Nicotinic Treatment of Post-Chemotherapy Subjective Cognitive Impairment

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CHAPTER I

INTRODUCTION

Advances in cancer treatment are producing a growing number of cancer survivors; therefore, issues surrounding quality of life during and following cancer treatment have become increasingly important. Chemotherapy-related cognitive impairment (CRCI) is one such quality of life issue that is commonly reported following the administration of chemotherapy in patients with cancer (Janelsins et al., 2011). Although studies reporting cognitive impairments associated with chemotherapy have been reported in patients with non-central nervous system (non-CNS) cancers since the 1980s (Silberfarb, 1983), the phenomenon commonly referred to as 'chemo brain' or 'chemo fog' is poorly understood and, until relatively recently, was largely unacknowledged (Ahles, 2012). Research suggests that CRCI can persist for months to years after finishing treatment (Ahles et al., 2002), which may have implications for the trajectory of cognitive aging for the growing number of long-term cancer survivors (Mandelblatt et al., 2013). As the number of cancer survivors who have will have to cope with CRCI is likely to increase, it is crucial to understand how CRCI presents clinically and to develop therapeutic interventions for CRCI.

The data obtained for this dissertation is from a pilot study evaluating the use of transdermal nicotine treatment to improve symptoms of pCRCI in breast cancer, colon cancer, lymphoma, and ovarian cancer survivors. Chapter II will provide a typical patient case summary to illustrate how CRCI often presents clinically, as well as an overview of CRCI, discuss risk factors for CRCI, factors that influence cognitive aging and CRCI, and will highlight the cholinergic system as a potential therapeutic target for CRCI. Chapter III presents the data from the primary double-blind, randomized, placebo-controlled, parallel group pilot study to evaluate the effect of transdermal nicotine to 1) produce positive effects on subjective complaints and 2) enhance cognitive performance on laboratory measures of cognitive performance in breast cancer, colon cancer, lymphoma, and

ovarian cancer patients with pCRCI. Chapter IV presents exploratory analyses examining subjective cognition and mood. Chapter V presents a cross-sectional study examining the similarities and differences between subjective and objective cognitive complaints in cancer patients with pCRCI (using baseline data from the primary study) and non-cancer patients from a separate study with subjective cognitive decline following menopause. Chapter VI gives perspective to pCRCI based on the three studies that comprise this dissertation. A summary of findings from each study is given and future directions are discussed.

CHAPTER II

BACKGROUND

Patient Case Summary

The patient is a 68-year-old, married woman employed as a teacher at a high school with a history of breast cancer. At 65-years of age, she presented with an abnormal routine mammogram screening; subsequent diagnostic imaging revealed a suspicious abnormality in her right breast. She underwent lumpectomy with axillary lymph node dissection, and pathology revealed stage IIa (pT1c, pN1, cM0), estrogen receptor-positive and progesterone receptor-positive (ER+/PR+), human epidermal growth factor receptor 2-positive (HER-2/neu+), invasive ductal carcinoma. The patient received chemotherapy and targeted therapy consisting of 6 cycles of taxotere, carboplatin, and trastuzumab, as well as radiotherapy to the right breast and underarm. Chemotherapy and radiotherapy were followed by adjuvant endocrine therapy with letrozole and completion of one year of maintenance trastuzumab to reduce risk of breast cancer recurrence. During chemotherapy, the patient reported worsening fatigue and cognitive complaints, including greater difficulty with memory, attention, concentration, and ability to multitask. The patient was advised that cognitive complaints during chemotherapy are not uncommon and would likely improve following completion of chemotherapy.

Follow-up with the patient 2-years post-chemotherapy revealed that the patient's cognitive complaints have not improved. She has stated that her symptoms have negatively impacted her job as a teacher. She denies receiving complaints about her work performance, but suspects that her coworkers are aware of changes. Upon questioning, she states that she has difficulty with word finding, needs reminders and notes to complete tasks, frequently loses paperwork, reports being easily distracted, has forgotten events and conversations, has trouble learning new work-related tasks, and that it takes greater cognitive effort to complete work-related tasks. She denies trouble recognizing faces, getting lost while navigating in familiar places, or any change in ability to

manage household chores. She ambulates, dresses, bathes, drives, and shops independently. She states that she has been less interested in socializing, due to anxiety and distress surrounding her cognitive functioning.

She stated that at a breast cancer support group, the topic of "chemobrain" was discussed, prompting her concerns that the changes in her cognitive functioning were a consequence of her breast cancer treatment. She was referred for neuropsychological evaluation by her primary care physician. Neuropsychological testing revealed that she performs below expectations for age and education level on measures of memory, executive function, and attention, however her performance was within the normative range. Despite performance within the normative range on objective cognitive testing, subjective cognitive (self-report) measures reveal endorsements of cognitive complaints. (Vega, Dumas, & Newhouse, 2017)

Overview of Chemotherapy-Related Cognitive Impairment (CRCI)

The American Cancer Society defines CRCI as: increased forgetfulness, trouble concentrating and remembering details, difficulty with multi-tasking word finding, and taking longer to finish tasks (Craig, Monk, Farley, & Chase, 2014). Although changes across various domains on objective testing have been reported for CRCI, effects have been reported most prominently in the domains of attention, working memory, executive function, and processing speed (Mandelblatt et al., 2013). To date, the majority of CRCI research has involved women with breast cancer (Janelsins et al., 2011; Wefel & Schagen, 2012), who (as of January 2016) represent approximately 23% (3.6 million) of the 15.5 million cancer survivors in the US alone (Miller et al., 2016). Although it is likely that patients who receive chemotherapy for any type of cancer may experience CRCI, much of the literature in populations other than breast cancer is preliminary (Wefel, Kesler, Noll, & Schagen, 2015). However, research in patients with other types of cancer reveal similar results (Ahles et al., 2002; Chao et al., 2012; Correa et al., 2010; D. Jones et al., 2013; Pedersen et al., 2009; Vardy & Tannock, 2007; Wefel et al., 2014). Estimates of the prevalence of CRCI in cancer patients vary widely across studies (Wefel et al., 2015). Current longitudinal studies suggest that approximately 40% of breast cancer patients have evidence of cognitive impairment prior

to cancer treatment, up to 75% exhibit cognitive decline during treatment, and 35-60% exhibit cognitive decline following completion of chemotherapy (Wefel et al., 2015). Severity of CRCI is typically mild to moderate in nature, such that impairments experienced would not typically qualify for a diagnosis of mild cognitive impairment (MCI) (Vega & Newhouse, 2014) or dementia, however even subtle impairments in cognitive functioning can greatly influence quality of life (Wefel et al., 2015).

Risk Factors for CRCI

Research suggests that the causes of CRCI are likely multifactorial and a number of biological mechanisms have been suggested to play a role in the development of CRCI, including blood brain barrier (BBB) damage, neurotoxic cytokines, changes in hormones, DNA damage, oxidative stress, reduced synaptic plasticity, altered growth factor levels, and impaired hippocampal neurogenesis (Ahles & Saykin, 2007; Janelsins et al., 2014; Loh et al., 2016). Additionally, certain alleles in the *Apolipoprotein E* (*APOE)* and *Catechol-O-methyltransferase* (*COMT)* genes have been associated with increased risk for CRCI (Ahles et al., 2003; Small et al., 2011). Neuroimaging studies in patients with cancer have revealed white and gray matter loss, altered white matter integrity, altered resting state connectivity changes and brain activation during tasks (Mandelblatt, Stern, et al., 2014). The question of why some cancer patients continue to experience CRCI for years following completion of chemotherapy has led to the examination of additional risk factors for CRCI, discussed below.

Interaction of Aging and CRCI

Aging is the most significant risk factor for developing cancer ("Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Mortality - All COD, Aggregated With State, Total U.S. (1969-2010) <Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance Re," n.d.). Although the mechanisms that underlie the increased risk for cancer that accompanies increased age

are not fully understood, there is considerable overlap in common biological changes that occur in the development of cancer, normal aging, and following chemotherapy treatment (Table 1).

Table 1. Summary of Biological Changes Associated with Normal Aging, Chemotherapy, and MCI/AD

Biological Changes	Normal Aging	After Chemotherapy	MCI	AD
Increased Cell Senescence	✓	✓		
Increased DNA Damage	✓	✓	✓	✓
Increased Oxidative Stress	✓	✓	✓	✓
Increased Pro-inflammatory Cytokines	✓	✓		✓
Decreased Telomere Length	✓	✓		✓
Increased Mitochondrial Dysfunction	✓	✓		✓

Aging is associated with increased cell senescence, DNA damage, oxidative stress, inflammation, mitochondrial dysfunction, and decreased telomere length (Campisi & Yaswen, 2009; Irminger-Finger, 2007; Kowald, 1999; Ramsey & Sharpless, 2006; Singh, 2006; von Zglinicki & Martin-Ruiz, 2005). Chemotherapy has been similarly associated with increased cell senescence (Campisi & d'Adda di Fagagna, 2007), DNA damage (Blasiak et al., 2004; Nadin, Vargas-Roig, Drago, Ibarra, & Ciocca, 2006), oxidative stress (Maccormick, 2006), inflammation (Bower et al., 2002; Collado-Hidalgo et al., 2006; Ganz, Bower, et al., 2013; Kesler et al., 2013; Penson et al., 2000; Pusztai et al., 2004; Tsavaris et al., 2002), mitochondrial dysfunction (Wardell et al., 2003), and decreased telomere length (Lahav et al., 2005; Maccormick, 2006; Schröder et al., 2001). It is important to note that all of the processes mentioned above, including age, have also been implicated as risk factors in cognitive decline and the development of neurodegenerative diseases, such as Alzheimer's disease (AD) (Ahles & Saykin, 2007; Keller et al., 2005; Maccormick, 2006; Mariani et al., 2005; Migliore et al., 2005; Tan et al., 2007; Tonelli, Postolache, & Sternberg, 2005; von Zglinicki & Martin-Ruiz, 2005; Wang et al., 2013). There is also overlap in alleles in the *APOE* gene that have been associated with both increased risk for CRCI and AD (Ahles et al., 2003). Further, neuroimaging studies have revealed similar changes observed following chemotherapy treatment and in normal aging, including gray and white matter loss, altered white matter connectivity, altered resting state connectivity changes and brain activation during tasks (Ahles, Root, & Ryan, 2012; Ahles & Saykin,

2007; Koppelmans et al., 2012; Mandelblatt, Stern, et al., 2014; McDonald et al., 2010, 2012; McDonald et al., 2013; Silverman et al., 2007). Together, this research suggests that the biological processes that underlie normal aging, brain response to chemotherapy, cognitive decline, and neurodegeneration overlap, leading to the hypothesis that chemotherapy may modify the normal aging trajectory (Ahles, 2012; Ahles et al., 2012; Maccormick, 2006; Mandelblatt et al., 2013).

Interaction of Cognitive Aging and CRCI

Aging is also associated with increased risk for cognitive impairment. Increasing evidence suggests that older patients are more susceptible to cognitive decline associated with chemotherapy and adjuvant endocrine therapies for breast cancer than younger patients (Ahles et al., 2010; Schilder et al., 2010). Additionally, age appears to interact with cognitive reserve, a predictor of future cognitive decline, to increase risk for cognitive decline following chemotherapy (Ahles et al., 2010). A study by Ahles et al demonstrated that older patients with lower cognitive reserve prior to chemotherapy treatment showed reduced performance on measures of processing speed (Ahles et al., 2010). This point is illustrated in Figure 1a where the effect of chemotherapy on cognitive performance may differ depending on level of pretreatment cognitive reserve (Ahles, 2012). Investigators have proposed several models illustrating how cancer treatment may modify the trajectory of normal cognitive aging (Figure 1b; for a more extensive review, see (Mandelblatt et al., 2013). Briefly, the phase shift hypothesis postulates that cancer patients treated with chemotherapy will experience greater decline in cognitive function compared to non-cancer/chemotherapy treated persons, and that the trajectory of decline will parallel normal aging and will remain constant over time (Ahles, 2012). Alternatively, the accelerated aging hypothesis proposes that treatment with chemotherapy may accelerate the normal aging process (Maccormick, 2006). This model predicts that the slope of cognitive decline will be steeper for cancer patients treated with chemotherapy compared to non-cancer/chemotherapy treated patients. It is important to note that the phase shift and accelerated aging hypotheses are not mutually exclusive hypotheses (Mandelblatt, Jacobsen, & Ahles,

2014). It is likely that some cancer patients may experience decline that follows the phase shift trajectory, while other cancer survivors may experience decline that follows the accelerated aging trajectory.

Whether or not cognitive decline associated with cancer treatments are similar to and/or increase the risk for MCI or dementia is a common concern voiced by older cancer patients. However, this issue appears to be complex given evidence that there may be an inverse relationship between risk of cancer and risk of developing dementia (Ganguli, 2015). In a prospective study of over 62,000 older women with breast cancer, no significant association between chemotherapy and drug-induced dementia or "other cognitive disorders" and in fact a significant reduction in the incidence of AD and vascular dementia was observed (Du, Xia, & Hardy, 2010), however this finding should be further evaluated.

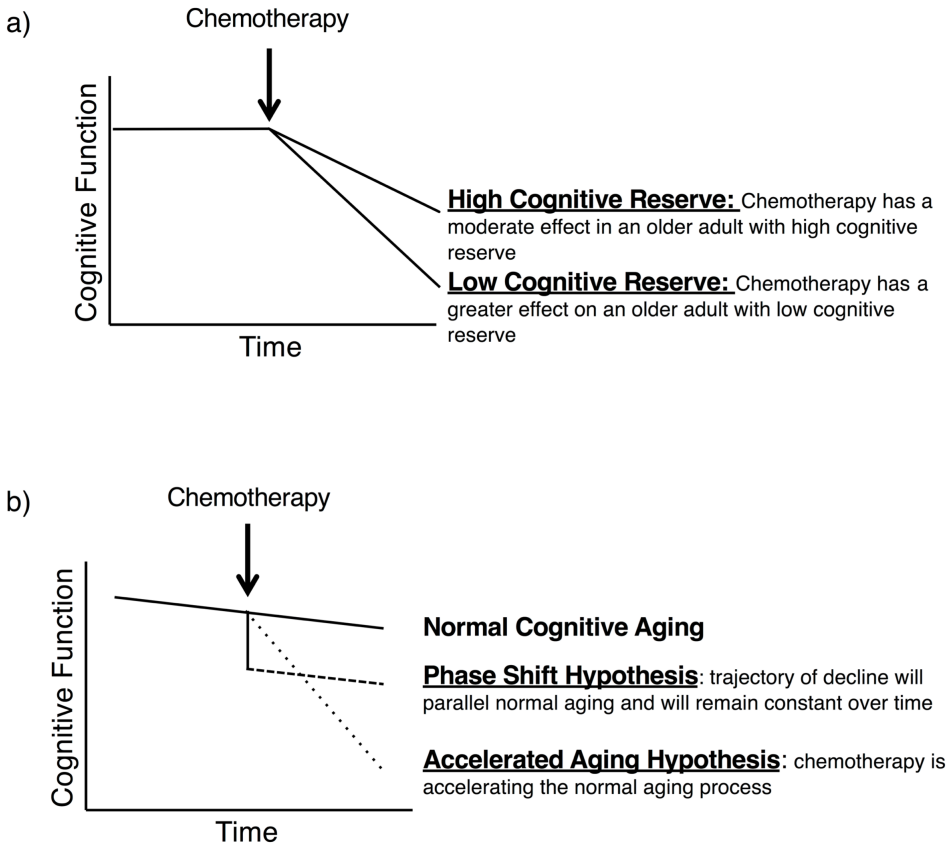


Figure 1. Interaction of chemotherapy with factors that affect normal cognitive aging. a) Effect of chemotherapy on cognitive performance may differ depending on pretreatment level of cognitive reserve. **b)** Possible trajectories of cognitive decline based on theories how chemotherapy interacts with normal cognitive aging. Figures adapted from (Ahles, 2012).

Pre-Morbid Cognitive Functioning

A common challenge for clinicians evaluating patients for CRCI is that, as in the case example, in normal clinical practice, cancer patients rarely receive cognitive assessment or neuropsychological testing prior to the initiation of chemotherapy. The importance of obtaining pretreatment neuropsychological assessment has been demonstrated by studies that have found that up to 41% of breast cancer patients perform below expectations for age and education prior to receiving chemotherapy (Ahles et al., 2008; Lange et al., 2014; Wefel, Lenzi, Theriault, Buzdar, et al., 2004), even when controlling for psychological factors, such as depression or anxiety, fatigue, or surgical factors (Ahles et al., 2008). Of additional importance, without pretreatment assessment for comparison, declines in cognitive functioning that occurred during and following completion of chemotherapy treatment may go unnoticed. This is of particular importance when interpreting the test results of individuals with greater pretreatment cognitive reserve, such as individuals with high education levels (Janelsins et al., 2014). Individuals with high pre-morbid cognitive functioning prior to chemotherapy may also be more likely to express subjective cognitive complaints *before* objective cognitive measures can detect impairment (Saykin et al., 2006), as may be the situation for the above case example. That is, due to the case example's high pre-morbid cognitive functioning, her lower than expected performance may reflect a change from a previously high to mid-range normal individual; therefore, the patient could be accurately perceiving an alteration in her perceived cognitive abilities, which is reflected as cognitive complaints on subjective (self-report) measures. fMRI studies have demonstrated the potential for compensatory activation after chemotherapy, which may maintain normal performance on neuropsychological testing, but reflect a change in resource utilization, similar to what is seen in normal aging (Ferguson et al., 2007; Kesler et al., 2009; Kesler, Kent, & O'Hara, 2011; McDonald et al., 2012). Such findings suggest that the patient's neuropsychological testing may fall in the normal range despite being associated with additional resource utilization and experienced as more effortful by patients. Further, there is increasing evidence that subjective (self-report) cognitive complaints, even with normal

performance on objective neuropsychological tests, is associated with an increased risk for developing late-life cognitive decline and AD (Saykin et al., 2006; Vega & Newhouse, 2014).

Pre-Existing Cognitive Impairment

As our population ages, increasing numbers of patients with pre-existing MCI or dementia will be diagnosed with cancer, which represents a challenge in studying the role that cancer diagnosis and cancer treatment may play in the exacerbation of cognitive impairment in older adults (Magnuson, Mohile, & Janelsins, 2016). SEER Medicare studies suggest that the estimated prevalence of dementia in cancer patients age 65 and over ranges from 3.8 to 7% (Gorin et al., 2005; Gupta & Lamont, 2004; Raji et al., 2008), although these estimates may be lower than true prevalence due to lack of reporting of these diagnoses within Medicare claims (Magnuson et al., 2016). Few studies have examined how a prior diagnosis of MCI or dementia specifically impacts treatment decision-making for cancer and what percentage of these patients are offered various types of cancer therapies, such as surgery or chemotherapy (Magnuson et al., 2016). Gupta and Lamont found that colon cancer patients with a pre-existing dementia diagnosis were more likely to be diagnosed without biopsies and less likely to be treated with curative intent, compared to non-dementia colon cancer patients (Gupta & Lamont, 2004). Chemotherapy and radiation are administered less frequently to breast cancer patients with a preexisting dementia diagnosis compared to non-dementia breast cancer patients (Gorin et al., 2005). Raji et al found that presence of a preexisting dementia diagnosis was associated with decreased survival after a diagnosis of breast, colon, or prostate cancer, increased mortality from cancer and from non-cancer causes, and increased odds of being diagnosed at an unknown stage of cancer (Raji et al., 2008). The issue of providing cancer treatment to patients with pre-existing dementia is a complex balancing act in terms of considering quality of life vs. quantity of life for the patient, and certainly stage of dementia at the time of cancer diagnosis should be taken into consideration. However, further research on the overall benefits, risks, and tolerance of cancer treatment in dementia patients at different stages of cancer is needed to better inform treatment decision

making for such patients and to better inform the role of health care professionals involved in the care of cancer patients with preexisting dementia.

Effects of Endocrine Therapy on CRCI

While the majority of evidence for cognitive difficulties in cancer patients and survivors is attributed to chemotherapy, there is growing evidence to suggest that adjuvant endocrine therapy for hormone-receptor positive (HR+) breast cancer, which account for approximately 70-75% of breast cancers (Harvey, Clark, Osborne, & Allred, 1999), may impact cognitive function, either alone or in combination with chemotherapy (Bender et al., 2006; Castellon et al., 2004; Collins et al., 2009b; Jenkins et al., 2008; Palmer et al., 2008; Schilder et al., 2009, 2010). However, such effects observed may not occur equally with all endocrine therapies (Mandelblatt et al., 2013). Adjuvant endocrine therapies for HR+ breast cancer act by blocking or lowering hormonal levels in patients with ER/PR+ tumors and include: 1) selective estrogen receptor modulators (SERMs), such as tamoxifen and 2) aromatase inhibitors (AIs), such as letrozole, which our case example received. Typically, studies provide evidence that tamoxifen adversely affects cognitive functioning (Collins et al., 2009b; Jenkins et al., 2004; Paganini-Hill & Clark, 2000), but have yielded inconclusive results with respect to AIs (Bender et al. 2007; Collins et al., 2009b; Jenkins et al., 2008; Jenkins et al., 2004). However, it is important to note that breast cancer patients are often maintained on endocrine therapy for extended periods of time; the current American Society of Clinical Oncology guidelines now recommend 10 years total duration (Burstein et al., 2014). Therefore, it is possible that CRCI associated with endocrine therapy for breast cancer may develop over time as patients age, although more research is needed.

Another area of growing concern is the effect of androgen-deprivation therapy (ADT) in men with prostate cancer. As of January 2016, there are more than 3.3 million men estimated to be living with prostate cancer in the United States, with the majority (64%) of these prostate cancer survivors over the age of 70 years (Miller et al., 2016). ADT is used to lower male androgens in order to treat prostate cancer and is a mainstay of

treatment for both metastatic and localized disease (Bolla et al., 2002; Jones et al., 2011). ADT can produce effects, such as depression and fatigue (Lee et al., 2015; Storey et al., 2012), that may indirectly affect cognitive functioning, and may also directly affect cognitive functioning as studies suggest that lower testosterone levels are associated with worse cognitive functioning in healthy older men (Holland, Bandelow, & Hogervorst, 2011). In addition, both low testosterone levels and ADT increase the risk of cardiovascular disease (Keating et al., 2010; Tsai et al., 2007), which is a known risk factor for dementia (Justin, Turek, & Hakim, 2013). Studies examining the effects of ADT on cognitive functioning have yielded inconclusive results (Alibhai et al., 2010; Gonzalez et al., 2015; Jim et al., 2010; Joly et al., 2006), however a meta-analysis of 14 studies concluded ADT in patients with prostate cancer had a significant impact on visuomotor ability (McGinty et al., 2014), and ADT has been associated with increased risk for dementia (Nead et al., 2017).

Effects of Targeted Therapies on Cognition

The majority of CRCI research has focused on understanding the effects of traditional chemotherapy on cognition. By contrast, there is little to no published data on the effects of newer targeted therapies on cognitive performance after treatment. Types of targeted therapies include immunotherapies, such as monoclonal antibodies and checkpoint inhibitors, and small molecule signaling pathway inhibitors, such as tyrosine kinase (TK) inhibitors. The appeal of targeted therapies is that they aim at targeting genes or proteins specific to cancer cells or activating immune mechanisms to attack cancer cells, thus reducing off-target side effects in normal tissues.

Although such strategies may be generally less cytotoxic than traditional chemotherapy drugs, targeted cancer therapies are not without risk and can have substantial, and in some cases, life-threatening side effects. Targeted therapies also have the potential to either directly affect brain function or indirectly effect cognition through peripheral extra-CNS mechanisms. For example, sunitinib, a TK inhibitor capable of crossing the BBB used to treat a number of cancers, has been shown to have negative effects on cognitive functioning, specifically

in the areas of learning, memory, and executive functioning in treated cancer patients (Mulder et al., 2014; van der Veldt et al., 2007). A subsequent mouse study revealed that sunitinib impaired spatial cognition as evidenced in Morris water maze, T-maze, and a passive avoidance task, and adversely affected cortical and hippocampal neurons (Abdel-Aziz et al., 2016). In a study evaluating the effect of antiangiogenic targeted therapy (primarily TK inhibitors), more than 30% of patients treated with such drugs developed cognitive decline (Joly et al., 2016).

As targeted therapy use becomes increasingly more common, how these drugs affect cognition will need to be addressed, especially given that they are often used in conjunction with traditional chemotherapy. In the case example, the patient received trastuzumab in conjunction with chemotherapy followed by completion of one year of maintenance trastuzumab. Trastuzumab, a monoclonal antibody, is the most commonly used targeted therapy to treat HER-2/neu+ breast cancer, however there is no published data on the effects of trastuzumab on cognition. As the role of targeted therapy expands, cognitive performance follow-up will become increasingly important.

Interventions

Non-Pharmacological Interventions

There is some evidence that suggests that nonpharmacological interventions such as cognitive behavioral therapy, cognitive brain training, mindfulness based stress reduction, and physical activity may be beneficial for patients with patients with CRCI (Janelsins et al., 2014; Joly et al., 2015). Two pilot studies examining cognitive behavioral therapy in breast cancer patients demonstrated improvement on both objective and subjective (self-report) measures of cognitive function (Ferguson et al., 2012; Ferguson, Ahles, et al., 2007). Computerized cognitive brain-training studies suggest improvement in executive functioning (Kesler et al., 2013), and yoga may reduce subjective memory complaints (Janelsins et al., 2015). The application of non-pharmacological interventions may be promising and should be tailored to each individual patient.

