A longitudinal assessment of cytokines and prospective memory functioning in chemotherapy exposed breast cancer patients

By

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Abstract

The present study sought to evaluate whether altered levels of cytokines may be associated with prospective memory (PM) deficits among breast cancer patients, as examined subjectively and objectively in a longitudinal case-control design, and to investigate possible predictors of these disturbances. As patients often complain of cognitive dysfunction, a secondary aim was to examine whether PM may better account for the self-reported deficits, or if dissociations may be attributable to reduced memory self-awareness. Seventeen women with breast cancer were assessed before chemotherapy and three months post-chemotherapy, and were compared with 17 age- and education-matched healthy controls. Patient PM deficits were found to emerge prior to chemotherapy, and IL-18 may be associated with changes in aspects of PM. Patients did not report more difficulties in PM, and subjective-objective associations were not apparent or explained by memory self-awareness. Interventions to ameliorate PM and associates of systemic inflammation should be investigated.

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Introduction

The lifetime probability of women in Canada developing cancer is currently estimated to be about 41%, of which the most prevalent diagnosis is breast cancer (Canadian Cancer Society, 2013). With advancements in cancer treatment there has been growing survivorship, such that the overall 5-year survival rate in breast cancer patients now approaches 90 percent (Canadian Cancer Society, 2013). Despite increases in lifespan, women often complain of persistent disturbances following treatment for breast cancer, particularly poor memory, which can interfere with daily activities, relationships, occupational tasks, thus resulting in diminished quality of life (Boykoff, Moieni, & Subramanian, 2009; Von Ah, Habermann, Carpenter, & Schneider, 2013; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004).

A central paradox remains regarding the nature and time course of treatment-related cognitive deficits. Studies that have assessed memory disturbances have found that breast cancer survivors are more likely to exhibit memory disturbances in comparison to healthy women, with deficits having been reported in immediate and delayed verbal memory (Bender, Sereika, Berga, & Vogel, 2006; Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004; Schagen et al., 1999; van Dam et al., 1998), visual memory (Bender et al., 2006; Castellon et al., 2004; van Dam et al., 1998), as well as in attention and concentration (Schagen et al., 1999; van Dam et al., 1998). It is also generally accepted that cognitive changes remit following the termination of chemotherapy (Ahles et al., 2010; Weis, Proppelreuter, & Bartsch, 2009), although a subgroup of patients may continue to exhibit persistent dysfunction (Kesler & Blayney, 2016; Wefel & Schagen, 2012; Weis et al., 2009).

However, the existing literature on memory functioning in breast cancer survivors has yielded mixed results, as several prospective studies have not found evidence of such impairment

(Hermelink et al., 2007; Jenkins et al., 2006; Mehlsen Pedersen, Jensen, & Zachariae, 2009; Tager et al., 2010). When apparent, memory deficits may be subtle (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Hodgson, Hutchinson, Wilson, & Nettlebeck, 2013; Jim et al., 2012; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006), at least when they are assessed with conventional neuropsychological tests, as was the case in the majority of studies on neurocognitive functioning in chemotherapy treated breast cancer patients (Cheung, Tan, & Chan, 2012). The neuropsychological batteries employed in these studies typically consisted of measures for the assessment of the ability to remember facts from the past when asked to do so (i.e., *retrospective memory*) (Baddeley, 1998). However, it has been consistently reported that the memory complaints of breast cancer survivors have not actually been good predictors of objective memory performance (Ahles et al., 2002; Bender et al., 2006; Castellon et al., 2004; Collins, Paquet, Dominelli, White, & Mackenzie, 2015; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Jenkins et al., 2004; Mehnert et al., 2007; Prokasheva, Faran, Cwikel, & Geffen, 2011; Pullens, De Vries, & Roukema, 2010; Schagen et al., 1999; van Dam et al., 1998; Vardy, Xu, & Booth, 2008; Weis et al., 2009). In fact, complaints have correlated more strongly with measures of mood disturbances (i.e., fatigue and depression) rather than with objective memory functioning (Castellon et al., 2004; Jansen et al., 2008; van Dam et al., 1998; Vardy et al., 2008; Weis et al., 2009). Given the discordant findings regarding subjective reports and objective neuropsychological performance, it has been speculated that the objective measures used in previous studies may not have targeted the primary memory deficits that gave rise to complaints (Pullens et al., 2010; Vardy, 2009).

Prospective memory functioning

Despite the limited evidence for cognitive impairment, breast cancer survivors frequently report clinically important disturbances in their cognition, including difficulties in remembering what they need to do in future instances, such as forgetting scheduled appointments or to return items to the store (Shilling, & Jenkins, 2007; Von Ah et al., 2013). These are examples of failures of *prospective memory*, which comprises the ability to remember to carry out intentions at appropriate times in the future, without being explicitly prompted to do so (Ellis & Kvavilashvili, 2000). Prospective memory may be time-based when it involves remembering that an action must be performed at a particular time (e.g., to take medication at a specific time) or it may be event-based when one has to remember to complete an action in the presence of a future cue (e.g., remembering to tell the doctor to refill a prescription at the next appointment), and it is essential for everyday independent living (Kliegel, Jäger, Altgassen, & Shum, 2008).

Prospective memory is considered to be a domain of metamemory, which involves the self-awareness and self-monitoring of memory functioning, and as is the case with metamemory functioning (Pannu & Kaszniak, 2005; Pannu, Kaszniak, & Rapcsak, 2005), prospective memory is mediated by prefrontal cortical areas of the brain (Burgess, Gonen-Yaacovi, & Volle, 2011; Carey, Woods, Rippeth, Heaton, & Grant, 2006; Costa, Peppe, Caltagirone, & Carlesimo, 2008; McFarland & Glisky, 2009; Momennejad & Haynes, 2012; Raskin, Buckheit, & Waxman, 2012; Raskin et al., 2011; Zogg et al., 2011). Consequently, other patient populations including those with Parkinson's disease (Costa et al., 2008; Raskin et al., 2011; Smith, Souchay, & Moulin, 2011), human immunodeficiency virus infection (Carey et al., 2006; Zogg et al., 2011), and Alzheimer's disease (Troyer & Murphy, 2007), which have been shown to have abnormal structural and functional connectivity of the frontal lobe, exhibit deficits relative to healthy controls when performing prospective memory tasks. Alterations in frontal areas of the brain

have also been reported in neuroimaging studies of breast cancer patients following chemotherapy (Ganz et al., 2013; Jenkins et al., 2016; Kesler, Kent, & O'Hara, 2011; Kesler et al., 2013b; McDonald, Conroy, Smith, West, & Saykin, 2013; Troyer & Murphy, 2007; Wefel & Schagen, 2012), supporting a notion for the presence of prospective memory deficits among breast cancer survivors.

Prospective memory and breast cancer. Several recent cross-sectional studies have shown that breast cancer survivors exhibit deficits on prospective memory tasks when they were assessed within one year of adjuvant chemotherapy exposure (Bedard et al., in press; Cheng et al., 2013; Paquet et al., 2013). In fact, breast cancer survivors have been found to be significantly impaired on a composite score of time- and event-based prospective memory, being 5.5 times more likely to score greater than two standard deviations below the mean of a control reference group (Paquet et al., 2013). In consideration of the specific nature of prospective memory deficits, differentially localized prospective memory impairments have been observed, with deficits only being evident during event-based tasks, at least in one study (Cheng et al., 2013), when prospective memory was evaluated using an adapted experimental paradigm (Katai, Maruyama, Hashimoto, & Ikeda, 2003) that had participants tapping on a desk while categorizing words. In this manner, time-based tasks consisted of instructing participants to tap on a desk every five minutes, while event-based tasks required participants to tap at the occurrence of two animal names appearing during the word categorizations. However, it has been well established that time-based tasks are generally more reliant on frontal areas of the brain (Burgess, Quale, & Frith, 2001; Burgess Gonen-Gonnaud et al., 2014; Carey et al., 2006; Costa et al., 2008; Mcfarland & Glisky, 2009; Volle, Gonen-Yaacovi, Costello Ade, Gilbert, & Burgess, 2011; Zogg et al., 2011), as they place greater demands on self-initiated cue monitoring

and intention retrieval processes (Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997), and so it is a contention of the present study that the differential impairments observed may have been the result of a differential cognitive load imposed between the time- and event-based tasks as a result of task selection (Henri, MacLeod, Phillips, & Crawford, 2004).

Consonant with this line of thinking, similar differential event-based deficits have been observed to occur among patients with Parkinson's disease (Katai et al., 2003) when evaluated with the tapping paradigm employed by Cheng et al. (2013), but when prospective memory is assessed with varied time- and event-based tasks, which increases demands on self-initiated encoding and retrieval (Einstein et al., 1995; Einstein, et al., 2005), patients with frontal abnormalities exhibit deficits in both time-based and event-based functioning (Carey et al., 2006; Costa et al., 2008; Raskin et al., 2011; Zogg et al., 2011). Consequently, in yet unpublished data involving comparisons between 80 breast cancer survivors and age- and education-matched controls, using the Memory for Intentions Screening Test (Raskin, 2004; Raskin et al., 2010; Raskin et al., 2011), a measure of prospective memory which includes a variety time-based and event-based tasks, survivors were found to exhibit deficits in both prospective memory subtypes (Bedard, 2014).

Moreover, preliminary evidence suggests that in consideration of the prospective memory deficits that are observed post-chemotherapy, breast cancer survivors display reductions in self-initiated retrieval processes, rather than encoding and the retention of intentions (Bedard et al., in press). This is to say that survivors exhibit deficits in their ability to "remember to remember" a future intention (i.e., referred to as a prospective component), as opposed to failing to remember what they were supposed to remember to do (i.e., retrospective component). In the seminal work

of prospective memory functioning among breast cancer survivors, from which findings of impaired self-initiated retrieval processes were based and which the present study is greatly influenced, it was found that poorer prospective memory performance was predicted by increased fatigue symptomology, which partially mediated the prospective memory deficits evident between survivors and controls (Paquet et al., 2013). These co-occuring disturbances may therefore be part of a psycho-neurological symptom cluster, which is suggestive of a possible common underlying mechanism (Kim, Barsevick, Fang, & Miaskowski, 2012). In this regard, elevations of peripheral pro-inflammatory cytokines have previously been suggested to play a role in depressive symptoms (Wefel, Witgert, & Meyers, 2008; Ganz et al., 2013), fatigue (Alfano et al., 2012) and memory functioning (Ahles & Saykin, 2007; Ganz et al., 2013; Wefel et al., 2008) among cancer patients, and elevated cytokines might similarly be a factor related to the prospective memory deficits evident in chemotherapy exposed breast cancer survivors.

