burgess (2001) explained, PM deficits are not usually well represented on neuropsychological batteries, but patients do show significant impairment in daily life performance.

Consistent with the fact that participants from the cancer group sleep for more hours than the healthy group are the sleepiness during the day scores from ESS. Mean results exposed that healthy controls are more sleepy during the day than the cancer group, and this might be a result of significantly decreased sleep hours (patient baseline mean 4.96 time 2 mean = 5.79; healthy controls baseline mean = 6.39 time 2 mean = 6.68. Higher scores indicate sleepiness.

In our sample, breast cancer patients showed in our objective measure of ME that they have a tendency of oversleeping; however, their perceived sleep is poorer than healthy controls. This might be due to several reasons, one being that at the time of testing, patients were recovering from the chemotherapy cycle, and no assessment

was conducted precisely at the time of treatment. Anecdotal reports of participants suggested that their sleep patterns were completely different immediately after the treatments, when the worst of the physiological side effects were taking place. On the other hand, studies of sleep and PM indicate that long sleep might be also associated with impairments to PM. Scullin and colleagues (2014) found that hypersomnia patients (9> hrs/night) performed significantly worse than healthy controls ($p < .05$). Contrary to these results, these same authors found that short sleep is also associated with nonfocal PM decline. In a sample of college students, those who slept for <7 hrs per night showed poorer performance than normal sleepers (7–9 hrs per night) ($p < .001$).

Our hypothesis that patient group will show poorer sleep patterns, which in turn will affect PM, has not been confirmed by ME; however, these results might be affected by the fact that sleep was not measured objectively exactly during treatment. On the other hand, PSQI results confirm our hypothesis, and the patient group showed impaired levels of sleep (>5 on PSQI scoring,), when compared to controls. These contradictory results between objective and subjective results might be due to the fact that it is not uncommon that participants have the tendency to overemphasize their symptoms, and the results should be considered with caution.

The relevance of this study is that to the best knowledge of the author of this work, no study has previously been conducted using the CAMPROMPT test within the context of chemo brain, and it is only the second time that PM testing has been used in the study of participants in the area of chemo brain.

To date, the literature on chemo brain has demonstrated that there is subtle cognitive impairment in some breast cancer patients. It remains unknown which are the mechanisms underlying this phenomenon, but fMRI has provided deeper insight into the phenomenon, suggesting that some brain structures might be affected (Deprez *et al.*, 2012).

It is suggested that more sensitive memory measures are needed to better understand the MCI as a by-product of chemotherapy.

A deeper study focusing on PM is suggested using PM self-reports, a combination of PM batteries (suitable for re-testing), along with PM experimental tasks and fMRI analyses in longitudinal studies with larger sample sizes.

The DSM-5 (American Psychiatric Association, 2013), states that due to the fact that major and mild neurocognitive disorder (MND) states that due to the fact that major and MND exist in a continuum, precise thresholds are difficult to determine, and perhaps that is one reason that neuropsychological batteries have failed to detect cognitive impairment in some studies on chemo brain. They suggest that careful history taking, observation, and integration of other findings are required for diagnosis. For this reason, the PI would like to stress on the importance of qualitative studies along with quantitative measures to better understand the phenomenon of chemo brain.

10.1.2 Qualitative: Emerging themes

Contrary to the quantitative findings, patients' interview results showed that cognitive failures are present in their everyday life, and that at times they could be debilitating. Patients' responses confirmed the research question that chemo brain failures are in fact PM failures in everyday life functioning. Emerging themes from thematic analysis involved attention deficits, inability to multitask and over-reliance on reminders as coping strategies, all pertaining to PM deficits (Mulrooney, 2007; Silverman *et al.*, 2009; Cohen *et al.*, 2008). An interesting theme that emerged, is related to breast cancer patients having trouble retrieving common words and names, which could be associated with the TOT phenomenon, because patients described the problem as "having the word in the back of your head" and "you know that you know the word", which have been associated with TOT (Kykyio *et al.*, 2001).

Scientific evidence suggests that this memory problem might be due to the TOT phenomenon (Kikyio *et al.*, 2001). The TOT phenomenon has been described as "a situation that occurs when a person cannot remember a specific piece of information but can provide information about that item and can accurately predict whether the answer will be recognised" (Neath *et al.*, 2003). This is also one of the forms of metamemory (self-knowledge of how the memory of an individual works) (Neath *et al.*, 2003; Oh-Lee *et al.*, 2012). Oh-Lee *et al.* (2012) explained that the TOT experience reflects a state of mind in which people are unable to think of target words, but feel that retrieval is

imminent. The experience results in frustration because of the inability to retrieve the word, but the patients have the strong feeling that the information will pop into their minds at any moment. Kikyo *et al.* (2012) argued that the retrieval effort and the successful retrieval are temporarily dissociated.

Of special interest is that neural correlates associated with TOT are anterior cingulate cortex (ACC), right dorsolateral PFC and right inferior cortex (Oh-Lee *et al.*, 2012). The relevance of this to this study is that these same areas appear to be involved in PM and chemo brain (Burgess *et al.*, 2012; Sherling *et al.*, 2013). Therefore, the author suggests that TOT should be analysed further within the context of PM and chemo brain to fully understand the problems that cancer patients report with word and name retrieval. Supporting this statement, research on metacognition and brain imaging suggests that EF and metacognitive regulation (processes that coordinate and monitor goal-directed behaviour, i.e. PM) are based on similar cognitive and neural mechanisms related to prefrontally mediated executive control processes, and that impairment of metamemory judgments is related to frontal-lobe lesions (Mantyla *et al.*, 2010; Kikyo *et al.*, 2012).

Furthermore, Mantyla *et al.* (2010) suggested that self-reports on PM and metacognitive regulation play an important role in self-belief of efficacy, meaning that individuals with effective control functions, such as multitasking and metamemory capabilities, have a stronger assurance of their cognitive capabilities. This might explain why some cancer patients report feeling like a lesser person than they used to be when faced with PM difficulties.

The fact that our participants reported forgetfulness may be due to divided attention, which interferes with monitoring processes (Parasuraman *et al.*, 1977) and disrupts spontaneous retrieval due to highly demanding tasks (Harrison *et al.*, 2013). Those highly demanding tasks may include their treatment and its implications and that, all in all, life and work become more difficult due to impaired PM or side effects, not to mention emotional processes such as anxiety and depression. All of these combined might be preventing the participants from noticing PM cues in their environment.

The use of reminders also indicated that PM was involved, because it showed that patients were lacking monitoring strategies, so they needed to rely on reminders to be able to remember their intentions.

Feeling anxious and frustrated were also the themes that emerged; however, those feelings were frequently counterbalanced through resilience and acceptance.

10.1.3 Case studies: Integration of results

The case studies showed how patients who undergo cancer treatment experience memory difficulties regardless of their neuropsychological tests results. PM is one of the cognitive domains affected and patients also face problems with words, which might be a problem of the TOT phenomenon, associated with LTM. This finding also gives insight to explore a new theory in the context of chemo brain, which is the TOT

phenomenon, and which, to our knowledge, has not been addressed as such in the chemo brain literature.

Our findings derived from the six case studies presented here provide clear evidence that chemo brain is a real phenomenon, despite the fact that our quantitative study showed the opposite. Our qualitative analysis explains the struggles cancer patients face with PM deficits after undergoing chemotherapy.

10.1.4 Implications of the current findings

Our results show that there is evidence that PM failure might be one of the underlying causes of chemo brain. The patients' reports relate to those of PM lapses. The examples provided by this sample showed that these PM failures, such as the ability to multitask or divided attention affect patients' lives significantly and at times, these failures might be stressful and even life threatening (e.g. difficulties with driving instructions, forgetting to take the medication or taking it twice).

Although participants showed a tendency to accept their situation, which helped them cope with these problems, feelings of frustration and anxiety were present most of the times, which could lead to feelings of inadequacy. Another detrimental effect of PM failures in chemo brain patients was that their self-esteem was in jeopardy. They tended to feel "stupid" or "less than", and they had to reduce or limit their span of activities or perform them more slowly. However, most of the participants reported

not being significantly affected in their social lives or at work, and that they only needed to learn or develop strategies of how to cope.

On a positive note, some of the cancer patients with memory difficulties approached the issue with a sense of humour and became very resilient when facing adversity. Almost intuitively, they developed coping strategies to help with PM failures, such as keeping reminders and lists at home and at work.

Due to the nature of this phenomenon, and because of the inconsistencies in neuropsychological test results, the author recommends that more mixed methods studies in the area of chemo brain should be conducted to better understand the phenomenon and to counterbalance the fact that MCI might be overlooked by neuropsychological tests. The use of more studies integrating patients' lived experiences, laboratory assessments and imaging techniques as well as the use of new technologies are suggested. This research was partly conducted online, and it was demonstrated to be highly effective and non-intrusive for participants, who could respond to the questionnaires at their own pace (Das 2012; Procter et al., 2013).

The lack of ecological validity when trying to assess cognitive deficits in breast cancer patients is of extreme importance for this type of study, mainly because in order to be able to better help patients to cope with their memory problems, it is important to consider how patients experience cognitive difficulties in their everyday life situations, and not only under laboratory conditions. It is very important that

neuropsychological assessment reflects the reality of these experiences, which would lead to more conclusive and valid results.