Pharmacological Interventions

Currently, there is no pharmacological treatment that is specific for CRCI. Most pharmacological treatment studies of cancer patients and survivors have centered on treating side effects of chemotherapy such as fatigue (Kohli et al., 2009; Lower et al., 2009; Lundorff, Jønsson, & Sjøgren, 2009; Mar Fan et al., 2008) and anemia (Fan et al., 2009; O'Shaughnessy, 2002), and have largely not focused on treating cognitive symptoms associated with chemotherapy. Studies evaluating the efficacy of stimulants, such as methylphenidate, dexmethylphenidate, and modafinil, for the treatment of CRCI have yielded mixed results with respect to cognition, therefore it remains unclear whether these medications are useful in treating CRCI (Fan et al., 2009; Kohli et al., 2009; Lower et al., 2009; Lundorff et al., 2009; Mar Fan et al., 2008; O'Shaughnessy, 2002). Other pharmacologic treatment studies have evaluated donepezil, an acetylcholinesterase inhibitor approved to treat mild to severe AD (Castellino et al., 2012; Shaw et al., 2006). Both open-label and placebo controlled studies in glioma patients suggested statistically significant improvements in cognitive performance (Castellino et al., 2012; Shaw et al., 2006). Additionally, a study in breast cancer survivors suggested improved verbal memory in those who had poorer cognitive functioning at baseline (Lawrence et al., 2016). Cholinesterase inhibitor studies provide support for the cholinergic system as a therapeutic target for improving cognitive functioning in CRCI (Castellino et al., 2012; Lawrence et al., 2016; Shaw et al., 2006). More selective cholinergic stimulation may potentially be useful for certain cognitive symptoms.

Overlap between CRCI Symptoms and the Cholinergic System

Table 2. Overlap between Domains Affected in CRCI & Cholinergically Modulated Cognitive Function

	Domains Affected in CRCI	Cholinergically Modulated Cognitive Function
Attention	✓	✓
Working Memory	✓	✓
Episodic Memory		✓
Executive Function	✓	✓
Speed of Processing	✓	✓
Spatial Learning		✓

Although studies often find a lack of association between objective and subjective measures of cognitive function, there is increasing evidence that subjectively reported cognitive complaints, even with normal performance on cognitive tests, is associated with an increased risk for developing late-life cognitive decline and Alzheimer's disease (AD)(Saykin et al., 2006). Interestingly, there is a large amount of overlap between the types of objective impairments and subjective cognitive complaints commonly reported in patients with CRCI and cholinergically modulated cognitive functions (Table 2). **Although changes across various domains have been reported for CRCI, effects have been reported most prominently in the domains of attention, working memory, executive function, and processing speed** (Ahles et al., 2002; Ahles & Saykin, 2002; Anderson-Hanley et al., 2003; Brezden et al., 2000; Castellon et al., 2004; Donovan et al., 2005; Downie et al., 2006; Ferguson & Ahles, 2003; Jansen et al., 2008; McDonald et al., 2010; Schagen et al., 1999; Tannock et al., 2004; van Dam et al., 1998; Wefel et al., 2004; Wefel et al., 2011; Yamada et al., 2010) (Table 2). Cognitive abilities such as attention, executive control, and memory rely heavily on the cholinergic neurotransmitter system (Ellis et al., 2006). Recently, a study has shown that smoking history moderated the detrimental effect of the CRCI risk allele *APOEε4* (Ahles et al., 2003) on cognitive performance in breast cancer patients treated with chemotherapy, suggesting a link between nicotinic cholinergic system functioning and CRCI (Ahles et al., 2014). Given the overlap between domains affected in CRCI and cholinergically modulated cognitive functions and the potential link between the nicotinic cholinergic system and CRCI (Ahles et al., 2014), the nicotinic cholinergic system represents a potential therapeutic target for improving cognitive functioning in cancer patients with CRCI.

The Cholinergic System as a Therapeutic Target for CRCI

The cholinergic system has been studied extensively in relation to cognitive aging and is the primary neurotransmitter system responsible for cognitive changes in both normal aging and dementia (Dumas & Newhouse, 2011). Given that cholinergic system integrity influences cognitive aging, it may also interact with chemotherapy treatment. Cognitive abilities such as attention, executive control, and memory rely heavily on

the cholinergic neurotransmitter system integrity, which modulates other neurotransmitter systems and overall cognition via nicotinic (and muscarinic) acetylcholinergic receptors (Ellis et al., 2006). The importance of the nicotinic cholinergic system was first understood using temporary blockade studies; antagonist drugs such as mecamylamine result in performance deficits across several cognitive domains, such as learning, memory, psychomotor speed, and attention (Newhouse et al., 1994; Vitiello et al., 1997). Drugs that stimulate the nicotinic cholinergic system have the opposite effect, acting as cognitive enhancers (Heishman, Kleykamp, & Singleton, 2010). A recent meta-analysis of over 41 double-blind placebo-controlled laboratory studies by Heishman and colleagues concluded that there are significant positive effects of nicotinic stimulation with nicotine on motor abilities, attention, and memory (Heishman et al., 2010).

Nicotinic agonists have been shown to improve cognitive performance in several clinical populations with cognitive impairment, including AD (Dawkins et al., 2007; Engeland et al., 2002; Howe & Price, 2001; Newhouse et al., 1988; Wilson et al., 1995), mild cognitive impairment (MCI) (Newhouse et al., 2012), and attention deficit hyperactivity disorder (ADHD) (Potter, Bucci, & Newhouse, 2012). However, nicotine has not been explored as a potential treatment for CRCI. Studies have shown that nicotinic agonists may exert differential effects on domains of cognition; certain cognitive domains tend to see more benefit than others (Potter et al., 2012; Wignall & de Wit, 2011). The pattern of response to nicotine may follow an inverted 'U' shape model (Newhouse, Potter, & Singh, 2004), where nicotinic treatment tends to improve performance only in those with some level of baseline impairment, and can actually decrease performance in otherwise healthy individuals. Therefore, cancer patients with *persistent* CRCI (pCRCI; continued impairment 1-5 years post chemotherapy) may derive therapeutic benefit from nicotine treatment compared to those without cognitive impairment.

CHAPTER III

NICOTINIC TREATMENT OF POST-CHEMOTHERAPY SUBJECTIVE COGNITIVE IMPAIRMENT: A PILOT STUDY

Introduction

Specific Aims

The purpose of this study was to evaluate the following specific aims: **Specific Aim 1)** assess if nicotine treatment will reduce subjective cognitive complaints in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI; and **Specific Aim 2)** assess if nicotine treatment will enhance performance on laboratory measures of cognitive performance in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI. The **primary hypothesis** (Specific Aim 1) is that nicotine treatment will reduce subjective cognitive complaints in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI following 6 weeks of treatment. The **secondary hypothesis** (Specific Aim 2) is that nicotine treatment will enhance cognitive performance on measures of attention and/or processing speed in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI following 6 weeks of treatment.

Methods

Study Design

The data obtained for this dissertation is from a double-blind, randomized, placebo-controlled, parallel group pilot study. Participants were randomized to either placebo or nicotine with equal allocation for 6-weeks, followed by 2 weeks of treatment withdrawal (for a total of 8 weeks). Participants were assessed both pre-, during, and post- treatment (see Figure 2 for overview of study design and study visits). At the end of the 8-week study, participants had the option to take part in the open-label portion of the study for an additional 6 weeks.

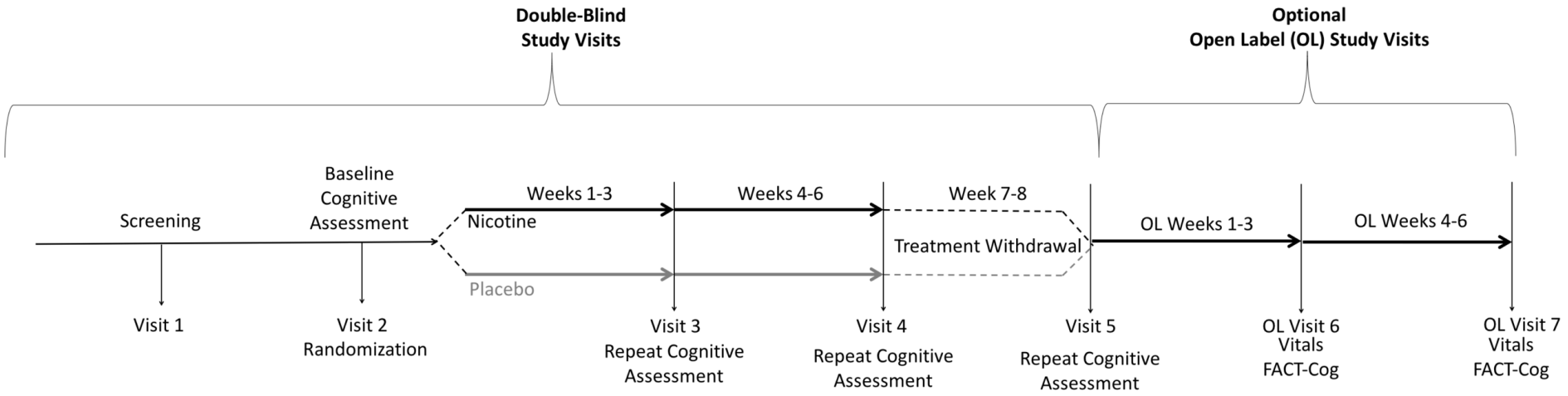


Figure 2. Overall pCRCI Study Design. The study consisted of two phases, a double-blind portion and an optional open-label portion. In the double-blind portion of the study, participants were first screened (Visit 1) to determine study eligibility. Once cleared for the study, participants completed a baseline visit (Visit 2) and then were randomized (50/50) to receive either transdermal nicotine or placebo patches. Participants then repeated their baseline cognitive assessment at Visits 3 and 4 following 3-weeks and 6-weeks on patches, respectively. After completing 6 weeks on patches, participants went off patches for 2-weeks, then repeated their baseline cognitive testing at their final double-blind study visit (Visit 5). At the end of the double blind, placebo controlled 8-week study participants had the option to take part in the open-label portion of the study for an additional 6 weeks. For all open label visits (Visits 6 and 7) only vitals were collected and one subjective test was completed.

Recruitment and Inclusion/Exclusion Criteria

Participants were recruited through Vanderbilt University-affiliated clinics and the greater Nashville, TN community. Recruitment strategies included: Facebook advertisements, the use of fliers in strategic locations and clinics, and recruitment databases such as ResearchMatch.org, the Vanderbilt Email Distribution List, news articles, as well as existing collaborations between our lab and the Vanderbilt Breast Center. Inclusion criteria for pCRCI study participants were as follows:

1) between the ages of 35 to 80
2) previously diagnosed with noninvasive or invasive breast cancer, ovarian cancer, or lymphoma
3) undergone treatment with systemic chemotherapy within the last 1-5 years
4) endorsed pCRCI subjective complaints (as defined below)
5) current non-smokers (no nicotine use within the last 5 years)
6) fluent in and able to read English

Following initial pre-screening, a review of medical records and cancer medical records was conducted to ensure good general health and to confirm that pCRCI participants met criteria for breast cancer, ovarian cancer, or lymphoma and had received systemic chemotherapy. Participants were cognitively and behaviorally screened to rule out dementia and active psychiatric disorders (see below). pCRCI participants were excluded for:

1) any <u>active</u> neurologic and/or psychiatric disease, history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities,
2) <u>current</u> major depression or another major psychiatric disorder as described in DSM-5 (use of psychotropic medications (e.g. antidepressants) was permitted, provided dosing has been stable for at least 3 months),
3) any history of alcohol or substance abuse or dependence within the past 2 years,

4) any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol including:

   4a) history of myocardial infarction in the past year or unstable, severe cardiovascular disease including angina or CHF with symptoms at rest, or clinically significant abnormalities on the electrocardiogram (ECG)

   4b) clinically significant and/or unstable pulmonary, gastrointestinal, hepatic, or renal disease

   4c) insulin-requiring diabetes or uncontrolled diabetes mellitus

   4d) uncontrolled hypertension (systolic BP> 170 or diastolic BP> 100)

5. use of any investigational drugs within 30 days or 5 half-lives, whichever is longer, prior to screening,
6. use of any drugs with pro-cholinergic properties (e.g. donepezil).

Double-Blind Study Visits

Screening (Visit 1) Measures

Participants were screened to exclude individuals with evidence of clinically significant cognitive impairment or dementia. Participants were evaluated using the Wechsler Abbreviated Scale of Intelligence (WASI), Mini Mental State Exam (Folstein, Folstein, & McHugh, 1975) (MMSE; score ≥ 26), Brief Cognitive Rating Scale (Reisberg et al., 1988) (score ≤ 2), and the Mattis Dementia Rating Scale (Jurica, Leitten, & Mattis, 2001) (minimum score 125) to establish a Global Deterioration Scale score (Reisberg, Ferris, & Sclan, 1993) (GDS; score ≤ 1) which rates the degree of cognitive impairment. To rule out the presence of current mood disorders, all participants were psychiatrically assessed using a portion of the Structured Clinical Interview (First et al., 2002) for DSM disorders and diagnoses (SCID-IV), the Beck Depression Rating Scale (Beck et al., 1961) (BDI; score ≤ 9). The BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression. The menopause symptom checklist (Newhouse et al., 2010) (Modified from Sherwin, 1991), a 60-item self-report rating inventory was used to assesses frequency of menopausal symptoms in the last 4 weeks.

Defining pCRCI

Although the definition for CRCI is evolving, for the purposes of the current study pCRCI was defined as follows: 1) endorsed change in cognitive functioning (self-report) the participant directly links to chemotherapy treatment received in the last 1-5 years; 2) evidence of substantial subjective impairment on the Cognitive Complaint Index (described below); 3) subjective complaints not better accounted for by presence of depression and/or another psychiatric or neurologic condition.

The Cognitive Complaint Index (CCI; Visit 1) (Saykin et al., 2006) was used to operationalize breast cancer patients as having subjective complaints. The CCI was chosen as the screening measure because previous research has shown that CCI score correlates with underlying neurodegenerative changes even when unaccompanied by deficits on formal testing (Saykin et al., 2006) and it has been used in previous studies by Newhouse and colleagues examining cognitive complaints in postmenopausal women (Dumas et al., 2012). The CCI consists of multiple inventories including the Memory Functioning Questionnaire (Gilewski et al., 1990), Memory Self-Rating Questionnaire (Squire, Wetzel, & Slater, 1979), the Neurobehavioral Function and Activities of Daily Living Rating Scale (ADL-self) (Saykin AJ, n.d.), the Informant Questionnaire on Cognitive Decline in the Elderly (IQCDE) (Jorm et al., 1994), the 30 items from the Geriatric Depression Scale (GDS) (Yesavage et al.), 12 items from a telephone-based screening for mild cognitive impairment (MCI), and 20 items from the Memory Assessment Questionnaire adapted in part from the Functional Activities Questionnaire (Pfeffer et al., 1982). Only items relevant to cognitive functioning are included from the GDS. A CCI score was calculated as the percentage of all items endorsed. pCRCI participants were required to have a CCI that includes endorsement of at least 20% of all items to be considered as having persistent chemotherapy-related subjective complaints (Saykin et al., 2006).

Baseline Assessment (Visit 2-5) Measures

Subjective (Self-Report) Measures

A summary of all subjective (self-report) measures is listed in Table 3. The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) (Jacobs et al., 2007) scale was used as the primary outcome measure for Specific Aim 1 to monitor change in pCRCI subjective complaints. This instrument has been used to monitor change in CRCI subjective complaints in previous studies and has demonstrated good internal consistency, test-retest reliability, and discriminant and convergent validity (Lai et al., 2009; Sanford et al., 2014; Wagner et al., 2009). This 37-item questionnaire is a self-report measure of cognitive function that aims to evaluate the "real world" impact of CRCI. It consists of four subscales: PCI: Perceived Cognitive Impairments; PCA: Perceived Cognitive Abilities; QOL: Impact on quality of life; and CFO: Comments from Others) and evaluates memory, concentration, mental acuity, verbal fluency, functional interference, and multitasking ability. At each double-blind visit (Visits 2-5), participants were asked to rate on a 5-point Likert scale how they assessed various aspects of their cognitive functioning over the last 7 days. Higher scores indicate better ratings of cognitive functioning.

The Profile of Mood States (POMS) (McNair et al., 1971) was used to monitor change in mood. The POMs is a psychological rating scale used to assess transient, distinct mood states. It is specifically intended for use as a research instrument in assessing changes in affective states across events or interventions in psychologically healthy adults. The 65 items on the POMs form 6 subscales, 5 negative mood states, and one positive mood dimension. The 5 negative mood state subscales are: Tension/Anxiety (assessed as both subjective state and somatic experience of anxiety); Depression (assesses feelings of inadequacy, isolation, guilt, futility, and sadness), Anger/Hostility (examines overt hostility and irritability); Fatigue (assesses feelings of exhaustion); Confusion (assesses efficiency and clarity of thinking). The positive mood state subscale is Vigor/Activity, which examines well-being, enthusiasm, liveliness, energy, and optimism. At each double-blind visit (Visits 2-5), participants were asked to rate, 'How are you feeling right now?' for each item using a five-point scale ranging from 0 (not at all) to 4 (extremely). All subscale scores are calculated by summing the items endorsed for each individual subscale. A total score of mood disturbance (TMD) score can also be calculated by summing the scores

of the 5 subscales for the negative mood states and subtracting from it the score for the positive subscale. For Tension/Anxiety, Depression, Anger/Hostility, Fatigue, Confusion and TMD, higher scores indicate greater mood disturbance. Conversely, for the Vigor/Activity subscale, higher scores indicate greater levels of enthusiasm and optimism.

Table 3. Summary of Self-Report and Cognitive Performance Measures

Self-Report Measure	**Administration**	
Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)	Self-Report	Consists of 4 subscales: • PCI: Perceived Cognitive Impairments • PCA: Perceived Cognitive Abilities • QOL: Impact on quality of life • CFO: Comments from Others
Profile of Mood States (POMS)	Self-Report	Consists of 6 subscales: • Tension/Anxiety • Depression • Anger/Hostility • Fatigue • Confusion • Vigor/Activity
Cognitive Performance Measure	**Administration**	**Cognitive Domain/Function**
Groton Maze Learning Test	CogState Battery (Computerized)	Executive Function/ Spatial Problem Solving
Set-Shifting Task		Executive Function
Detection Task		Psychomotor Function/ Speed of Processing
Identification Task		Visual Attention/Vigilance
Two Back Task		Attention/Working Memory
Conners Continuous Performance Task (CPT)	Computerized	Sustained Attention/Vigilance
Choice Reaction Time Task (CRT)		Attention /Psychomotor Speed
Critical Flicker Fusion Task (CFF)		Attention/Vigilance
Selective Reminding Task (SRT)	Verbal	Immediate/Delayed Memory Recall

Cognitive Performance Measures

To characterize the effects of nicotine on cognitive functioning in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI, we utilized measures that met one or more of the following criteria: 1) targeted domains most likely to be endorsed by patients with pCRCI (i.e. attention, working memory, executive function, and processing speed); 2) prior demonstration of response to nicotinic stimulation or blockade in nicotine studies. The cognitive performance battery (Table 3) consisted of computerized and verbal

tests, as well as tests from the CogState battery.

Computerized and Verbal Tests

The Conners Continuous Performance Test (CPT) ("The Conners Continuous Performance Test," 1994, "The Continuous Performance Test," 1995) was used as the outcome measure for Specific Aim 2. The CPT is a computerized task measures sustained attention/vigilance. Participants see a series of letters appearing one at a time on a computer screen. Participants are instructed to press a button for every letter that appears on the screen, except for "X". The primary outcome variable for this task is CPT reaction time standard error divided by interstimulus interval (a measure of variability of reaction time); lower scores indicate better performance. We have previously found this CPT outcome variable to be sensitive to nicotine-induced attentional improvements in people with ADHD, AD (White & Levin, 1999), healthy young adults (Levin et al., 1998), and in nicotine-treated MCI patients (Newhouse et al., 2012); improvements in performance on this measure have been shown to correlate with clinical improvement.

The Critical Flicker Fusion (CFF) task (Kupke & Lewis, 1989) was used as a test of attention/vigilance. In an ascending trial, the participant presses a button indicating when the frequency of flashing lights, (beginning at 12 Hz and increasing to 50 Hz), has increased to the point that the lights appear to be no longer flashing but rather appear continuously on ("fused"). In a descending trial, beginning at 50 Hz, the participant presses a button when the frequency of apparently fused lights is decreased such that lights begin to appear to be flashing. The participant needs to respond before the frequency hits the upper or lower limit in each trial. The outcome variable for CFF is frequency (Hz) for ascending and descending trials.

The Choice Reaction Time (CRT, (Hindmarch, 1984)) task was used as a measure of attention and psychomotor speed. The CRT task is a reaction time task in which participants are asked to keep their index finger on a "home" key next to a liquid crystal diode (LCD) until one of 6 LCDs arrayed in a semicircle, approximately 25 cm from the "home" key, was lit on the response box. When one of the 6 LCDs arrayed in a

semicircle lights up, the participant is asked to lift her index finger and press the corresponding button next to the illuminated LCD, then return her finger to the "home" LCD button. This pattern continues for 50 trials. Outcome variables on the CRT included the mean and median processing reaction time (RT) (time from stimulus onset to initiation of movement), the mean and median motor RT (time from initiation of movement to stimulus termination), and mean and median total reaction time, with lower scores indicating better performance.

The Selective Reminding Task (SRT) (Buschke & Fuld, 1974) was used to assess immediate and delayed memory recall. Participants are read a list of 16 words and must immediately recall the list across 8 trials. Every trial after the first involves selectively reminding the participant of the words she did not recall on the immediately preceding trial. The SRT is continued until either the participant is able to correctly recall all 16 words on three consecutive trials, or until 8 trials have been completed. Upon completing the immediate recall portion of the SRT, and after a 20-minute delay, participants are asked to complete a single delayed recall trial. SRT total immediate recall was analyzed using the number of correctly recalled words across trials 1-8 (referred to as Total Recall), total immediate recall consistency was analyzed using the number of words correctly recalled on two trials in a row across trials 1-8 (referred to as Total Consistency), SRT total immediate recall failure was analyzed using the number of words not recalled two trials in a row across trials 1-8 (referred to as Total Recall Failure), and total delayed recall was analyzed using the number of words correctly recalled after a 20-minute delay (referred to as Delayed Recall).

CogState Battery

The CogState battery (CogState Ltd., Melbourne, Australia) is comprised of tasks that includes measures of various cognitive domains (Maruff et al., 2009). The tasks in the CogState battery have been specifically designed to assess the presence or absence of cognitive change. The specific tasks from this battery were selected to specifically target the domains most likely to be endorsed by breast cancer patients with persistent CRCI and because they are brief and can be given repeatedly without eliciting practice effects over time (Darby

et al., 2002; Tannock et al., 2004).

CogState Detection Task: The Detection task is a measure of information processing speed and uses a well-validated simple reaction time paradigm using playing card stimuli. In this task, the playing cards are all red and black jokers. The participant is asked to press a "*Yes"* key as soon as the card in the center of the screen flips over. The dependent variable is performance speed, defined for this task as the mean of the log10 transformed reaction times for correct responses. Lower transformed scores indicate better (i.e., faster) performance.

CogState Identification Task: The Identification task is a measure of visual attention and uses a well-validated choice reaction time paradigm using playing card stimuli. In this task, the playing cards are all either red or black jokers. The participant is asked whether the card currently being presented in the center of the screen is red. The participant responds by pressing a "*Yes"* key when the joker card is red and "*No*" when it is black. The dependent variable is performance speed, defined as the mean of the log10 transformed reaction times for correct responses. Lower transformed scores indicate better (i.e., faster) performance.

CogState Two Back Task: The Two Back Memory Task is a measure of working memory and uses a well-validated n-back paradigm using playing card stimuli. In this task, the playing cards are identical to those found in a deck of playing cards, with the exception of the joker. The participant is asked whether the card currently shown is the same as the card two cards prior ("two back"). The participant responds by pressing *Yes* or *No* keys. The first two responses is always treated as *No,* since there are no preceding cards for comparison. The dependent variable for the Two Back Task is performance accuracy, defined for this task as the mean of the arcsine transformed proportion of correct responses; higher scores indicate better performance.

CogState Set Shifting Task: The Set Shifting Task is a measure of executive function. In this task, playing cards are presented on the screen one at a time. Participants are required to determine if each playing card is 'correct' or 'incorrect', selecting *Yes* or *No* keys, respectively. These decisions are based on underlying rule sets

related to either the color of the card (red or black) or the number shown on the card. Participants learn test rules through trial-and-error strategies, and by using feedback from the computer; when a wrong choice is made, an error tone is sounded and the participant must correct his or her response in order for the test to proceed. In addition, test rules change over time at a general level (whether color or number is the rule), and at a more specific level (which color or number is correct, within the respective general rule). The dependent variable is performance accuracy, defined for this task as the mean of the arcsine transformed proportion of correct responses; higher scores indicate better performance.

Groton Maze Learning Test (GMLT): The GMLT is a measure of problem solving and reasoning and uses a well-validated maze-learning paradigm. Participants are required to learn a 28-step pathway hidden within a 10 x 10 grid of squares, observing specific rules for moving across the grid (e.g., do not skip tiles, no diagonal moves). Correct choices are rewarded with a green check mark and the ability to continue learning subsequent steps of the maze. Incorrect choices require the participant to return to the last correct move and explore other options to learn the path. Thus, through trial-and-error learning, participants identify the path. Participants repeat the same path several times in succession using the same trial-and-error learning approach and are expected to complete these subsequent trials ever more efficiently as they learn the path. The primary dependent variable is a measure of accuracy, defined as the total number of errors across all learning trials.

Treatment Assignment and Management

Nicotine was delivered by a transdermal patch delivery system for topical application, available in sizes of 10, 20cm^2. Each patch contained approximately 1.75mg nicotine/cm^2, and releases 7, and 14mg of nicotine, respectively, over 24 hours. Participants were randomized

Table 4. Drug Titration Schedule

Week(s)	Dose
Week 1	½ 7 mg patch per day (for 16 hours per day)
Week 2	7 mg patch per day (for 16 hours per day)
Weeks 3-4	¾ 14 mg patch per day (for 16 hours)
Weeks 5-6	14 mg per day (for 16 hours)
Weeks 7-8	Treatment withdrawal

(50/50) to receive either blinded nicotine or placebo skin patches. A random number generator was used to assign participants to either the treatment or placebo group. The titration administration pattern was as indicated in Table 4 to help to avoid initial side effects. Patches were applied for 16 hours per day and participants were contacted by phone or email weekly to assess tolerability and answer questions. If a participant appeared to be suffering persistent side effects at any dose, the dose was reduced to the previous dose until they were free of side effects. At each visit, vital signs (blood pressure, pulse) and weight were collected. Adverse events were recorded and categorized by body system, event type, attribution, frequency, severity, and course.