Pro-inflammatory cytokines and cancer

Although most chemotherapeutic agents have not been shown to cross the blood brain barrier (BBB), cytotoxic effects in the central nervous system have been documented following chemotherapy administration. In this regard, signaling molecules of the immune system, cytokines, may be transported across the BBB, bind to cytokine receptors, and promote local inflammation in the frontal lobe (Myers, 2010; Pomykala et al., 2013). Although fairly impermeable to cytokines due to their size and hydrophilic nature, cytokines may enter the brain at spots where the BBB is more vulnerable, including the circumventricular organs (Goehler, Lyte, & Gaykema, 2007), and additional saturated transport mechanisms may allow for cytokine penetration in a limited capacity (Pan et al., 2011). In addition, cytokines may also have indirect effects, with peripheral cytokines stimulating visceral branches of the vagus nerve which may

lead to the release of central cytokines, modulating neurochemical states and altering brain processes (Wilson, Finch, & Cohen, 2002; Wieczorek, Swiergiel, Pournajafi-Nazarloo, & Dunn, 2005). It should be noted that stressful events might also compromise the permeability of the BBB, and allow for greater cytokine activation in the brain parenchyma. Not surprisingly, the diagnosis of cancer and subsequent treatment are both profound psychological stressors (Payne, Sullivan, & Massie, 1996; Hermelink et al., 2015; Reid-Arndt & Cox, 2012), which may be associated with elevated levels of circulating pro-inflammatory cytokines (Denaro, Tomasello, & Russi, 2014).

Standard dose chemotherapy regimens may activate nuclear factor kappa beta (NfKβ), which regulates pro-inflammatory gene products (Aggarwal, Shihodia, Sandur, Pandey, & Sethi, 2006), and standard-dose chemotherapy treatment has been associated with elevated cytokine levels in the periphery (Ahles & Saykin, 2007). Increased pro-inflammatory cytokine concentrations have been suggested to play a role in depressive symptoms (Wefel et al., 2008; Ganz et al., 2013), fatigue (Alfano et al., 2012; Bower et al., 2011), and among breast cancer patients that have been treated with adjuvant chemotherapy, reduced verbal memory has been observed in relation to elevated interleukin (IL)-6 (Kesler et al., 2013a), tumor necrosis factor alpha (TNF-α; Kesler et al., 2013a; Patel et al., 2015), and interferon-α (IFN-α; Ahles & Saykin, 2007). Moreover, higher levels of circulating pro-inflammatory cytokines, including TNF-α (Ganz et al., 2012; Ganz et al., 2013; Pomykala et al., 2013) and IL-6 (Cheung et al., 2015; Pomykala et al., 2013) have been associated with increased memory complaints in chemotherapy-exposed patients.

Given these associations, an assessment of the relationships between cytokine concentrations and objectively measured as well as subjectively reported prospective memory

functioning may offer important insights into possible mechanisms of cognitive deficits experienced by breast cancer patients. Moreover, it remains unclear whether the prospective memory deficits are a result of chemotherapeutic treatments or if they are exacerbated by chemotherapy, and this uncertainty is additionally confounded as an increasing number of studies have revealed that patients may exhibit cognitive deficits prior to the initiation of chemotherapy (Ahles et al., 2008; Hermelink et al., 2007; Jansen, Cooper, Dodd, & Miaskowski, 2011; Mandelblatt et al., 2014), which is documented to occur in up to a third of individuals (Ahles et al., 2008; Janelsins et al., 2011). Breast cancer patients exhibit more diffuse functional and structural frontal connectivity prior to starting chemotherapy (Askren et al., 2014; Menning et al., 2015; Scherling et al., 2012), which has also been associated with greater levels of fatigue (Askren et al., 2014; Menning et al., 2015). Thus, it is conceivable to expect that prospective memory deficits may be present prior to chemotherapy among breast cancer patients. Although fatigue may predict prospective memory functioning following chemotherapy (Paquet et al., 2013), it is not certain whether this may be the case as assessed subjectively and objectively prior to chemotherapy, what the temporal nature of these relationships may be, and whether changes in levels of circulating pro-inflammatory cytokines are associated with changes of these factors.

As indicated earlier, lower quality of life has been observed following chemotherapy treatment (Byar, Berger, Bakken, & Cetak, 2006; Ganz et al., 2002; Jenkins et al., 2016), which may be linked to levels of pro-inflammatory cytokines among breast cancer survivors (Sprod et al., 2012). Preliminary work indicated that increases in pro-inflammatory cytokines and decreases in quality of life occur from pre- to post-chemotherapy for some breast cancer patients, but limitations of sample size have precluded an evaluation of correlations between these factors (Jenkins et al., 2016). Breast cancer survivors that report cognitive dysfunction exhibit lower

quality of life (Boykoff et al., 2009; Debess, Riis, Pedersen, Ewertz, 2009; Von Ah et al., 2013), and may also exhibit dysregulated levels of pro-inflammatory cytokines (Cheung et al., 2015; Ganz et al., 2012; Ganz et al., 2013; Pomykala et al., 2013), but it remains unclear whether self-reported prospective memory deficits may be associated with changes in quality of life, and similarly if changes in circulating cytokines may correspond with alterations in reported quality of life.

Present study

As metamemory processes including prospective memory are reliant on the frontal lobe (Fleming & Dolan, 2012), it may be that the lack of an association between subjective and objective measures of cognitive functioning in previous studies may have been due to the measures used not being sufficiently sensitive to neuropsychological deficits that are experienced by breast cancer survivors in daily life (Pullens et al., 2010; Vardy, 2009), and thus it has been proposed that investigations of prospective memory may be more consonant with complaints (Collins et al., 2015; Paquet et al., 2013). Alternatively, the subjective-objective dissociation may have stemmed from decreased self-awareness or memory self-monitoring abilities. Among patients with Parkinson's (Smith et al., 2011; Souchay, Isingrini, & Gil, 2006) and Alzheimer's diseases (Moulin, 2004; Souchay, Isingrini, & Gil, 2002; Shaked et al., 2014), metamemory impairments in the judgement of neuropsychological test performance have been observed, such that these patients have a tendency to overestimate cognitive performance (Smith et al., 2011; Souchay et al., 2002; Souchay et al., 2006). To date, there has only been one published study that has examined metamemory functioning in breast cancer patients (Collins et al., 2015), and although breast cancer survivors exhibited a greater discrepancy between subjective and objective measures, having reported more dysfunction than was actually observed, patient

metamemory functioning did not differ from controls, and no evidence of a correlation between metamemory indices and subjective-objective disparities were found. Given the paucity of data on metamemory in breast cancer patients, and as metamemory deficits have been found to co-occur with prospective memory impairments among patients with Parkinson's disease (Smith et al., 2011), evidence for disruptions in metacognition should still be explored.

Prospective memory is a central aspect of successful daily functioning, but it remains unclear whether deficits originate prior to chemotherapy and what mechanisms may possibly underly prospective memory impairments and associative symptoms. As such, the primary objective of the present investigation was to assess if changes in pro-inflammatory cytokines are associated with changes in prospective memory functioning, as assessed subjectively and objectively, as well as with levels of fatigue, depressive symptomology, and quality of life. This is, as it seems, the first longitudinal study examining these factors before chemotherapy and after chemotherapy for breast cancer. Moreover, it is of interest to examine whether the prospective memory deficits may be more broadly based across time- and event-based tasks, as has been evidenced in previous work (Bedard et al., 2014), and to examine whether findings of deficits in self-initiated retrieval (i.e., the prospective component) may be corroborated (Bedard, in press), as well as evaluate for the presence of any temporal variations that may exist.

A final aim of this study was to explore the potential influence of metamemory accuracy in explaining any relationship between subjective and objective prospective memory performance.

Materials and methods

Participants

This study was approved by the Research Ethics Boards at our institutions which are responsible for reviewing studies involving human participants. A convenience sample of 17 breast cancer (stage I, II or IIIa) patients, which had already received local treatment (i.e., surgery), and for whom a course of standard adjuvant chemotherapy was planned were recruited by their medical oncologist at The Ottawa Hospital Cancer Centre. Seventeen healthy controls age-matched (within five years) to patients were recruited from public recruitment notices and at community events. Participants were excluded if they had a prior history of any other cancer, metastatic disease, prior exposure to chemotherapy or radiation therapy, or had documented depression, psychiatric, or substance abuse disorders. Thirty-one patients were approached, of these, 13 refused to participate and one patient was withdrawn from the study as they were not administered chemotherapy. Of the 23 eligible controls, six refused to participate.

Study procedure

Patients were informed of the study at an appointment with their oncologist prior to the initiation adjuvant chemotherapy. Interested participants were sent written consent forms and questionnaire packages by mail, which were returned during subsequent memory testing sessions. Data collection for the patients was carried out at two time-points. The first testing session (T1) was at baseline prior to chemotherapy, and the second time-point (T2) occurred at three months after the final cycle of chemotherapy, a time of assessment chosen as it has been used in previous cross-sectional studies of prospective memory among breast cancer (Bedard et al., in press; Paquet et al., 2013). The healthy controls completed one testing session.