According to Schagen *et al.* (1998), the ecological validity of most neuropsychological tests is low due to the fact that the cognitive domains assessed by traditional tests of cognitive function have little overlap with everyday experiences on which patients base their self-reports, and hence the lack of correlation between self-reports and standardised assessment as opposed to neuropsychological tests, which are highly artificial because of the way the material is presented to the patients and show little resemblance to everyday memory performance.

On the other hand, interviews are more focused on problems in daily life. The problem with self-reports is that they depend on patients' reports and if a patient has memory problems, he/she will forget to report it and will compromise the objectivity of the assessment. Moreover, personal beliefs and personality traits may compromise objectivity, influencing the responses on self-reports. It is believed that patients have a strong tendency to overemphasize their memory problems, but this could be overcome by the opinion of relatives or a person close to the patient (Schagen *et al.*, 1998; Cull *et al.*, 1996).

In the current study, it was decided to contrast neuropsychological assessment with interviews to get a deeper understanding of this controversial finding between neuropsychological tests and self-reports. It was decided to conduct online and face-to-face interviews rather than standardised self-reports, in order to gain a deeper

insight into patients' everyday life situations. Our findings suggest a significant discrepancy between tests and interviews (Downie *et al.2006*; Shilling *et al.,* 2007).

10.2 Strengths and limitations

10.2.1 Strengths

One of the strengths of this study was the use of multiple sources of data collection by examining test results, questionnaires and interviews as well as analysis of the literature on the various areas of study (PM, chemo brain, TOT, sleep time). This allowed the issue of chemo brain to be addressed in a broader manner by presenting objective and subjective evidence together. Data triangulation was achieved by using multiple sources, which helped to corroborate that PM failures and chemo brain present the same cognitive disadvantages to sufferers, that chemo brain patients show the TOT phenomenon and that neuropsychological tests might not be sensitive enough to detect MCI (Patton, 1987; Yin, 1994; Burgess *et al.*, 2004). Issues regarding construct validity were also addressed with data triangulation, because multiple sources of evidence provided multiple measures of the same phenomenon, enhancing the quality of the case studies presentation (Yin, 2004).

The strength of this type of study was the ability to analyse in depth the PM aspect of chemo brain using a mixed methods design, which was aimed at addressing the whole spectrum of the problem, by studying the patients' experiences in their daily lives as well as self-reports and neuropsychological batteries.

10.2.2 Limitations

Recruitment and assessment of patients after being diagnosed with cancer may be challenging. For the patients, this is a very traumatic time and they often do not want to participate in studies. A more convenient time for recruitment is after surgery, because they have already accepted the fact that they have cancer. However, assessment after surgery also has its drawbacks. Recent experience of general anaesthetic and the shock of diagnosis may alter cognitive status, thereby affecting test scores, but the use of a control group helped resolve this as well as the possibility of practice effects (Mar Fan *et al.,* 2005). For the reasons stated above, the qualitative study conducted for this work was limited by a relatively small sample size. When breast cancer patients were approached before surgery, they refused to take part; therefore, the study was limited to patients who had already undergone breast surgery, and together with NHS ethics procedures, recruitment became a very slow process. Our results might have also been influenced by the effects of surgery, in which breast cancer patients showed significantly poorer scores than the controls at baseline.

10.2.2.1 Methodological issues

Due to the challenges with recruitment of our patient population and time constraints regarding PhD studentship along with patients' duration of chemotherapy treatment, neuropsychological assessment was only possible during patients' cancer treatment

and not after it. Our study was limited by a small sample size, but in the study of chemo brain, there are many comparable studies with relatively small samples sizes (Wefel *et al.*, 2004; Bender *et al.*, 2006; Downie *et al.*, 2006; Menheret *et al.*, 2006; Hurria *et al.*, 2006; Mehelsen *et al.*, 2009; Tager *et al.*, 2009). However, this study stands out from the others in that it longitudinally assesses participants' PM and sleep changes in the middle of the treatment cycle in an attempt to explore when changes in cognition begin. However, further studies are needed with larger sample sizes that include assessment of neuropsychological measures of PM before, during and after treatment within different populations and that consider cultural and ethnic variability.

On the other hand, despite the fact that CAMPROMPT test's ecological validity seems to accurately reflect situations similar to those experienced in real life situations, it is not a good measure for retesting due to high familiarity effect. This could be because versions A and B of the tests are almost identical rather than alternate and equivalent. Furthermore, distractor tasks do not seem to be very reliable due to the fact that test instructions require participants to choose which distractor task to work on, lacking standardisation of the ongoing activity for all participants. In addition, the cost of the ongoing activity could be one of lesser value than other activities, meaning that while working on an ongoing activity, some participant could have chosen to work on a very demanding task, whereas others might have chosen to work on a much less attention demanding task. Moreover, participants are provided by a clock and timers to constantly monitor the time; therefore, it is difficult to conclude whether automatic monitoring is in place or if it is prompted by cues provided by clock or timer observations.

As an example, and contrary to our results, in a study conducted to assess PM decline in patients with Parkinson's disease, Foster *et al.*'s (2009) results showed that event-based tasks required more attentional monitoring (nonfocal tasks). Their results also suggested that patients in their sample showed worse performance than controls in such tasks. Foster and colleagues (2009) argued that although time-based task are thought to require more attentional control than event-based tasks, the presence of an external cue such as the clock in such tasks could reduce the "need for internally-guided monitoring".

However, the author of this thesis argues that in CAMPROMPT tests, the time-based tasks are nonfocal and require self-initiating monitoring despite the fact that the clock is present during the testing session. When participants are working on the ongoing tasks, they need to remember to monitor the clock while their attention is focused on the ongoing task. In the literature, it has been very well stablished that self-initiating monitoring is a strong predictor of time-based PM performance (Einstein *et al.*, 1995; Phillips *et al.*, 2004; Mioni *et al.*, 2013). The TWTE (Harris *et al.*, 1982) is based on the assumption that participants synchronise their internal clock with an external clock, and that test takers rely more on their internal clock during testing, and when the time to give a response approaches, they start to rely more on the external clock; this can be observed by the rate of clock checking observations (Mioni *et al.*, 2013). In our sample, participants were more engaged in working on the ongoing activity rather than on checking the clock; however, it is suggested that CAMPROMPT test developers should add a clock checking recording to address this situation.

In order to investigate how attentional and WM resources are allocated in time monitoring strategies, it is suggested that studies on chemo brain patients focus on time perception, attention shifting and differences in monitoring. In our sample, the fact that patients showed lower performance than healthy controls in time-based tasks could indicate that patients have trouble inhibiting the ongoing activity to shift their attention to check the clock in order to perform the PM task (Mioni *et al.*, 2013).

A more reliable neuropsychological measure of PM could be the MIST, which has shown promising results for breast cancer patients (Paquet, 2013). This test controls better for the ongoing tasks by using word search puzzles and also assesses time-based and event-based PM. However, there is no evidence of its efficacy for retesting on breast cancer patients. The author of this thesis suggests that assessment of PM should be carried out by using PM neuropsychological assessment together with well validated PM paradigms that assess attention and EFs and try to replicate real life situations. One of the PM tools that might be useful for the study of PM and chemo brain along with neuroimaging techniques is the Virtual Reality-based Prospective Memory Test (VRPMT-CV), which has shown promising results with the rehabilitation of cancer survivors (Alana *et al.*, 2013), schizophrenic patients (Man *et al.*, 2014) and TBI patients (Yip *et al.*, 2013). Man *et al.* (2014) suggested that VRPMT is a reliable and sensitive tool for the assessment of PM, and that its concurrent validity was established by computing scores with that of the CAMPROMPT, with a significant correlation found between both the tests ($r = 0.90$, $p < 0.001$). The VRPMT consists of a computer-based test in which participants go shopping in a convenience store, providing an everyday PM scenario, where event-based and time-based PM tasks can be assessed. The author of this thesis suggests that

VRPMT, along with neuroimaging tools, should be used in further studies of chemo brain and PM as a more sensitive measure of chemo brain.

Other limitations of the current study were that breast cancer patients were not assessed at exactly the same time as the treatment, but a few weeks after having chemotherapy, when the recovery phase was taking place. Anecdotal reports in our laboratory indicated that patients' sleep and cognition were worst exactly during treatment, when the common side effects of chemotherapy were taking place. However, for ethics purposes, it was decided not to intrude in the patients' lives while they were experiencing such discomfort. It is worth noting that in the literature on chemo brain, it is not possible to ascertain when exactly in the treatment cycle the patients are being assessed. The patients may be assessed a few hours before their chemotherapy begins, a few hours after the treatment, one, two or three weeks after treatment, or immediately before the next cycle. It is imperative to be clearer in identifying at which stage of the treatment patients are being assessed to gain further understanding about the effects that chemotherapy-related side effects such as nausea and lack of sleep have on cognition.

Our thematic analysis comprised a convenience sample of 12 participants who provided insight into their memory difficulties after experiencing cancer treatment. However, some limitations were observed. Firstly, the study was conducted several months after treatment only; therefore, no baseline assessment with interviews was provided, and secondly, we do not know how participants rated their memory before treatment, although they did mention that their memories were better before commencing treatment.