Optional Open-Label Study Visits (Visits 6-7)

At the end of the double blind, placebo controlled 8-week study participants had the option to take part in the open-label portion of the study for an additional 6 weeks. Since it was not known which condition (nicotine or placebo) the participant was randomized to during the blinded portion of the study, all participants were treated as though they received placebo and thus followed the titration administration pattern as indicated in Table 4 to help to avoid initial side effects. As in the double-blind portion, patches were applied for 16 hours per day. Participants were contacted by phone weekly to assess tolerability and answer questions. If a participant appeared to be suffering persistent side effects at any dose, the dose was reduced until they were free of side effects. During this time, participants came in for 2 additional study visits at weeks 11 and 14 weeks (see Figure 2), during which safety data (heart rate, blood pressure, and weight) and FACT-Cog scores were collected. Adverse events were recorded and categorized by body system, event type, attribution, frequency, severity, and course.

Statistical Analyses

Analyses were performed using IBM SPSS Statistics for Mac, version 25 (IBM Corp., Armonk, N.Y., USA) to evaluate group differences between nicotine and placebo groups on self-report and cognitive performance

outcome measures. Group demographic differences were evaluated using independent samples *t*-tests and chi-square tests. Group differences in screening and baseline cognitive test scores were evaluated using independent samples *t*-tests. All outcome variables of interests are shown in Table 5. Data were included from all participants that had completed Visits 1-3. Two participants (0003 and 0023) had missing data from Visits 4-5, therefore SPSS was used to impute the missing data from Visits 4-5 for those participants. Briefly, using SPSS, the data are first analyzed for patterns in the missing data. Then, multiple imputation (MI) proceeds with replicating the incomplete dataset multiple times and replacing the missing data in each replicate with plausible values drawn from an imputation model. The imputation model is chosen automatically by SPSS based on whether the data have an arbitrary pattern of missing values (Markov chain Monte Carlo method, number of iterations = 5) or a monotone pattern of missing values (Monotone Method). Constraints on missing values (e.g. minimum values and maximum values) can be specified to ensure that the MI returns appropriate values. The number of case draws and parameter draws is also specified (50 and 2, respectively). The MI output returns values pooled (over the five iterations) for the missing data and statistical analyses of interest were then performed on each completed dataset.

Primary Aim (Specific Aim 1)

For the Primary Aim (Specific Aim 1), a mixed-models repeated measures ANOVA was used to assess the interaction of treatment group (nicotine, placebo) with time (Visit), using change from baseline PCI FACT-Cog score (Visit 3, Visit 4, and Visit 5) as the dependent measure. t-tests were used to look at post-hoc pair-wise differences. All pairwise comparisons were Sidak corrected for multiple comparisons at the $p < 0.05$ level. Unpaired t-tests were used to conduct a pre-treatment/baseline (Visit 2) and post-treatment (Visit 4) comparison.

Principle Secondary Aim (Specific Aim 2)

For the Principle Secondary Aim (Specific Aim 2), a mixed-models repeated measures ANOVA was used to assess the interaction of treatment group (nicotine, placebo) with time (Visit), using change from baseline

score for CPT reaction time standard error divided by interstimulus interval (a measure of variability of reaction time) (Visit 3, Visit 4, and Visit 5) as the depended measure. Unpaired t-tests were used to conduct a pre-treatment/baseline (Visit 2) and post-treatment (Visit 4) comparison.

Secondary Analyses

Mixed-models repeated measures ANOVA was used to assess the interaction of treatment group (nicotine, placebo) with time (Visit), using change from baseline scores (Visit 3, Visit 4, and Visit 5) for the CRT, CFF, SRT, and CogState tasks listed in Table 5. t-tests were used to look at post-hoc pair-wise differences. All pairwise comparisons were Sidak corrected for multiple comparisons at the $p < 0.05$ level. Unpaired t-tests were used to conduct a pre-treatment/baseline (Visit 2) and post-treatment (Visit 4) comparison. Differences for rates of adverse events or other safety abnormalities between groups were assessed using chi-square analysis. Mixed-models repeated measures ANOVA was used to assess treatment group differences (nicotine, placebo) in change from baseline systolic blood pressure (Visit 3, Visit 4, Visit 5).

Table 5. Primary and Secondary Outcome Variables

Measure	Task/Test	Cognitive Domain/Function	Primary Outcome Variables
Specific Aim #1	FACT-Cog	Perceived Cognitive Impairments	PCI Component Score (Increase in score = improvement)
Specific Aim #2	CPT	Sustained Attention/Vigilance	Reaction time Standard Error/Interstimulus Interval (Decrease in score = improvement)
Secondary	CRT	Attention/Psychomotor Speed	Reaction Time (ms) (Lower score = better performance)
	CFF	Attention/Vigilance	Correct Detections (Higher score = better performance)
	SRT	Immediate/Delayed Memory Recall	8 Trial Total Recall, Immediate/Delayed Recall (Higher score = better performance)
	Detection Task	Psychomotor Function/ Speed of Processing	Speed of Performance (ms) (Lower score = better performance)
	Identification Task	Visual Attention/Vigilance	Speed of Performance (ms) (Lower score = better performance)
	Two Back Task	Attention/Working Memory	Accuracy of Performance (Higher score = better performance)
	Groton Maze Learning Test	Executive Function/ Spatial Problem Solving	Total # of Errors (Lower score = better performance)
	Set-Shifting Task	Executive Function	Total # of Errors (Lower score = better performance)

FACT-Cog: Function Assessment of Cancer Therapy-Cognitive Function, PCI: Perceived Cognitive Impairment, CPT: Continuous Performance Task, CRT: Choice Reaction Time Task, CFF: Critical Flicker Fusion Task, SRT: Selective Reminding Task

Results

Participant, Screening, and Baseline Demographics

See Consort Diagram (Figure 3) for details regarding participant enrollment. Of the 106 people pre-screened for the study, 37 were screened at Visit 1. Of the 37 screened at Visit 1, 25 people passed screening criteria and were randomized to treatment after completing Visit 2. Twelve were randomized to nicotine treatment (9 completed all visits, 2 completed 3 visits and therefore had usable data) and 13 were randomized to placebo treatment (11 completers). The mean ages for the nicotine and placebo treated groups were 56.00 ± 11.58 and 52.55 ± 7.66, respectively. There was no difference in mean age between groups ($t(20) = 0.83$, $p = 0.42$). There were no group differences on any demographic variables (Table 6), screening variables (Table 7), or the majority of baseline variables (Table 8). However, there was a difference between groups in baseline SRT Total Recall Failure performance (Table 8). At baseline, the placebo group had a greater number of recall failures compared to the nicotine group (Figure 4).

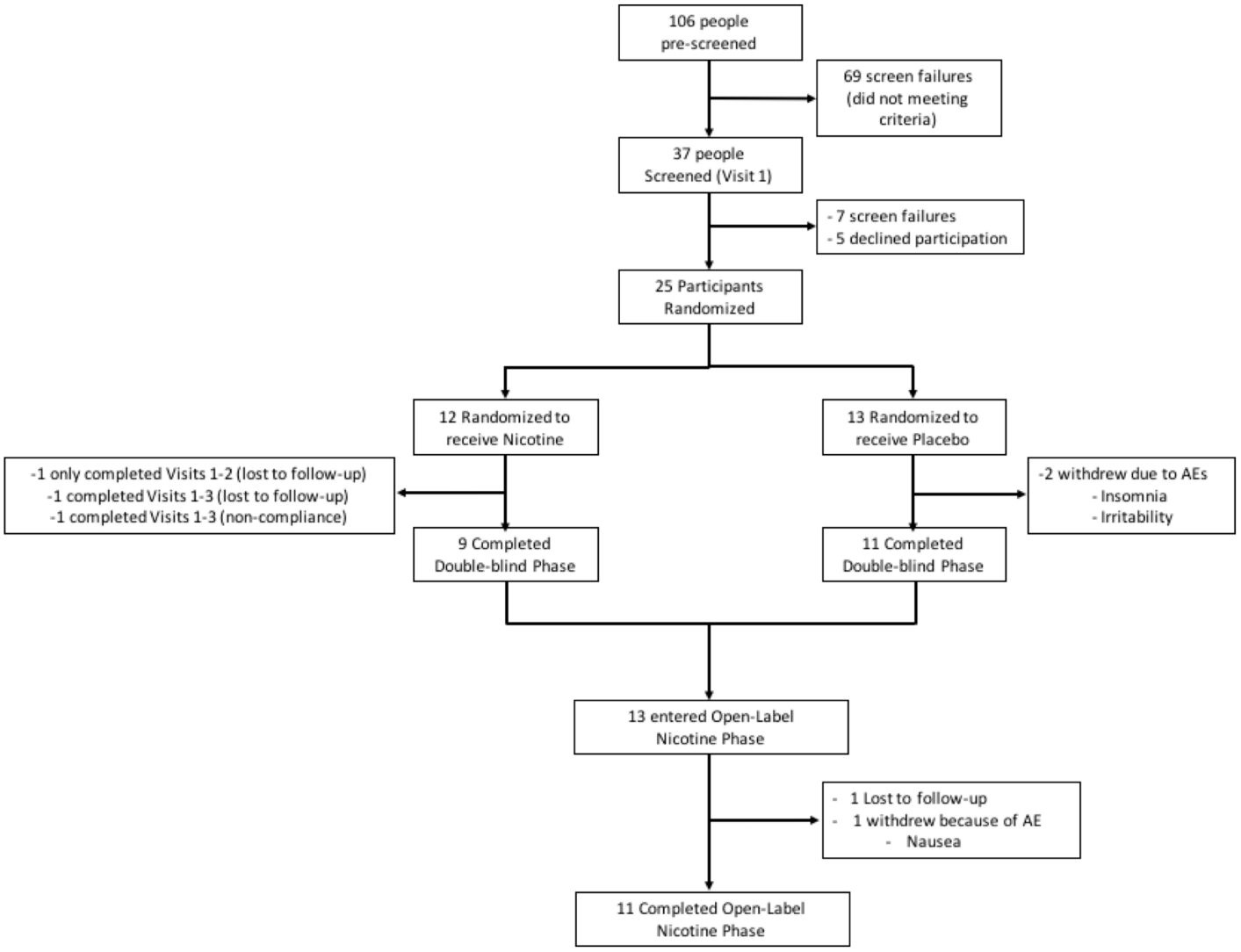


Figure 3. Consort Diagram. Of the 106 people pre-screened for the study, 37 were screened at Visit 1. Of the 37 screened at Visit 1, 25 people passed screening criteria and were randomized to treatment after completing Visit 2. Twelve were randomized to nicotine treatment (9 completers, 11 with usable data) and 13 were randomized to placebo treatment (11 completers).

Table 6. pCRCI Participant Demographics

		Nicotine (n=11)	Placebo (n=11)	Group Difference Statistics
Age in years (mean ± S.D.)		56.00 ± 11.58	52.55 ± 7.66	$t(20) = 4.22$, $p = 0.24$
Years Since Completed Chemotherapy (mean ± S.D.)		2.49 ± 1.42	2.87 ± 173	$t(20) = -0.56$, $p = 0.58$
Cancer Type	Breast	8	10	$\chi(3) = 4.22$, $p = 0.24$
	Lymphoma	2	0	
	Ovarian	0	1	
	Colon	1	0	
Cancer Stage	I	3	5	$\chi(3) = 2.44$, $p = 0.48$
	II	3	4	
	III	4	1	
	IV	1	1	
Cancer Treatment	Chemotherapy	11	11	-
	Surgery	10	11	$\chi(1) = 1.05$, $p = 0.31$
	Radiation	5	7	$\chi(3) = 0.73$ $p = 0.39$
Current Endocrine Therapy	Yes	6	7	$\chi(2) = 1.28$, $p = 0.53$
	No	5	4	
Received Targeted Therapy	Yes	4	2	$\chi(2) = 2.27$, $p = 0.32$
	No	7	9	
Menopausal Status Prior to Chemotherapy	Pre-Menopausal	5	6	$\chi(1) = 0.18$, $p = 0.67$
	Post-Menopausal	6	5	

*Table only includes demographic data from the 22 participants that had usable data

Table 7. Screening Visit Cognitive Assessment Scores

	Drug Group	N	Mean	Std. Deviation	Min	Max	Group Difference Statistics
CCI Score (% Endorsed)	Nicotine	11	0.54	0.11	0.31	0.73	$t(20) = 0.13$, $p = 0.90$
	Placebo	11	0.53	0.11	0.29	0.72	
WASI-II FSIQ-2 Composite Score	Nicotine	11	111.00	7.00	98	122	$t(20) = -0.18$, $p = 0.86$
	Placebo	11	111.82	13.11	95	141	
DRS Total Raw Score	Nicotine	11	141.27	0.91	140	143	$t(20) = -1.71$, $p = 0.10$
	Placebo	11	142.09	1.30	140	144	
MMSE Score	Nicotine	11	28.36	1.29	26	30	$t(20) = -0.67$, $p = 0.51$
	Placebo	11	28.73	1.27	26	30	
BDI Score	Nicotine	11	5.36	3.93	0	13	$t(20) = 0.34$, $p = 0.74$
	Placebo	11	4.82	3.68	0	10	
BAI Score	Nicotine	11	6.73	6.71	0	20	$t(20) = 0.88$, $p = 0.38$
	Placebo	11	4.73	3.26	0	11	
MSC Score	Nicotine	11	32.00	15.76	7	60	$t(20) = 1.15$, $p = 0.27$
	Placebo	11	24.82	13.55	7	42	

CCI: Cognitive Complaint Index, WAIS-II FSIQ-2:, DRS: Dementia Rating Scale, MMSE: Mini Mental State Exam, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, MSC: Menopause Symptom Checklist

Table 8. Baseline Cognitive Assessment Scores

Measure	Outcome Variable	Drug Group	N	Mean	Std. Deviation	Min	Max	Group Difference Statistic
FACT-Cog	PCI Score	Nicotine	11	39.64	15.91	16	66	$t(20) = -0.40$, $p = 0.69$
		Placebo	11	42.00	11.52	21	63	
	CFO Score	Nicotine	11	14.00	1.61	12	16	$t(20) = -.074$, $p = 0.47$
		Placebo	11	14.64	2.34	8	16	
	PCA Score	Nicotine	11	12.91	3.94	8	20	$t(20) = 0.33$, $p = 0.74$
		Placebo	11	12.36	3.88	7	19	
	QOL Score	Nicotine	11	10.64	3.85	5	16	$t(20) = 0.32$ $p = 0.76$
		Placebo	11	10.18	2.79	7	15	
	Total Score	Nicotine	11	77.18	23.37	42	118	$t(20) = -0.24$ $p = 0.81$
		Placebo	11	79.18	14.44	61	108	
SRT	Total Recall	Nicotine	11	83.55	12.84	71	113	$t(20) = 1.02$ $p = 0.32$
		Placebo	11	77.64	14.31	53	103	
	Total Consistency	Nicotine	11	48.73	19.09	25	89	$t(20) = 0.25$ $p = 0.81$
		Placebo	11	46.82	16.91	21	80	
	Total Recall Failure	Nicotine	11	12.18	5.36	1	19	$t(20) = -2.26$ $p = 0.04$*
		Placebo	11	20.64	11.19	7	40	
	Delayed Recall	Nicotine	11	10.45	3.56	5	16	$t(20) = 1.11$ $p = 0.28$
		Placebo	11	8.82	3.34	4	14	
CPT	Reaction Time SE/Interstimulus Interval	Nicotine	11	0.04	0.14	-0.19	0.20	$t(20) = -0.13$ $p = 0.90$
		Placebo	11	0.04	0.13	-0.14	0.26	
CFF	Mean Ascending (Hz)	Nicotine	11	35.63	5.14	24.00	42.60	$t(20) = 1.52$ $p = 0.14$
		Placebo	11	32.75	3.57	28.10	39.60	
	Mean Descending (Hz)	Nicotine	11	37.48	4.59	28.70	45.40	$t(20) = 1.97$ $p = 0.06$
		Placebo	11	33.75	4.30	25.70	38.80	
CRT	CRT Recognition Time (ms)	Nicotine	11	477.41	112.76	372.50	767.00	$t(20) = 0.78$ $p = 0.45$
		Placebo	11	447.55	58.69	368.00	580.00	
	Motor Reaction Time (ms)	Nicotine	11	371.05	103.76	243.50	637.50	$t(20) = -0.30$ $p = 0.77$
		Placebo	11	382.05	63.67	254.00	472.00	
	Total Reaction Time (ms)	Nicotine	11	857.18	202.54	665.00	1414.00	$t(20) = 0.24$ $p = 0.82$
		Placebo	11	840.82	109.25	642.50	990.00	
CogState	ID Task (Speed)	Nicotine	11	2.77	0.09	2.70	3.03	$t(20) = -0.12$ $p = 0.91$
		Placebo	11	2.78	0.08	2.67	2.96	
	Detection Task (Speed)	Nicotine	11	2.59	0.09	2.51	2.75	$t(20) = -0.16$ $p = 0.88$
		Placebo	11	2.59	0.10	2.50	2.79	
	Two Back (Accuracy)	Nicotine	11	1.16	0.13	0.89	1.33	$t(20) = -0.09$ $p = 0.93$
		Placebo	11	1.17	0.30	0.36	1.57	
	Set Shifting (Errors)	Nicotine	11	31.91	15.65	14	54	$t(20) = 1.15$ $p = 0.26$
		Placebo	11	23.64	17.96	9	60	
	Groton Maze (Errors)	Nicotine	11	58.91	17.88	27	83	$t(20) = 1.52$ $p = 0.14$
		Placebo	11	48.27	14.70	22	75	

FACT-Cog: Function Assessment of Cancer Therapy-Cognitive Function, PCI: Perceived Cognitive Impairments, PCA: Perceived Cognitive Abilities, QOL: Impact on quality of life, and CFO: Comments from Others, SRT: Selective Reminding Task, CFF: Critical Flicker Fusion Task, CRT: Choice Reaction Time Task, GMLT: Groton Maze Learning Task

* Significant at $p < 0.05$ level

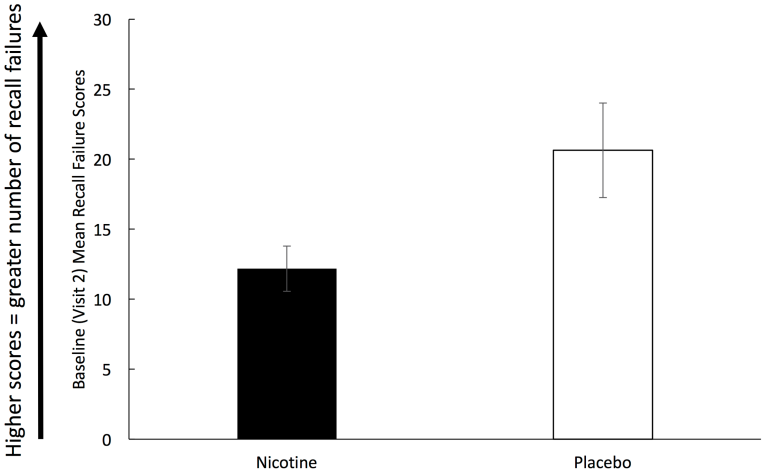


Figure 4. Baseline (Visit 2) performance differences on the Selective Reminding Task (SRT) Total Recall Failure. Treatment groups are distinguished by the following colors: nicotine (black) and placebo (white). Error bars indicate SE. Higher scores indicate greater number of recall failures (i.e. worse performance). At baseline, the placebo group had a greater number of recall failures compared to the nicotine group.

Primary Aim (Specific Aim 1)

Results for the primary outcome measure are shown in Figure 5. Data were analyzed using a mixed-models repeated measures ANOVA with a within-subjects factor of FACT-Cog PCI change from baseline score over time (Visit 3, Visit 4, and Visit 5) and a between-subject factor of drug treatment group (nicotine, placebo). Mauchly's test indicated that the assumption of sphericity had been violated ($\chi 2(2) = 12.22$, $p < .05$), therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.72$). There was a main effect of FACT-Cog PCI change from baseline score, $F(2.16, 43.11) = 23.39$, $p < .001$, however there was no main effect of drug treatment group ($F(1,20) = 0.47$, $p = 0.50$), or interaction between FACT-Cog PCI change from baseline score over time and drug treatment group $F(2.16, 43.11) = 0.93$, $p = 0.41$). Post-hoc comparisons revealed significant differences in FACT-Cog PCI change from baseline scores between Visit 2 and all visits, as well as a significant difference between Visit 3 and Visit 4 (Table 9). *t*-tests were used to look at post-hoc pair-wise differences. All pairwise comparisons were Sidak corrected for multiple comparisons at the $p < 0.05$ level. Asterisks indicated significant pairwise differences between groups, $*p < 0.05$. Additionally, data were analyzed using an unpaired t-test to conduct a pre-treatment/baseline (Visit 2) and post-treatment (Visit 4) comparison. No significant difference was found between treatment groups ($t(20) = 0.32$, $p = 0.98$).

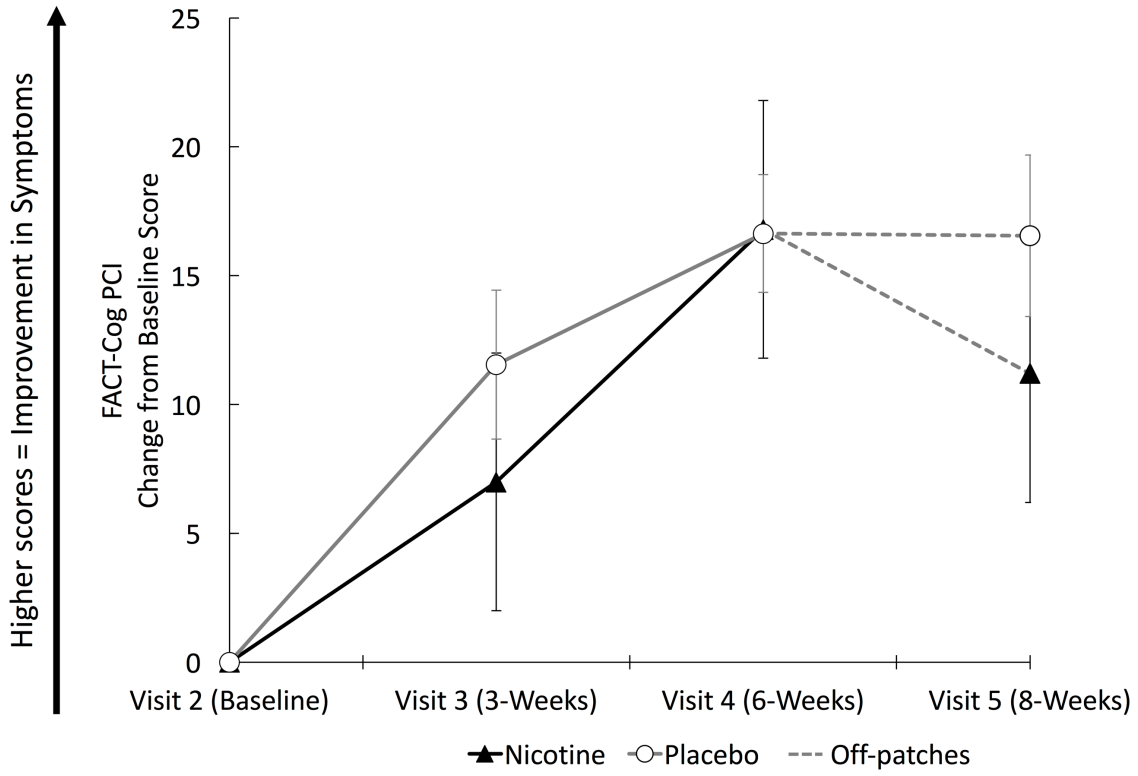


Figure 5. FACT-Cog Perceived Cognitive Impairment (PCI) Change from Baseline Scores. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Positive change scores indicate improvement in symptoms.

Table 9. Post-hoc pair-wise differences for Main effect of FACT-Cog PCI Change from Baseline Score

Visit (PCI Change from Baseline Score)	Visit (PCI Change from Baseline Score)	Mean Difference	Std. Error	Sig.[b]	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
Visit 2	Visit 3	-9.273*	2.316	0.004	-16.031	-2.515
	Visit 4	-16.718*	2.597	0.000	-24.294	-9.142
	Visit 5	-13.873*	2.678	0.000	-21.686	-6.059
Visit 3	Visit 2	9.273*	2.316	0.004	2.515	16.031
	Visit 4	-7.445*	1.327	0.000	-11.318	-3.573
	Visit 5	-4.6	1.858	0.127	-10.021	0.821
Visit 4	Visit 2	16.718*	2.597	0.000	9.142	24.294
	Visit 3	7.445*	1.327	0.000	3.573	11.318
	Visit 5	2.845	1.728	0.52	-2.195	7.886
Visit 5	Visit 2	13.873*	2.678	0.000	6.059	21.686
	Visit 3	4.6	1.858	0.127	-0.821	10.021
	Visit 4	-2.845	1.728	0.52	-7.886	2.195

Based on estimated marginal means

* The mean difference is significant at the

[b] Adjustment for multiple comparisons: Sidak.

Principle Secondary Aim (Specific Aim 2)

Results for the principle secondary outcome measure are shown in Figure 6. Data were analyzed using a mixed-models repeated measures ANOVA with a within-subjects factor of time (Visit), using change from baseline score for CPT reaction time standard error divided by interstimulus interval (a measure of variability of reaction time; Visit 3, Visit 4, and Visit 5) and a between-subject factor of drug treatment group (nicotine, placebo). No significant main effects were observed for CPT reaction time standard error divided by interstimulus interval ($F(3,60) = 0.18$, $p = 0.91$) or drug treatment group ($F(1,20) = 0.34$, $p = 0.57$), and no interaction was observed between CPT reaction time standard error divided by interstimulus interval and drug treatment group ($F(3,60) = 0.35$, $p = 0.79$). Additionally, data were analyzed using an unpaired t-test to conduct a pre-treatment/baseline (Visit 2) and post-treatment (Visit 4) comparison. No significant difference was found between treatment groups ($t(20) = 0.75$, $p = 0.48$).