Measures

Quality of life. Quality of life was measured with the Functional Assessment of Cancer Therapy - General (FACT-G; Cella et al., 1993; see Appendix A), which is a 27-item five-point

likert-scale, which comprises four subscales including: physical well-being (PWB), functional well-being (FWB), emotional well-being (EWB), and social well-being (SWB). Responses may be summed for a total ranging from 0-108, with higher scores indicating greater quality of life. The FACT-G has excellent internal reliability (Cronbach's alpha of .91), and each of the subscales have demonstrated good Cronbach's alphas ranging from .68 to .90 (Cella, Hahn, & Dineen, 2002). In the present study, Cronbach's alpha for the FACT-G at T1 was .88, .95 at T2, and .84 for controls.

Fatigue. Fatigue was measured with the Functional Assessment of Chronic Illness Therapy – Fatigue scale (FACIT-F; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997) which is a self-reported measure comprising 13 items rated on a five-point likert-scale ranging from zero to four, and a copy of which is presented in Appendix E. Higher scores on the FACIT-F indicate *less* fatigue. The FACIT-F has demonstrated internal consistency with Chronbach's alpha of .91 (Butt et al., 2013), and in the present study, Cronbach's alphas were .81 for controls, and .93 and .96 for patients at T1 and T2, respectively.

Depression. Depressive symptomology was assessed by the Center for Epidemiologic Studies Depression (CES-D; Radloff, 1977; Appendix F) scale, a 20-item self-report scale used to measure depressive symptomatology in the general population. Items are scored on a 4-point likert scale ranging from zero to three, with higher scores indicating more depressive symptoms. The CES-D has excellent internal consistency with a Chronbach's alpha of .91 and a retest reliability of .87 (Miller, Anton, & Townson, 2008). In the present study, the CES-D demonstrated acceptable internal reliability with a Cronbach's alpha of .65 for controls, .94 for patients at T1, and .81 at T2.

Prospective memory. Participants were administered the Memory for Intentions Screening Test (MIST; Raskin, 2004; Raskin et al., 2010), a standardized clinical test of prospective memory. Administration instructions for the MIST are provided in Appendix H. Briefly, the test requires participants to complete eight PM tasks while working on a word search as an ongoing task. Briefly, the MIST is composed of four event-based tasks (e.g., "When I hand you a red pen, sign your name on your paper"), which are accorded a score of two if performed correctly, or zero if incorrect. In addition, four of the tasks are time-based (e.g., "In 15 minutes, tell me that it is time to take a break"), which were given a score of 2 if the task was performed at the correct time, 1 if either the correct task was performed at an incorrect time, or if the participant remembered the time, but forgot the task or substituted the task with another one. A score of zero for time-based trials is given if the time and the task were both incorrect. Total scores on the MIST range from 0 to 48, higher scores indicating better prospective memory. At the baseline assessment, participants were administered Form A, and at T2, Form B was used, which includes different four different event-based and four new time-based tasks, in addition to a separate word search form to limit practice effects (Raskin et al., 2010).

At the completion of the MIST, 8 multiple choice items are given to assess recognition of the prospective memory intentions, which provides a measure of cue encoding and retention. Therefore, deficits noted from the recognition test are indicative of impairments of the retrospective component. Furthermore, the MIST includes a set of error codes that are accorded for trials in which errors were made. The error codes included: omission errors (i.e., failing to respond to a cue), task substitutions (e.g., replacement of the response on a trial by an intention for another trial), loss of content (e.g., recognizing that a response is required, but failing to recall the intention), loss of time (i.e., performing an intention greater than one minute before or

after the cue). Omission errors are indicative of a failure of the prospective component, whereas task substitution and loss of content errors likely reflect failure of the retrospective component (although task substitution may also indicate deficits in executive control), and loss of time errors reflect difficulty with strategic time monitoring (Raskin et al., 2010; Raskin et al., 2011).

Everyday memory. The Prospective and Retrospective Memory Questionnaire (PRMQ; Smith, Della Sala, Logie, & Maylor, 2000; Appendix G) was used to measure self-reported prospective memory functioning as it occurs in everyday life. The scale consists of 16 items scored on a 5-point likert scale, with 8 items summed to form a retrospective memory scale and another 8 items used to create a prospective memory subscale.

The only objective index of retrospective memory in the present study is the recognition test as part of the MIST, included to measure the retrospective component of prospective memory. However, previous studies among Parkinson's patients (Raskin et al., 2011) and breast cancer survivors (Bedard et al., in press) have shown that both controls and respective patients make very few mistakes on this recognition test, such that it is not a sensitive measure of general retrospective memory functioning. Thus, as the present study is only interested in associations between subjective and objective measures of prospective memory as well as predictors of subjective memory, having not otherwise evaluated retrospective memory, only scores corresponding to the prospective memory subscale were examined. Higher scores on this subscale are indicative of more prospective memory slips in everyday life. The prospective memory subscale of the PRMQ has evidenced acceptable Chronbach's alpha of .84 (Crawford, Smith, Maylor, Della Salla, & Logie, 2003), which was also observed in the present study as items on the prospective memory subscale for controls had a Chronbach's alpha of .84, and .82

and .89 for patient T1 and T2 time-points, respectively. T1 Chronbach's alpha of .82, T2 Chronbach's alpha of .89, control Chronbach's alpha of .84.

Metamemory judgements. Prior to starting the MIST, participants were asked to provide a percentage prediction of the tasks that they expected to remember to perform on the MIST, on a 100-point scale. After completion of the MIST, participants were then asked to indicate a postdiction for the percentage of tasks they feel that they performed, which was rated on the same percent scale as the prediction. Accuracy of memory predictions may be operationalized as signed or unsigned differences between predictions and actual performance (Hertzog, Dixon, & Hultsch, 1990), however, the use of signed differences does not allow for the interpretation of group means (Moulin, 2004). Therefore, as with previous studies assessing metamemory accuracy in breast cancer (Collins et al., 2015), as well as other patient populations (Moulin, Perfect, & Jones, 2000; Smith et al., 2011; Souchay et al., 2006), unsigned absolute difference scores were evaluated in the present study.

Cytokine analysis. At each time-point, a 10-ml sample of blood was drawn from the participants before the memory test, placed in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 1140 g (2500 RPM) for 15 minutes within 30 minutes of collection. Plasma was then immediately aliquoted into Eppendorf tubes and stored at -80^{o}C until analysis. Cytokine levels were quantified in duplicate with high sensitivity Quantikine ELISA kits obtained through R&D Systems, Inc. (Minneapolis MN, USA), according to the manufacturer's instructions. Each cytokine was assessed in a single run to eliminate inter-assay variability, and intra-assay variability was less than 12%.

Statistical analyses

All statistical analyses were performed using SPSS version 21. The significance level

was set at $p < .05$ for all tests. A-priori power analyses with the use of G*Power (version 3.1.9.2), demonstrated that a sample size of 17 case-control pairs was capable of detecting only large size effects (between-group differences and changes between time-points) with a power > 0.80. The accuracy of prediction and postdiction judgements were measures of non-directional discrepancy, such that they were calculated as the unsigned difference (i.e., absolute difference) between the MIST summary scores (converted to a percentage of the total possible MIST score) and each of the predictions and postdictions, respectively, for each participant. Change scores taking the difference between T2 and T1 were also calculated for each of the cytokines, subjective and objective prospective memory variables, fatigue, depression, and quality of life variables.

All continuous data were screened for normality using skewness z-tests, and most were found to skewed with the exception of age, years of education, MIST total scores, scores on the time-based scales, and control event-based scores, scores on the PRMQ, and levels of IL-18. Moreover, T1 scores of total quality of life, physical well-being, emotional well-being, and functional well-being, in addition to T2 levels of functional well-being and physical well-being, scores for control social well-being, emotional well-being were not found to be skewed. However, evaluation of the difference scores for within-subject analyses between time-points for each variable, and for between-subject analyses for each variable, revealed that most were normally distributed with the exception of all prediction and postdiction accuracy scores, which were positively skewed, and scores on the recognition test which were negatively skewed. In addition, skewed difference scores were found for IL-6, physical well-being and emotional well-being which were positively skewed within patients at T1 and T2, and between time-point scores on IL-18, EPO which were negatively skewed, as well as depressive scores which were

negatively skewed, and positive skew was noted for loss of time and task substitution errors between controls and patients at T1, and finally, task substitution errors between controls and patients at T2 were positively skewed.

Transformations. Normality was achieved for most of the skewed variables using logarithm and square root transformations, as indicated below, according to recommendations by Tabachnick and Fidell (2013), by first applying square root transformations and then logarithmic transformations for variables that remained skewed. Normality was again checked following transformations with the use of skewness z-tests.

Square root transformations. Square root transformations on associated variables were found to alleviate T2-T1 skewed difference scores for emotional well-being, physical well-being, and EPO, as well as control and T1 difference scores for loss of time and task substitution errors, and for task substitution difference scores between controls and patients at T1. Square root transformations were also applied to T1, T2, and control levels of fatigue (negatively skewed), pre- as well as postdiction accuracy scores (positive skew), in addition to alleviate negative skew observed among T2 levels of emotional well-being, and control levels of functional well-being.

Logarithmic transformations. Logarithmic transformations were applied on associated variables, such that difference scores between controls and patients at T1 for recognition and depression scores, as well as T2-T1 difference scores for concentrations of IL-6 were found to be normally distributed. Logarithmic transformations normalized the T1, T2, and control variable data involving BDNF, TNF- α, EPO, IL-6, and levels of depression, which exhibited positive skew, with the exception of T1 levels of IL-6, and T2 levels of EPO which remained skewed following logarithmic transformation. Logarithm transformation was also applied to control and T2 levels of total quality of life, control levels of physical well-being, and T1 and T2 levels of

social well-being, which were all previously negatively skewed.

Transformations were not found to normalize the data involving T2-T1 difference scores on the recognition test, or for levels of IL-18, in addition to control and T2 differences on recognition test scores.

Analyses. Consequently, Wilcoxon Signed Ranks Tests for paired samples were used for differences between controls and patients at T2 and for within-patient differences between time-points involving recognition test scores, and IL-18. All other between group comparisons and mean changes between T1 and T2 were based on paired-sample t-tests (using the transformed variables as indicated above), and categorical data were analyzed with McNemar χ^2. For each participant, MIST total scores were transformed into Z-scores, using the control group mean and standard deviation. Moderate impairment was defined as scoring two standard deviations below the mean performance of the control group on the MIST, as outlined in international recommendations (Wefel, Vardy, Ahles, & Schagen, 2011) and used in other studies (Ahles et al., 2008; Paquet et al., 2013). McNemar χ^2 was used to determine differences in impairment rates between groups.