One of the advantages of this study was the possibility of carrying out online questionnaires; however, this technique also had its limitations. A lot of relevant information might have been lost through conducting research online, because the possibility of deriving information from facial expressions and non-verbal behaviour was not available. Furthermore, it was not possible to ask the participants if they could expand on their answers if they gave short responses. However, despite these limitations, it is recommended that online resources are more commonly used, as they tend to be cost effective and convenient for participants, especially when they are dealing with an illness. Another disadvantage might be that some participants might not have access to a computer or they might not be computer literate. In our sample, all the participants who were invited from the previous study had access to a computer, but were invited to go to their local library in case they needed access to a computer and assistance in using it.

Another limitation was that we did not use PM self-reports for analysis but only for screening participants for the case studies. We wanted to keep our study as objective as possible and did not want to influence the qualitative study responses while taking part in the neuropsychological assessment. Self-reports were used in the qualitative study as screening measures and to direct the conversation of the interviews to be able to ask questions related to PM in open-ended, semi-structured interviews and to give a sense to the topic of the case studies. The author suggests that future assessment of PM and chemo brain would be based on a self-report questionnaire that is developed and validated to aid chemo brain research, and for an accurate assessment of patients

to receive proper healthcare when they come to the clinics and report memory complaints.

10.3 Future directions and further research

Although this study was the first of its kind to use the CAMPROMPT test to investigate PM in chemo brain patients in a mixed methods methodology, including a biological marker to observe if sleep was an intervening factor leading to PM complaints, further studies that increase power using these measures are needed once CAMPROMPT is revised by its developers. The author of this thesis believes that CAMPROMPT is in fact a sensitive measure, but alternative forms should be more reliable.

10.3.1 APOE, dopamine and neural correlates

Similar lines of research in the areas of chemo brain and PM had been separately analysed in the literature in both the areas: the study of their relationship with APOE allele e4, the role of dopamine in PM and the analysis of neural correlates (Ahles *et al.* (2014; Foster *et al.*,2009; Keser *et al.*, 2011; Inagaki *et al.*, 2007) . An examination combining these areas in future studies is suggested by the author of this thesis.

10.3.1.1 Neural correlates

In the past few years, there has been an increase in studies looking for structural brain changes associated with cancer treatment. A comparison of those studies with the ones conducted in relationship to PM would be useful to observe if there is an overlap between both the areas of study.

Among cancer patients, Inagaki *et al.* (2007) reported decreased PFC volume and/or tissue and white matter bilateral middle frontal gyri. McDonald *et al.* (2010) found decreased bilateral middle frontal gyri, while McDonald *et al.* (2012) found left middle frontal gyrus (Sherling *et al.*, 2013). Using PET and fMRI studies, Silverman *et al.* (2007) found increased activity in the left inferior frontal gyrus (near Brodmann areas 44 & 45) and right superior frontal gyrus; Ferguson *et al.* (2007) found widespread increased activity on bilateral PFC; Ruiter *et al.* (2010) found decreased activity in the dorsolateral PFC; and Keser *et al.*, 2011) found decreased caudal lateral PFC (Sherling *et al.*, 2013). Based on this evidence and the evidence provided above with regard to PM neural correlates, it can be concluded that there is a structural correlation between PM and chemo brain activity.

Burgess *et al.* (2001) argued that delayed intentions are supported by brain structures located in the frontal lobes and related structures such as frontal pole (Brodmann area 10), where they found increased blood flow bilaterally in the right lateral prefrontal and inferior parietal regions and the precuneus (Brodmann area 7), with all of these involved in the maintenance of the intention. Activation in the thalamus and PFC have been found to be involved in the realisation of the intention and reported a decrease in activation in the right lateral PFC (Burgess *et al.*, 2012). Other regions of the brain

involved in PM are the anterior PFC during transient clock-related activity (before clock monitoring activity takes place) (Oksanen *et al.*, 2014) and the medial temporal lobes and hippocampus (McDaniel *et al.*, 2007; Gordon *et al.*, 2011). The parietal lobes (Brodmann area 40) and the anterior cingulate (Brodmann area 32) were found to be activated during PM paradigms by Burgess *et al.* (2011).

Studies of PM involving breast cancer patients are suggested to further analyse the structures of the brain involved during PM paradigms and to observe in further detail the regions of the brain that might be affected while executing PM tasks. These kinds of studies might provide a more ecologically valid assessment of neuroimaging and PM assessment of patients suffering from chemo brain. While neuroimaging techniques provide a clear observation of the regions of the brain involved during psychological assessment, they might still lack ecological validity. That is, psychological assessment is still being conducted under laboratory conditions, and therefore, no accurate analysis of patients' daily activities is taking place. According to our findings that PM decline is implicated in chemo brain, the author of this thesis suggests that involvement of neuroimaging studies using more ecologically valid psychological measures are combined for more accurate results.

10.3.1.2 Neural correlates for name and word finding failures or tip-of-the-tongue states

Our thematic analysis and interview results showed that one of the most common difficulties reported by patients was the problem of remembering words and names of familiar people. Interestingly, this area of research has been neglected in the study of

chemo brain, and to our knowledge, this is the first study considering its analysis as a result of our case studies interviews.

A word finding problem, TOT is the inability to produce a well-known word, despite the strong feeling that recall of the word is imminent, and occurs when a familiar word temporarily fails to come to mind (Shafto *et al.*, 2009; James, 2006); it is most noticeable with aging (James, 2006). This age-related word retrieval has been associated with neural atrophy in the left anterior insula (Shafto *et al.*, 2007) and with reduction and atrophy of grey matter (Resnick *et al.*, 2003). Furthermore, substantial grey matter atrophy across the brain has been related to age-related cognitive decline in EF and verbal memory, and the neural correlates involved are mostly prefrontal and medial-temporal regions (Shafto *et al.*, 2009; Resnick *et al.*, 2003; Raz *et al.*, 1998). On the other hand, face naming has been associated with the posterior temporal region, the insula, lateral and medial prefrontal areas and the medial temporal lobe in successful retrieval of information about a person's name, and TOT has been a valuable tool for studying these processes (Galdo-Alvarez *et al.*, 2011). Galdo-Alvarez *et al.* (2011) reported that successful name retrieval and naming are associated with interaction of a brain network involving occipital areas, occipital parietal areas, the anterior cingulate, the PFC and the insula.

Taken together, some areas of the brain associated with TOT and face naming have been considered in chemo brain studies; however, they have not been associated with TOT and chemo brain. The author of this thesis suggests that more emphasis is placed on the study of TOT and chemo brain neural correlates to better understand the

aetiology of the most commonly reported complaint from breast cancer patients, which is face and word naming failure.

10.3.1.3 The presence of the e4 allele of the apolipoprotein E (APOE e4) and dopamine

Another line of research that should be analysed is the relationship between chemo brain, PM and APOE e4, which is a genetic risk factor for developing Alzheimer's disease (McDaniel *et al.*, 2005). According to Ahles *et al.* (2003), only a percentage of cancer patients who receive chemotherapy present the phenomenon of chemo brain, and they suggested that this might be due to the presence of the APOE e4 gene in some patients, which might be a potential risk factor. They explained that chemotherapy is considered as a type of insult to the brain, and patients with APOE e4 will be more vulnerable to cognitive decline associated with chemotherapy. On the other hand, they argued that patients with MCI, who are APOE e4 carriers, had smaller baseline brain volumes. Furthermore, Archer *et al.* (2006) found that MCI had an increased prevalence in healthy APOE e4 carriers. On the other hand, McDaniel *et al.* (2005) found a significant deficit in PM for APOE e4 carriers failing to perform an intended action at the appropriate moment. Further research in this area is suggested by the author of this thesis, inviting APOE e4 carriers who have undergone chemotherapy assisted by PM tools to further analyse the involvement of APOE e4 genotype on chemo brain as a PM failure.

In a study conducted by Ahles *et al.* (2014) to assess whether breast cancer treatment and nicotine interact with APOE e4 carriers, thereby decreasing neuropsychological tests performance, they suggested that dopaminergic activity could be one mechanism that can explain post-treatment cognitive decline in breast cancer patients. Their conclusions are in agreement with previous studies that suggest that low dopamine levels in the PFC negatively affect cognitive performance in breast cancer patients undergoing chemotherapy treatment (Small *et al.*, 1995; McDonald *et al.*, 2012. Ahles *et al.*, 2014).

Research suggests that the PFC plays an important role in cognitive functions, such as PM, inhibition and goal maintenance (Cabeza *et al.*, 2013; Beck *et al.*, 2016). Furthermore, there are indications that dopamine in the PFC modulates cognitive control, influencing attention, inhibition, PM and cognitive flexibility (Foster *et al.*,2009, Costa *et al.*, 2008; Beck *et al.*, 2016).

Foster *et al.* (2009) found that Parkinson's disease participants fail to efficiently perform monitoring strategies in PM tasks, and they suggested that this might be due to the fact that patients were unable to retrieve the intention on nonfocal cues, reflecting difficulty in shifting their attention. They also suggested that this impairment in cognitive flexibility has been associated with dopamine depletion in the PFC.

On the other hand, Costa *et al.* (2008) also investigated impaired executive control abilities involved in PM in Parkinson's disease participants and found that dopamine

alterations play a critical role in cognitive deficits in PM. However, when they administered the medication Levadopa, patient's PM performance was significantly improved; in fact, previous PM deficits were restored.