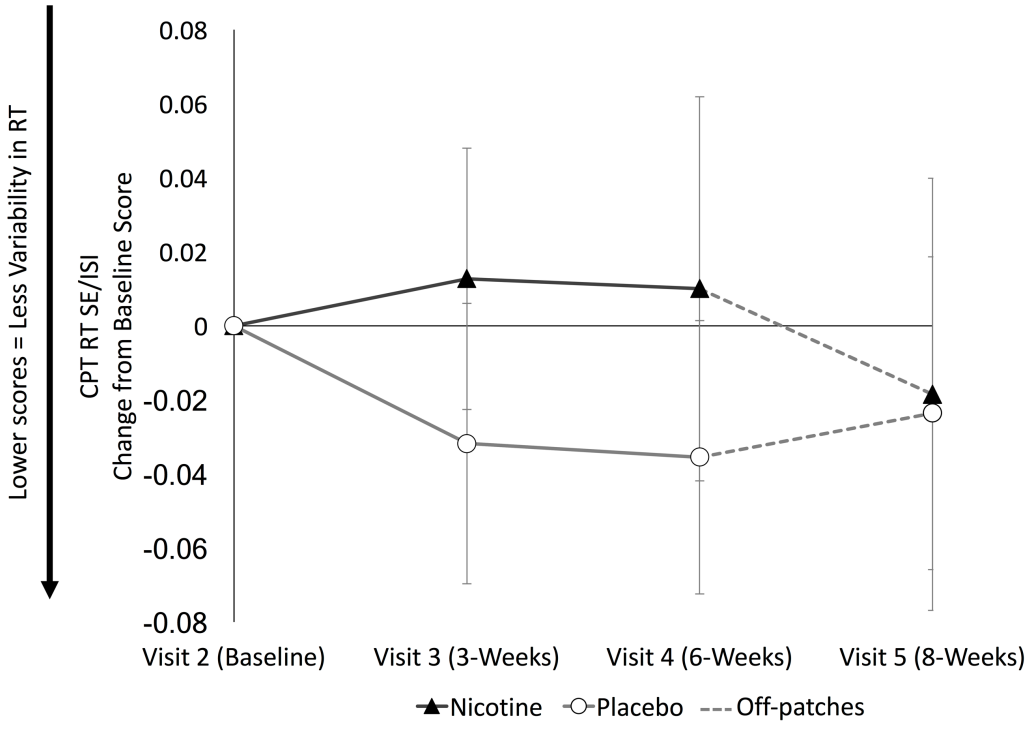


Figure 6. Conner's Continuous Performance Task (CPT) Reaction Time (RT) Standard Error (SE) Divided by Interstimulus Interval (ISI) Change from Baseline Scores. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Negative change scores indicate improved performance.

Secondary Analyses

Results for the secondary outcome measures are shown in Table 10. Each measure was analyzed using a mixed-models repeated measures ANOVA with a within-subjects factor of time (Visit) using change from baseline score for each respective measure (see Table 9; Visit 3, Visit 4, and Visit 5) and a between-subject factor of drug treatment group (nicotine, placebo). No significant effects were observed for CFF, CRT Recognition Reaction Time, CRT Total Reaction Time, SRT Total Consistency, SRT Delayed Recall, or on any CogState measures (Table 10). Within-Subjects main effects of time were observed for FACT-Cog PCA, QOL, and Total Scores, (Table 10). Scores on the FACT-Cog PCA (Figure 7a), QOL (Figure 7b) and Total Scores (Figure 7c) improved in both groups over time. A main effect of time was also observed for CRT Motor Reaction Time (Table 10), with CRT Motor Reaction times improving in both groups over time (Figure 8). All other main effects and interactions were non-significant (Table 10).

Time ($F(3,60) = 2.84$, $p = 0.04$) and group ($F(1,20) = 5.28$, $p = 0.03$) main effects were observed for SRT Total Recall change from baseline score and treatment group, where the placebo group improved more than the nicotine group. There was no significant interaction between SRT Total Recall Score and drug treatment group, however a trend was observed ($F(3,60) = 2.35$, $p = 0.08$; Table 10, Figure 9). Additionally, SRT Total Recall data were analyzed using an unpaired t-test to conduct a pre-treatment/baseline (Visit 2) and post-treatment (Visit 4) comparison, and revealed a significant difference between groups ($t(20) = -2.49$, $p = 0.02$) (Figure 10), where the placebo group performed better at Visit 4 (compared to Visit 2) than the nicotine group.

To account for differences between treatments group in baseline (Visit 2) SRT Total Recall Failure Score (Table 8, Figure 4), a mixed-models repeated measures ANCOVA with a within subjects factor of raw SRT Total Recall Failure Scores (Visit3, Visit 4, Visit 5), and a between subjects factor of treatment group (nicotine, placebo), co-varied for raw baseline (Visit 2) SRT Total Recall Failure Score was used. After controlling for the effect of baseline (Visit 2) SRT Total Recall Failure Score, there were no significant main or interaction effects observed.

Table 10. Mixed-Models Repeated ANOVA Results for Secondary Outcome Measures

	Measure	Time Main Effect	Interaction Effect	Treatment Group Main Effect
FACT-Cog	CFO Score	$F(3,60) = 2.18$, $p = 0.10$	$F(3,60) = 0.96$, $p = 0.42$	$F(1,20) = 0.18$, $p = 0.67$
	PCA Score	$F(1.90,37.94) = 11.61$, $p < 0.001^{*+}$	$F(1.90,37.94) = 1.05$, $p = 0.38^{+}$	$F(1,20) = 0.75$, $p = 0.40$
	QOL Score	$F(2.18,43.62) = 17.66$, $p < 0.001^{*+}$	$F(2.18,43.62) = 0.72$, $p = 0.72^{+}$	$F(1,20) = 0.14$, $p = 0.72$
	Total Score	$F(2.20,43.94) = 24.25$, $p < 0.001^{*+}$	$F(2.20,43.94) = 1.18$, $p = 0.320^{+}$	$F(1,20) = 0.66$, $p = 0.43$
SRT	Total Recall	$F(3,60) = 2.84$, $p = 0.04^{*}$	$F(3,60) = 2.35$, $p = 0.08$	$F(1,20) = 5.28$, $p = 0.03$*
	Total Consistency	$F(3,60) = 0.97$, $p = 0.41$	$F(3,60) = 1.25$, $p = 0.30$	$F(1,20) = 5.28$, $p = 0.31$
	Delayed Recall	$F(3,60) = 2.55$, $p = 0.06$	$F(3,60) = 1.24$, $p = 0.30$	$F(1,20) = 4.31$, $p = 0.06$
CFF	Ascending Mean (Hz)	$F(1.88,37.57) = 0.58$, $p = 0.56^{+}$	$F(1.88,37.57) = 0.36$, $p = 0.78^{+}$	$F(1,20) = 0.12$, $p = 0.73$
	Descending Mean (Hz)	$F(2.06,41.18) = 0.74$, $p = 0.49^{+}$	$F(2.06,41.18) = 0.73$, $p = 0.49^{+}$	$F(1,20) = 0.74$, $p = 0.73$
CRT	Recognition Reaction Time (ms)	$F(1.90,37.91) = 1.67$, $p = 0.20^{+}$	$F(1.90,37.91) = 0.83$, $p = 0.44^{+}$	$F(1,20) = 1.07$, $p = 0.31$
	Motor Reaction Time (ms)	$F(1.92,38.39) = 3.68$, $p = 0.04^{*+}$	$F(1.92,38.39) = 0.46$, $p < 0.63^{+}$	$F(1,20) = 0.12$, $p = 0.73$
	Total Reaction Time (ms)	$F(1.73,34.58) = 3.16$, $p = 0.06^{+}$	$F(1.73,34.58) = 0.35$, $p = 0.68^{+}$	$F(1,20) = 0.50$, $p = 0.49$
CogState	ID Task (Speed)	$F(2.08,41.59) = 0.84$, $p = 0.44^{+}$	$F(2.08,41.59) = 0.51$, $p = 0.61^{+}$	$F(1,20) = 0.11$, $p = 0.75$
	Detection Task (Speed)	$F(3,60) = 1.18$, $p = 0.32$	$F(3,60) = 0.50$, $p = 0.99$	$F(1,20) = 0.32$, $p = 0.86$
	Two Back (Accuracy)	$F(1.57,31.39) = 3.35$, $p = 0.06^{+}$	$F(1.57,31.39) = 0.45$, $p = 0.59^{+}$	$F(1,20) = 0.09$, $p = 0.77$
	Set-Shifting Task (Errors)	$F(2.02,40.48) = 3.07$, $p = 0.06^{+}$	$F(2.02,40.48) = 0.26$, $p = 0.78^{+}$	$F(1,20) = 0.35$, $p = 0.56$
	GMLT (Total Errors)	$F(3,60) = 2.71$, $p = 0.05^{+}$	$F(3,60) = 1.78$, $p = 0.16^{+}$	$F(1,20) = 1.79$, $p = 0.20$

FACT-Cog: Function Assessment of Cancer Therapy-Cognitive Function, PCI: Perceived Cognitive Impairments, PCA: Perceived Cognitive Abilities, QOL: Impact on quality of life, and CFO: Comments from Others, SRT: Selective Reminding Task, CFF: Critical Flicker Fusion Task, CRT: Choice Reaction Time Task, GMLT: Groton Maze Learning Task

[+] Adjusted for Greenhouse-Geisser estimates of sphericity

[*] Significant at $p < 0.05$ level

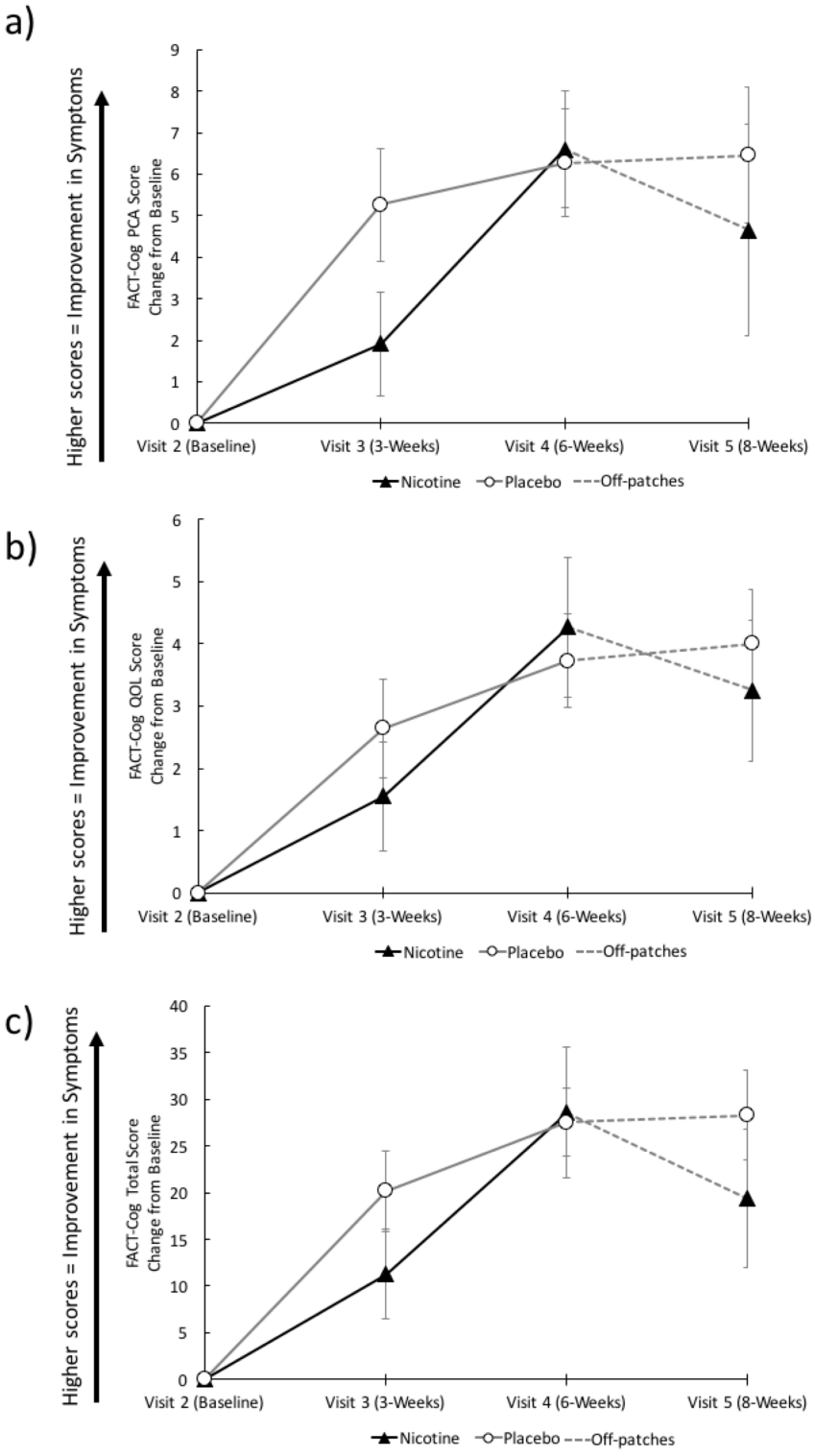


Figure 7. Secondary FACT-Cog Change from Baseline Scores. a) FACT-Cog Perceived Cognitive Abilities (PCA) change from baseline scores. b) FACT-Cog Quality of Life (QOL) change from baseline scores. c) FACT-Cog Total change from baseline scores. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Positive change scores indicate improvement in symptoms.

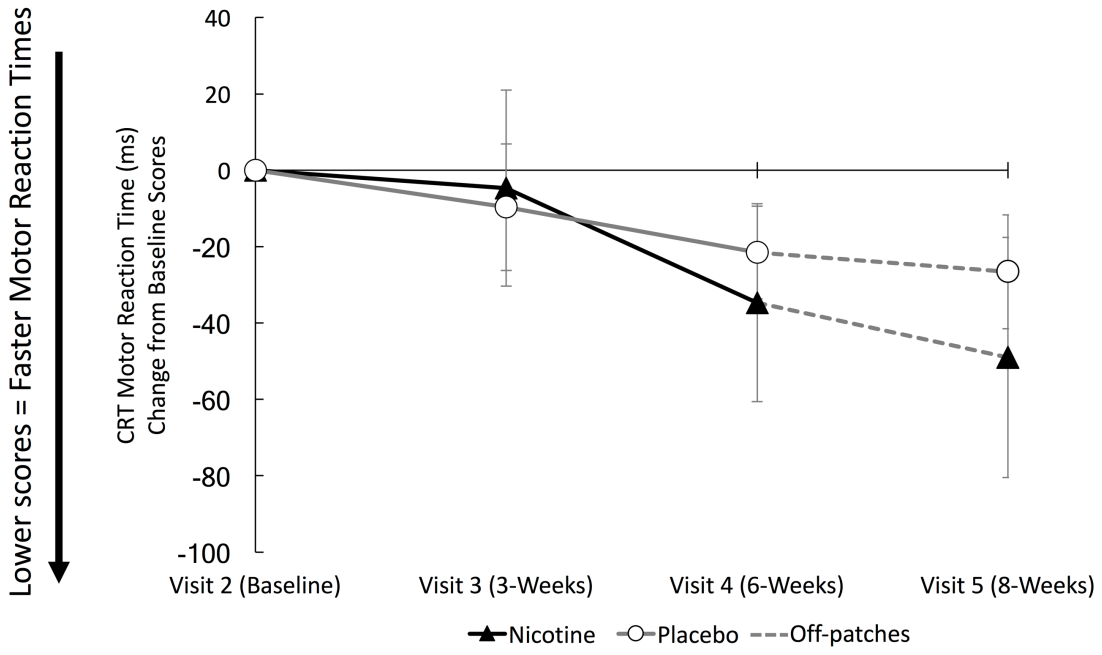


Figure 8. Choice Reaction Time (CRT) Task Motor Reaction Time (ms) Change from Baseline Scores. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Negative change scores indicate improved performance (i.e. faster reaction times).

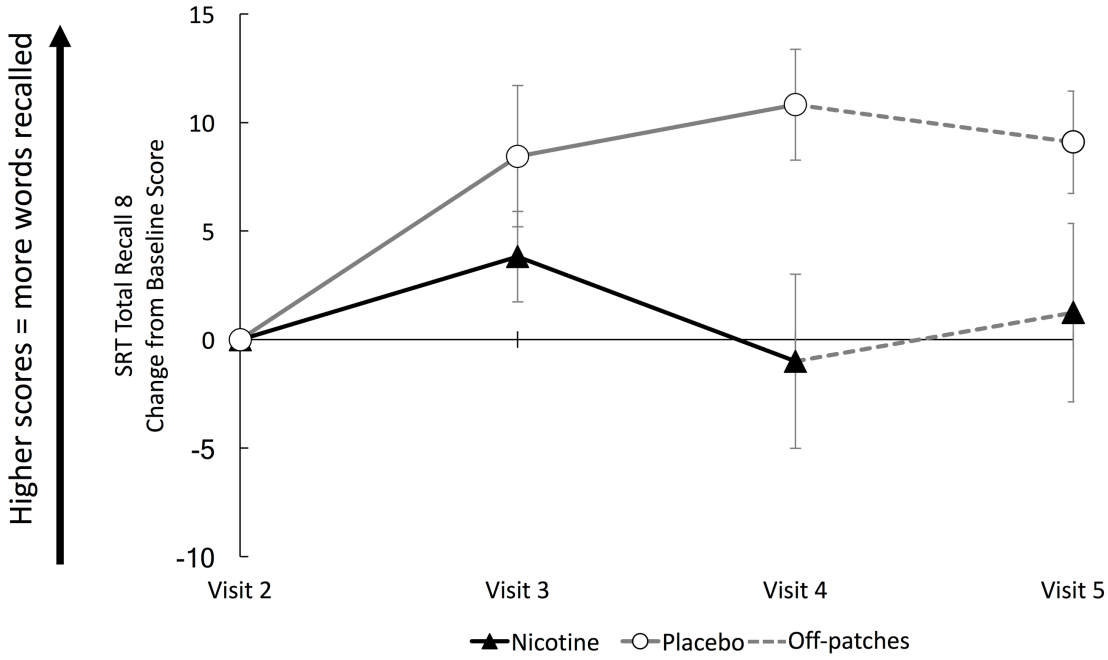


Figure 9. Selective Reminding Task (SRT) Total Recall Change from Baseline Scores. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Positive change scores indicate improved performance (i.e. more words recalled).

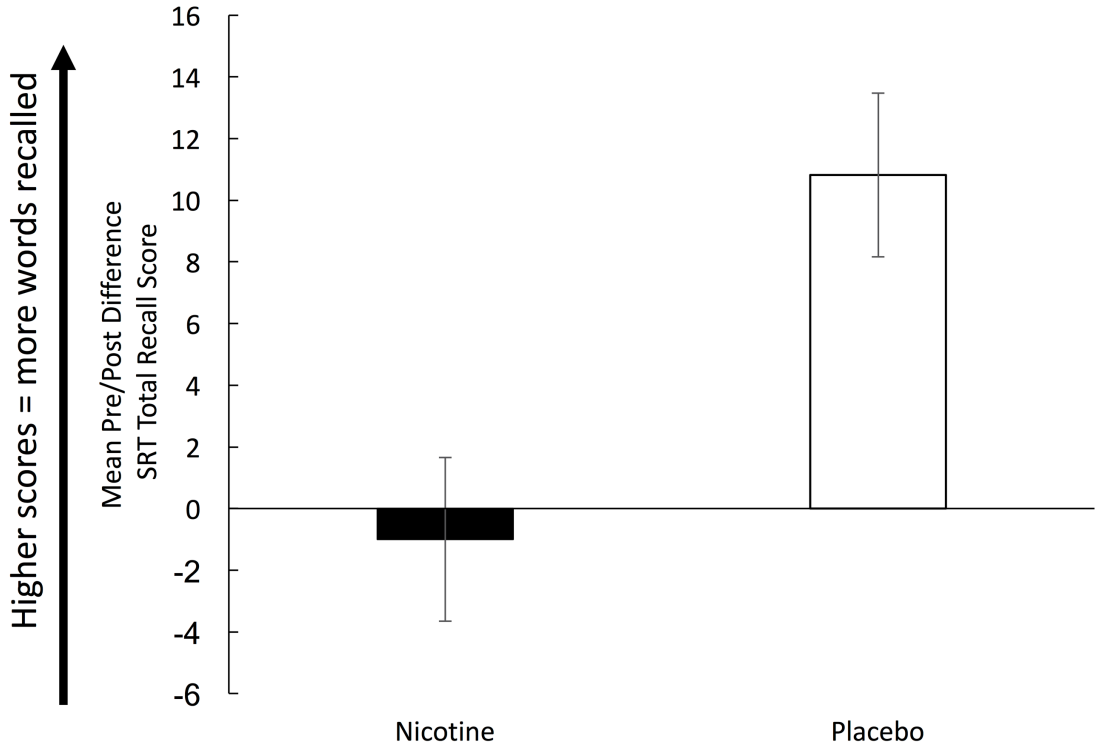


Figure 10. Selective Reminding Task (SRT) Pretreatment/Baseline (Visit 2) and Posttreatment (Visit 4) Comparison. Treatment groups are distinguished by the following colors: nicotine (black) and placebo (white). Error bars indicate SE. Higher scores indicate greater number of words recalled (i.e. better performance). The placebo group performed better at Visit 4 (compared to Visit 2) than the nicotine group.

Differences for rates of adverse events (AEs) or other safety events between groups were assessed using chi-square analysis (Table 11). AEs were assessed across all double-blind study visits and categorized according to body system for all participants who received at least one dose of patches (nicotine n = 12, placebo n = 13). The total number AEs for the double-blind treatment period were 11 for nicotine group compared to 12 for the placebo group (p = 0.85). There was no significant difference in AEs between groups in any body system (Table 11, Figure 11). The majority of AEs experienced by both groups were mild in nature, with skin irritation being the most common AE. Mixed-models repeated measures ANOVA was used to assess treatment group differences (nicotine, placebo) in change from baseline systolic blood pressure (Visit3, Visit 4, Visit 5), weight (kg), and pulse (bpm) There were no significant main or interactions effects between treatment group and mean systolic blood pressure change from baseline (Figure 12a), weight (kg; Figure 12b), or pulse (bpm; Figure 12c).

Table 11. Adverse Events Across Double-Blind Visits (Visit 2-5)

		Nicotine (n = 12)	Placebo (n = 13)	Chi Square Statistic
Number of AEs	No	20	24	$\chi(1) = 0.03$, $p = 0.85$
	Yes	11	12	
Dermatologic/Skin	No	23	33	$\chi(1) = 2.03$, $p = 0.71$
	Yes	6	2	
Gastrointestinal	No	26	32	$\chi(1) = 0.59$, $p = 0.81$
	Yes	3	3	
Musculoskeletal	No	29	34	$\chi(1) = 0.84$, $p = 0.36$
	Yes	0	1	
Neurologic	No	27	33	$\chi(1) = 0.04$, $p = 0.85$
	Yes	2	2	
Mood	No	29	33	$\chi(1) = 1.71$, $p = 0.19$
	Yes	0	2	
Insomnia	No	29	33	$\chi(1) = 1.71$, $p = 0.19$
	Yes	0	2	
Severity of AE	Mild	10	11	$\chi(1) = 0.01$, $p = 0.95$
	Moderate	1	1	

AE: Adverse Event

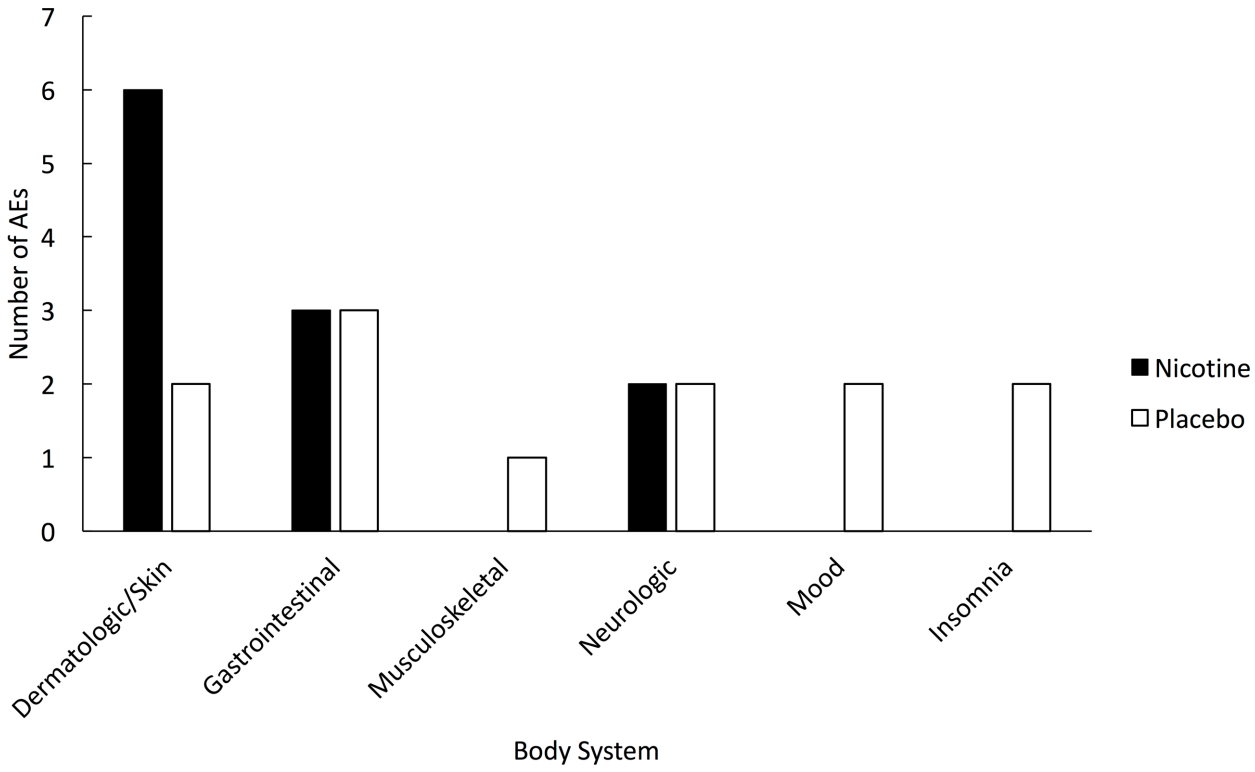


Figure 11. Number of Adverse Events According to Body System. Treatment groups are distinguished by the following colors: nicotine (black) and placebo (white).