To evaluate whether prospective memory functioning among breast cancer patients were impaired in event-based versus time-based tasks, two repeated measures analyses of variance using group (patient versus control) and cue type (time-based versus event-based) as within-subjects variables were performed separately for T1 and T2. Although event-based prospective memory variables for patients at both time-points were found to be skewed, results did not change when a nonparametric approach to testing the statistical interaction was used. Planned follow-up pairwise comparisons were conducted using paired-samples t-tests for analyses involving the time-based scales, and differences on the event-based scale were assessed with

Wilcoxon Signed Ranks Tests.

To assess relationships between changes in cytokine levels and prospective memory as well as fatigue, depression, and quality of life, change scores were calculated taking the difference between T2 and T1 scores for each of these variables. Correlation was used to evaluate the predictors of objective and subjective prospective memory as well as to evaluate bivariate correlations between changes in cytokines to changes in objectively and subjectively measured prospective memory, fatigue, depression, and quality of life (Pearson product moment for parametric data and Spearman's rho for non-parametric). Bivariate relationships between levels of fatigue, depression and the quality of life measures were also examined with Pearson's product-moment correlations.

As it was of interest to assess whether prediction and postdiction accuracy differed between groups at T1 and at T2, two repeated measures analyses of variance were conducted using group (patient versus control) and unsigned accuracy scores (prediction versus postdiction) as within-subjects variables, separately for each time-point.

Results

Participant demographics

Participant demographic and clinical characteristics are summarized in Table 1. The two groups were similar with regard to age, $t(16) = -0.139$, $p = .891$, and perhaps due to older age ($M = 57.82$), a large majority of the patients (88.2% vs. 11.8%) as well as controls (100% vs. 0%) were post-menopausal at the time of the baseline assessment, proportions of which were not found to differ between groups (McNemar χ^2, $p = .50$). Moreover, evaluation of confidence intervals indicated that, as the 95% confidence intervals included values between -2 and 2, the control-patient pairs were also found to be matched within two years of education, $t(16) = 2.41$,

95% CI = 4.19 to .63. At T2, all patients had completed chemotherapy with a mean time of 3.4 months since their last chemotherapy treatment. Fifty-nine percent of the patients were receiving endocrine therapy, and 82% had been given radiotherapy.

Table 1

Demographic and Clinical Characteristics of the Breast Cancer Patients and Healthy Controls

	Total sample (N = 34)	Patients (n = 17)	Control (n = 17)	p-value
Age, mean (SD, range)	57.82 (6.033, 45-69)	57.76 (7.30, 45-69)	57.88 (4.66, 50-69)	.891
Education, mean (SD, range)	16.38 (3.26, 10-21)	15.18 (3.63, 10-21)	17.59 (2.37, 12-21)	.011
Menopausal status				
Pre-menopausal (%)	5.9	11.8	0	.500
Post-menopausal (%)	94.1	88.2	100	
Treatment received				
Chemo only (%)		0		
Chemo & radiation (%)		41		
Chemo & endocrine (%)		18		
Chemo & radiation, & endocrine (%)		41		
Months elapsed since end of chemo, mean (SD, range)		3.47 (.72, 3-5)		

Depressive symptoms and fatigue

As displayed in Table 2, breast cancer patients had more fatigue at T1 (i.e., lower FACT-F scores), $t(16) = -3.016$, $p = .008$, and higher levels of depressive symptomology compared to the controls, $t(16) = 2.417$, $p = .029$. At T2 follow-up, the breast cancer patients had greater depressive symptomology compared to the controls, $t(16) = 5.118$, $p < .001$, but also in comparison to their baseline levels of depression, $t(16) = 3.766$, $p = .002$. Levels of fatigue at T2 were not found to differ from patient baseline levels, $t(16) = .167$, $p = .870$, such that patients were also more fatigued than controls at T2, $t(16) = -2.326$, $p = .033$. As can be seen in Table 3, levels of fatigue and depression were found to be significantly correlated at both T1 ($p < .01$) and T2 ($p < .05$), such that greater fatigue symptomology co-occurred with greater levels of depression.

Quality of life

Breast cancer patients had lower total quality of life at baseline as compared to controls, $t(16) = -3.543$, $p = .003$ (see Table 2). At T2, overall quality of life among patients exhibited a trend toward higher scores from baseline levels, $t(16) = 1.861$ $p = .081$, such that patients evidenced a lower trend toward significance as compared to controls, $t(16) = -1.899$, $p = .076$.

Patients reported lower physical well-being ($p = .026$), emotional well-being ($p < .001$), and functional well-being ($p < .001$) in comparison to controls at baseline, although scores on social well-being did not differ between groups *(*$p = .722$). At T2, Patients were found to have increased emotional well-being ($p = .007$), and functional well-being ($p = .040$) compared to baseline levels, such that they no longer differed from controls with regards to emotional well-being ($p = .135$), but were still lower than controls on functional well-being ($p = .009$). Social well-being and physical well-being at T2 were not found to differ from levels at T1 ($p = .608$ and

p = .540, respectively), such that physical well-being was still lower amongst patients (p = .019), and social well-being did not differ compared to controls (p = .923).

Correlations between fatigue, depression, and the measures of quality of life at T1 and T2 are presented in Table 3. Of note, positive bivariate relationships were established between levels of fatigue and total quality of life, as well as physical well-being, functional well-being, and social well-being at both T1 and T2 (ps < .01), indicating that lower fatigue symptomology was associated with these indices of quality of life. However, fatigue was not found to be associated with emotional well-being at either time-point (ps > .05). Negative correlations were observed between total quality of life (p < .01), as well as physical well-being (p < .05), and functional well-being (p < .01) with levels of reported depression at both time-points, in addition to emotional well-being and social well-being at T2 (ps < .05). Depression was however not found to be related with emotional or social well-being at T1 (ps > .05).

Table 2

Means and Standard Deviations Across Measures as a Function of Group Membership and Time-point

	Breast cancer (*n* = 17)				Controls (*n* = 17)	
	T1		T2			
	Mean	SD	Mean	SD	Mean	SD
Depression (0-60)	11.35	9.67	17.23	6.88	6.41	4.57
Fatigue (0-52)	39.61	8.83	39.88	11.71	47.23	4.84
Total quality of life (0-108)	82.42	13.32	86.71	15.52	95.45	10.89
PWB (0-28)	23.55	3.67	23.0	4.31	26.21	2.44
SWB (0-28)	23.16	4.64	23.58	5.15	23.74	4.03
EWB (0-24)	17.07	3.33	19.54	3.24	21.35	3.07
FWB (0-28)	18.65	4.90	20.59	4.90	24.14	3.18
Objective PM						
MIST summary score (0-48)	35.65	10.28	35.47	7.74	43.76	4.25
Impairment rates (%)	35.30		29.40		5.90	
Time-based (0-8)	5.06	1.95	5.24	1.44	7.18	0.95
Event-based (0-8)	6.82	2.01	6.59	1.70	7.41	0.94
Ongoing word search (0-40)	28.88	5.88	29.94	6.33	30.71	4.04
Recognition (0-8)	7.53	1.01	7.35	0.79	7.82	0.39
24-hour delayed task (0-2)	0.71	0.99	0.88	0.99	0.59	0.99
MIST error types						
Omission	0.59	0.71	0.41	0.51	0.29	0.51
Loss of content	1.00	1.06	0.76	0.83	0.41	0.71
Task substitution	0.59	0.94	0.59	0.87	0.06	0.24
Loss of time	0.88	0.86	0.88	0.99	0.12	0.33
Subjective PM	17.88	4.14	19.35	5.31	18.06	4.34
Metamemory						
Prediction (0-100)	65.59	22.19	68.53	27.40	74.71	23.55
Postdiction (0-100)	78.82	25.19	74.12	23.55	80.88	22.17
Prediction accuracy	22.65	22.50	18.90	12.30	20.44	19.02
Postdiction accuracy	11.32	10.94	21.54	14.66	13.68	17.52
Cytokine levels						
TNF-α (pg/mL)	1.91	1.42	2.27	1.78	2.23	0.85
Il-6 (pg/mL)	5.69	16.22	5.87	9.34	1.55	1.09
Il-18 (pg/mL)	272.96	52.20	322.02	90.87	240.84	34.79
BDNF (pg/mL)	4326.76	2810.68	3329.63	3034.19	3802.68	2484.23
EPO (mIU/mL)	10.60	4.38	17.11	18.48	7.53	3.34

Note. PM = prospective memory; PWB = physical well-being; SWB = social well-being; EWB = emotional well-being; FWB = functional well-being.

Table 3

Bivariate Correlations Between Measures of Fatigue, Depression, and Quality of Life at T1 and T2 for Breast Cancer Patients

	Fatigue	Depression	TQOL	PWB	FWB	EWB	SWB
Fatigue	-	-.596*	.733**	.920**	.829**	.253	.723**
Depression	-.647**	-	-.440	-.666**	-.701**	-.584*	-.490*
TQOL	.809**	-.684**	-	.744**	.860**	.653**	.814**
PWB	.767**	-.596*	.811**	-	.842**	.403	.728**
FWB	.756**	-.659**	.945**	.711**	-	.636**	.759**
EWB	.293	-.341	.607**	.427	.489*	-	.385
SWB	.667**	-.318	.867**	.417	.745**	.236	-

Note. TQOL = total quality of life; PWB = physical well-being; SWB = social well-being; EWB = emotional well-being; FWB = functional well-being; Correlations below the diagonal represent bivariate relationships at T1, whereas those above the diagonal indicate those at T2; * $p < .05$, ** $p < .01$.