In lieu of these results, the author of this thesis suggests that in future studies, the assessment of dopamine levels should be included along with measures of PM that focus on nonfocal cues related to attentional monitoring, cognitive flexibility and attention shifting.

10.4 Conclusion

To date, the literature on chemo brain has demonstrated that there is a subtle cognitive impairment in some breast cancer patients. Our findings suggest that the problem is real and affects breast cancer patients' quality of life. Although the underlying mechanisms in this phenomenon remain unknown, there is evidence about which areas of the brain get affected. Our findings suggest that the type of memory that is affected in chemo brain patients is PM. A vast majority of the research has focused on general cognitive dysfunction, although some studies have started adding neuroimaging technologies to their assessments. More specific and comprehensive studies that include experimental PM tools and PM neuropsychological assessment, along with neuroimaging techniques, are necessary to deeply analyse the relationship between PM and chemo brain. More sensitive memory measures are also needed to better understand the phenomenon. It is recommended that more focus on the study of PM and chemo brain be placed in future longitudinal and imaging studies in order to

replicate current findings and to include the analysis of TOT and face and word naming failures.

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APPENDIX I Recruitment Materials

I-1 Invitation to participate in the study

STUDY TITLE: THE EFFECTS OF CANCER TREATMENT ON MEMORY

INVITATION

We would like to invite you to take part in the above-named research study, as you have recently been diagnosed with breast cancer.

The purpose of the study is to observe if cancer treatment has an effect on memory processes. We will be using a series of tests and questionnaires to help us understand this better with the aim of trying to improve care/treatment for this group of patients.

The duration of the study will be 9 months. During this time, you will be required to attend on four occasions to complete the study procedures.

Your participation is entirely voluntary; no payment will be given for participation.

All screening and tests will take place at this hospital, and we will arrange schedules at your convenience and availability.

If you decide you would like to participate, you will be given an information sheet to keep and asked to sign a consent form.

We hope that this study will help cancer patients understand how to improve their quality of life.

If you think you would like to take part, please contact Liliana Moyers at

lmoyers@bournemouth.ac.uk

Phone 01202514903 Mobile 07427869252

Chief investigator: Dr Tamas Hickish
Principal researcher: Liliana Moyers

I-2 **Invitation to participate in online questionnaires**

Dear Mrs_____

We are inviting you to take part in the second part of the memory study on the effects of chemotherapy on memory. You have been invited because you have already completed your treatment, and completed the first part of the study, in which you took a series of psychology test.

Your participation in this second part is entirely optional, and consists of an online interview and questionnaires.

This study will be used as a follow up for the first one, and both complement each other. The principal investigator will be comparing results from each study as case studies.

If you do not have access to a computer or Internet, you can go to your local library where you can use computers with free Internet access.

In order to access the online interview, please follow this link_____ and write the following access code_____

Please email lmoyers@bournemouth.ac.uk or ring 07427869254 as soon as you have completed the interview, or in case you find any difficulty, or have any further questions.

Your information will be confidential and only the principal investigator and advisors from Bournemouth University will have access to it.

Invitation
Version 2
Date 08/04/13
REC Ref: 10/H0502/92

I-3 **Invitation to participate in face-to-face interview**

Invitation to participate in face-to-face interview

Bournemouth University

NHS

The Royal Bournemouth Hospital
Castle Lane East
Bournemouth
Dorset
United Kingdom
BH7 7DW
Tel: 01202 303626
www.rbch.nhs.uk

Dear Mrs_____,

We are grateful for your participation so far. Your contribution has helped us to better understand the effects of cancer treatment on memory.

To continue our investigation, we are inviting you to take part on a face-to-face interview. You have been invited because you have already completed your treatment, and completed the on-line interview.

Your participation is entirely optional, and consists on a face-to-face interview which will last about one hour. The interview will take place at Bournemouth University, and will involve a few questions related to your experience with your treatment, and how this has impacted you memory.

After receiving this letter, the principal investigator will contact you to confirm your participation, and to arrange the most convenient schedule for the interview.

Your information will be confidential and only the principal investigator and advisors from Bournemouth University will have access to it.

If you have further questions, please do not hesitate to contact Liliana Moyers at lmoyers@bournemouth.ac.uk or at 07427869254

Sincerely,

Liliana Moyers, principal investigator.

Invitation Face-to face interview
Version 2
Date 08/01/14
REC Ref: 10/H0502/92

I-4 Consent form

Bournemouth University

Dorset County Hospital NHS
NHS Foundation Trust

Patient Identification Number:

CONSENT FORM

STUDY TITLE: **INVESTIGATION OF PROSPECTIVE AND WORKING MEMORY AND THE IMPACT OF IMPAIRED SLEEP AND/OR IMPAIRED GLUCOSE METABOLISM IN RECENTLY DIAGNOSED BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY: A LONGITUDINAL STUDY**

Chief Investigator: Dr Tamas Hickish

Name of Researcher: Liliana Moyers-Ruiz

Please initial box

1. I confirm that I have read and understood the information sheet dated.....for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Bournemouth University, Bournemouth and Poole hospital, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study. ☐
5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Person taking consent	Date	Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

I-5 Participant information sheet

Bournemouth University

Dorset County Hospital NHS
NHS Foundation Trust

PARTICIPANT INFORMATION SHEET

STUDY TITLE: **INVESTIGATION OF PROSPECTIVE AND WORKING MEMORY AND THE IMPACT OF IMPAIRED SLEEP AND/OR IMPAIRED GLUCOSE METABOLISM IN RECENTLY DIAGNOSED BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY: A LONGITUDINAL STUDY**

Chief investigator: Prof. Tamas Hickish

Principal researcher: Liliana Moyers-Ruiz, PhD student

INVITATION

We would like to invite you to consider taking part in the above research study. Before you decide whether or not you would like to take part, we would like to explain what the research is about, why it is important and what is involved.

A member of the research team will go through the information sheet with you in case you have any questions; this will take approximately 10 minutes. You can talk about the study with others if you wish and please ask any questions. You can contact the principal researcher and/or the chief investigator with any queries. If you decide not to participate, your care will not be affected in any way.

PART 1

What is the purpose of the study?

Sleep and glucose regulation are frequently altered in breast cancer patients who receive chemotherapy. The purpose of this project is to observe the effects of chemotherapy on sleep and glucose regulation, and observe whether or not these have an effect on memory processes in breast cancer patients during and after chemotherapy treatment.

Why have I been invited?

You have been invited as you have been diagnosed with breast cancer and are scheduled to begin treatment soon. If you were invited to take part but do not have breast cancer is because your participation will help us to compare your results with cancer patients. Participants in this project will include individuals who have been diagnosed with breast

cancer and are receiving chemotherapy treatment, individuals who have been diagnosed with breast cancer who are receiving treatment other than chemotherapy, and a group of individuals who do not have cancer.

Do I have to take part?

No. Your participation in this project is entirely voluntarily. If you agree to participate, you can withdraw at any time without affecting your medical treatment, or your chance to participate in another study. If you decide to participate and later do not want to continue, you have the right to withdraw without giving any further explanation. This decision will not affect your medical treatment.
We will describe the study in this information sheet, and if you decide you would like to take part, we will ask you to sign a consent form.

What will happen to me if I take part?

Your participation in this project will not represent any greater risk than in those encountered under normal daily activities. We will give you two copies of a consent form to sign: one or your own records and one for our file. You will be required to attend on four occasions to complete the study procedures, which include

1. Filling out 7 questionnaires
2. Performing some psychology tests
3. Wear a SenseWear® armband
4. Measurements taken of your pupils
5. Blood tests to measure your glucose levels

These four visits will take place over approximately a 9-month period.

What will I have to do?

The questionnaires will take approximately 10 minutes to complete, and you need to complete these before we go on to the following tests.

For the psychology tests, the researcher will need to ask you questions following a certain format to make sure that all participants are treated in the same way. Each of these sessions will take approximately one hour to complete and will take place at the hospital. You will also be asked to perform some tasks at this time.

You will be required to wear an apparatus called SenseWear®, which resembles an armband for a 7-day period before you attend the above session. This piece of equipment will not cause you any discomfort or harm, and it is easy to wear. Measurements of your pupil will be taken; this assessment takes about 15 minutes to complete and will take place in a dark room at the hospital. You will have to wear a

goggle-like mask with web cams attached to it. You will need to stay awake during this assessment while measurements of your pupil dilation are taken by the web cams on the mask.

We will also take some blood samples at each visit to measure your glucose levels.

Duration of participation

The four visits will take place as follows: one before chemotherapy, one after the second or 3rd cycle, one immediately after your last cycle, and the last one six months after completing your treatment.

Time 1 **Baseline Testing** (10 days prior to 1st cycle)	**Time 2** **Mid-term Testing** (11 days before 4th cycle)	**Time 3** **Post-treatment testing** (11 days after 6th cycle)	**Time 4** **6 months follow-up** (6 months after 6th cycle)
2 Screening Questionnaires (10 min) At any time before testing	**1 Screening questionnaire**	**1 Screening questionnaire**	**1 Screening questionnaire**
Psychology tests (1 hr)	**Psychology tests** (1hr)	**Psychology tests** (1 hr)	**Psychology tests** (1hr)
Questionnaires: **2 Sleep scales** (5 min. Day of testing)	Questionnaires: **2 Sleep scales** (5 min. Day of testing)	Questionnaires: **2 Sleep scales** (5 min. Day of testing)	Questionnaires: **2 Sleep scales** (5 min. Day of testing)
Sensewear (7 days before testing) **Pupil measurement** (15 min. Day of testing) **Blood test**	**Sensewear** (7 days before testing) **Pupil measurement** (15 min. Day of testing) **Blood test**	**Sensewear** (7 days before testing) **Pupil measurement** (15 min. Day of testing) **Blood test**	**Sensewear** (7 days before testing) **Pupil measurement** (15 min. Day of testing) **Blood test**

What are the possible disadvantages and risks of taking part?