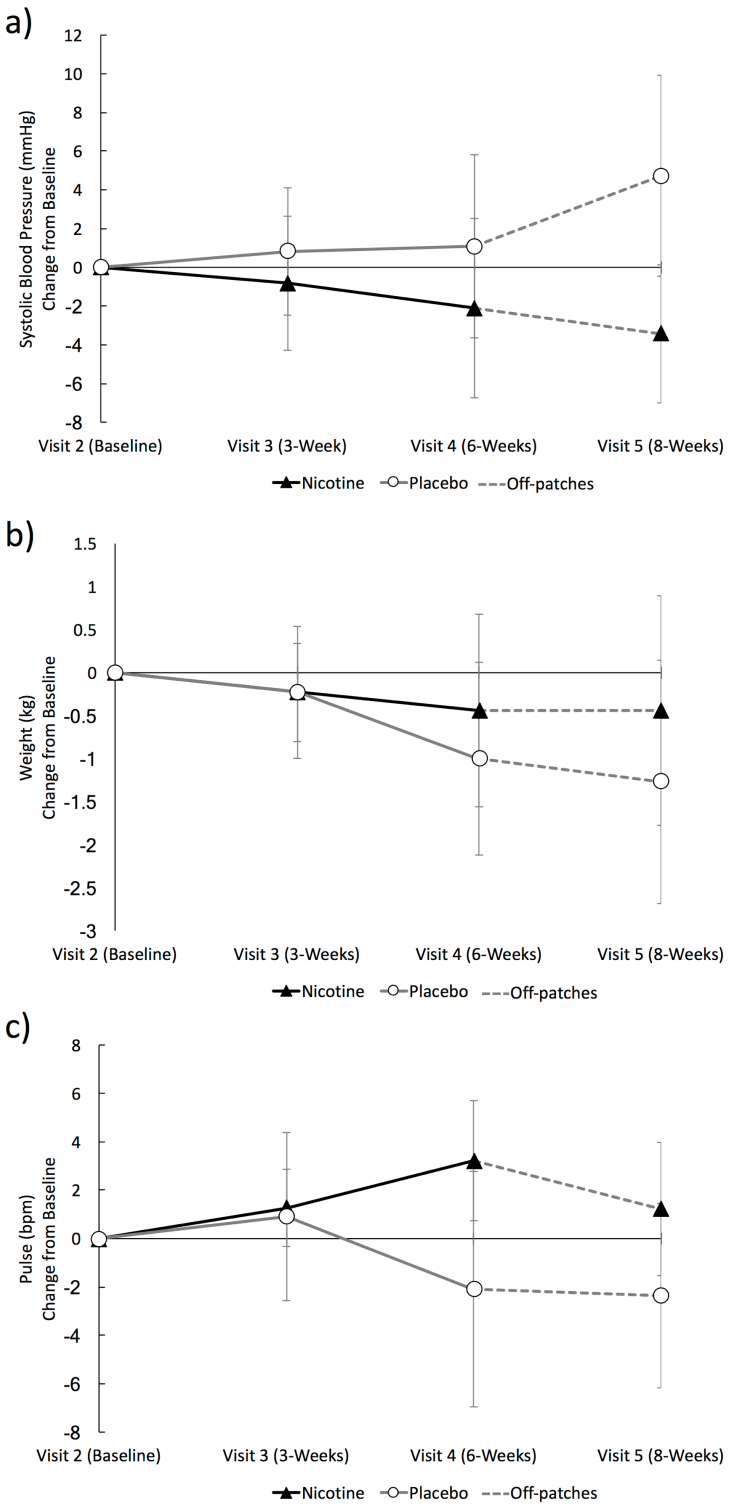


Figure 12. Vitals Change from Baseline. a) Systolic blood pressure change from baseline. Negative change scores indicate a reduction in systolic blood pressure. b) Weight (kg) change from baseline. Negative change scores indicate weight loss c) Pulse (bpm) change from baseline. Negative change scores indicate reduction in pulse. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE.

Discussion

Summary of Findings

The primary aim (Specific Aim 1) of the study was to determine if transdermal nicotine treatment would reduce subjective cognitive complaints in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI. The primary hypothesis (Specific Aim 1) was that nicotine treatment would reduce subjective cognitive complaints in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI following 6 weeks of treatment compared to placebo. Although there was a main effect of FACT-Cog PCI change from baseline score across subsequent visits, there was no main effect of drug group, or interaction between FACT-Cog PCI change from baseline score and drug group. In other words, participants in both groups improved in terms of self-reported cognitive complaints over the course of the study regardless of treatment.

The principle secondary aim (Specific Aim 2) of the study was to determine whether nicotine treatment would enhance performance on laboratory measures of cognitive performance in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI. The principle secondary hypothesis (Specific Aim 2) was that nicotine treatment would enhance cognitive performance on measures of attention and/or processing speed in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI following 6 weeks of treatment compared to placebo. However, no significant main effects were observed for CPT reaction time standard error divided by interstimulus interval or treatment group, and no interaction was observed between CPT reaction time standard error divided by interstimulus interval and treatment group. In other words, there was no difference between treatment groups over the course of the study in terms of performance on the CPT.

Secondary analyses revealed that like FACT-Cog PCI score, scores on the FACT-Cog PCA, QOL, and Total Scores improved in both groups over time, regardless of treatment group. CRT Motor Reaction times also improved in both groups over time, however this may be related to a practice effect. The only difference between treatment groups observed was for SRT Total Recall Score, where the placebo group performed better

at Visit 4 (compared to Visit 2) than the nicotine group. While there was no statistically significant baseline difference between treatment groups on SRT Total Recall, there was, a baseline difference between treatment groups on SRT Recall Failure. SRT Total Recall is defined as the number of correctly recalled words across trials 1-8; conversely SRT Total Recall Failure is defined as the number of words not recalled in two consecutive trials across trials 1-8. Given the difference in SRT Total Recall Failure at baseline, the analysis for SRT Total Recall was re-run with baseline score as a covariate in a mixed-models repeated measures ANCOVA with a within subjects factor of time (Visit) using raw SRT Total Recall Scores (Visit3, Visit 4, Visit 5), and a between subjects factor of drug treatment group (nicotine, placebo). After adjusting for the effect of baseline (Visit 2) SRT Total Recall Score, there were no significant main or interaction effects observed. Therefore, this suggests that the effects observed for SRT Total Recall may reflect baseline differences between groups.

In terms of AEs, the study medication was well tolerated. There was no significant difference in number of AEs between groups in any body system. The majority of AEs experienced by both groups were mild in nature, with skin irritation being the most common AE. There were also no differences between treatment groups in mean systolic blood pressure (mmHg), mean weight in kg, or pulse (bpm) change from baseline.

To date, previous pharmacological treatment studies of cancer patients and survivors have centered on treating side effects of chemotherapy such as fatigue (Kohli et al., 2009; Lower et al., 2009; Lundorff et al., 2009; Mar Fan et al., 2008) and anemia (Fan et al., 2009; O'Shaughnessy, 2002), and have largely not focused on treating cognitive symptoms associated with chemotherapy. Studies evaluating the efficacy of stimulants, such as methylphenidate, dexmethylphenidate, and modafinil, for the treatment of CRCI have yielded mixed results with respect to cognition, therefore it remains unclear whether these medications are useful in treating CRCI (Fan et al., 2009; Kohli et al., 2009; Lower et al., 2009; Lundorff et al., 2009; Mar Fan et al., 2008; O'Shaughnessy, 2002). Treatment studies that have evaluated donepezil, an acetylcholinesterase inhibitor approved to treat mild to severe Alzheimer's disease, and both open-label and placebo controlled studies suggested

improvements in cognitive performance (Castellino et al., 2012; Lawrence et al., 2016; Shaw et al., 2006). While these various treatment studies have yielded mixed-results, a strong placebo effect such as observed in the current study has never been previously reported for this population. Aspects of the current study design that potentially contributed to the observed placebo response in the current study are discussed below.

Length of Study

The study that provided a template for the current study design was a 6-month treatment study evaluating transdermal nicotine as a treatment for mild cognitive impairment (MCI) (Newhouse et al., 2012). The study by Newhouse et al., observed improvements in attention, memory, psychomotor speed and subjective ratings of cognition after 6-months of treatment with transdermal nicotine compared to placebo. At the time the current study was designed, the study length of 6-weeks on treatment and 8-weeks total was chosen because it was felt that it was a sufficient amount of time to detect a change using the principle measures, yet short enough to make the study feasible. Although we were able to detect a change/improvement in self-reported cognitive complaints, the current treatment duration of 6-weeks may simply not have been enough time to distinguish between the drug and placebo response. For example, when FACT-Cog PCI change from baseline scores from open-label study visits were included in a graph with the double-blind data (Figure 13), the open-label scores for the group that received nicotine during both the double-blind portion and open-label portions of the study (i.e. participants who received 12 weeks of nicotine vs 6 weeks) start to rise above those that received placebo. It may be the case that placebo effects are strong early-on in the study, but plateau or dissipate over longer study lengths. This may suggest that, in future, longer treatment duration could potentially help separate the drug response from the placebo response.

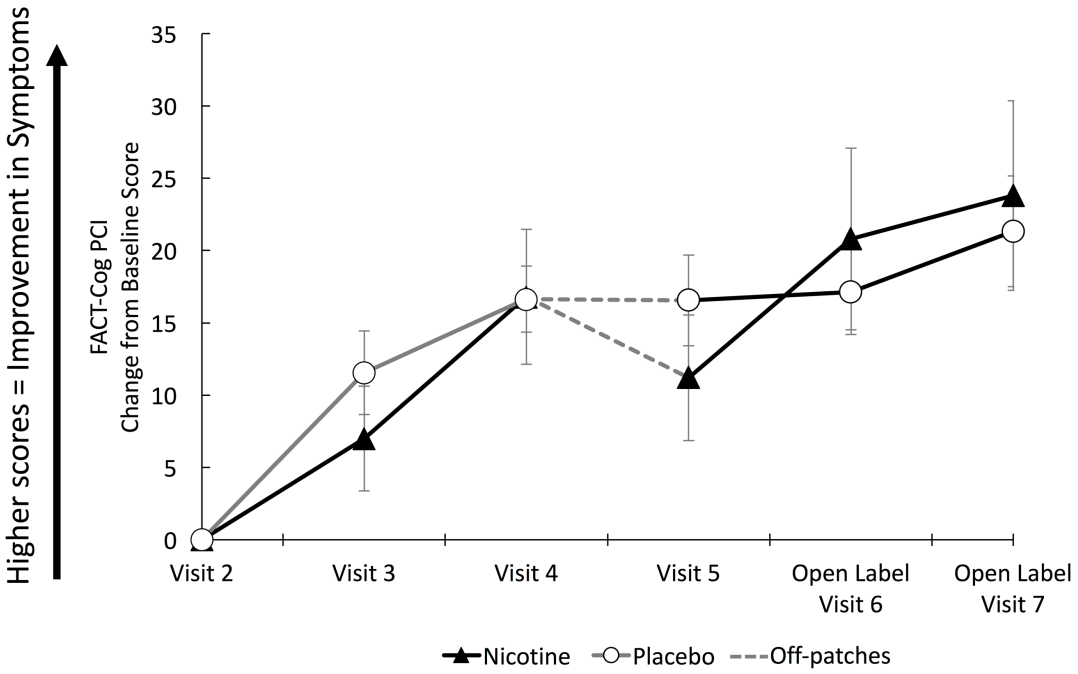


Figure 13. Open-Label FACT-Cog Perceived Cognitive Impairment (PCI) Change from Baseline Scores. Treatment groups during the double-blind portion of the study are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). Double-blind visits are Visits 2-5, open-label visits are Visits 6 (n=13) and 7 (n=11). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Positive change scores indicate improvement in symptoms.

Study Dosing

The Nicoderm patches that were used in the current study are available in 7mg, 14mg, and 21mg doses. A titration schedule (Table 4) was used help avoid initial side effects. Participants were started off on a ½ of a 7mg patch and were titrated up to 14mg by week 5 of the study. The maximum dose for the previous 6-month nicotine treatment study in MCI done by Newhouse was higher than the current study (Newhouse et al., 2012). However, at the time we were designing the current study, it was felt that a maximum dose of 14mg would be most tolerable (in terms of side effects) given the shorter study length and younger age of the participants. In terms of AEs, the study medication was very well tolerated. The only participants to withdraw due to AEs during the double-blind portion of the study were in the placebo group and there was no significant difference in number of AEs between groups in any body system. In hindsight, however, it may be the case that 14mg was not a sufficient. The fact that substantial weight changes in the nicotine group were not observed also supports

that the participants were under dosed since weight changes were observed in the MCI study conducted by Newhouse. In future, in addition to a longer study duration the dosing plan should be altered to include a maximum dose of 21mg/24 hours.

Placebo Response

The strong placebo response observed in this population was unexpected. Factors that potentially contributed to the observed placebo response in the current study are discussed below. Placebo response can be defined as the change in symptoms that occurs during a clinical trial in patients/research participants who have been randomized to receive placebo treatment (Rutherford & Roose, 2013). Placebo responses are commonly reported in treatment studies across a wide range of medical conditions, particularly for mood disorders such as depression (Peciña et al., 2015), but have also been observed in a wide range of other medical disorders (Agid et al., 2013; Colagiuri et al., 2015; Mestre et al., 2014).

Placebo response in clinical trials is a fascinating and complex phenomenon. It has been hypothesized that a number of potential factors that contribute to observed placebo response in clinical trials (Figure 14, adapted from Rutherford & Roose, 2013. Briefly, 'Treatment Factors' consist of all study interventions/procedures experienced by a patient/research participant in a clinical trial. Placebo effects are often attributed to expectancy, a form of conscious or unconscious reactivity that occurs when a research participant or patient expects a given result and therefore unconsciously affects the outcome, or reports the expected result. Placebo effects can also be affected by the frequency of patient–clinician interactions (Posternak & Zimmerman, 2007). For example, a meta-analysis investigating the influence of therapeutic contact frequency in 41 randomized-control trials for major depressive disorder (MDD) observed greater reduction in symptom severity in the placebo group that had more frequent patient-clinician interactions (Posternak & Zimmerman, 2007). Participants receiving antidepressants also experienced greater symptomatic change with increased numbers of follow-up visits, but the relative effect of this increased therapeutic contact

was approximately 50% less than that observed in the placebo group (Posternak & Zimmerman, 2007). The intensive nature of the clinical management that research participants often receive in clinical trials may provide non-specific benefits such as stress reduction, decreased anxiety or improvement of mood, thus contributing to placebo response (Oken, 2008). In addition, clinician/researcher attributes (e.g. personality, interaction style) may also contribute to placebo response (Oken, 2008). For example, optimistic or enthusiastic physician attitudes are associated with greater clinical improvements compared to neutral or pessimistic attitudes in a number of medical conditions, such as pain, hypertension, and obesity (Di Blasi & Kleijnen, 2003). Additional Treatment Factors that may contribute to placebo responses are physical aspects of the treatment such as route of administration (Khan et al., 2004), the pill dosing regimen, the color of pills, and the technological sophistication of the treatment procedures (Benedetti, 2008). These treatments factors may be moderated by 'Participant Characteristics,' such as personality, demographics, self-efficacy, stress, previous experiences/personal history of patient–clinician/researcher interactions, as well as shared experiences of the patient and clinician/researcher (Brody, 2000; Colagiuri et al., 2015; Di Blasi et al., 2001; Rutherford & Roose, 2013). 'Measurement Factors,' which represent sources of bias and error inherent in measuring subjective symptoms, and 'Natural History Factors,' such as spontaneous improvement or worsening in condition, provide additional sources of placebo effects (Rutherford & Roose, 2013). The sum effects and the interactions of the aforementioned treatment, patient characteristic, measurement, and natural history factors result in the placebo response observed in clinical trials (Figure 14).

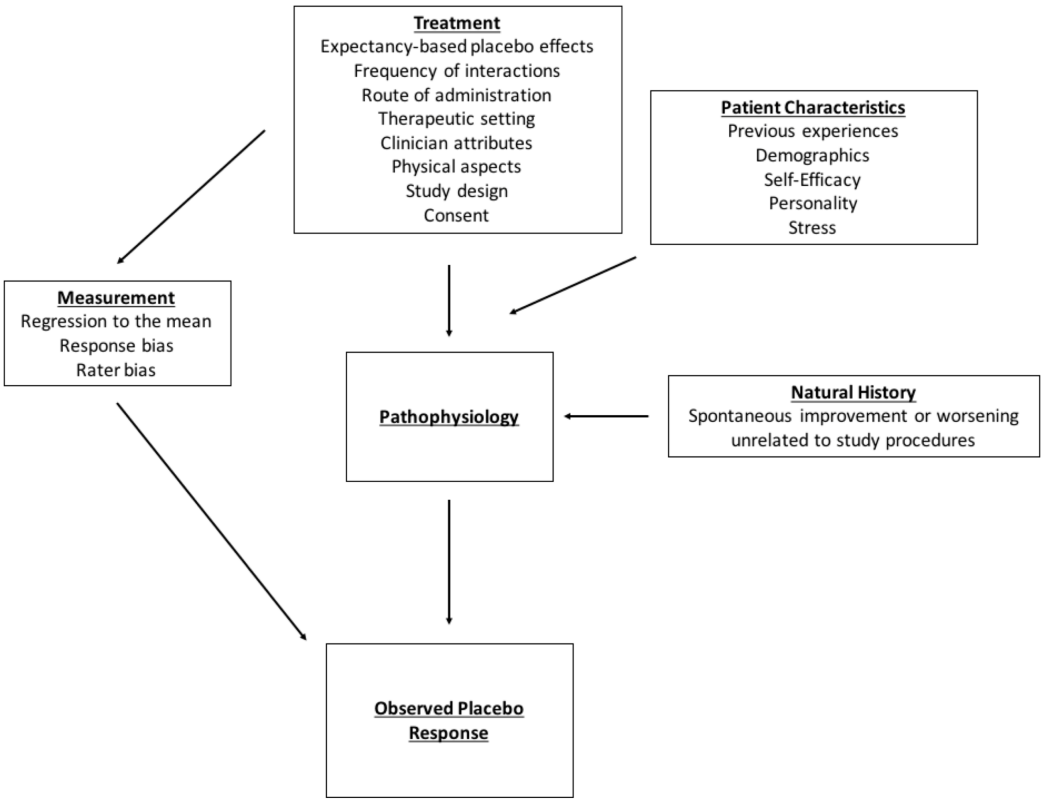


Figure 14. Model of Placebo Response in Clinical Trials Measuring Subjective Symptoms (adapted from (Rutherford & Roose, 2013). The sum effects and the interactions of treatment, patient characteristic, measurement, and natural history factors result in the placebo response observed in clinical trials.

Research into the underlying neurobiology of placebo responses has largely focused on pain (placebo analgesia) (Colagiuri et al., 2015), in which the μ-opioid receptor system has been implicated as the primary receptor system involved in placebo analgesia (Wager, Scott, & Zubieta, 2007). However, it may be most appropriate to compare the placebo response observed in the current study with placebo responses observed in clinical trials for depression. One study by Pecina et al., sought to examine the neurochemical mechanisms underlying placebo response in patients with MDD (Peciña et al., 2015). The study design consisted of a single-blinded 2-week crossover placebo lead-in phase with the administration of two identical placebos: an "active" placebo (described to participants as having fast-acting antidepressant effects) and an "inactive" placebo (described to participants as being a placebo with no antidepressant effects). PET imaging with the μ-opioid receptor-selective radiotracer [$^{(11)}$C]carfentanil (Wager et al., 2004) was completed after each 1-week "inactive" and "active" oral placebo treatment. Following the 2-week placebo lead-in phase, patients then completed a

10-week open label trail trial in which they received SSRI treatment. The researchers found that the participants reported significant decreases in depression symptoms when they took the "active" placebo, compared to when they took the "inactive" placebo. These reductions were linked to increased μ-opioid receptor brain activity in regions of the brain associated with emotion and stress regulation (Peciña et al., 2015). These results suggest that some people may be more responsive to the ***intention*** to treat their depression, and that such people may benefit most from the combination of antidepressant medications and cognitive therapies that enhance the patient-clinician relationship (Peciña et al., 2015).

Similarly, it may be the case that women with pCRCI could benefit from the incorporation of cognitive rehabilitation/therapies, that enhance the patient-clinician relationship, into their post-cancer care. Cognitive rehabilitation refers to a clinic-based, therapeutic program aimed at improving cognitive abilities, functional capacity, real-world skills (Wefel et al., 2015). There is some evidence that suggests that nonpharmacological interventions such as cognitive behavioral therapy, cognitive brain training, mindfulness based stress reduction, and physical activity may be beneficial for patients with patients with CRCI (Janelsins et al., 2014; Joly et al., 2015). For example, two pilot studies examining cognitive behavioral therapy in breast cancer patients demonstrated improvement on both objective and subjective (self-report) measures of cognitive function (Ferguson et al., 2012; Ferguson et al., 2007). Computerized cognitive brain-training studies suggest improvement in executive functioning (Kesler et al., 2013) and yoga may reduce subjective memory complaints (Janelsins et al., 2015). It may also be the case that for a syndrome such as pCRCI, for which no current treatment exists and is only now becoming increasingly recognized and accepted, that the intensive nature of clinical management that these participants received (which is likely beyond the level of individual attention they might have received in a typical clinical setting) may have provided benefits such as stress reduction, decreased anxiety, and improvement of mood, thus contributing to the strong placebo response observed. The issue of mood improvement will be further discussed further in Chapter IV.

CHAPTER IV

EXPLORATORY ANALYSES: SUBJECTIVE COGNITION AND MOOD IN CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENT

Introduction

Rationale

As discussed in Chapter III, the strong placebo response observed in this population was unexpected. One potential reason for the observed placebo response could potentially be that participation in the current study provided benefits such as stress reduction, decreased anxiety, and improvement of mood. Previous studies have found that affective symptoms, fatigue, and poorer quality of life (QOL) are associated with subjective cognitive complaints, but usually not with objective cognitive impairment on neuropsychological tests (Hutchinson et al., 2012). A study by Dhillon et al., 2017 found that total FACT-COG and PCI scores were associated with depression/anxiety, fatigue, and poorer QOL but had little or no association with results of neuropsychological testing (Dhillon et al., 2017). As an exploratory analysis, we evaluated change in mood across visits. In addition, we evaluated the association between mood measures and FACT-Cog scores, and between FACT-Cog scores and objective measures of cognitive functioning.

Methods

Outcome Measures

As mentioned previously, the FACT-Cog (Jacobs et al., 2007) scale was to monitor change in pCRCI subjective complaints. The FACT-Cog consists of four subscales (PCI: Perceived Cognitive Impairments, PCA: Perceived Cognitive Abilities, QOL: Impact on quality of life, and CFO: Comments from Others) and evaluates memory, concentration, mental acuity, verbal fluency, functional interference, and multitasking ability. At each double-blind visit (Visits 2-5), participants were asked to rate on a 5-point Likert scale how they felt about

various aspects of their cognitive functioning over the last 7 days. Higher scores indicate better self-reported cognitive functioning.

The Profile of Mood States (POMS) (McNair et al., 1971) was used to monitor change in mood across Visits 2-5. The POMs is a psychological rating scale used to assess transient, distinct mood states. It is specifically intended for use as a research instrument in assessing changes in affective states across events or interventions in psychologically healthy adults. The 65 items form 6 subscales, 5 negative mood states, and one positive mood dimension. The 5 negative mood state subscales are: Tension/Anxiety (assessed as both subjective state and somatic experience of anxiety), Depression (assesses feelings of inadequacy, isolation, guilt, futility, and sadness), Anger/Hostility (examines overt hostility and irritability), Fatigue (assesses feelings of exhaustion), and Confusion (assesses efficiency and clarity of thinking). The positive mood state subscale is vigor/activity, which examines well-being, enthusiasm, liveliness, energy, and optimism. At each double-blind visit (Visits 2-5), participants were asked to rate, 'How are you feeling right now?' for each item using a five-point scale ranging from 0 (not at all) to 4 (extremely). All subscale scores are calculated by summing the items endorsed for each individual subscale. A total score of mood disturbance (TMD) score can also be calculated by summing the scores of the 5 subscales for the negative mood states and subtracting from it the score for the positive subscale. For Tension/Anxiety, Depression, Anger/Hostility, Fatigue, Confusion, and TMD higher scores indicate greater mood disturbance. Conversely, for the Vigor subscale, higher scores indicate greater levels of enthusiasm and optimism.

To characterize the effects of nicotine on cognitive functioning in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI, we utilized measures that met one or more of the following criteria: 1) targeted domains most likely to be endorsed by patients with pCRCI (i.e. attention, working memory, executive function, and processing speed); 2) prior demonstration of response to nicotinic stimulation or blockade in nicotine studies. See Table 3, Chapter III for an overview of the objective cognitive performance battery.

Statistical Analyses

Analyses were performed using IBM SPSS Statistics for Mac, version 25 (IBM Corp., Armonk, N.Y., USA). Two participants (0003 and 0023) had missing data from Visits 4-5, therefore SPSS was used to impute the missing data from Visits 4-5 for those participants (see Chapter III). Group differences in screening, baseline, and POMS scores were evaluated using independent samples t-tests. A mixed-models repeated measures ANOVA with a within-subjects factor of time (Visit) using change from baseline scores for POMS-TMD and on each of the 6 POMS subscales (Visit 3, Visit 4, and Visit 5) and a between-subject factor of drug treatment group (nicotine, placebo). POMS data from both groups were combined and a repeated measures ANOVA was used to assess change from baseline scores for POMS-TMD and on each of the 6 POMS subscales. t-tests were used to look at post-hoc pair-wise differences. All pairwise comparisons were Sidak corrected for multiple comparisons at the $p < 0.05$ level. Correlations between POMS and FACT-Cog and the FACT-Cog and objective measures were performed using Pearson product-moment correlations. All correlation analyses were performed for each FACT-Cog subscale according to visit. The alpha level for rejection of the null hypothesis for all correlation analyses was Bonferroni corrected at the $p < 0.05$ level.