Prospective memory test

As shown in Table 2, at baseline the breast cancer patient group performed more poorly than controls on the MIST, $t(16) = -2.985$, $p = .009$, Cohen's $d = 0.72$. Although patients had lower mean scores on the MIST at T2 compared to patient baseline scores, paired-samples t-tests revealed that MIST performance did not significantly differ between time-points, $t(16) = .074$, $p = .942$, such that the patients at T2 performed more poorly than controls on the MIST, $t(16) = 3.53$, $p = .003$, Cohen's $d = 0.85$. As also indicated in Table 2, after applying the criteria for the classification of moderate impairment, 5% of the controls exhibited prospective memory impairment compared to 35.3% of the patients at T1 (McNemar χ^2, $p = .063$, OR = 8.72, 95% CI = 0.918 to 82.962) and 29.4% at T2 (McNemar χ^2, $p = .219$, OR = 6.67, 95% CI = 0.686 to 64.775).

Differences between breast cancer patients and controls on the components of the MIST are presented in Table 2. There was no difference between groups at either time-point on the on-going word search (ps > .05), or between time-points for patients ($Z = -1.403$, $p = .161$). Patients did not differ from controls on the multiple-choice recognition test at baseline ($t = -.940$, $p = .361$) and similarly did not exhibit any significant change across time-points ($Z = -1.136$, $p = .256$).

The baseline repeated measures ANOVA revealed a main effect of group $F(1,16) = 8.909$, $p = .009$, $\eta^2 = .358$, with patients performing worse than controls, and a main effect of task type was found, $F(1,16) = 16.000$, $p = .001$, $\eta^2 = .500$, with lower time-based performance at T1. These main effects were accompanied by a significant interaction between group and cue type, $F(1,16) = 5.878$, p .028, $\eta^2 = .269$. Subsequently, pairwise comparisons indicated the presence of a significant effect of patients on the time-based scale ($p = .002$, Cohen's $d = -0.90$),

however, the effect of patients on the event-based scale was not significant (p = .305, Cohen's d = -0.26).

Similarly, in evaluating performance at T2, a repeated measures ANOVA uncovered a main effect of group $F(1,16) = 12.445$, $p = .003$, $\eta^2 = .438$, with poorer performance amongst patients, and a main effect of task, $F(1,16) = 7.967$, $p = .012$, $\eta^2 = .332$, with lower performance on time-based tasks. Once again, a significant interaction between group and task type was found, $F(1,16) = 5.014$, $p = .040$, $\eta^2 = .239$. Pairwise comparisons revealed a significant effect of patients on the time-based scale (p = .001), which was accompanied by a large Cohen's d (Cohen's d = -0.99) corresponding to a large effect. In contrast, the patient effect on the event-based scale was found to be on trend (p = .083, Cohen's d = -0.44).

Analyses of error types revealed that the patients made more errors of task substitution (p = .044) and loss of time ($p < .001$) at baseline and at T2 (p = .012 and p = .008, respectively at T2) as compared to controls. In addition, "omission" and loss of content errors at T1 exhibited higher trends towards significance as compared to controls (both ps = .096). No other error types differed across groups or time-points for patients (ps >.05).

Self-reported prospective memory

Subjective prospective memory functioning was not found to differ between groups at baseline, $t(16) = .154$, $p = .879$, or between the controls and patients at T2, $t(16) = .797$, $p = .437$ (Table 2). Although the patients reported having experienced slightly more prospective memory slips at T2 as compared to baseline levels, the difference was not statistically significant, $t(16) = 1.180$, $p = .255$.

Baseline prediction and postdiction accuracy

Analyses of raw predictions indicate that the patient group made lower predictions on

MIST performance at baseline than the control group although this difference was not statistically significant, $t(16) = -1.981$, $p = .065$ (Table 2). Following administration of the MIST, raw postdictions were not found to differ between the patient group and the control group, $t(16) = 0.268$, $p = .792$.

The ANOVA uncovered a main effect of prediction/postdiction accuracy, $F(1, 16) = 7.196$, $p = .016$ $\eta^2 = .310$, with postdictions being more accurate than predictions in relation to actual performance on the MIST (Table 2). There was no main effect of group, $F(1, 16) = 0.20$, $p = .890$, $\eta^2 = .001$, for prediction/postdiction accuracy, and the interaction between group and prediction/postdiction accuracy was not significant, $F(1, 16) = 0.50$, $p = .825$, $\eta^2 = .003$.

T2 prediction and postdiction accuracy

At T2 follow-up, the patient raw predictions were not found to differ from patient baseline raw predictions, $t(16) = 0.560$, $p = .583$, and although lower, patient raw postdictions at T2, were not found to differ significantly from those at baseline, $t(16) = -0.607$, $p = .553$ (see Table 2).

The repeated measures ANOVA did not reveal a main effect of prediction/postdiction accuracy, $F(1, 16) = 1.390$, $p = .256$ $\eta^2 = .080$, such that predictions and postdictions for controls and patients at T2 did not differ in terms of accuracy in relation to actual performance on the MIST. The ANOVA did not reveal a main effect of group, $F(1, 16) = 1.623$, $p = .221$, $\eta^2 = .092$, for prediction/postdiction accuracy, such that the interaction between group and prediction/postdiction accuracy was also not significant, $F(1, 16) = 1.533$, $p = .234$, $\eta^2 = .087$.

Cytokine levels

Means and standard deviations of cytokine levels are displayed in Table 2. No statistically significant differences were observed across the time-points or between the controls

and patients at either time-point for concentrations of IL-6, TNF-α, and BDNF (*p*s > .05). A non-significant trend towards higher levels of IL-18 at T1 as compared to controls was evidenced (*p* = .071), which at T2 was found to be significant (*p* = .009), as patients had greater concentrations of IL-18 at T2 as compared to T1 levels (*p* = .028). Compared to controls, concentrations of EPO at T1 were found to be higher among patients (*p* = .026), and were found to increase from baseline levels (*p* = .037), such that patients also had higher concentrations of EPO at T2 as compared to controls (*p* = .044). Of note, a large proportion of the participants had IL-10 (patients = 58.8%; controls = 88.2%), and IFN-α (patients = 82.4%-100%; controls = 82.4%) concentrations that were below the detection limit at T1 and T2. As a result, intra-assay variability for those cytokines was markedly higher (over 47%) and so they were not considered in further analyses.

Predictors of objective prospective memory

As can be seen in Table 4, neither age, menopausal status, education, depressive scores, levels of fatigue, subjective prospective memory, total quality of life or any of the subscales of the FACT-G were found to predict objective prospective memory as assessed with the MIST, at any of the time-points for patients or for controls (all *p*s >.05). All of the controls were post-menopausal, which precluded correlational analyses for this factor among controls. In addition, the number of months since the completion of chemotherapy at T2 was not found to influence MIST scores (*p* = .259). Univariate analyses of the relationship between concentrations of circulating cytokines and MIST summary scores revealed that none of the cytokines predicted prospective memory functioning for controls or at any time-point for patients (*p*s > .05).

Table 4

Predictors of MIST Summary Scores for Patients and Controls

	Breast cancer (n = 17)					
	T1		T2		Controls (n = 17)	
Variables	r	p-value	r	p-value	r	p-value
Age	-.089	.735	-.355	.162	.191	.463
Menopausal status	.244	.346	.191	.463	-	-
Education	.102	.696	-2.77	.282	.077	.770
Months elapsed	-	-	-.290	.259	-	-
Depression	-.150	.567	.243	.348	-.091	.727
Fatigue	.165	.527	-.127	.626	-.236	.361
Subjective PM	-.208	.422	-.406	.106	.350	.168
Total quality of life	.066	.800	.334	.191	-.179	.491
PWB	.095	.717	.118	.652	-.247	.339
FWB	.035	.895	-.174	.504	-.032	.902
EWB	-.096	.715	.295	.251	-.245	.344
SWB	.020	.940	.395	.116	-.066	.801
Cytokine levels						
TNF-α	-.065	.804	.269	.296	-.328	.198
Il-6	.032	.903	.172	.509	.154	.568
Il-18	-.282	.272	.189	.467	-.119	.650
BDNF	.086	.742	.276	.283	-.213	.413
EPO	.140	.592	.118	.652	.298	.245

Note. r indicates Pearson's correlation except for correlations involving menopausal status, T1 IL-6 and T2 EPO levels, in which case r indicates Spearman's rho; PM = prospective memory; PWB = physical well-being; SWB = social well-being; EWB = emotional well-being; FWB = functional well-being.

Predictors of subjective prospective memory

Results from univariate analyses including predictors of self-reported subjective prospective memory are presented in Table 5. Age, education, and menopausal status were not found to predict subjective prospective memory complaints at any of the observation points (all *p*s > .05), and time elapsed since chemotherapy was not found to predict subjective prospective memory at T2 ($p = .860$). However, greater depressive symptoms were found to be associated with lower subjective prospective memory at T1 ($p = .002$) and at T2 ($p = .002$), but this was not the case for controls ($p = .107$). Reported levels of fatigue at T1 or for controls were not found to be predictive of subjective complaints (*p*s > .05), but more fatigue at T2 was associated with greater subjective complaints at T2 ($p = .001$).

Correlations between measures of quality of life and subjective complaints revealed that lower total quality of life, as well as physical well-being and functional well-being on the FACT-G were associated with greater subjective prospective memory scores across all observations (all *p*s < .05), with the exception of controls, for which functional well-being was on trend to predicting subjective reports ($p = .070$). Although social well-being was not found to be predictive at T1 or for controls (*p*s > .05), lower social well-being did significantly predict elevated complaints at T2 ($p < .001$). Emotional wellbeing was not found to be correlated with subjective prospective memory functioning for controls or for patients at either time-point (*ps* > .05). Moreover, none of the cytokine concentrations were found to be associated with self-reported prospective memory functioning for the controls or at any time-point for the patients (*p*s > .05).