You may find that some of the questionnaires ask for sensitive information, and it is possible that you might feel overwhelmed by answering a scientific test battery (what's this!). You may also experience some inconvenience whilst wearing the SenseWear® for 7 days and you might feel uncomfortable and sleepy being in a dark room for 15 minutes during the pupil measurement. You may experience some slight bruising or discomfort from the blood samples. To reduce the risks for you, only experienced and qualified members of the research team will perform these procedures. Please discuss any concerns with a member of the research team who will do their best to help you.

What are the possible benefits of taking part?

We hope that the information we obtain from this study will help us understand more about memory processes in patients who are undergoing chemotherapy. You will gain understanding on how psychological tests and experiments are used to gain knowledge in psychology research. There may not be any direct benefit to you, but we hope that this study will help us improve care for patients in the future.

What if there is a problem?
If you have any complaint about the way you have been dealt during your participation in the study or any possible harm you might suffer, it will be addressed (detailed information on this is given in Part 2).

Will my taking part in the study be kept confidential?
Yes. All information will be kept strictly confidential. Your name will not be used, as a unique code number will be used to identify your data. We will adhere to ethical and legal practice to keep your information confidential.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

What will happen if I don't want to carry on with the study?
If, for any reason, or at any time, you decide that you no longer wish to be involved in this study, you are free to withdraw without giving a reason. Deciding to withdraw from the trial will not affect your care. If you do decide to withdraw from the study, we will ask for your consent to allow us to use the data collected up to your withdrawal with your permission.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak with the researchers, who will do their best to answer your questions:

Liliana Moyers (Principal investigator): 01202 514903.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from

Professor Tamas Hickish (Chief investigator): 01202 704789.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence, then you may have grounds for compensation, but you may have to pay your legal cost. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from Bournemouth University and Bournemouth and Poole hospitals. They may also be looked at by authorised staff employed by the regulatory authorities to check that the study is being carried out correctly. All will have a duty of confidentiality towards you as a research participant, and we will do our best to meet this duty.

All completed questionnaires, tests and other collected data will be stored at Bournemouth University in a secure locked cabinet for a period of 5 years after the end of the trial and then destroyed.

All electronic data will be kept on a secure computer, and access to the data will be secured by use of specific passwords known only to authorised persons within the research team. We will ensure that you are not named in any publications that may result from this research.

Involvement of the General Practitioner/Family doctor.

If you agree to participate, we will write to your GP to let him/her know that you are taking part in this study.

What will happen to any samples I give?

The blood samples that you will provide for routine tests will be analysed locally at the hospital laboratory. Tests will be conducted to analyse your glucose levels, to see if there have been any changes that may be affecting memory. After the tests have been completed, these samples will be destroyed.

What will happen to the results of the research study?

The results of this research will be used as a part of a PhD dissertation and might be published in relevant scientific journals. They may also be presented at scientific conferences. You will not be named in this or any study results. When available, a summary of the results of the study may be obtained from the principal researcher.

Who is organising and funding the research?

This research is organised by Bournemouth University as a part of a PhD grant and sponsored by The Royal Bournemouth Hospital.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favorable opinion by Southampton REC A Research Ethics Committee.

Physical Exercise
Evidence indicates that exercising 3 times a week helps maintain cognitive health, and we would encourage you to do so. We also will be collecting information regarding your exercise levels by asking about your exercise habits in some of your diaries.

Further information and contact details
You can contact the principal investigator for more information about this study.

Thank you for taking the time to read this information sheet. If you decide to take part in the study, you will be given a copy of this information sheet and the signed consent form to keep for your own records.

I-6 Letter to patient's doctor

Dr

Dear Dr _____

We would like to inform you that your patient _____ will be taking part in a research study at Poole Hospital looking at the effects of chemotherapy on memory. This is a 9-month longitudinal study where participants will be asked to undergo the following:

1. a series of neuropsychological tests
2. complete sleep and sleepiness questionnaires and diaries
3. complete screening questionnaires.
4. provide blood samples.

We will also record sleep wake/activity and take measurements of pupil aperture.

Your patient has been invited to participate in this project, as she has been recently scheduled to begin breast cancer treatment with chemotherapy.

If you have any questions or require any further information, please do not hesitate to contact me.

Yours sincerely,

Liliana Moyers Ruiz

Principal Investigator

Email: lmoyers@bournemouth.ac.uk

Tel: 01202 514903

Chief Investigator: Professor Tamas Hichkish

I-7 **Patient background information request**

Bournemouth University

Dorset County Hospital NHS
NHS Foundation Trust

BACKGROUND INFORMATION

Participant ID number_____ DOB_____
Weight_____Height_____Contact No.___ Hospital No. _

In order to be able to have a better understanding of your participation on this study, we require this basic background information. Please circle the response that best describes you.

1) What is your age?
   a. 18–30
   b. 31–40
   c. 41–50
   d. 50–60
   e. 60+

2) What is your gender?

   a. Female
   b. Male

3) What is your current marital status?

   a. Married
   b. Single
   c. Divorced
   d. Widow
   e. Patternship
   f. Separated

4) What is your highest level of education?

   a. Less than upper school
   b. Upper school
   d. College
   e. Bachelors
   f. Masters
   g. Postgraduate
   f. Other Explain_____

5) Have you been previously diagnosed with?
1. Cancer
2. Diabetes

3. Mental or psychiatry disorder
4. Mood disorder (i.e. depression, anxiety)
5. Any other medical condition Explain_____

6) Do you have a significant other supporting you while you receive your cancer treatment?

a. Yes
b. No

7) Do you consider yourself a multitasking person?

1. Yes
2. No

8) What is your current employment status?
a. Full time
b. Part time
c. Self-employed
d. Unemployed
e. Volunteer
f. Care taker
g. Do not work

9) Do you smoke?
a. Yes
b. No

10) If yes, how much?

11) Do you drink alcohol?
a. Yes
b. No

12) If yes, how much?

13) Do you exercise regularly?
a. Yes
b. No

14) If yes, how often? And how much?

15) Are you currently taking any medication?

1. Yes
2. No

16) If yes, explain

17) What is your current menopausal status?

18) Have you previously had breast surgery?

19) If yes, when?_____

APPENDIX II Ethics Submissions

II-1 Reply from National Research Ethics Service

NHS
National Research Ethics Service
Southampton & South West Hampshire REC (A)
Building L27
University of Reading
London Road
Reading
RG1 5AQ

Telephone: 0118 918 0567
Facsimile: 0118 918 0559

21 December 2010

Professor Tamas Hickish
Consultant in Medical Oncology,
Visiting Professor to Bournemouth University
Royal Bournemouth Hospital
Castle Lane East
Bournemouth , Dorset
BH7 7DW

Dear Professor Hickish

Study Title: **The Influence of impaired sleep and/or impaired glucose metabolism on Prospective and Working Memory in Breast cancer patients receiving chemotherapy treatment: A Chemo-Brain longitudinal study.**
REC reference number: **10/H0502/92**
Protocol number: **10/H0505/92**

The Research Ethics Committee reviewed the above application at the meeting held on 07 December 2010. Thank you for attending to discuss the study.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Questionnaire: Depression Scale (HADS)		
Questionnaire: CAMPROMPT Record Form		
Questionnaire: Background information (participant)		18 November 2010
Letter of invitation to participant	Women recently diagnosed with breast cancer	18 November 2010
Letter of invitation to participant	Women with no medical condition	18 November 2010
GP/Consultant Information Sheets		18 November 2010
CV James Lecouteur (research assistant)		
Participant Information Sheet		18 November 2010
REC application		18 November 2010
Questionnaire: National Adult Reading Test (NART)		
Questionnaire: Benton Visual Retention Test		

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Questionnaire: Pittsburg Sleep Quality Index (PSQI)		
Questionnaire: Epwoth Sleepiness Scale		
Questionnaire: Karolinska Sleepiness Scale		
Questionnaire: Digit Span		
Questionnaire: Digit Symbol - Coding		
Questionnaire: Karolinska Sleep Diary		
Protocol		18 November 2010
Letter from Statistician		18 November 2010
Referees or other scientific critique report		18 November 2010
Investigator CV	Tamas Hickish	18 November 2010
Investigator CV	Simon Thompson	18 November 2010
Investigator CV	Liliana Moyers Ruiz	18 November 2010
Participant Consent Form		18 November 2010
Covering Letter		18 November 2010
Summary/Synopsis		18 November 2010
Letter from Sponsor		

Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

The Committee delegated authority to confirm its final opinion on the application to the Chair.