Results

Demographics

The participants used in the current analysis were the same as those used in Chapter III. See consort diagram (Chapter III, Figure 3) for details regarding participant enrollment. Briefly, twelve were randomized to nicotine treatment (9 completers, 11 with usable data) and 13 were randomized to placebo treatment (11 completers). The mean ages for the nicotine and placebo treated groups were 56.00 ± 11.58 and 52.55 ± 7.66, respectively. There was no difference in mean age between groups ($t(20) = 0.83$, $p = 0.42$). There were no group differences on any demographic (Chapter III, Table 6) factors, CCI scores (Chapter 3, Table 7) or baseline FACT-Cog scores (Chapter III, Table 8). There were also no baseline group differences on any of the POMS subscales. (Table 12, Figure 15).

Table 12. POMs Baseline Group Differences

	Drug Group	N	Mean	Std. Dev	SEM	*t* Statistic
Total Mood Disturbance	Nicotine	11	12.09	20.94	6.31	$t(20) = 0.11$, $p = 0.91$
	Placebo	11	11.18	16.76	5.05	
Tension/Anxiety	Nicotine	11	5.00	3.32	1.00	$t(20) = 0.12$, $p = 0.90$
	Placebo	11	4.82	3.66	1.10	
Depression	Nicotine	11	4.64	4.27	1.29	$t(20) = 0.62$, $p = 0.54$
	Placebo	11	3.64	3.23	0.98	
Anger/Hostility	Nicotine	11	2.00	3.58	1.08	$t(20) = 0.49$, $p = 0.63$
	Placebo	11	1.36	2.38	0.72	
Fatigue	Nicotine	11	7.55	7.33	2.21	$t(20) = 0.06$, $p = 0.95$
	Placebo	11	7.36	6.28	1.89	
Confusion	Nicotine	11	7.45	4.78	1.44	$t(20) = 0.44$, $p = 0.66$
	Placebo	11	6.73	2.61	0.79	
Vigor/Activity	Nicotine	11	14.55	5.84	1.76	$t(20) = 0.67$, $p = 0.51$
	Placebo	11	12.73	6.86	2.07	

POMS: Profile of Mood States

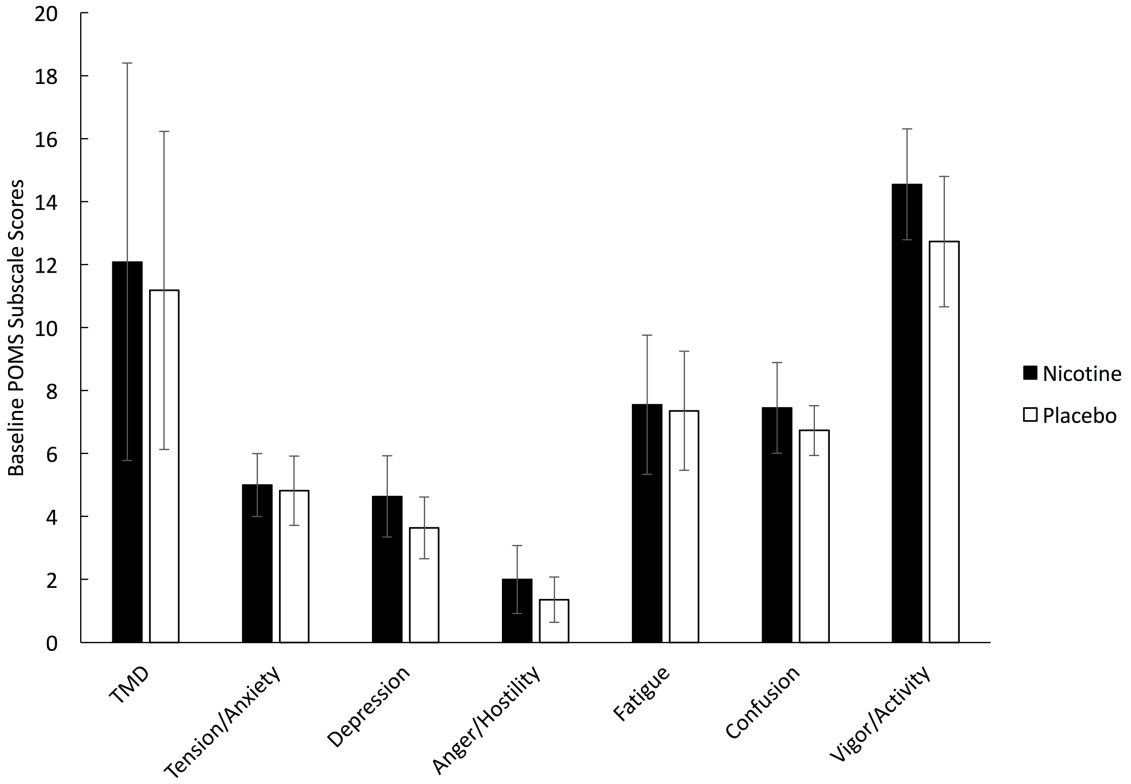


Figure 15. POMS Subscale Baseline Scores. Treatment groups are distinguished by the following colors: nicotine (black) and placebo (white). Error bars represent SEM. For Total Mood Disturbance (TMD), Tension/Anxiety, Depression, Anger/Hostility Fatigue, and Confusion, higher scores indicate greater mood disturbance. Conversely, for the Vigor/Activity subscale, higher scores indicate greater levels of enthusiasm and optimism. There were no baseline differences on any POMS subscales between treatment groups.

POMs ANOVA Results

Mixed-model repeated measure ANOVA results evaluating drug treatment group differences in change from baseline scores for POMS-TMD and on each of the 6 POMS subscales are presented in Appendix Table 1 and Appendix Figures 1-2. No differences with respect to drug treatment group were observed, therefore data was combined for subsequent ANOVA and correlation analyses presented in this chapter. Combined data were analyzed using a repeated measures ANOVA was used to assess change from baseline scores for POMS-Total Mood Disturbance (TMD) and each of the 6 subscales over time (Visit 3, Visit 4, and Visit 5). Combined data ANOVA results for POMS subscales are shown above in Table 13. Significant changes observed on POMS are discussed below. All post-hoc pairwise differences were corrected for multiple comparisons using the Sidak correction, $p < 0.05$.

POMS-Total Mood Disturbance (TMD) Score

There was a significant decrease in TMD scores compared to baseline ($F(3,63) = 7.49$, $p < 0.001$). Negative TMD change scores indicates improved mood. Post-hoc comparisons revealed significant differences between Visit 2 and Visit 4 ($p = 0.003$, mean diff = -14.09), and Visit 2 and Visit 5 ($p = 0.03$, mean diff = -13.74) (Figure 16).

POMS-Depression Score

Mauchly's test indicated that the assumption of sphericity had been violated ($\chi2(5) = 14.08$, $p < 0.05$), therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.69$). There was a significant decrease in POMS-Depression scores compared to baseline ($F(2.09, 43.96) = 3.39$, $p < 0.05$). Negative POMS-Depression change scores indicate improved mood. Post-hoc comparisons revealed significant differences between Visit 2 and Visit 5 ($p = 0.02$, mean diff = -2.25) (Figure 17a).

POMS-Fatigue Score

Mauchly's test indicated that the assumption of sphericity had been violated ($\chi2(5) = 13.65$, $p < 0.05$), therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.73$). There was a significant decrease in POMS-Fatigue scores compared to baseline ($F(2.19, 45.96) = 3.37$, $p < 0.05$). Negative POMS-Fatigue change scores indicate improved mood. Post-hoc comparisons revealed a trend for a difference between Visit 2 and Visit 5 ($p = 0.09$, mean diff = -2.25) (Figure 17b).

POMS-Confusion Score

Mauchly's test indicated that the assumption of sphericity had been violated ($\chi2(5) = 24.99$, $p < 0.05$), therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.57$). There was a significant decrease in POMS-Confusion scores compared to baseline ($F(1.70, 35.74) = 11.68$, $p < 0.001$). Negative POMS-Fatigue change scores indicate improved mood. Post-hoc comparisons revealed significant differences between Visit 2 and Visit 3 ($p = 0.02$, mean diff = -1.14), Visit 2 and Visit 4 ($p = 0.002$, mean diff = -3.10), Visit 2 and Visit 5 ($p = 0.004$, mean diff = -2.88) (Figure 17c).

POMS-Vigor/Activity Score

There was a significant increase in POMS-Vigor/Activity scores compared to baseline ($F(3,63) = 7.25$, $p < 0.001$). Positive POMS-Vigor/Activity change scores indicate improved mood. Post-hoc comparisons revealed significant differences between Visit 2 and Visit 4 ($p = 0.001$, mean diff = 5.65), Visit 2 and Visit 5 ($p = 0.03$, mean diff = 3.66) (Figure 17d).

POMs Anxiety/Tension and POMs Anger/Hostility Scores

No significant changes in POMS-Tension/Anxiety ($F(2.10, 44.04) = 1.74$, $p = 0.19$) or POMS-Anger/Hostility scores over time were observed ($F(2.04, 42.82) = 0.85$, $p = 0.44$).

Table 13. POMS-Subscale Change from Baseline ANOVA Results

POMS Subscale	ANOVA Result
Total Mood Disturbance	***F*(3,63) = 7.49, *p* < 0.001****
Tension/Anxiety	$F(2.10, 44.04), = 1.74, p = 0.19^{+}$
Depression	***F*(2.09, 43.96) = 3.39, *p* < 0.05*$^{+}$**
Anger/Hostility	$F(2.04, 42.82), = 0.85, p = 0.44^{+}$
Fatigue	***F*(2.19, 45.96), = 3.37, *p* < 0.05*$^{+}$**
Confusion	***F*(1.70, 35.74) = 11.68, *p* < 0.001**$^{+}$**
Vigor/Activity	***F*(3,63), = 7.25, *p* < 0.001****

POMS: Profile of Mood States

$^{+}$Adjusted for Greenhouse-Geisser estimates of Sphericity

*Significant at p < 0.05 level

**Significant at p < 0.001 level

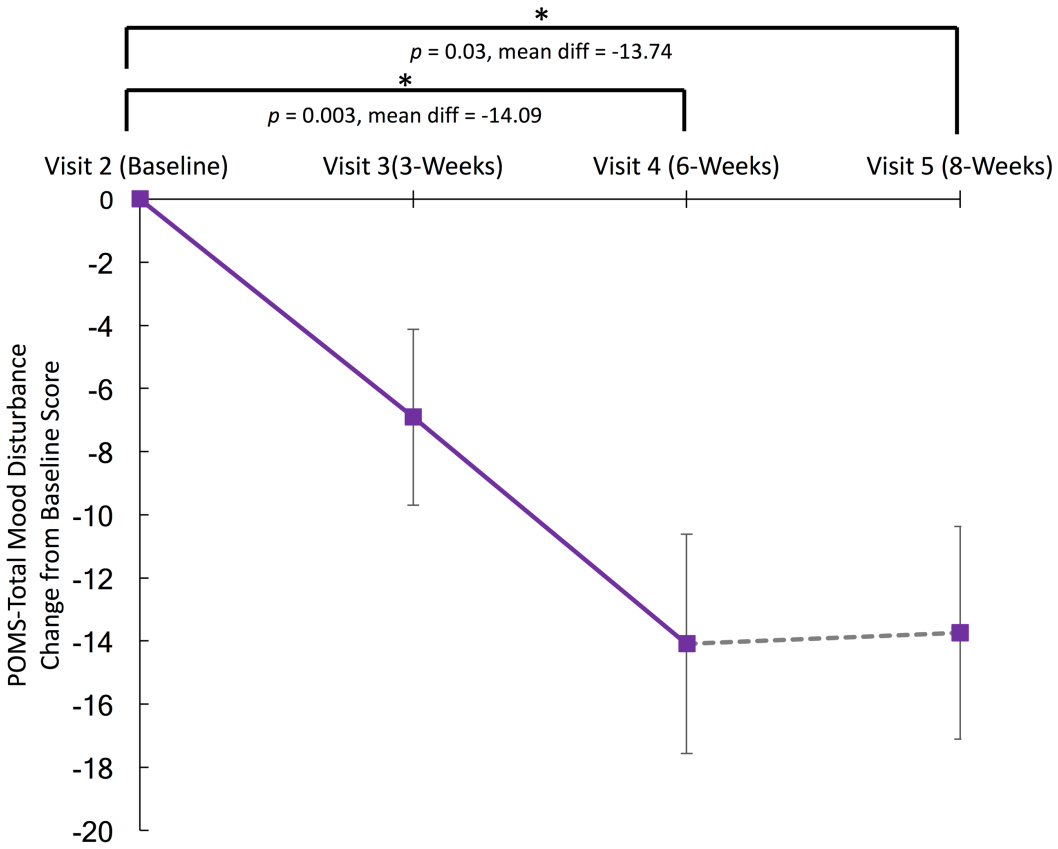


Figure 16. POMS Total Mood Disturbance (TMD) Change from Baseline Scores. TMD score is calculated by summing the scores of the 5 subscales for the negative mood states and subtracting from it the score for the positive subscale. Purple square markers indicate combined nicotine and placebo group data. The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Asterisks indicated significant pairwise differences between visits, **p* < 0.05. All post-hoc pairwise comparisons are Sidak corrected for multiple comparisons. Negative TMD change scores indicates improved mood.

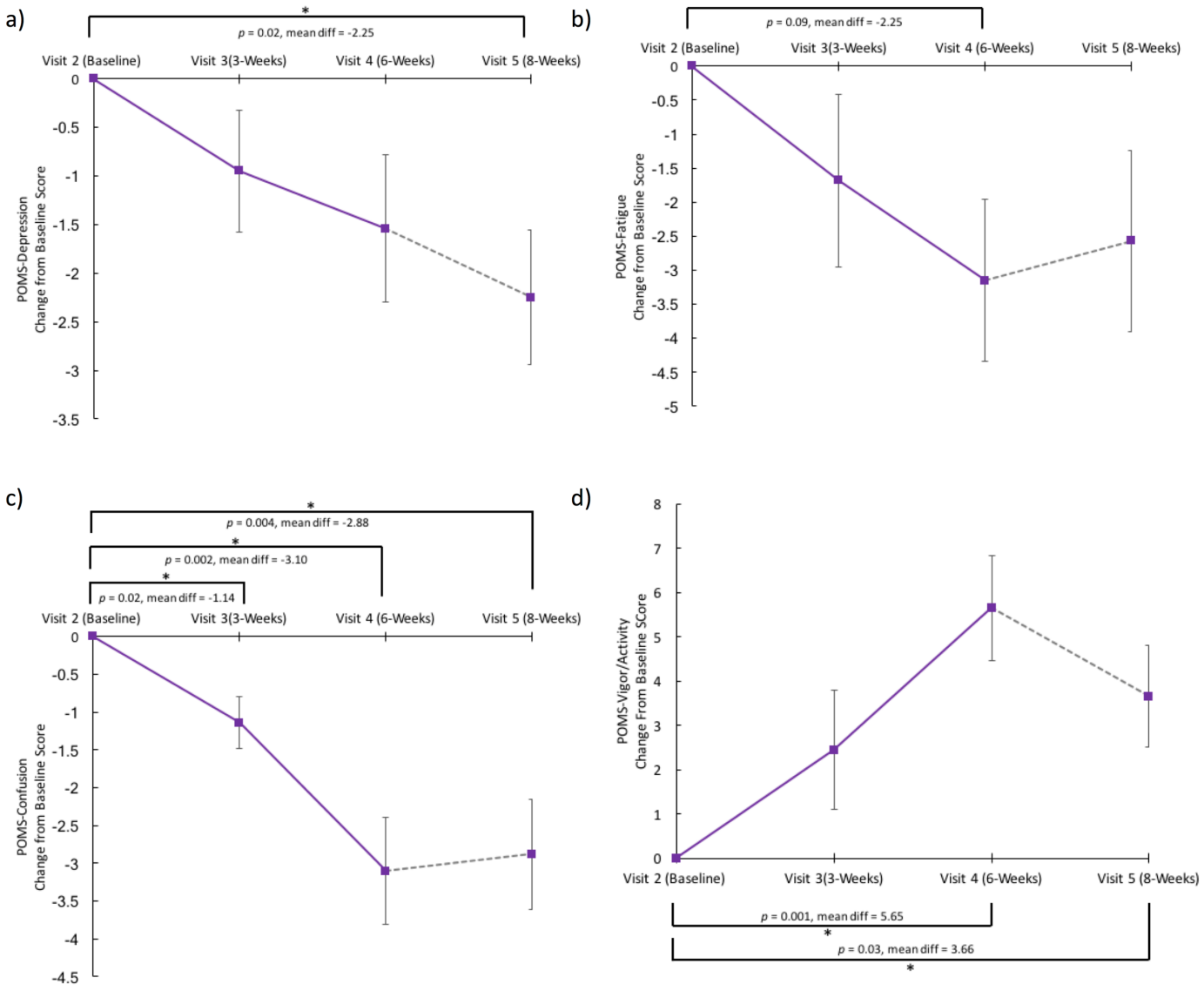


Figure 17. Significant POMS Subscales Change from Baseline Scores. a) POMS-Depression change from baseline scores, negative change scores indicate improvement in mood b) POMS-Fatigue change from baseline scores, negative change scores indicate improvement in mood c) POMS-Confusion change from baseline scores, negative change scores indicate improvement in mood and d) POMS-Vigor/Activity change from baseline scores, positive change scores indicate improvement in mood. For all graphs, purple square markers indicate combined nicotine and placebo group data. The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Asterisks indicate significant pairwise differences between visits, *$p < 0.05$. All post-hoc pairwise comparisons are Sidak corrected for multiple comparisons.

Relationship Between FACT-Cog and POMS

Correlations between POMS and FACT-Cog measures were performed using Pearson product-moment correlations. Pearson correlation coefficient results are shown in Appendix Tables 2-6. Scatter plots for significant correlations that survived Bonferroni correction are shown in Figure 18. There were significant negative associations between the following FACT-Cog and POMS measures: Visit 3 FACT-Cog PCI score and Visit 3 POMS-Confusion score ($r(20) = -0.68$ $p < 0.001$) (Figure 18a), Visit 3 FACT-Cog PCA score and Visit 3 POMS-Confusion score ($r(20) = -0.69$ $p < 0.001$) (Figure 18b), and Visit 3 FACT-Cog Total score and Visit 3 POMS-Confusion score ($r(20) = -0.75$ $p < 0.001$) (Figure 18c).

Relationship Between FACT-Cog and Cognitive Performance Measures

Correlations between FACT-Cog subscales and objective measures were performed using Pearson product-moment correlations. Pearson correlation coefficient results are shown in Appendix Tables 7-11. No significant correlations were observed between any FACT-Cog subscale and any cognitive performance measure.

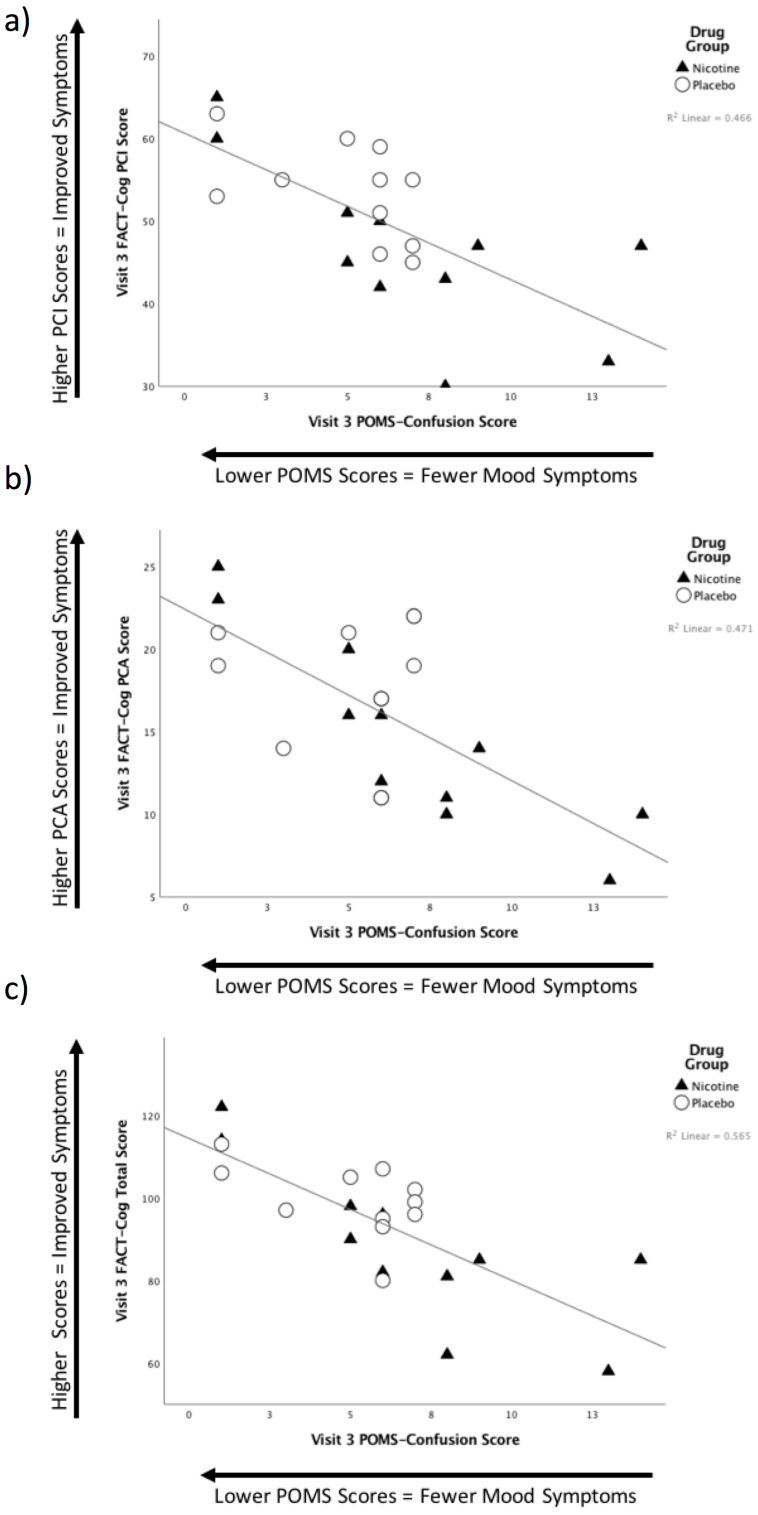


Figure 18. Scatterplots for Significant Correlations between FACT-Cog Subscales and Profile of Mood States (POMS)-Confusion Scores. a) Correlation between Visit 3 FACT-Cog Perceived Cognitive Impairment (PCI) score and Visit 3 POMS-Confusion score, b) Correlation between Visit 3 FACT-Cog Perceived Cognitive Abilities (PCA) score and Visit 3 POMS-Confusion Score, and c) Correlation between Visit 3 FACT-Cog Total score and Visit 3 POMS-Confusion Score. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). For all graphs, lower FACT-Cog scores were associated with higher POMS-Confusion scores. Higher FACT-Cog PCI scores indicate better subjective cognition. Lower POMS – Confusion scores indicates better mood.

Discussion

Summary of Findings

As an exploratory analysis, we evaluated change in mood across visits. The following POMS subscales improved significantly from baseline: Total Mood Disturbance**,** Depression**,** Fatigue**,** Confusion**,** Vigor/Activity. There were no differences between drug treatment groups. In other words, all participants improved in terms of some aspects of mood over the course of the study regardless of drug treatment group. In addition, we evaluated the association between mood measures and FACT-Cog scores, and between FACT-Cog scores and objective measures of cognitive functioning. There were significant negative correlations between Visit 3 POMS-Confusion scores and the following Visit 3 FACT-cog subscales: PCI, PCA, and Total. Lower FACT-Cog scores (poorer subjective cognition) were associated with higher POMS-Confusion scores (poorer mood). No significant correlations were observed between any FACT-Cog subscale and any cognitive performance measure.

These results suggest that one potential reason for the observed placebo response could potentially be that participation in the current study provided benefits such as stress reduction, decreased anxiety, and improvement of mood. The finding that the FACT-Cog correlated with mood measures, but did not correlate with cognitive performance measures, suggests that the subjective symptoms measured by the FACT-Cog may actually reflect fatigue, anxiety/depression, and poorer quality of life, as opposed to cognitive performance measured on neuropsychological testing. This finding supports previous research that found that total FACT-Cog and FACT-Cog PCI scores were associated with depression/anxiety, fatigue, and poorer QOL but had little or no association with results of neuropsychological testing (Dhillon et al., 2017).

CHAPTER V

PERSISTENT SUBJECTIVE CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENT: COMPARISON WITH SUBJECTIVE COGNITIVE DECLINE FOLLOWING MENOPAUSE

Introduction

Menopause Associated Subjective Cognitive Decline (maSCD)

Complaints of cognitive dysfunction are also commonly reported by women during and following the menopause transition in non-cancer patients (Weber & Mapstone, 2009), and may be related to the decline in circulating estrogen levels (Paul Newhouse et al., 2013). The transition from pre- to post-menopausal status is associated with cognitive difficulties in learning and memory (Greendale et al., 2009). For example, approximately 60% of middle-aged women reported cognitive changes in the Seattle Midlife Women's Health Study (ME & Woods, 2001), and 42% of postmenopausal women reported a negative change in cognition in the Study of Women Across the Nation (SWAN) (Bromberger et al., 2011). There is also increasing evidence that SCD, even with normal performance on objective neuropsychological tests, is associated with an increased risk for developing late-life cognitive decline and Alzheimer's disease (AD) in female non-cancer patients (Pérès et al., 2011). In addition to naturally occurring menopause, surgically induced menopause has been found to be detrimental to cognitive functioning, particularly on verbal memory tasks (Phillips & Sherwin, 1992; Sherwin, 2006). as well as being associated with fewer improvements with practice compared to age-matched women who underwent a natural menopause (Rice et al., 2000). Although not universally agreed upon (Kok et al., 2006; Polo-Kantola et al., 1998), it has been suggested that chemotherapy-induced menopause might have similar effects on cognitive functioning (Vearncombe et al., 2011).