Table 5

Predictors of Subjective Prospective Memory for Patients and Controls

	Breast cancer (n = 17)					
	T1		T2		Controls (n = 17)	
Variables	r	p-value	r	p-value	r	p-value
Age	-.244	.386	-.204	.443	-.272	.292
Menopausal status	-.318	.213	-.168	.519	-	-
Education	-.273	.288	-.042	.872	-.095	.718
Months elapsed	-	-	-.046	.860	-	-
Depression	**.706**	**.002**	**.684**	**.002**	-.404	.107
Fatigue	-.434	.082	**-.709**	**.001**	-.369	.145
Total quality of life	**-.508**	**.037**	**-.735**	**.001**	**-.584**	**.014**
PWB	**-.508**	**.038**	**-.728**	**.001**	**-.521**	**.032**
FWB	**-.567**	**.018**	**-.661**	**.004**	-.450	.070
EWB	-.294	.252	-.482	.050	-.445	.073
SWB	-.168	.520	**-.820**	**.001**	-.416	.097
Cytokine levels						
TNF-α	-.256	.322	.198	.447	-.363	.152
Il-6	-.203	.434	.165	.526	-.086	.750
Il-18	.049	.851	.146	.575	-.163	.533
BDNF	.275	.286	.283	.271	-.349	.170
EPO	-.258	.318	.096	.714	.341	.180

Note. r indicates Pearson's correlation except for correlations involving menopausal status, T1 IL-6 and T2 EPO levels, in which case r indicates Spearman's rho; PWB = physical well-being; SWB = social well-being; EWB = emotional well-being; FWB = functional well-being.

Correlational analyses of changes between T1 and T2

Correlations of the relationships between changes in each of the cytokines, subjective and objective prospective memory, fatigue, depression, and each of the quality of life variables are reported in Table 6. Of note, changes in circulating IL-6 and BDNF were not found to be associated with changes in any of the other variables, and changes in IL-18, TNF-α and EPO were not associated with changes in prospective memory as assessed subjectively with the PRMQ or objectively with the MIST summary score or event-based scale (*p*s > .05). Changes in IL-18 were, however, negatively associated with changes in time-based scores ($p = .040$), whereas the other cytokines were not (*p*s > .05). Most of the changes in cytokine concentrations were not found to be correlated with changes in depression or fatigue (*p*s > .10) with the exception of TNF-α, which exhibited a negative trend with FACIT-F scores (i.e., greater fatigue symptomology) ($p = .09$). Neither any changes in total quality of life, emotional well-being, subjective well-being, or physical well-being were found to be significantly associated with changes in circulating cytokines, although a negative correlation between physical well-being and TNF-α was found to be marginally significant ($p = .054$), and trends were found between total quality of life and EPO (positive correlation, $p = .096$), as well as between physical well-being and IL-18 (negative correlation, $p = .067$). Differential functional well-being was also found to be positively correlated with EPO changes ($p = .010$), but was not associated with the other cytokines (*p*s > .05).

Table 6

Correlations Between Changes in Cytokines and Prospective Memory, Fatigue, Depression, and Quality of Life

		csIL-6	csIL-18	csTNF-α	csEPO	csBDNF
csMIST summary	*r*	0.058	-0.357	0.238	0.032	0.039
score	*p*-value	.824	.160	.358	.902	.881
csTime-based	*r*	-0.196	**-0.502**	0.142	0.188	-0.132
	p-value	.452	**.040**	.588	.470	.613
csEvent-based	*r*	0.251	-0.042	0.097	-0.197	0.299
	p-value	.332	.873	.711	.449	.243
csSubjective	*r*	0.209	0.248	0.321	-0.249	0.294
	p-value	.420	.338	.209	.336	.251
csFatigue	*r*	-0.216	0.079	-0.424	0.250	-0.226
	p-value	.404	.764	.090	.334	.382
csDepression	*r*	-0.305	0.229	-0.168	0.205	-0.376
	p-value	.234	.377	.519	.429	.137
csTQOL	*r*	-0.161	0.167	-0.216	0.417	-0.234
	p-value	.538	.522	.405	.096	.365
csPWB	*r*	-0.141	-0.454	-0.474	-0.151	-0.144
	p-value	.590	.067	.054	.564	.580
csFWB	*r*	-0.045	-0.072	-0.115	**0.605**	-0.163
	p-value	.845	.784	.660	**.010**	.532
csEWB	*r*	-0.052	-0.318	-0.216	0.386	-0.175
	p-value	.842	.213	.405	.126	.502
csSWB	*r*	-0.249	-0.198	-0.007	0.171	-0.157
	p-value	.335	.447	.978	.513	.546

Note. cs = change scores (i.e., T2-T1); *r* indicates Pearson's correlation, except for those involving csIL-6, csIL-18, csEPO, csPWB, csEWB, which were not normally distributed and for those *r* indicates Spearman's rho; Time-based and Event-based are referent to the subscale scores on the MIST; Subjective = subjective prospective memory; TQOL = total quality of life; PWB = physical well-being; SWB = social well-being; EWB = emotional well-being; FWB = functional well-being.

Discussion

While investigations into post-chemotherapy cognitive deficits have burgeoned over the last two decades, only a small number of studies have included assessments prior to chemotherapy (Ahles et al., 2008; Askren et al., 2014; Cheung et al., 2015; Hermelink et al., 2007; Hermelink et al., 2015; Jansen et al., 2011; Jenkins et al., 2006; Jenkins et al., 2016; Patel et al., 2015; Scherling et al., 2012) in the investigation of breast cancer treatment related cognitive impairments, a phenomenon which patients have purported to be due to chemotherapy, describing the experiences with the terms "chemofog" or "chemobrain." Given findings of frontal lobe abnormalities prior to chemotherapy as evidenced in recent neuroimaging studies (Askren et al., 2014; Menning et al., 2015; Scherling et al., 2012), an objective of the present study was to examine whether prospective memory deficits that have been reported to occur among chemotherapy exposed breast cancer survivors (Bedard et al., in press; Cheng et al., 2013; Paquet et al., 2013) may be evident prior to chemotherapy treatment. This is the first study to evaluate prospective memory functioning prior to chemotherapy, and the first longitudinal assessment of prospective memory in breast cancer patients.

Compared to age- and education-matched healthy controls, this study revealed a pattern of prospective memory deficits in breast cancer patients prior to the initiation of chemotherapy, similar in magnitude to those in a previous cross-sectional study of post-chemotherapy prospective memory functioning (Paquet et al., 2013), with 35% of the patients (only 5% of controls) meeting criteria for the classification of having moderate prospective memory impairments. As the prospective memory deficits were not found to change at three months post-chemotherapy, which corresponds to a similar time interval of assessment as in previous cross-sectional evaluations of post-chemotherapy prospective memory (Bedard et al., in press; Paquet

et al., 2013), the data from the present study suggest that prospective memory impairments manifest due to other factors prior to chemotherapy treatment. This is consonant with findings from other studies that have measured pre-treatment neuropsychological functioning among breast cancer patients (Ahles et al., 2008; Askren et al., 2014; Hermelink et al., 2007; Jansen et al., 2011; Patel et al., 2015; Scherling et al., 2012), as well as patients of colorectal cancer (Vardy et al., 2014). In fact, cognitive deficits have been reported to occur in newly diagnosed breast cancer patients prior to receiving any local or systemic treatment (Hermelink et al., 2015; Patel et al., 2015), which may be attributable to increased stressor experiences (Hermelink et al., 2015) or perhaps to elevations of cytokines including TNF-α (Patel et al., 2015). Future longitudinal studies including earlier pre-treatment assessments will be needed to evaluate whether prospective memory deficits may also be present in newly diagnosed breast cancer patients, and to examine associated temporal mechanistic factors.

Moreover, it was of interest to extend prior work on time-based and event-based prospective memory, as disproportionate event-based deficits have been observed post-chemotherapy (Cheng et al., 2013), which preliminary work suggests may not be the case when survivors are evaluated with varied time- and event-based tasks (Bedard, 2014). Using a naturalistic test of prospective memory that encompasses a set of varied tasks, it was found that patients exhibit a differential deficit while completing time-based tasks prior to chemotherapy exposure. Although not originally anticipated as both time- and event-based impairments have been noted to occur among breast cancer survivors (Bedard, 2014) and other neurological patients (Carey et al., 2006; Zogg et al., 2011), this finding is in line with findings involving Parkinson's disease patients (Raskin et al., 2011), as they have exhibited preferential deficits on tasks that place greater demands on the frontal lobe (Foster, McDaniel, Repovŝ, & Hershey,

2009). The differential impairments among patients in the present study were observed again at T2, although a trend of lower event-based performance emerged. As previous work of post-chemotherapy functioning with adequately powered analyses did not find evidence of disproportionate deficits (Bedard et al., 2014), the trend level group differences on event-based tasks evidenced in the present study may be significant in future studies with larger samples. As chemotherapy exposure has been associated with greater frontal lobe abnormalities than are observed pre-chemotherapy (de Ruiter & Schagen, 2013), it is possible that chemotherapy may contribute to prospective memory deficits that are observed prior to the receipt of treatment, leading to prospective memory impairments that are more broadly based.

Investigation into the cognitive operations that may underlie these prospective memory deficits in the present study revealed that breast cancer patients exhibited more loss of time errors at both time-points, which may indicate difficulties in time monitoring (i.e., clock checking). Although task substitution errors were also found to be lower among patients, the absence of group differences on the recognition test indicate that failure of the retrospective component was not a contributor to the prospective memory deficit (Raskin et al., 2010), which corroborates previous findings among breast cancer survivors (Bedard et al., in press). In this light, the task substitution errors may indicate deficits in executive control (Raskin et al., 2011), which may include difficulties in the planning of intentions, or perhaps in cognitive flexibility, which has been shown to be highly associated with the execution of delayed intentions (Kliegel, Martin, McDaniel, & Einstein, 2002). Moreover, as the groups were similar with regards to the ongoing word search task, the cognitive load imposed during the ongoing activity does not appear to have disproportionately affected the ability of the breast cancer survivors to carry out delayed intentions.