Further information or clarification required

1. The Committee recognised that the first approach to potential participants was from a member of both the research team and the clinical team. The Committee acknowledge the importance of getting the right information to participants, but wish to emphasise the need to avoid coercion when approaching.
2. The Committee believed that whilst 'Chemo-Brain' was recognised terminology, it would be potentially offensive or worrying to participants and was not a clinical term. The use of this term in Patient Documents should be removed.
3. The Committee request that the GP letters should be tailored to each participant group.
4. The Committee wished to highlight their concern at the level of academic supervision the application seems to have received. The Committee wish to see evidence that the application has been proof read by someone with English as their first language.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

If the committee has asked for clarification or changes to any answers given in the application form, please do not submit a revised copy of the application form; these can be addressed in a covering letter to the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 10 May 2011.

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

10/H0502/92	**Please quote this number on all correspondence**

Yours sincerely

Dr Iain MacIntosh
Chair

Email: scsha.SWHRECA@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments.*

Copy to: *Dr. Simon Thompson*

Southampton & South West Hampshire REC (A)

Attendance at Committee meeting on 07 December 2010

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Richard Andoh	Pharmacist	No	
Rev'd Dr Rosemary Baker	Consultant in Learning Disabilities	No	
Mrs Ita Berry	Retired Clinical Psychologist	Yes	
Dr Stewart Bruce-Low	Laboratory Director & Senior Lecturer	Yes	
Dr Paul Diprose	Consultant Anaesthetist	Yes	
Mrs Grania Howard	Operating Department Practitioner	No	
Dr Simon Kolstoe	Academic Research Scientist	Yes	
Dr Mary Lanyon	Retired Veterinarian	Yes	
Dr Iain MacIntosh	Consultant Paediatric Intensive Care	Yes	
Dr Chris Markham	Senior Lecturer in Health Service & Research	Yes	
Mrs Lucy Sayer		Yes	
Mrs Margaret Stephens	Senior Specialist, Speech & Language Therapist (Adult Neurology & Elderly Care)	Yes	

II-2 Reply to amendment from National Research Ethics Service

NHS
Health Research Authority
NRES Committee South Central - Southampton A
Bristol Research Ethics Committee Centre
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Tel: 0117 342 1381
Fax: 0117 342 0445

16 May 2013

Professor Tamas Hickish
Consultant in Medical Oncology, Visiting Professor to Bournemouth University
Poole Hospital
Royal Bournemouth Hospital
Castle Lane East
Bournemouth , Dorset
BH7 7DW

Dear Professor Hickish

Study title:	**The Influence of impaired sleep and/or impaired glucose metabolism on Prospective and Working Memory in Breast cancer patients receiving chemotherapy treatment: A Chemo-Brain longitudinal study.**
REC reference:	**10/H0502/92**
Protocol number:	**10/H0505/92**
Amendment number:	**6**
Amendment date:	**08 April 2013**
IRAS project ID:	**60838**

Thank you for submitting the above amendment, which was received on 07 May 2013. It is noted that this is a modification of an amendment previously rejected by the Committee.

The modified amendment has been considered on behalf of the Committee by the Vice-Chair.

Ethical opinion

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved are:

Document	Version	Date
Invitation Letter	2	08 April 2013
Modified Amendment	6	08 April 2013

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/H0502/92:	**Please quote this number on all correspondence**

Yours sincerely

Dr Simon Kolstoe
Vice-Chair

E-mail: nrescommittee.southcentral-southamptona@nhs.net

Copy to: *Dr. Simon Thompson*

II-3 Notice of substantial amendment

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm.

Details of Chief Investigator:

1. Name: Dr Tamas Hickish

Address:

Telephone:

Email:

Fax:

Full title of study:	Previous version: THE INFLUENCE OF IMPAIRED SLEEP AND/OR IMPAIRED GLUCOSE METABOLISM ON PROSPECTIVE AND WORKING MEMORY IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY TREATMENT: A LONGITUDINAL STUDY Revised version: PROSPECTIVE AND WORKING MEMORY DECLINE AND IMPAIRED SLEEP AND/OR IMPAIRED GLUCOSE METABOLISM IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY TREATMENT: A LONGITUDINAL STUDY
Name of main REC:	Southampton & South West Hampshire REC (A)
REC reference number:	10/H0502/92
Date study commenced:	Not yet started
Protocol reference *(if applicable),* current version and date:	10/H0502/92
Amendment number and date:	

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the NRES Application Form

Yes *No*

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes *No*

If yes, please submit <u>either</u> the revised protocol with a new version number and date, highlighting changes in bold, <u>or</u> a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes *No*

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

Yes ***No***

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

REC Form

1. The sponsor information provided on the initial application form was incorrect. This should have indicated Dr Robert Chapman, Head of Research, Royal Bournemouth Hospital as the sponsor representative and should have been signed accordingly.

2. The R&D Lead has been corrected from Dr Tamas Hickish to Dr Robert Chapman.

3. The filter question form was completed incorrectly.

Question 2 – tick should have been entered in 'other study' instead of 'Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology'.

Question 2a(c) – this should have been 'no'. By making this change, some questions were added to the form. Copies of the original forms and the amended form have been included. Changes have been highlighted in both forms.

Protocol

1. We have amended the title slightly to accurately emphasize the study.

Previous version:

THE INFLUENCE OF IMPAIRED SLEEP AND/OR IMPAIRED GLUCOSE METABOLISM ON PROSPECTIVE AND WORKING MEMORY IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY TREATMENT: A LONGITUDINAL STUDY

Revised version:
PROSPECTIVE AND WORKING MEMORY DECLINE AND IMPAIRED SLEEP AND/OR IMPAIRED GLUCOSE METABOLISM IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY TREATMENT: A LONGITUDINAL STUDY

Participant Information Sheet and Consent Form (dated 24/03/11 version 3) in which the title was changed are included with this submission. Only study title was changed.

Demographics Questionnaire:

2. Further questions have been added to the background information. We have included a copy of the original submission (dated 18/11/10) and the amended submission (dated 24/03/11 version 2), in which additional questions are highlighted.
3. All information regarding actiwatch has been changed to Sensewear.
4. All information regarding sleep diaries (KSS and KSD) has been removed.
5. After proofreading, some typographical changes had been made. Original submission (dated 18/11/10) and the amendment version (dated 24/03/11 v. 2) have been submitted. The original submission highlights the changes and omissions; the amendment submission underlies the changes.

Equipment

1. It has been decided to use the "SenseWear®" device instead of the "actiwatch" to observe sleep/wake activity. The SenseWear® is worn on the arm of the patient, being more reliable and comfortable.

Methodology

2. Sleep diaries will be taken out of the study (they were going to be used to support actiwatch data).
3. Days of using SenseWear® will change from 10 days to 7 days.
4. Research Assistant James Le couteur will not be taking part in the study.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

Document	*Version*	*Date*

Declaration

1. I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.

2. I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: ……..……

Print name: ……..……

Date of submission: …….

II-4 Data controller register

Royal Bournemouth & Christchurch Hospitals NHS Foundation Trust

DRC DORSET RESEARCH CONSORTIUM

DATA PROTECTION ACT 1998

DATA CONTROLLER REGISTER

Use this form to summarise details about each collection of (or system containing) person-identifiable data. Include details of all manually held and computerised personal data involved. Use a new form for each collection/system.

For help in completing this form, please contact:
Bournemouth & Christchurch Hospitals: Mike Riding, 01202 704461
Poole Hospital: Richard Hatton, 01202 448689/442866

Department	Oncology	Location	Poole Hospital
Name of person completing form		Liliana Moyers-Ruiz	
Project title	**INVESTIGATION OF PROSPECTIVE AND WORKING MEMORY DECLINE AND THE IMPACT OF IMPAIRED SLEEP AND/OR GLUCOSE METABOLISM IN RECENTLY DIAGNOSED BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY: A LONGITUDINAL STUDY**		

REC Approval	**X** YES	NO	N/A
If YES, REC Reference No. 10/H0502/92	REC Reference Number: 10/H0502/92		

1.	Details of the system and ownership	
1.	*Who is collecting the data?*	Principal Investigator: Liliana Moyers-Ruiz
2.	*Where is the data being held?*	In Locked cabinets at Bournemouth hospital

3.	Details of the data processing	
1.	*Is the data held on a computer, manually or both?*	Both
2.	*If computerised, which IT systems will be used to the capture the data e.g. Excel, Access, Electronic CRF or other database?*	SPSS (Statistical Program for the Social Sciences) latest version, excel
3.	*Is any of the data processed externally? i.e. does an outside bureau or agency or other NHS organisation do some or all of the data processing?*	Yes Pupillometry analyses at Poole Hospital
4.	*If the data is processed externally, please give the name of the company, university or other NHS organisation that processes it.*	Poole Hospital
5.	*Does a written contract or an agreement exist with the company or NHS organisation?*	Yes

6.	Information recorded and disclosed				
		Recorded		**Disclosed**	
	Patients' name	*YES*	*NO X*	*YES*	*NO X*
	Initials	*YES*	*NO X*	*YES*	*NO X*
	Address	*YES*	*NO X*	*YES*	*NO X*
	Hospital number	*YES*	*NO X*	*YES*	*NO X*
	Date of birth	*YES*	*NO X*	*YES*	*NO X*
	Post Code	*YES*	*NO X*	*YES*	*NO X*