Rationale for Study

Although the majority of evidence for cognitive difficulties in cancer patients and survivors is attributed to chemotherapy, there is growing evidence to suggest that menopausal status and/or endocrine therapy can also influence cognitive function in cancer patients (Janelsins et al., 2011). Case studies in breast cancer reveal that cognitive difficulties can vary among patients who received the same course of chemotherapy, suggesting that this could be related to menopausal status (Paraska & Bender, 2003). The effect of menopause may be particularly relevant for breast cancer patients since adjuvant endocrine therapy for hormone-receptor positive (HR+) breast cancer, which account for approximately 70-75% of breast cancers (Harvey et al., 1999), has been shown to impact cognitive function, either alone or in combination with chemotherapy (Bender et al., 2006; Castellon et al., 2004; Collins et al., 2009b; Jenkins et al., 2008; Palmer et al., 2008; Schilder et al., 2009, 2010). For example, neuroimaging research in breast cancer patients has shown that changes in the patterns of brain activity from pre- to post-chemotherapy treatment varies according to pre-treatment menopausal status (Conroy et al., 2013). Given that there is this question of how much menopause contributes to the pCRCI phenotype (e.g. subjective cognitive complaints) in women, we compared a group of primarily post-menopausal women with subjective pCRCI to two groups of post-menopausal women without a history of cancer: women who endorse maSCD (maSCD+) and women who do not (maSCD) to explore the similarities and differences between SCD following chemotherapy and SCD following menopause. This comparison is unique because the majority of CRCI research has compared cancer patients to completely healthy controls. While our maSCD- group serves as a healthy control group, the addition of a comparison group of otherwise healthy women without a history of cancer who also endorse subjective cognitive decline (maSCD+ group), to our knowledge, has never been previously examined (Vega, Dumas, & Newhouse, 2018).

Methods

Participants

This study included data from 63 total participants who were recruited for two separate studies in the lab; 1) the pCRCI study discussed in previous chapters and 2) a maSCD study. maSCD study participants were recruited as part of a larger study examining the ability of estrogen to enhance cholinergic-related cognitive function (Dumas, Kutz, et al., 2013). Only screening (Visit 1) and baseline (pre-treatment, Visit 2) data for pCRCI participants is presented in this chapter.

Of the 37 women recruited and screened for the pCRCI study, 24 cancer (breast cancer = 20), ovarian cancer = 1, lymphoma = 3) patients completed both a screening and baseline visit and were included in the current analysis. Twelve were excluded because they did not meet inclusion/exclusion criteria. The pCRCI study was conducted at Vanderbilt University. The maSCD study was conducted at both Vanderbilt University and University of Vermont. A total of 53 healthy, post-menopausal women were recruited and screened for the maSCD study. Of this sample, 39 women completed both a screening and baseline visit and were included in the current analysis. Fourteen were excluded because they did not meet inclusion/exclusion criteria. Both studies were carried out in accordance with the recommendations of University of Vermont and Vanderbilt University Institutional Review Boards with written informed consent from all participants.

Inclusion and Exclusion Criteria

Since the pCRCI and maSCD studies shared the same principle investigator (PN), both studies had very similar exclusion criteria, which allowed for the comparison between studies. Both studies excluded for: 1) any active neurologic and/or psychiatric disease, history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities, 2) current major depression or another major psychiatric disorder as described in DSM-5 (use of psychotropic medications (e.g. antidepressants) was permitted, provided dosing has been stable for at least 3 months), 3) any history of alcohol or substance abuse

or dependence within the past 2 years, 4) any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol including: 4a) history of myocardial infarction in the past year or unstable, severe cardiovascular disease including angina or CHF with symptoms at rest, or clinically significant abnormalities on the electrocardiogram (ECG) 4b) clinically significant and/or unstable pulmonary, gastrointestinal, hepatic, or renal disease 4c) insulin-requiring diabetes or uncontrolled diabetes mellitus, 4d) uncontrolled hypertension (systolic BP> 170 or diastolic BP> 100), 5) use of any investigational drugs within 30 days or 5 half-lives, whichever is longer, prior to screening, and 6) use of any drugs with pro-cholinergic properties (e.g. donepezil). Exclusion criteria for the maSCD participants included all of the above criteria for the pCRCI study with the following additional criteria: 1) use of hormone therapy during the last year, 2) a history of breast cancer, and 3) and a history or presence of severe menopausal symptoms.

Differences in the inclusion criteria for two studies were as follows: 1) pCRCI study participants were required to be between 35 and 80 years of age, been diagnosed with noninvasive or invasive breast cancer, ovarian cancer, or lymphoma, undergone treatment with systemic chemotherapy within the last 1-5 years, endorsed pCRCI subjective complaints, current non-smokers (no nicotine use within the last 5 years), and were fluent in and able to read English, 2) maSCD study participants were required to be between 50-60 years of age, and postmenopausal (i.e., without menses for one year and without surgically induced menopause). Exclusion criteria for the maSCD participants included all of the above criteria for the pCRCI study with the following additional criteria: 1) use of hormone therapy during the last year, 2) a history of breast cancer, and 3) and a history or presence of severe menopausal symptoms.

Outcome Measures

Behavioral

The Cognitive Complaint Index (CCI) (Saykin et al., 2006) was used to operationalize both study participants as having subjective complaints. The CCI was chosen to operationalize participants as having

subjective complaints because previous research has shown that this measure correlates with underlying neurodegenerative changes even when unaccompanied by deficits on formal testing

For both the pCRCI study and maSCD study, a CCI score was calculated as the percentage of all items endorsed. For the pCRCI study, participants were required to have endorsement of at least 20% of all items to be considered as having chemotherapy-related subjective complaints (Saykin et al., 2006) (n = 24). For the maSCD study, participants were categorized in the maSCD+ group (n = 16) if they endorsed more than 20% of the items on these questionnaires. Conversely, participants were categorized in the maSCD- group (n = 23) group if they endorsed less than 20% of items on the CCI. BDI scores were calculated according to Beck et al., 1961 with higher scores indicating more severe depressive symptoms. The MSC score was calculated according to (Newhouse et al., 2010), with higher scores indicating greater menopausal symptoms.

Cognitive

The two studies shared similar cognitive testing batteries enabling comparison of the datasets. These cognitive domains included tests of simple attention and verbal episodic memory. Each task is described below. The cognitive battery was performed at numerous visits, however only baseline data are included.

The Critical Flicker Fusion (CFF) task (Kupke & Lewis, 1989) was used as a test of attention/vigilance. In an ascending trial, the participant presses a button indicating when the frequency of flashing lights, (beginning at 12 Hz and increasing to 50 Hz), has increased to the point that the lights appear to be no longer flashing but rather appear continuously on ("fused"). In a descending trial, beginning at 50 Hz, the participant presses a button when the frequency of apparently fused lights is decreased such that lights begin to appear to be flashing. The participant needs to respond before the frequency hits the upper or lower limit in each trial. The outcome variable for CFF is frequency (Hz) for ascending and descending trials.

The Choice Reaction Time (CRT task (Hindmarch, 1984)) was used as a measure of attention and psychomotor speed. The CRT task was a reaction time task in which participants are asked to keep their index

finger on a “home” light sensitive diode (LSD) until one of 6 LSDs arrayed in a semicircle, approximately 25 cm from the “home” key, was lit on the response box. When one of the 6 LSDs arrayed in a semicircle lit up, the participant is asked to lift her index finger and press the corresponding button to the illuminated LCD, then return her finger to the “home” LSD button. This pattern continues for 50 trials. Outcome variables on the CRT included the mean and median processing reaction time (RT) (time from stimulus onset to initiation of movement), the mean and median motor RT (time from initiation of movement to stimulus termination), and mean and median total reaction time, with lower scores indicating better performance.

The Selective Reminding Task (SRT) (Buschke & Fuld, 1974) was used to assess immediate and delayed memory recall. Participants are read a list of 16 words and must immediately recall the list across 8 trials. Every trial after the first involves selectively reminding the participant of the words she did not recall on the immediately preceding trial. The SRT is continued until either the participant is able to correctly recall all 16 words on three consecutive trials, or until 8 trials have been completed. Upon completing the immediate recall portion of the SRT, and after a 20-minute delay, participants are asked to complete a single delayed recall trial. SRT total immediate recall was analyzed using the number of correctly recalled words across trials 1-8 (Refered to as Total Recall), total immediate recall consistency was analyzed using the number of words correctly recalled on two trials in a row across trials 1-8 (referred to as Total Consistency), SRT total immediate recall failure was analyzed using the number of words not recalled two trials in a row across trials 1-8 (Referred to as Total Recall Failure), and total delayed recall was analyzed using the number of words correctly recalled after a 20-minute delay (referred to as Delayed Recall).

Statistical Analysis

One-way ANOVAs were performed using IBM SPSS Statistics for Mac, version 24 (IBM Corp., Armonk, N.Y., USA) to evaluate group differences between pCRCI study participants and maSCD study participants (categorized as either maSCD+ or maSCD-) on behavioral and cognitive outcome measures. Correlations between behavioral and cognitive measures were performed using Pearson product-moment correlations. For

correlation analyses, CCI was analyzed as a continuous variable. The alpha level for rejection of the null hypothesis was set at $p < 0.05$. All behavioral analyses and the SRT analysis included data from all 63 participants. Three participants from the maSCD- group failed to complete the CRT and CFF and were therefore excluded from those analyses. Sidak corrected t-tests were used to look at post-hoc pair-wise differences.

Results

Demographics

Demographics for each group are shown in Table 14. There was no difference in mean age between groups $F(2,60) = 0.927$, $p = 0.401$. The mean ages for each group are as follows: maSCD+ = 56.75, maSCD- = 56.04, and pCRCI = 54.21. A total of 36 were recruited and screened for the pCRCI study. Of this sample, 24 cancer (breast cancer = 19), ovarian cancer = 1, lymphoma = 3) patients completed both a screening and baseline visit and were included in the current analysis. A total of 53 healthy, post-menopausal were recruited and screened for the maSCD study. Of this sample, 39 women completed both a screening and baseline visit and were included in the current analysis. pCRCI participants were an average of 2.5 years post-chemotherapy.

Table 14. pCRCI and maSCD Participant demographics

		pCRCI (n=24)	maSCD+ (n=16)	maSCD- (n=23)
Age in years (mean ± S.D.)		54.21 ± 9.38	56.75 ± 2.70	56.04 ± 2.94
Years Since Completed Chemotherapy (mean ± S.D.)		2.50 ± 1.84	-	-
Cancer Type	Breast	20	-	-
	Lymphoma	3		
	Ovarian	1		
Current Endocrine Therapy	Yes	14	-	-
	No	10		
Menopausal Status Prior to Chemotherapy	Pre-Menopausal	13	-	-
	Post-Menopausal	11		
Current Menopausal Status	Pre-Menopausal	2	-	-
	Post-Menopausal	22	16	23

pCRCI: persistent Chemotherapy-Related Cognitive Impairment, maSCD: Menopause-Associated Subjective Cognitive Decline

Behavioral

Results for behavioral descriptive statistics and ANOVA results are shown in Table 15. Significant ANOVA results are displayed on Figure 19. There was a statistically significant difference between pCRCI, maSCD+ and maSCD- groups ($F(2,60) = 70.73$, $p < 0.0001$) in CCI score. Post-hoc analyses revealed that pCRCI participants had a higher mean CCI score (mean = 0.4466, $p < 0.001$) compared to both maSCD+ (mean = 0.275) and maSCD- (mean = 0.088). There was statistically significant difference between both pCRCI and maSCD+ groups, compared to the maSCD- group on BDI $F(2,60) = 8.70$, $p = 0.001$. Post-hoc analyses revealed that pCRCI participants (mean = 4.92, $p < 0.01$) and the maSCD+ group (mean = 5.13, $p < 0.001$) both had a higher mean BDI score compared to the maSCD- group (mean = 1.83). There was a statistically significant difference between pCRCI, maSCD+ and maSCD- groups on the MSC score ($F(2,60) = 10.63$, $p < 0.0001$). Post-hoc analyses revealed that the pCRCI (mean = 27.88, $p < 0.001$) group had a higher mean MSC score compared to the maSCD- (mean

= 12.96) group, but not the maSCD+ (mean = 21.00) group. There was no significant difference between pCRCI participants who received endocrine therapy and those who did not on any behavioral measure (see Appendix Table 12). There was also no significant difference between pCRCI participants based on menopausal status prior to chemotherapy on any behavioral measure (see Appendix Table 13).

Table 15. pCRCI and maSCD Behavioral and CRT Descriptive Statistics and ANOVA Results

		N	Mean	Std. Deviation	Std. Error	Minimum	Maximum	ANOVA Result
CCI Score	maSCD+	16	0.28	0.09	0.02	0.18	0.47	$F(2,60) = 70.73$, $p<0.0001$
	maSCD-	23	0.09	0.06	0.01	0.00	0.18	
	pCRCI	24	0.45	0.14	0.03	0.09	0.67	
Age	maSCD+	16	56.75	2.70	0.67	51.00	60.00	$F(2,60) = 0.927$, $p=0.401$
	maSCD-	23	56.04	2.95	0.61	50.00	60.00	
	pCRCI	24	54.21	9.38	1.92	38.00	73.00	
BDI Score	maSCD+	16	5.13	2.19	0.55	1.00	10.00	$F(2,60) = 8.70$, $p=0.001$
	maSCD-	23	1.83	2.27	0.47	0.00	9.00	
	pCRCI	24	4.92	3.75	0.77	0.00	13.00	
MSC Score	maSCD+	16	21.00	9.63	2.41	6.00	37.00	$F(2,60) = 10.63$, $p<0.0001$
	maSCD-	23	12.96	7.25	1.51	4.00	30.00	
	pCRCI	24	27.88	14.50	2.96	7.00	60.00	
CRT Median Processing Reaction Time	maSCD+	16	399.84	37.42	9.35	325.00	452.50	$F(2,57) = 6.21$, $p=0.004$
	maSCD-	20	405.30	68.26	15.26	318.00	588.50	
	pCRCI	24	467.08	84.53	17.26	368.00	767.00	
CRT Median Motor Reaction Time	maSCD+	16	394.06	85.67	21.42	257.00	585.50	$F(2,57) = 0.98$, $p=0.380$
	maSCD-	20	358.20	64.12	14.34	273.00	523.50	
	pCRCI	24	376.65	79.58	16.24	243.50	637.50	
CRT Median Total Reaction Time	maSCD+	16	801.84	111.35	27.84	584.50	1046.50	$F(2,57) = 2.22$, $p=0.118$
	maSCD-	20	770.80	120.61	26.97	633.50	1115.00	
	pCRCI	24	852.79	148.62	30.34	642.50	1414.00	

CCI: Cognitive Complaint Index, BDI: Beck Depression Inventory, MSC: Menopause Symptom Checklist, CRT: Choice Reaction Time Task

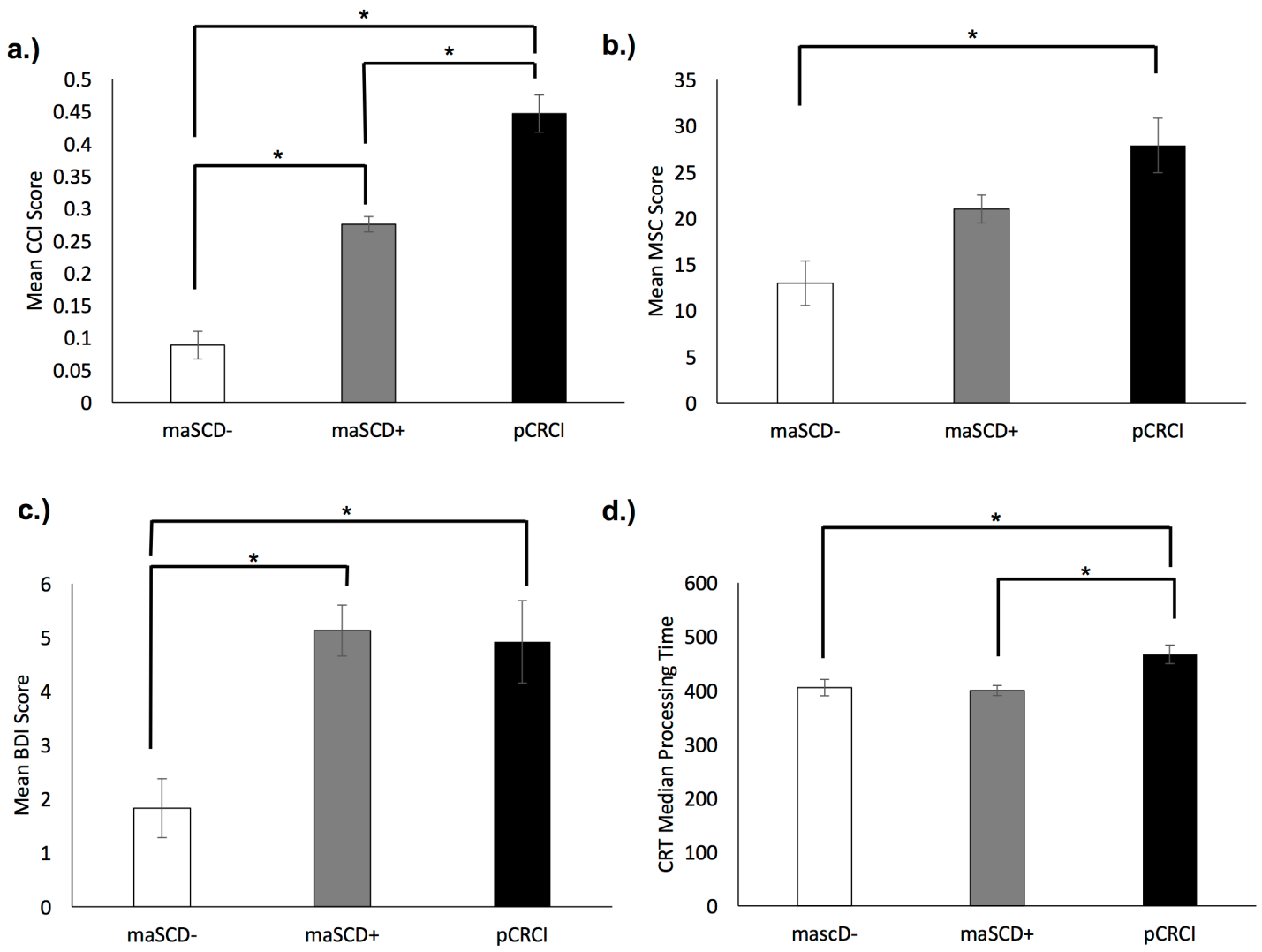


Figure 19. pCRCI and maSCD Comparison Graphs showing significant ANOVA Results. a) Group differences in mean (± SE) Cognitive Complaint Index (CCI) score. b) Group differences in mean (± SE) Menopause Symptom Checklist (MSC) score. c) Group differences in mean (± SE) Beck Depression Inventory (BDI) score, and d) Group differences in Choice Reaction Time (CRT) median processing reaction time (± SE). For all graphs, groups are distinguished by the following colors: pCRCI (black), maSCD+ (gray), and maSCD- (white). For all bar graphs, Sidak corrected t-tests were used to look at post-hoc pair-wise differences. Asterisks indicated significant pairwise differences between groups, *$p < 0.05$.

Cognitive

Results for CRT descriptive statistics and ANOVA results are shown in Table 15. There was a statistically significant difference between pCRCI, maSCD+ and maSCD- groups ($F(2,57) = 6.21$, $p = 0.004$) for CRT median processing reaction time. Post-hoc analyses revealed that pCRCI participants had a higher median processing reaction time (mean = 467.08ms) compared to both maSCD+ (mean = 399.84ms, $p < 0.05$) and maSCD- (mean = 405.30ms, $p < 0.05$) groups. However, there was no significant difference between groups on CRT median motor reaction times or CRT median total reaction time. Both CFF and SRT results are included in supplemental materials (Appendix Table 14). There was no significant difference between groups on CFF mean ascending or descending variables, and no significant difference between groups on SRT Total Recall, Total Consistency, Total Recall Failure, and Delayed Recall. There was no significant difference between pCRCI participants who received endocrine therapy and those who did not on any cognitive measure (see Appendix Table 12). There was also no significant difference between pCRCI participants based on menopausal status prior to chemotherapy on any cognitive measure (see Appendix Table 13).

Relationship Between Behavioral and Cognitive Outcome Measures

Pearson correlation coefficient results are shown in supplemental materials (Appendix Table 15). Scatter plots for significant correlations are shown in Figure 20. There was a significant positive association between the following behavioral outcome measures: BDI score and CCI score ($r(61) = 0.502$, $p < 0.0001$), BDI score and MSC score ($r(61) = 0.583$, $p < 0.0001$), and MSC score and CCI score ($r(61) = 0.597$, $p < 0.0001$). CCI score was also significantly positively associated with CRT median processing reaction time ($r(58) = 0.355$, $p = 0.005$).

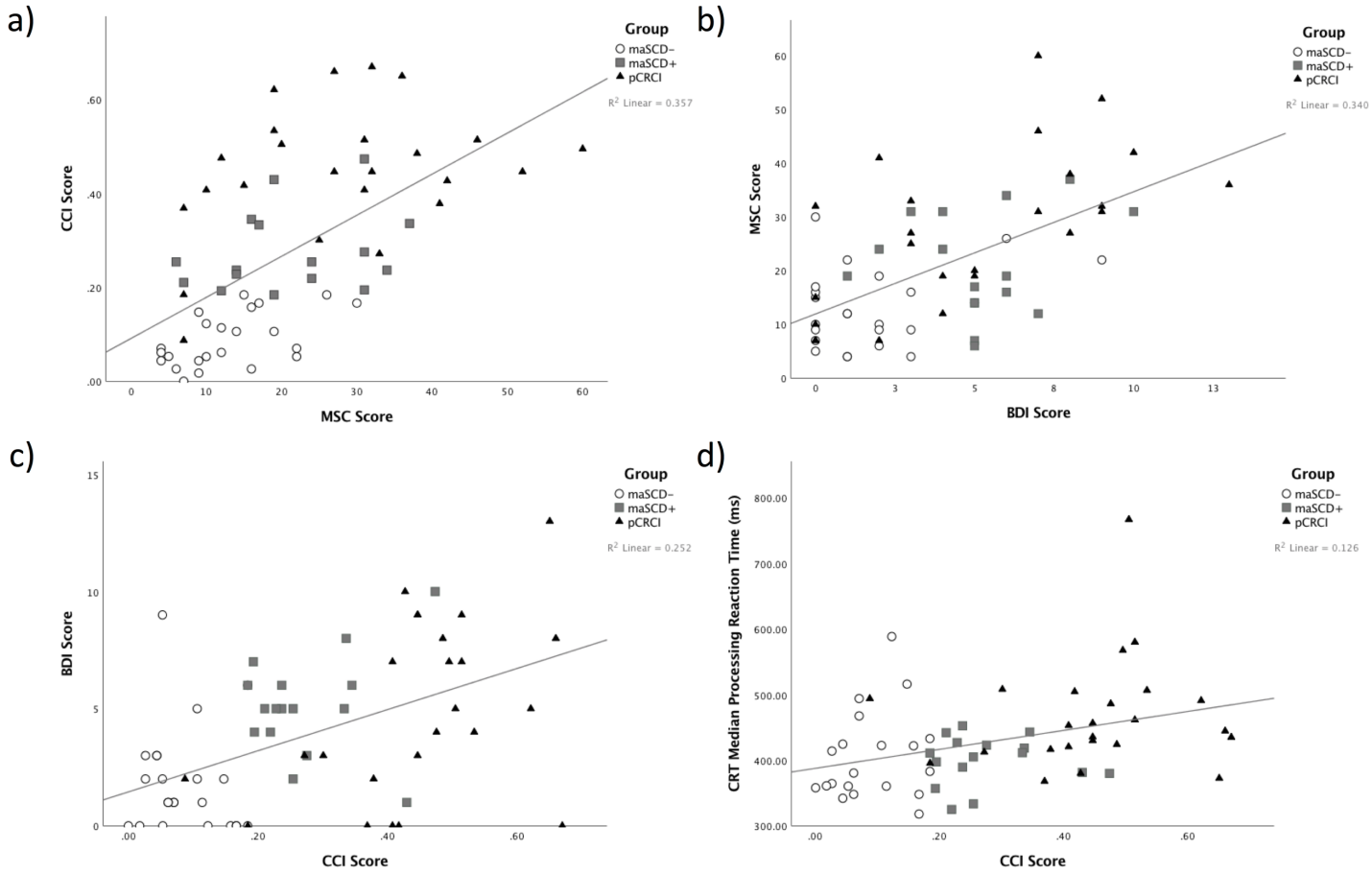


Figure 20. Scatterplots Showing Significant Correlations Between Cognitive and Behavioral Measures. a) Correlation between Menopause Symptom Checklist (MSC) Score and Cognitive Complaint Index (CCI) Score. b) Correlation between Beck Depression Inventory (BDI) Score and MSC Score. c) Correlation between CCI Score and BDI Score d) Correlation between CCI Score and Choice Reaction Time (CRT) Task Median Processing Reaction Time (in ms). For all graphs, groups are distinguished by the following colors: pCRCI (black triangles), maSCD+ (gray squares), and maSCD- (white circles).

Exploratory Analyses

Menopause Symptom Checklist Individual Items

Items on the MSC endorsed by more than 50% of participants were as follows for each group. pCRCI participants endorsed weight gain and backache (50%), insomnia (54.2%), hot flashes, bladder control, and sinus problems (58.3%), cold hands and feet (62.5%), joint pain and muscle stiffness (66.7%), craving for sweets (75%), can't concentrate (79.2%), forgetfulness and fatigue (87.5%). The maSCD+ group endorsed night sweats, nervous tension, joint pain, muscle stiffness, and intestinal gas (50%), increased appetite, insomnia and fatigue (56.2%), hot flashes and vaginal dryness (56.2%), irritability (62.5%), craving for sweets (75%), and forgetfulness (100%). The maSCD- group endorsed night sweats and early awakening (60.9%) and hot flashes (69.6%). The only MSC item all three groups endorsed was hot flashes. Since more than 50% of participants in both the maSCD+ and pCRCI groups endorsed cognitive items on the MSC, we removed the "forgetfulness" and "can't concentrate" items from the total MSC scores for each group to determine if a significant difference between groups remained and to determine if CCI score still correlated with MSC score. After removing the cognitive items from MSC score, there was still a statistically significant different between pCRCI, maSCD+ and maSCD- groups (($F(2,60) = 8.10$, $p = 0.001$) in MSC score. pCRCI participants had a higher mean modified MSC score (mean = 24.71) compared to both maSCD+ (mean = 19.19) and maSCD- (mean = 12.48). The correlation analyses also revealed that the modified MSC score was still significantly correlated with CCI score ($r(61) = 0.540$, $p < 0.0001$) and BDI score ($r(61) = 0.566$, $p < 0.0001$).