Concurrent with evaluating alterations in prospective memory functioning, a primary objective of the present study was to investigate predictors of reported deficits. Significant increases in concentrations of circulating plasma IL-18 and EPO were observed from pre- to post-chemotherapy, and compared to controls, patients exhibited higher EPO levels at baseline. Although higher levels of IL-6 have been found post-chemotherapy in other studies (Cheung et al., 2015; Janelsins et al., 2012), evidence was not found in the present study to support this, possibly due to the great amount of variability in IL-6 concentrations, which may be a result of a smaller sample size. IL-18 is an important mediator of inflammatory processes, identified to promote IFNγ production and regulate IL-1 activity (Dinarello & Giamila, 2003), and has been associated with cognitive impairments in schizophrenia (Wu et al., 2016), Alzheimer's disease (Bossù et al., 2010), and in patients with HIV (Iannello et al., 2009). Although none of the cytokines in the present study were associated with objectively measured prospective memory functioning at any time-point, changes in circulating cytokines have been documented to co-occur with alterations in frontal areas of the brain among breast cancer patients (Pomykala et al., 2013). Interestingly, increases in levels of IL-18 from pre- to post-chemotherapy were found to be associated with decreases in time-based prospective memory performance. This finding is in line with those from other neurological patients that display altered neural activity of the frontal lobe (Bossù et al., 2010; Iannello et al., 2009; Wu et al., 2016), and support the notion of dysregulated cytokine activation that has been proposed as a mechanism underlying cognitive deficits in breast cancer (Ahles & Saykin, 2007), and indicate that this may be extended to account for alterations in prospective memory.

Although it is not the case amongst all studies, previous work into the associates of cognitive dysfunction in breast cancer have found that cognitive deficits, including prospective

memory, may co-occur with elevated fatigue symptomology (Bender, Ergÿn, Rosenzweig, Cohen, & Sereika, 2005; Kim et al., 2008; Paquet et al., 2013; Reidt-Arndt, Yee, Perry, Hsieh, 2009), suggesting the presence of a psycho-neurological symptom cluster, which may share a common biological correlate (Kim et al., 2012). In the present study, patients were found to be significantly more fatigued than controls, with levels remaining unchanged across time-points for patients. Although the present study did not find an association between objective prospective memory performance and fatigue symptomology, which is consistent with a number of other studies involving breast (Castellon et al., 2004; Jansen et al., 2011; Jenkins et al., 2006; Vardy et al., 2007) and colorectal cancer patients (Vardy et al., 2014), patients that exhibited more fatigue post-chemotherapy in the present study as compared to baseline levels were also observed to have associated increases in TNF-α, which is consonant with inflammatory associated (Alfano et al., 2012; Vardy et al., 2014) and TNF mediated fatigue symptomology, which have been observed among breast cancer patients (Bower et al., 2011).

In consideration of self-reported prospective memory, deficits were not found to differ for women from pre- to post-chemotherapy, or between groups at either time-point. However, as is consistent with other studies (Boykoff et al., 2009; Debess, Riis, Pedersen, Ewertz, 2009; Von Ah et al., 2013), patients that perceived greater prospective memory slips experienced lower total quality of life, as well as physical and functional wellbeing, which highlights the importance of evaluating prospective memory in a breast cancer population, as complaints of dysfunction in this cognitive domain are commonly reported by breast cancer survivors (Shilling, & Jenkins, 2007; Von Ah et al., 2013). As in other studies that found significant associations with self-reported cognitive functioning (Castellon et al., 2004; Jansen et al., 2008; van Dam et al., 1998; Vardy et al., 2008; Vardy et al., 2014; Weis et al., 2009), self-perceived prospective memory

deficits were found to be correlated with depressive symptoms and greater post-chemotherapy levels of fatigue.

It has been suggested that previous neuropsychological measures employed in the evaluation of correlations between objective and subjective functioning may have lacked ecological validity to uncover significant relationships (Pullens et al., 2010; Vardy, 2009). As a corollary, an additional aim of the present study was to examine whether, as has been proposed in other studies (Collins et al., 2015; Paquet et al., 2013), prospective memory may substantiate memory complaints among breast cancer patients. In the present study, prospective memory was assessed with the MIST, a highly ecological test that includes many tasks that may be encountered during everyday life (Raskin et al., 2010; Woods et al., 2008). However, contrary to what was hypothesized, a significant association between self-reported and objectively measured prospective memory functioning was not apparent, which requires inquiry into explanations to account for this subjective-objective discrepancy.

For instance, an aim of the study was to examine the role of metamemory accuracy in explaining the relationship between subjective and objective prospective memory performance. The patients were not found to differ from the controls in prediction or postdiction judgements at either time-point, and the evaluation of pre- and postdiction accuracy did not reveal any interactions or group differences, indicating that patients were as accurate as controls in predicting subsequent performance on the MIST, as well as in perceiving performance after completion. These results corroborate previous findings of intact metamemory performance among breast cancer survivors (Collins et al., 2015), and indicate that metamemory functioning may likely not account for the discrepancy between subjective and objective prospective

memory. Thus, other propositions advanced to account for the dissociation between subjective and objective measures of cognitive functioning should be considered.

For instance, it has been suggested that structural and functional abnormalities are often compensated with broader neural network activations following cancer treatments (de Ruiter & Schagen, 2013), such that individuals may feel as though cognitive processes are more effortful as a result of more diffuse neural correlates underlying neurocognition. However, this would likely only explain discrepancies between self-reported dysfunction in the absence of objectively measured deficits (Collins et al., 2015; Moore et al., 2014), which is not the case in the present study.

It may be that the disparity evidenced in the present study may be due to issues related to differing timeframes of assessment, as neuropsychological evaluations are completed at one particular instance in time, whereas self-report measures, including the PRMQ which was used in the present study, assess perceived performance over prolonged periods and may encompass multiple referent environments (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012). The MIST was designed to be as ecologically valid as possible within the context of clinical assessments of prospective memory (Raskin et al., 2010), encompassing intentions for a variety of tasks that may be encountered over multiple everyday situations. Thus it is a neuropsychological test that may adequately tap into the complexities of daily life (Woods et al., 2008), and so issues of referent environments may be minimized, at least in comparison to other conventional tests, which are not as ecologically valid (Chaytor & Schmitter-Edgecombe, 2003). Nonetheless, the MIST is a very standardized test that is completed face-to-face with an experimenter, and so it may also be of interest for future studies to implement non-laboratory measures of real-time data in natural settings over extended periods (see for example Barrett &

Barrett, 2001), as these may more closely account for the experiences that give rise to self-reported cognitive deficits and the subjective prospective memory complaints apparent in the present study, and which have been reported elsewhere (Shilling, & Jenkins, 2007; Von Ah et al., 2013).

It should be noted that the present study is subject to a number of limitations. Although the sample size was in line with other published longitudinal studies that have included pre-chemotherapy assessments (Askren et al., 2014; Jenkins et al., 2016; Scherling et al., 2012), the sample size was quite small limiting the ability to detect meaningful differences that may otherwise be present. For instance, a large sample may have revealed associations between objective and subjective indices of prospective memory, as well as event-based deficits following chemotherapy. Moreover, the study made use of convenience sampling, which may have introduced biases, particularly given the increased demands of participating in this time-sensitive study during a very stressful and busy period of treatment, and so caution should be applied to the generalizability of findings. However, it should be noted that, in agreement with Jenkins et al. (2016), the pre-chemotherapy assessment timeframe is a very challenging period from which to recruit patients. Thus, pre-chemotherapy assessments are not a very feasible assessment interval, and inclusion of assessments during this period in future studies may impact recruitment projections in the attainment of adequate sample sizes.

In addition, it is unclear in the present study whether increased stressor experiences associated with the breast cancer diagnosis itself may be implicated or whether the prospective memory deficits that have been observed may be associated with pre-chemotherapy local treatment, such as surgery. To better discern the exact root causes of prospective memory

impairments among breast cancer patients, future prospective studies will be needed including assessments with newly diagnosed, treatment naive breast cancer patients.

Furthermore, practice effects are a common problem in longitudinal designs and if not carefully controlled for, may lead to the concealment of group (or between time-point) differences. Of note, the control participants only completed the study procedure at one session as they were not assessed at two intervals, and so this precluded the calculation of reliable change indices, a standard assessment of intra-case change, which would enable the calculation of test-retest reliability based on standard errors of the difference between control assessments, used to account for the influence of practice effects. However, administration of the MIST in the present study employed two separate versions, which included different prospective memory tasks as well as ongoing word search puzzles, which mitigate the influence of practice effects (Goldberg, Harvey, Wesnes, Snyder, & Schneider, 2015; Raskin et al., 2010).

As it was not of *a priori* interest at the time of paradigm design to examine time- and event-based performance separately in this preliminary feasibility study, the metamemory measures in the present study should be interpreted with some caution as they do not map perfectly on to objectively measured MIST scores. As has been mentioned, the time- and event-based tasks include separate scoring instructions (i.e., time-based tasks may be given a score of one, but event-based are either accorded a score of zero or two), and participants were not privy to this when determining metamemory percentage judgements. Future studies may wish to assess metacognition on time- and event-based tasks separately, and may consider percentage judgements based on a likert scale, corresponding to the eight time- and event-based tasks.

Conclusions

Despite the limitations, the present study provides valuable information into the nature and mechanisms underlying cognitive dysfunction in breast cancer patients. In the first longitudinal assessment of prospective memory, this study uncovered prospective memory deficits prior to the initiation of chemotherapy, and that this deficit may initially be localized to time-based tasks, although further studies with larger samples will be needed to confirm this. This study also provides evidence in support of cytokine dysregulation underlying prospective memory deficits and co-morbid mood disturbances, as changes in IL-18 were associated with changes in time-based tasks, and TNF-α alterations were associated with changes in levels of fatigue. Remedial strategies including mindfulness-based stress reduction, which may ameliorate experiences of fatigue and cognitive outcomes among breast cancer survivors (Johns et al., 2016), or perhaps administration of polyunsaturated fatty acids to mitigate systemic inflammation (Alfano et al., 2010), may be investigated in future rehabilitation interventions aimed at improving memory functioning and quality of life in breast cancer survivors.