	Telephone number	*YES*	*NO X*	*YES*	*NO X*
	Age	*YES X*	*NO*	*YES*	*NO X*
	Sex	*YES X*	*NO*	*YES*	*NO X*

7.	Source of Data Please indicate which of the following you will be using		
1.	*Paper records*	*YES X*	*NO*
2.	*Hospital computer not attached to the network*	*YES*	*NO X*
3.	*Hospital computer attached to the network*	*YES X*	*NO*
4.	*Home or other personal computer not attached to the network*	*YES*	*NO X*
5.	*Home or personal computer attached to the network*	*YES*	*NO X*
6.	*Laptop, palmtop or hand held computer*	*YES*	*NO X*
7.	*University computer*	*YES X*	*NO*
8.	*Computer disk, CD or memory stick*	*YES X*	*NO*
9.	*Audio tapes*	*YES*	*NO X*
10.	*Digital camera (Pupillometry's webcam)*	*YES X*	*NO*
11.	*Images including x-ray*	*YES*	*NO X*

12.	Details required for the organisation to register with the Information Commissioner	
1.	*For what purpose is the data collected and held? E.g. health administration, personnel, employment, contractors, health research, accounts, crime prevention, etc. (e.g. is the data collected for the purpose of treating the patient?)*	Health Research
2.	*About whom is the data collected and processed? E.g. patients, complainants, relatives, staff, contractors, suppliers, etc.*	Breast cancer patients receiving chemotherapy treatment, breast cancer patients receiving treatment other than chemotherapy, healthy women

3.	*What sort of data is collected and held? E.g. health details, employment details, finance details, personal views, trade union membership, other personal details.*	Patient's background information, psychological tests and questionnaires, sleep/wake activity, sleepiness, blood samples	
4.	*To whom may the data be disclosed? E.g. other NHS depts or sites, social services, government, voluntary agencies, relatives, legal representatives, survey/research organisations.*	Pupillometry to Poole hospital staff	
5.	*How often will the data be shared or disclosed.*	Every time we collect this kind of data (4 times for each patient)	
6.	*Can you confirm that you keep a record of disclosures and associated reasons?*	*YES X*	*NO*
7.	*If you are collecting data directly from the patient, will you obtain written consent from the patient for the information stored and processed?*	*YES X*	*NO*
8.	*If you are collecting data directly from the patient, will you ensure the data is not used by anyone else for other purposes?*	*YES X*	*NO*

9.	Data Quality and Security		
1.	*If you are collecting data directly from the patient, will you have a method of checking data accuracy?*	*YES X*	NO
2.	*If the data is to be published, state where and if it will be completely anonymised*	*In PhD dissertation, scientific journals. It will be completely anonymised*	
3.	*How will the data be held? – personal laptop not attached to a network, laptop attached to network or other?*	*University's and Hospital's computers, CD*	
4.	*How is personal and sensitive data destroyed?*	*Files will be shredded, and blood samples will be destroyed according to NHS policies*	
5.	*When sending sensitive and bulk personal data by post, is it sent via Royal Mail Special Delivery or a Courier service?*	*YES X*	*NO*
6.	*Are staff aware of the security guidelines regarding e-mail i.e. sensitive and confidential data must be send via encrypted e-mail e.g. NHS.net?*	*YES X*	*NO*
7.	*Are staff aware of the Safe Haven policy?*	*YES X*	*NO*
8.	*What contingency arrangements are there to cover loss of records?*	*CD's and computers will have a password to access the information. Information will be also held in University and hospital's computers*	

9.	*If data is being submitted electronically, is it being done using secure send or the N3 network?*	*YES*	*NO*

10.	Compliance with Data Protection (DP) principles		
1.	*If you are collecting data directly from the patient or member of staff, have they been informed that it is being used?*	*YES X*	*NO*
2.	*Have the patients or members of staff given their consent to all processing and disclosure?*	*YES X*	*NO*
3.	*Have measures been taken to ensure that those to whom the data is disclosed will process it appropriately?*	*YES X*	*NO*
4.	*Are there routine audits of how the data is managed?*	*YES X*	*NO*
5.	*How is the data kept accurate and up to date?*	*Standardised measures will be used for accuracy and direct contact with Chief Investigator (patient's oncologist) to update treatment course.*	
6.	*Is the data archived in line with NHS guidelines?*	*YES X*	*NO*
7.	*Can patients or staff access their personal data within the 40 day limit set by the DP Act?*	*YES X*	*NO*
8.	*Is it possible to prevent processing that can cause damage or distress? i.e. If a person does not want to have their data processed, can their request be met without detriment to the service provided?*	*YES X*	*NO*
9.	*Are their procedures in place within the department to control security and access to personal and sensitive data?*	*YES X*	*NO*
10.	*Are departmental staff aware of their responsibilities under the DP Act?*	*YES X*	*NO*
11.	*Is data to be transferred outside the European Economic Area? If so, to which country?*	*No*	

Completed by the Data Protection Officer Initials:
……

Name of Data Protection Officer
……

Signed:
……

Register Reference Number:

……...

Date:

……

APPENDIX III Open ended questions and PM questionnaire

11.1. Online questionnaire

Welcome Page

Hello. I would like to thank you for accepting being part of this study. Your participation is greatly appreciated.

In the first section, you will be asked to complete a questionnaire about your memory.

The second part is an interview. You are encouraged to ask your family members to help you complete this interview and add some comments about your memory, but please specify whose response it is.

The response boxes for the interview will expand as needed, therefore there is no word limit.

Please indicate your type of treatment, dosages (if you are aware of them) and complementary therapies (Tamoxifen, etc) and when did you commence chemotherapy/radiotherapy/hormone treatment and when you finished it, or if you are still on it.

Please try to be as detailed as possible.

You have 2 weeks to complete this assignment. This is an off line interview, which means you can work on it at your own peace. In order to save your responses to continue in a later time, you must click the "next" icon at the bottom of the page every time you want to exit the questionnaire pages, and "Prev" for the interview page; failure to do this, will delete all the responses. To send the survey, click "Done" at the end of the interview.

Please feel free to write anything that comes to your mind about the topic and your experiences and feelings during and after treatment. Your responses will no be seen by anyone outside the research team, and will be anonymyzed. Only Principal Investigator knows your identity. We are not going to be judgmental of your responses, and will be treated objectively.

When you finish completing the questionnaire and interview, please e-mail Liliana Moyers at lmoyers@bournemouth.ac.uk indicating you have completed the assignment.

We greatly appreciate your participation and time dedicated to this study.

Information & Consent

In order to better understand memory difficulties that breast cancer patients experience during or after the course of chemotherapy we are conducting and on-line asynchonomous (Off-line, not real time) interview.

You have been invited because you have already completed your treatment or/and have reported memory difficulties to the Principal researcher, and have participated on the first part of this study.Your opinions and insight are highly valuable to help us develop a tool that assesses memory impairment after chemotherapy or cancer treatment

Your identity will be confidential throughout the duration of the study as well as in the reporting of findings. An ID will be assigned to you to be able to access the questionnaire and interview.
Your participation is voluntary and no payment will be provided. Please read the following and indicate whether I have your permission to use your responses on my reports, and consent to participate.

Description of the study:
1. The first part will require that you answer an online questionnaire.
2. Secondly you will be required to respond a few online questions, as detailed as possible, about your memory difficulties with examples (your family members, friends and co-workers might help you with the responses).

Duration of the study.
Access to the questionnaire and interview will be opened for 2 weeks. After you complete the questionnaire, you will gain access to the interview. If you leave the survey and want to come back, just click on the link provided on your email.

***1. Please answer.**

- ☐ Yes, I have read and understood the Participant Information sheet
- ☐ Yes, I consent to take part.
- ☐ Yes, I give you my consent to publish the content of my responses.
- ☐ No, I do not give you my consent to publish the content of my responses.

PRMQ

Please respond the following questions

You must complete the questionnaire before leaving the page. To save click "NEXT". You can always come back to the questionnaire by clicking "PREV"

***2. Do you decide to do something in a few minutes' time and then forget to do it?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***3. Do you fail to recognize a place you have visited before?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***4. Do you fail to do something you were supposed to do a few minutes later even though it is there in front of you, like take a pill or turn off the kettle?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***5. Do you forget something you were told a few minutes before?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***6. Do you forget appointments if you are not prompted by someone else or by a reminder such as a calendar or diary?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***7. Do you fail to recognize a character in a radio or television show from scene to scene?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***8. Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***9. Do you fail to recall things that have happened to you in the last few days?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***10. Do you repeat the same story to the same person on different occasions?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***11. Do you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it is there in front of you?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***12. Do you mislay something that you have just put down, like a magazine or glasses?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***13. Do you fail to mention or give something to a visitor that you were asked to pass on?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***14. Do you look at something without realizing you have seen it moments before?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***15. If you tried to contact a friend or relative who was out, would you forget to try again later?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***16. Do you forget what you watched on television the previous day?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

***17. Do you forget to tell someone something you had meant to mention a few minutes ago?**

○ Very often ○ Quite often ○ Sometimes ○ Rarely ○ Never

CAPM

Please tell us if you encounter the following situations

You must complete the questionnaire before leaving the page. To save click "NEXT". You can always come back to the questionnaire by clicking "PREV"