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Appendix A

Patient Time 1 Demographic Questionnaire

1. What is your age in years? _____years
2. Have you undergone menopause?
   A. Yes.
   B. No.
3. How many years of education have you completed? _____ years
4. What is your height in centimeters? _____cm
5. What is your weight in pounds? _____ lbs
6. What is your employment status?
   A. I work full-time.
   B. I work part-time.
   C. I am retired.
   D. I am on medical leave.
   E. I am not employed.

Appendix B

Patient Time 2 Demographic Questionnaire

1. Have you undergone menopause?

C. Yes.

D. No.

2. What is your height in centimeters? _____cm

3. What is your weight in pounds? _____ lbs

4. What is your employment status?

F. I work full-time.

G. I work part-time.

H. I am retired.

I. I am on medical leave.

J. I am not employed.

5. On what date did you receive your last chemotherapy treatment? ____ / ____/ _____ DD/MM/YYYY

6. Were you treated with radiation?

A. Yes.

B. No.

7. Are you currently taking endocrine therapy?

A. Yes.

B. No.

8. If you are taking endocrine therapy, please indicate what endocrine therapy you are taking.

A. Letrozole (Femara).

B. Exemestane (Aromasin).

C. Anastrozole (Arimidex).

D. Tamoxifen.

E. Other (please specify): _____

Appendix C

Control Demographic Questionnaire

1. What is your age in years? ____ years

2. What is your marital status?
   a. Single
   b. Married
   c. Separated
   d. Widowed

3. How many years of education have you completed? _____ years

4. What is your height in centimeters? _____ cm

5. What is your weight in pounds? _____ lbs

6. What is your employment status?

   K. I work full-time.

   L. I work part-time.

   M. I am retired.

   N. I am on medical leave.

   O. I am not employed.

7. Have you undergone menopause?

   E. Yes.

   F. No.

8. Are you currently taking hormone replacement therapy?

   C. Yes.

   D. No.

9. If you are taking hormone replacement therapy, please indicate what type you are taking.

   F. Estrogen

   G. Progesterone

   H. Both

   I. Other (please specify): _____

Appendix D

Functional Assessment of Cancer Therapy – General

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

PHYSICAL WELL-BEING

		Not at All	A Little Bit	Some-what	Quite a Bit	Very Much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at All	A Little Bit	Some-what	Quite a Bit	Very Much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends .	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person	0	1	2	3	4

	who is my main support)					
Q1	Regardless of your current level of sexual activity, please answer the following questions. If you prefer not to answer it, please mark this box □ and go to the next question.					
GS7						
	I am satisfied with my sex life	0	1	2	3	4

EMOTIONAL WELL-BEING

		Not at All	**A Little Bit**	**Some-what**	**Quite a Bit**	**Very Much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at All	**A Little Bit**	**Some-what**	**Quite a Bit**	**Very Much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4

GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things that I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix E

Functional Assessment of Chronic Illness Therapy – Fatigue scale

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

ADDITIONAL CONCERNS

		Not at All	A Little Bit	Some-what	Quite a Bit	Very Much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix F

Center for Epidemiological Studies – Depression

A number of statements which people have used to describe themselves are given below. Read each statement and then blacken the appropriate number to the right of the statement to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

		Almost Never	Sometimes	Often	Almost Always
1	I feel pleasant	0	1	2	3
2	I feel nervous and restless	0	1	2	3
3	I feel satisfied with myself	0	1	2	3
4	I wish I could be as happy as others seem to be	0	1	2	3
5	I feel like a failure	0	1	2	3
6	I feel rested	0	1	2	3
7	I am "calm, cool, and collected"	0	1	2	3
8	I feel that difficulties are piling up so that I cannot overcome them	0	1	2	3
9	I worry too much over something that really does not matter	0	1	2	3
10	I am happy	0	1	2	3
11	I have disturbing thoughts	0	1	2	3
12	I lack self-confidence	0	1	2	3
13	I feel secure	0	1	2	3
14	I make decisions easily	0	1	2	3
15	I feel inadequate	0	1	2	3
16	I am content	0	1	2	3

17	Some unimportant thought runs through my mind bothers me	0	1	2	3
18	I take disappointments so keenly that I can't put them out of my mind	0	1	2	3
19	I am a steady person	0	1	2	3
20	I get in a state of tension or turmoil as I think over my recent concerns	0	1	2	3

Appendix G

Prospective and Retrospective Memory Questionnaire

How often have each of these things happened to you?

		Never	Rarely	Sometimes	Quite Often	Very Often
1	Do you decide to do something in a few minutes' time and then forget to do it?	1	2	3	4	5
2	Do you fail to recognize a place you have visited before?	1	2	3	4	5
3	Do you fail to do something you were supposed to do a few minutes later even though it's there in front of you, like take a pill or turn off the kettle?	1	2	3	4	5
4	Do you forget something that you were told a few minutes before?	1	2	3	4	5
5	Do you forget appointments if you are not prompted by someone else or by a reminder such as a calendar or diary?	1	2	3	4	5
6	Do you fail to recognize a character in a radio or television show from scene to scene?	1	2	3	4	5
7	Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?	1	2	3	4	5
8	Do you fail to recall things that have happened to you in the last few days?	1	2	3	4	5
9	Do you repeat the same story to the same person on different occasions?	1	2	3	4	5
10	Do you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it's there in front of you?	1	2	3	4	5
11	Do you mislay something that you have just put down, like a magazine	1	2	3	4	5

	or glasses?					
12	Do you fail to mention or give something to a visitor that you were asked to pass on?	1	2	3	4	5
13	Do you look at something without realizing you have seen it moments before?	1	2	3	4	5
14	If you tried to contact a friend or relative who was out, would you forget to try again later?	1	2	3	4	5
15	Do you forget what you watched on television the previous day?	1	2	3	4	5
16	Do you forget to tell someone something you had meant to mention a few minutes ago?	1	2	3	4	5

Appendix H

Memory for Intentions Screening Test Administration Instructions

Items required for test administration:

- Tape recorder
- Red pen
- Digital clock, visible to both examiner and examinee (provided)
- Postcard (provided)
- Word search puzzle (provided)
- Request for records form (provided)
- Examiner record form (provided)

Seating/Clock arrangement during administration:

The test administration should be performed at a table, with the examiner seated directly across from the examinee. The digital clock is to be placed to the side of the table, visible to both the examiner and examinee. Please ensure that no additional clocks are visible to the examinee (with the exception of any timepiece they may be wearing) during the test administration. Provide the word search puzzle and a pen/pencil to the examinee, but instruct him/her not begin until instructed to do so.

Examiner Record Form Information:

Please review the examiner record form briefly to familiarize yourself with the form prior to the test administration. Note that on the examiner record form, there are several columns. The first column designates the Task (A-H, examiner administration and AA-HH, examinee responses). The second column will tell the examiner when to administer the Task or when the Task should be completed by the examinee. The third column, entitled "Prospective Memory Tasks", indicates what is to be stated verbally (in bold and quotations) or what action (in italics) is to be completed by the examiner, as well as, what action or verbal response should be provided by the examinee. The Score/Response column allows the examiner to circle the appropriate score obtained for each Task based upon scoring rules provided below, as well as, write incorrect responses provided by the examinee. The last column, titled E.C., indicates that an Error Code should be entered if the response to the Task was incorrect. An error code indicates what type of error was made on the Task; information on the error codes is provided below.

Administration Instructions:

1. Begin by ensuring that the proper seating arrangement is achieved and that all necessary materials have been gathered.

2. Read the instructions in bold on the front page of the test booklet to the examinee. Instruct the examinee to begin the Word Search Puzzle 1. If the examinee completes the word

search puzzle during the test, instruct them to turn it over and complete Puzzle 2 on the reverse side of the paper.

3. Wait until the clock display changes to the next minute and begin the test by administering Task A in the examiner record form. Do not allow the examinee to write notes regarding the test items.

4. Immediately after administering the first Task, fill in the time in the "Task Time" column on the examiner record form for A-FF. Begin by writing the current time for A. The amount of time is indicated by the letter of a task plus the number of minutes to be added. For example, the Task Time for B is A+:01. In other words, the Task Time for B is the time at A plus one minute. So, if the time at A (when A was administered) is 2:05, the time at B is 2:06. Complete the Task Time for all tasks now.

5. At the appropriate Task Time, as noted by the Task Time column completed in Step 4, administer the appropriate Prospective Memory Task. Verbal cues provided by the examiner are presented in **bold** and action cues are provided in *italics*.

6. Beginning with CC, indicate whether the appropriate response was provided by marking an X in either the Correct or Incorrect box. If Incorrect, write the incorrect response and the time of the incorrect response, use additional paper if necessary. Then, circle the appropriate score: 0, 1, or 2 based upon the information provided below. Scoring rules are also provided on the examiner record form.

    a. On Trials 1, 4, 7 and 8 (Time Cues), an incorrect response may be scored either a 0 or a 1.
    Responses on these items may be scored a 1 when the correct response is given at the incorrect time or the incorrect response is given at the correct time. Incorrect responses at the incorrect time are scored a 0.

    b. On Trials 2, 3, 5, and 6 (Associative Cues), responses may only be scored a 0 or 2. Responses that are correct following an associative cue may be scored a 2, otherwise they are considered incorrect.

7. Please also code each incorrect response based upon the error code table provided.

8. Instruct the examinee to stop working on the Word Search Puzzle.

9. Following the completion of the eight Trials, please read the eight multiple choice questions and possible responses aloud to the examinee. The correct response is presented in italics. Please circle
1 if the examinee chooses the correct response and 0 if the examinee chooses the incorrect response.

10. Prior to the departure of the examinee, administer the Delayed Prospective Memory Task. The examinee may make a notation or write down this task, but should not be prompted to do so by the examiner. Make a note on the record form of the time this prompt was administered and the time that the examinee called your office (leaving a message is acceptable). If the examinee contacts your office in 24hours (+/- 1), please circle 1 on the record form to indicate that they completed the task. If the examinee failed to call or did not call within the requisite time period (+/- 1 hour of the target time), circle a 0.