***18. Forgetting to buy an item at the grocery store**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***19. Forgetting an appointment with your doctor or therapist**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***20. Leaving the iron on**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***21. Forgetting to put the garbage bin out**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***22. Forgetting a change in your daily routine (e.g., turning up to a regular appointment when the regular day has been changed)**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***23. Not locking the door when leaving home**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***24. Walking into a room and forgetting why you went there**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***25. Mistakenly following your old routine, when it has been changed (e.g., putting out rubbish at the wrong time when the collection day has been changed)**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***26. Forgetting to water pot plants or the garden**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***27. Forgetting to pass on a message**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***28. Forgetting to take tablets at the prescribed time**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***29. Forgetting to take clothes off the line**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***30. Forgetting to have a shower or bath**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***31. Accidentally doing something twice by mistake (e.g., putting two lots of coffee in a cup)**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***32. Forgetting to eat a meal**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***33. Forgetting to get money from the bank/ATM**

○ Very often ○ Often ○ Occasionally ○ Rarely ○ Never ○ Not Applicable

***34. Accidentally forgetting to put a piece of clothing on when you get dressed (e.g., forgetting to put your socks on)**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***35. Forgetting to take your wallet or purse when you leave the house**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***36. Having trouble remembering personal dates at the right time, such as someone's birthday or anniversary**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***37. Accidentally forgetting a grooming activity (e.g., brushing your hair, shaving)**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***38. Forgetting to make a telephone call you intended to make**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***39. Forgetting to do cleaning chores**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***40. Leaving water taps on**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***41. Not remembering to bank a cheque**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***42. Leaving out an ingredient you planned to use while cooking or preparing a meal**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***43. Accidentally forgetting to brush your teeth**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***44. Arriving at a shop and forgetting what you planned to buy**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***45. Forgetting to mention a point you intended to make during a conversation**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***46. Forgetting to put petrol in your car**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***47. Not remembering to pay bills**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***48. Checking whether or not you have already done something you planned to do**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***49. Forgetting to do the laundry**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***50. Forgetting to meet a friend at a pre-arranged time**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***51. Leaving the stove on**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***52. Forgetting to post a letter**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***53. Not remembering to check the water levels/tyre pressure of your car**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***54. Forgetting to check your calendar or diary**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***55. Forgetting to turn the heater off**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

***56. Forgetting to take your diary**

Very often | Often | Occasionally | Rarely | Never | Not Applicable

On-Line Interview

57. Please indicate:

Age	
Chemotherapy treatment or other cancer treatment	
Dosage	
Number of cycles	
Other chemotherapy treatments (hormonal, tamoxifen, radiotherapy)	
Have you had surgery	
Date of surgery	
Type of cancer	
Stage	
Approximate date of diagnosis	
Date commencing treatment	
Date treatment finished	
Menopause status before treatment	
Menopause status after treatment	

58. Have you experienced any memory difficulties during or after your cancer treatment?

- ○ Yes
- ○ No

If you have not experienced memory difficulties, please do not continue with the interview.

On-Line Interview

For the following questions please write everything that comes to your mind, trying to be as detailed as possible, and give as many examples as you can. Your family members are encouraged to help you respond (indicate when they are responding). Please consider your experience during and after your treatment.

IMPORTANT NOTE:
You can leave the interview at anytime and continue later. To save click "PREV". To send the interview click "DONE"

59. Please explain whether your memory has been affected during or after your chemotherapy/radiotherapy treatment and how

60. Tell us about your family and friends reaction about your memory changes during and after your treatment, and how these reactions make you feel.

61. Explain how you noticed your memory has changed and when (after first cycle, second, third, months later...)and if it has continuing changing

62. Tell us how was your memory before the illness and your treatment

63. Could you explain how has your work been impacted?

64. Could you explain if this has impacted your social life, and how?

65. Could you let us know how do these memory changes make you feel?

66. In case you life has been impacted by memory difficulties, please explain how you are coping with these

APENDIX IV Example how themes emerged

1. **Identified categories for each question, per participant using a colour code:**

   Green: Problems with words

   Blue: When memory problems began

   Red: Problems with memory

   Purple: More difficulty, multitasking, slowness

   Example Question 1(Each question has its own colour code), Participant 1

Q1 Please explain whether your memory has been affected during or after your chemotherapy/radiotherapy treatment and how

Raw data analysis:

"Definitely during, I had real trouble remembering words, making a sentence was really hard work, and remembering people's names that I had known for years."

Identified categories

Purple: Inability to do things, more difficult, slowness (takes more time to do things), harder, cannot multitask (Multitasking)

Green: Problems with words and names, sentences (semantic)

Blue: During treatment (beginning of memory problems)

Red: Problems with memory and remembering, forgetfulness, concentration (Attention)

Words, names, sentences = semantic category

Remembering/forgetting = memory category

2. **Example question 1 raw data analysis:**

1. **Initial identification of key words**
2. **Paraphrases**

Participant 1

"Definitely during, I had real trouble remembering words making a sentence was really hard work, and remembering people's names that I had known for years."

During treatment, it became harder to make sentences and recalling the names of people I know well. I struggled retrieving words.

Memory problems started during treatment. I have trouble remembering words and names. I work harder to make a sentence.

3. **Summarize responses**

Example Participant 1 all responses from question 1 to question 7:

During treatment, it became harder to make sentences and recalling the names of people I know well. I struggled retrieving words.

Memory problems started during treatment. I have trouble remembering words and names. I work harder to make a sentence

My family and friends are aware of how my memory got bad, I feel stupid for the things I say.

My family notices. I feel stupid.

When I finished treatment, my memory started getting better, but I cannot say when it started to deteriorate.

I cannot recall when it started, and it is better now.

Before treatment and illness my memory was ok, but sometimes I forget what I was doing and started doing other things.

My memory was better before treatment.

4. Re-read–Re-write and making sense from summaries

Example Participant 1

It was very apparent that my memory problems began during treatment. Making sentences became a very difficult thing to do, as well as remembering names. My family and friends noticed that I had memory problems because I said stupid things.

Memory is getting better now, but I cannot recall exactly when the problems began after commencing treatment. Before treatment, I did not have bad memory, although sometimes I started some jobs but forgot about another one.

Problems with my shoulder due to treatment are preventing me to return to work, but not related to memory, although they affect my social life, and I find it difficult to keep up with conversations. All these memory changes make me feel frustrated and angry, but I am coping fine and I take my time to say things.

5. **Identification of key words and cluster into similar topics for data reduction.**

All participants' responses were analysed. Each and every raw response and participants' summaries were compared to identify key words for each question. Key words were identified according to the frequency of usage.

Examples of key words that emerged from summaries:

Key words: Remembering, forgetfulness

Clustered in memory construct

Key words: Attention, concentration

Clustered in PM construct

Key words: Problems with words and names, trouble making sentence

Clustered in semantic construct

Key words: Reminders, lists, write down

Clustered in dependency construct

Key words: Frustrated, angry, laugh

Clustered in mood

Key words: Difficulty, harder than before, slowness

Clustered multitasking constructs

Final Clusters: Mood, ability to multitask, semantic problems, use of reminders, attention, memory.

6. **Comparison of theme's clusters and reduction into small packets**

i.e. Semantic: problems with words and name

Semantic problems = Tip-of-the-tongue

7. **Code creation (themes):**

ATTENTION: FORGETFULNESS, LACK OF ATTENTION, CONCENTRATION

TIP OF THE TONGUE: DIFFICULTY FOLLOWING CONVERSATIONS AND COMPLETING SENTENCES, TROUBLE REMEBERING WORDS AND NAMES

MULTITASKING: DIFFICULTY DOING MY JOB, DIFFICULT TO MULTITASK, HARDER TO DO MY JOB, SLOWNESS

NEGATIVE MOOD, FRUSTRATION, ANXIETY: FRUSTRATION, CROSS, STUPID, BEWILDERED, WORRIED

POSITIVE MOOD, ACCEPTANCE: LAUGH, ACCEPT, NOT BOTHER, OPEN

REMIDER DEPENDENCY: WRITE IT DOWN, USE AIDS, CALENDAR

Glossary

ANOVA- Analysis of Variance

APOE -Apolipoprotein

BVRT -Benton Visual retention Test

CAMPROMPT -Cambridge Prospective Memory Test

CAPM-Comprehensive Assessment of Prospective Memory

COWAT -Controlled Oral Word Association Test

EF- Executive function

EEG- Electroencephalography

ESS-Epworth Sleepiness Scale

FIQ- Full IQ

HADS- Hospital Anxiety and depression Scale

HC-Healthy controls

ICT Information and Communication Technologies

IQ- Intelligence Coefficient

LTM- Long term memory

MCI- Mild cognitive impairment

MIST- Memory for Intention Screening test

ME- Measured sleep

NART- National Adult Reading test

NHS- National Health Service

PAM- Preparatory Attentional and Memory Processes

PFC- Prefrontal cortex

PM- Prospective memory

PIQ- Performance IQ

PRMQ- Prospective and Retrospective Memory Questionnaire

PSQI- Pittsburgh Sleep Quality Index

PT-Patient

QUAL- Qualitative

QUANT- Quantitative

RM- Retrospective memory

SAS- Supervisor attention system

SD- Standard Deviation

SPSS- Statistical Program for the Social Sciences

STM- Short term memory

TOT- Tip-of-the-tongue

VIQ- Verbal IQ

WAIS- Wechsler Adult Intelligence Scale

WM- Working memory