Discussion

Summary of Findings

pCRCI participants report more severe SCD symptoms than women after natural menopause, despite being on average 2.5-years post-chemotherapy, supporting previous findings that CRCI can persist for months to years after finishing treatment (Ahles et al., 2002). pCRCI participants not only endorsed greater SCD on the CCI, but also exhibited objective performance differences. pCRCI participants were slower on the processing

reaction time component (time from stimulus onset to initiation of movement). This finding supports previous research in breast cancer patients that also found evidence of cognitive impairment on attention and processing speed (Ahles et al., 2002; Cruzado et al., 2014; Hurria et al., 2006; Mandelblatt et al., 2013; Wefel, Saleeba, Buzdar, & Meyers, 2010). In addition, pCRCI participants endorsed significantly greater menopausal symptoms on MSC compared to the maSCD- group, but not the maSCD+ group. Results were not related to menopausal status prior to chemotherapy or current endocrine therapy use.

These results suggest that although menopausal symptoms may contribute to some of the SCD experienced by cancer patients after chemotherapy, they do not fully account for pCRCI. This suggests, at least in women, that menopause is only one component of pCRCI. The effects of cancer and chemotherapy treatment on brain function are likely multifactorial and a number of biological mechanisms have been suggested to play a role in the development of CRCI. These possible mechanisms for CRCI, including blood brain barrier (BBB) damage, neurotoxic cytokines, DNA damage, oxidative stress, reduced synaptic plasticity, altered growth factor levels, and impaired hippocampal neurogenesis (Ahles & Saykin, 2007; Janelsins et al., 2014; Loh et al., 2016), likely overlap with hormone changes following menopause, suggesting possible additive effects.

Neuroimaging studies have identified structural changes in the brain after chemotherapy in gray and white matter (de Ruiter et al., 2012; Deprez et al., 2012; Inagaki et al., 2007; McDonald et al., 2013), providing support for an anatomical basis to explain the functional impairments reported by cancer patients. In addition to structural brain changes, chemotherapy has also been shown to decrease task-related brain activation in regions of the parietal lobe that were involved in planning and episodic memory (de Ruiter et al., 2011). In a prospective longitudinal study, decreased working memory-related brain activity in the frontal lobes was seen one month after chemotherapy that partially recovered one year later (Collins et al., 2009a; McDonald et al., 2012). Studies examining the effects of chemotherapy on functional connectivity have revealed disrupted connectivity in frontal, temporal, and striatal brain regions and increased subjective complaints in executive functioning and memory difficulties compared to controls (Bruno, Hosseini, & Kesler, 2012). These findings

suggest a relationship between network connectivity and subjective reports of cognition in breast cancer patients five years post chemotherapy compared to healthy controls (Bruno et al., 2012). Longitudinal studies in breast cancer patients have revealed decreased functional connectivity one month after chemotherapy that partially returned to baseline at one year in the dorsal attention network (Dumas, Makarewicz, et al., 2013). In addition, increased memory complaints were noted at one month and one year post-chemotherapy. These findings suggest a detrimental effect of chemotherapy on brain functional connectivity that is related to self-assessment (Dumas, Makarewicz, et al., 2013). Thus, the impact of chemotherapy on network connectivity through its disruption of gray matter integrity and/or white matter connectivity may contribute to the functional impairments or subjective complaints endorsed by cancer patients during and after chemotherapy.

Although we did not obtain any neuroimaging in the pCRCI study, an fMRI study of working memory examining a subset of maSCD participants used in Chapter V (Dumas, Kutz, et al., 2013), found that women with substantial post-menopausal cognitive complaints showed greater cortical activity (measured via BOLD signal) during working memory performance than women without such complaints despite equivalent performance, suggesting that cognitive complaints may indicate increased neural effort, perhaps as a form of compensation. In addition, resting-state functional connectivity (rsFC) analyses conducted using the maSCD participants (Vega et al., 2016) indicated a positive correlation between the executive control network and cognitive complaint score, weaker negative functional connectivity within the frontal cortex, and stronger positive connectivity within the right middle temporal gyrus in postmenopausal women who report more cognitive complaints, supporting previous findings suggesting that high levels of cognitive complaints may reflect changes in brain connectivity. Although speculative, the performance deficits observed in this study may indicate long-term changes in reduced processing efficiency as a result of chemotherapy in pCRCI. These findings suggest that cortical connectivity changes or compensation may be responsible for the symptoms of maSCD and pCRCI.

Study Limitations

Although the pCRCI sample was primarily post-menopausal at the time of study (measured by FSH levels), two women included in the pCRCI sample were considered pre-menopausal, potentially increasing variability. However, analyses were repeated without the two pre-menopausal pCRCI participants and the results remained unchanged. While no difference on behavioral and cognitive measures was found based on pCRCI participants' menopausal status *prior* to chemotherapy, future studies with a larger number of currently pre-menopausal pCRCI participants would be informative. Additionally, a group of cancer patients that had undergone chemotherapy who *do not* endorse pCRCI would have been an additional comparison group. Finally, since the current study sample included participants recruited for two different studies, the cognitive and behavioral assessments that the two studies had in common were few, therefore only limited comparisons could be made between groups.

Study Strengths

This study also has several strengths. The majority of CRCI research has compared cancer patients to completely healthy controls. While our maSCD- group serves as a healthy control group, the addition of a comparison group of otherwise healthy women without a history of cancer who also endorse subjective cognitive decline, to our knowledge, has never been previously examined. Both studies had similar ages between groups and no differences based on age were found on any behavioral or cognitive measures. Finally, the correlation of a subjective measure of cognitive functioning (CCI) with objective test performance differences provides support that subjective complaints that persist following chemotherapy are indicative of attention and psychomotor changes.

Clinical Implications

There is increasing evidence that SCD, even with normal performance on objective neuropsychological tests, is associated with an increased risk for developing late-life cognitive decline and Alzheimer's disease (AD) in female non-cancer patients (Pérès et al., 2011). This is of particular importance to older cancer patients due to the age-associated increase in the risk for dementia. Increasing evidence suggests that older patients are more susceptible to cognitive decline associated with chemotherapy and adjuvant endocrine therapies for breast cancer than younger patients (Ahles et al., 2010; Schilder et al., 2010). Additionally, age appears to interact with cognitive reserve, a predictor of future cognitive decline, to increase risk for cognitive decline following chemotherapy (Ahles et al., 2010). A study by Ahles et al demonstrated that older patients with lower cognitive reserve prior to chemotherapy treatment showed reduced performance on measures of processing speed (Ahles et al., 2010). Thus, the persistence of a significant level of cognitive complaints in pCRCI or maSCD may indicate that such patients are at increased risk for late life cognitive impairment. The question of why some cancer patients experience persistent CRCI for years following completion of chemotherapy when others do not and whether these individuals are at higher risk for age-related cognitive decline will require further study.

CHAPTER VI

CONCLUSIONS AND FUTURE DIRECTIONS

Summary of Findings

The primary aim (Specific Aim 1) of the study was to determine if transdermal nicotine treatment would reduce subjective cognitive complaints in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI. The primary hypothesis (Specific Aim 1) was that nicotine treatment would reduce subjective cognitive complaints in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI following 6 weeks of treatment compared to placebo. Although there was a main effect of FACT-Cog PCI change from baseline score across subsequent visits, there was no main effect of drug group, or interaction between time and drug group on FACT-Cog PCI change from baseline score. In other words, participants improved in terms of subjective complaints over the course of the study regardless of treatment group.

The secondary aim (Specific Aim 2) of the study was to determine if nicotine treatment would enhance performance on laboratory measures of cognitive performance in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI. The secondary hypothesis (Specific Aim 2) was that nicotine treatment would enhance cognitive performance on measures of attention and/or processing speed in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with pCRCI following 6 weeks of treatment compared to placebo. However, no significant main effects were observed for time or treatment group, and no interaction was observed between time and treatment group on CPT reaction time standard error divided by interstimulus interval. In other words, there was no difference between treatment groups over the course of the study in terms of performance on the CPT.

Secondary analyses revealed that like FACT-Cog PCI score, scores on the FACT-Cog PCA, QOL, and Total Scores improved in both groups over time, regardless of treatment group. The only difference between treatment groups observed was for SRT Total Recall Score, where the placebo group performed better at Visit

4 (compared to Visit 2) than the nicotine group. While there was no statistically significant baseline difference between treatment groups on SRT Total Recall, there was, however, a difference between treatment groups on SRT Recall Failure. SRT Total Recall is defined as the number of correctly recalled words across trials 1-8; conversely SRT Total Recall Failure is defined as the number of words not recalled two trials in a row across trials 1-8. Given the difference in SRT Total Recall Failure at baseline, the analysis for SRT Total Recall was re-run with baseline score as a covariate in a mixed-models repeated measures ANCOVA with a within subjects factor of raw SRT Total Recall Scores (Visit3, Visit 4, Visit 5), and a between subjects factor of treatment group (nicotine, placebo). After adjusting for the effect of baseline (Visit 2) SRT Total Recall Score, there were no significant main or interaction effects observed. Therefore, this suggests that the effects observed for SRT Total Recall may reflect baseline differences between groups.

In terms of AEs, the study medication was well tolerated. There was no significant difference in number of AEs between groups in any body system. The majority of AEs experienced by both groups were mild in nature, with skin irritation being the most common AE. There were also no differences between treatment groups in mean systolic blood pressure (mmHg), mean weight in kg, or pulse (bpm) change from baseline.

As an exploratory analysis, we evaluated change in mood across visits. The following POMS subscales improved significantly from baseline: Total Mood Disturbance**,** Depression**,** Fatigue**,** Confusion**,** Vigor/Activity. There were no differences between treatment groups. In other words, participants improved in terms of some aspects of mood over the course of the study regardless of treatment group. In addition, we evaluated the association between mood measures and FACT-Cog scores, and between FACT-Cog scores and objective measures of cognitive functioning. There were significant negative correlations between POMS Confusion and FACT-Cog subscales. That is, lower FACT-Cog scores (poorer self-reported cognition) were associated with higher POMS-Confusion scores (poorer mood). Importantly, no significant correlations were observed between any FACT-Cog subscale and any objective measure of cognition, suggesting that the subjective symptoms measured

by the FACT-Cog may reflect fatigue, anxiety/depression, and poorer quality of life, as opposed to cognitive performance measured on neuropsychological testing.

When pCRCI participants were compared to two groups of women without a cancer history, one with subjective cognitive complaints (maSCD+) and one without (maSCD-), pCRCI participants reported more severe SCD symptoms than women after natural menopause, despite being on average 2.5-years post-chemotherapy, supporting previous findings that CRCI can persist for months to years after finishing treatment (Ahles et al., 2002). pCRCI participants not only endorsed greater SCD on the CCI, but also exhibited objective performance differences. pCRCI participants were slower on the processing reaction time component (time from stimulus onset to initiation of movement. This finding supports previous research in breast cancer patients that also found evidence of cognitive impairment on attention and processing speed (Ahles et al., 2002; Cruzado et al., 2014; Hurria et al., 2006; Mandelblatt et al., 2013; Wefel et al., 2010). In addition, pCRCI participants endorsed significantly greater menopausal symptoms on MSC compared to the maSCD- group, but not the maSCD+ group. Results were not related to menopausal status prior to chemotherapy or current endocrine therapy use. These results suggest that although menopausal symptoms may contribute to some of the SCD experienced by cancer patients after chemotherapy, it does fully not account for pCRCI, and suggests at least in women, menopause is only one component of pCRCI.

Future Directions

While the concept of nicotinic receptor stimulation for cognitive enhancement is not in itself novel, the idea of using nicotine treatment for non-smoking individuals with pCRCI has previously never been explored. Although the results were not as anticipated, due to the large placebo response, the results of this study still have clinical, scientific, and public health significance. In future, a number of things should be considered when designing a future clinical trial aimed at using transdermal nicotine to treat pCRCI.

Outcome Measures

The FACT-Cog (Jacobs et al., 2007) scale was used as the primary outcome measure for Specific Aim 1 to monitor change in pCRCI subjective complaints. This instrument was chosen as the primary outcome measure for a number of reasons: 1) it was developed specifically in cancer patients to evaluate the "real world" impact of CRCI, 2) it had been used to monitor change in CRCI subjective complaints in a previous number of studies, 3) it could be administered repeatedly, and 4) demonstrated good internal consistency, test-retest reliability, and discriminant and convergent validity in previous studies (Lai et al., 2009; Sanford et al., 2014; Wagner et al., 2009). Although we were able to measure a change in subjective functioning, the subjective symptoms measured by the FACT-Cog may actually reflect fatigue, anxiety/depression, and poorer quality of life, as opposed to cognitive performance measured on neuropsychological testing. While cognitive performance testing has shown an inconsistent correlation with patient self-report in CRCI studies (Castellon & Ganz, 2009; Vardy, 2009), several studies have demonstrated significant associations between various neuroimaging metrics, such as fMRI, structural MRI, EEG, and MRI spectroscopy, and subjective cognitive complaints (Deprez et al., 2014; Deprez et al., 2011; Hunter et al., 2014; Kesler, 2014; Kesler et al., 2013; Kesler et al., 2011; McDonald et al., 2013). In a future study, neuroimaging could be used as a biomarker to evaluate treatment effects.

Study Design

The study that provided a template for the current study design was a 6-month treatment study evaluating transdermal nicotine as a treatment for mild cognitive impairment (MCI) (Newhouse et al., 2012). The study by Newhouse et al., observed improvements in attention, memory, psychomotor speed and subjective ratings of cognition after 6-months of treatment with transdermal nicotine compared to placebo. At the time the current study was designed, the study length of 6-weeks on treatment and 8-weeks total was chosen because it was felt that it was a sufficient amount of time to detect a change, yet short enough to make

the study feasible for a dissertation study. Although we were successfully able to measure a change/improvement in subjective cognitive complaints, the current treatment duration of 6-weeks may simply not have been enough time to distinguish between the drug and placebo response. It may be the case that participation in the current study provided short terms benefits, thus contributing to the strong placebo response observed; however, it is possible that with an extended trial length, those initial short term benefits we observed may eventually plateau or wane, thus allowing for a drug effect (if any) to be measured. Therefore, in future, a longer study duration could potentially help separate the drug response from the placebo response.

One important consideration that could be made when extending a future trial length would be reducing the number of in-person study visits. Placebo effects can also be affected by the frequency of patient–clinician interactions (Posternak & Zimmerman, 2007). For example, a meta-analysis investigating the influence of therapeutic contact frequency in 41 randomized-control trials for major depressive disorder (MDD) observed greater reduction in symptom severity in the placebo group that had more frequent patient-clinician interactions (Posternak & Zimmerman, 2007). Participants receiving antidepressants also experienced greater symptomatic change with increased numbers of follow-up visits, but the relative effect of this increased therapeutic contact was approximately 50% less than that observed in the placebo group (Posternak & Zimmerman, 2007).

One solution could be to minimize the number of in-person study visits, thereby limiting benefits of patient-clinician/researcher interactions, by using ecological momentary assessment (EMA) or web-based testing (e.g. REDCap) to collect data. EMA, also referred to as experience sampling, permits the repeated sampling of a research participant's current behaviors and experiences in real time (e.g., self-report, actigraphy, psychophysiological variables), in their natural environments (Armey, Schatten, Haradhvala, & Miller, 2015). Although not required, EMA often uses mobile technology such as tablets and cell phones to collect these data (Armey et al., 2015). EMA aims to capture more accurate self-reports by asking people about their experiences closer to the time and the context they occur (Shiffman, Stone, & Hufford, 2008).

Study Dosing

The Nicoderm patches that were used in the current study are available in 7mg, 14mg, and 21mg doses. A titration schedule (Table 3) was used help avoid initial side effects. Participants were started off on a ½ of a 7mg patch and were titrated up to 14mg by week 5 of the study. The maximum dose for the previous nicotine treatment study for MCI done by Newhouse et al. was higher (Newhouse et al., 2012) than that used in the current study. However, at the time we were designing the current study, we felt that a maximum dose of 14mg would be most tolerable (in terms of side effects) given the shorter study length and younger age of the participants. In terms of AEs, the study medication was very well tolerated. The only participants to withdraw due to AEs were in the placebo group and there was no significant difference in number of AEs between groups in any body system. In hindsight, however, it may be the case that 14mg was not a sufficient dose in helping distinguish between a drug response and the strong placebo response observed. The fact that we did not see substantial weight changes in the nicotine group also supports that the participants were under dosed. In future, in addition to a longer study duration with less frequent visits, the dosing plan should be altered to include a maximum dose of 21mg.

Placebo Response

Although we did not see the drug treatment effect we anticipated, we were able to observe improvement in self-reported cognitive symptoms, likely resulting from participation in the trial itself. These results suggest that women with pCRCI would benefit from the incorporation of cognitive rehabilitation/therapies, which we may have inadvertently provided some aspects of throughout the course of the study, into their post-cancer care. Cognitive rehabilitation refers to a clinic-based, therapeutic program aimed at improving cognitive abilities, functional capacity, real-world skills (Wefel et al., 2015). It may also be the case that for a syndrome such as pCRCI, for which no current treatment exists and is only now becoming

increasingly recognized and accepted, that the intensive nature of clinical management that these participants received (which is likely beyond the level of individual attention they might have received in a typical clinical setting) may have provided benefits such as stress reduction, decreased anxiety, and improvement of mood, thus contributing to the strong placebo response observed.

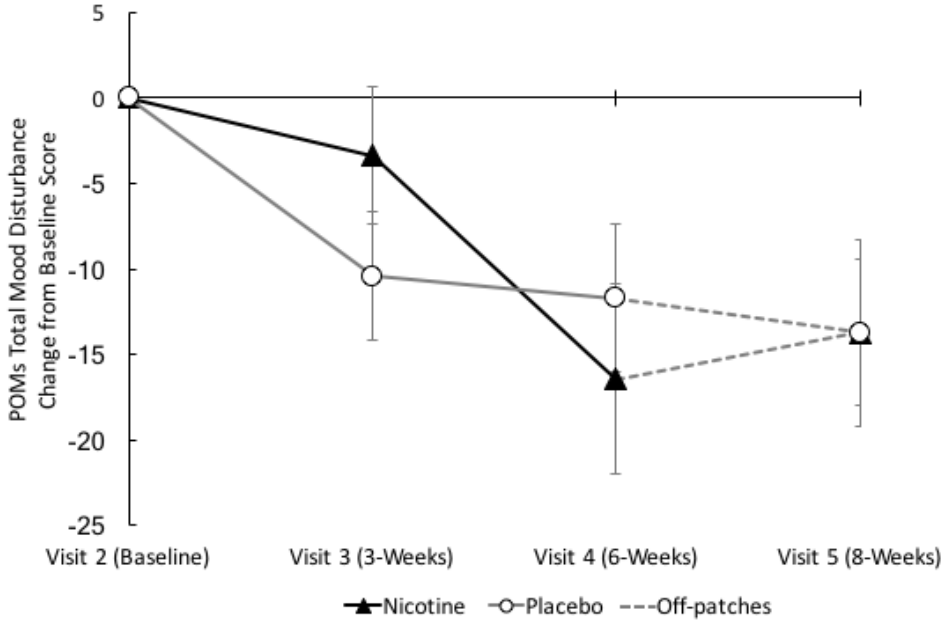
APPENDIX

Drug Treatment Group Differences on POMs

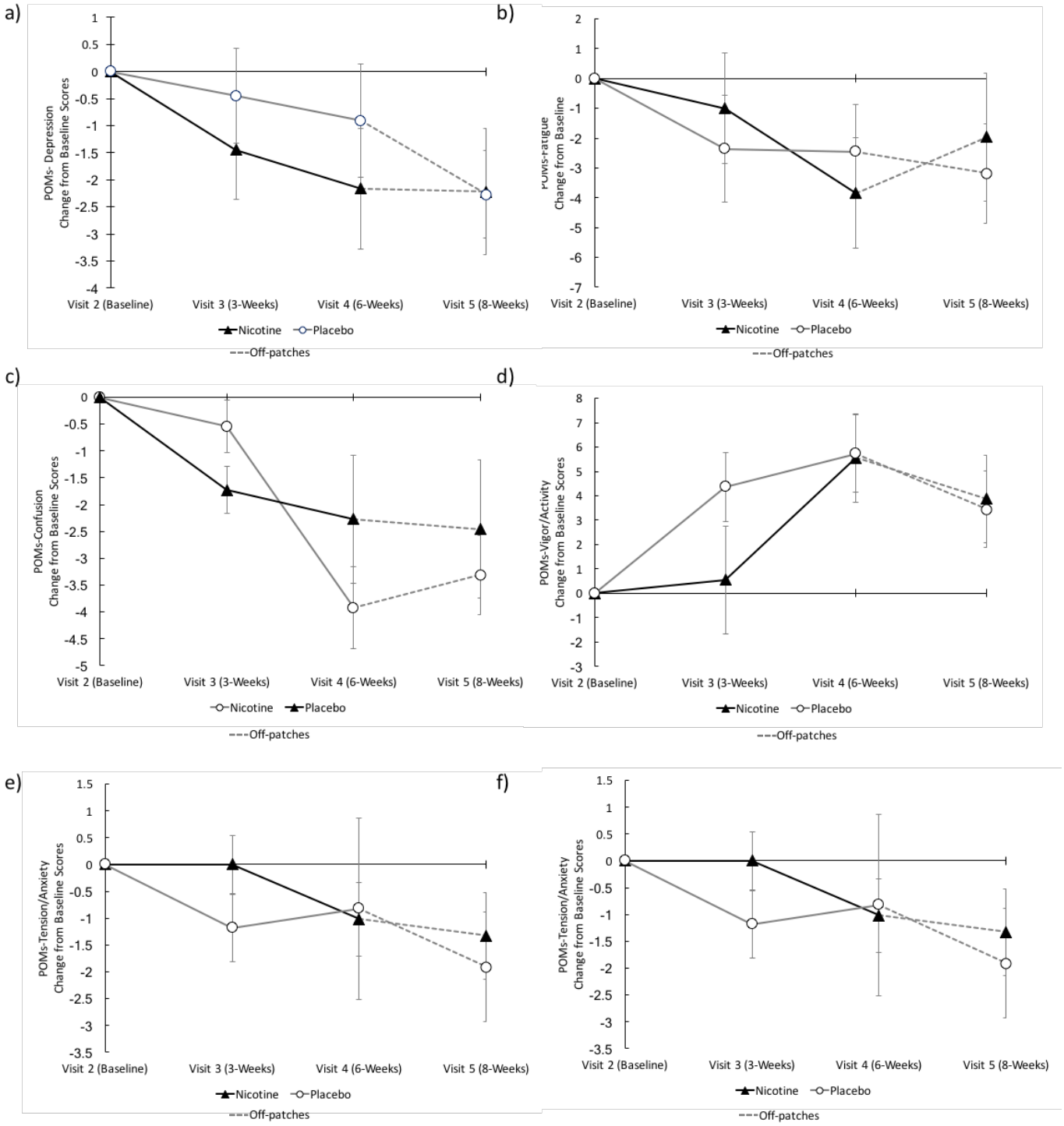
Appendix Table 1. Mixed-Models Repeated ANOVA Results for POMs

	Subscale	Time Main Effect	Interaction Effect	Treatment Group Main Effect
POMS	**Total Mood Disturbance**	$F(3,60) = 7.49$, $p < 0.001^{**}$	$F(3,60) = 1.00$, $p = 0.40$	$F(1,20) = 0.02$, $p = 0.88$
	Tension/Anxiety	$F(2.07,41.33) = 1.69$, $p = 0.18^{+}$	$F(2.07,41.33) = 0.36$, $p = 0.71^{+}$	$F(1,20) = 0.25$, $p = 0.63$
	Depression	$F(2.05,40.97) = 3.29$, $p < 0.05^{*+}$	$F(2.05,40.97) = 0.42$, $p = 0.67^{+}$	$F(1,20) = 0.45$, $p = 0.51$
	Anger/Hostility	$F(2.03,40.59) =$, $p = 0.56^{+}$	$F(2.03,40.59) = 0.24$, $p = 0.79^{+}$	$F(1,20) = 0.02$, $p = 0.90$
	Fatigue	$F(2.08,41.52) = 3.22$, $p < 0.05^{*+}$	$F(2.08,41.52) = 0.70$, $p = 0.51^{+}$	$F(1,20) = 0.03$, $p = 0.87$
	Confusion	$F(1.69,33.70) = 12.28$, $p < 0.001^{**+}$	$F(1.90,37.91) = 0.83$, $p = 0.44^{+}$	$F(1,20) = 1.07$, $p = 0.31$
	Vigor/Activity	$F(3,60) = 7.35$, $p < 0.001^{**}$	$F(3,60) = 1.27$, $p < 0.29$	$F(1,20) = 0.35$, $p = 0.56$

[+] Adjusted for Greenhouse-Geisser estimates of sphericity
[*] Significant at p < 0.05 level
[**] Significant at p < 0.001 level



Appendix Figure 1. POMS Total Mood Disturbance (TMD) Change from Baseline Scores. TMD score is calculated by summing the scores of the 5 subscales for the negative mood states and subtracting from it the score for the positive subscale. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE. Negative TMD change scores indicates improved mood.



Appendix Figure 2. POMS Subscales Change from Baseline Scores. a) POMS-Depression change from baseline scores, negative change scores indicate improvement in mood, b) POMS-Fatigue change from baseline scores, negative change scores indicate improvement in mood, c) POMS-Confusion change from baseline scores, negative change scores indicate improvement in mood, d) POMS-Vigor/Activity change from baseline scores, positive change scores indicate improvement in mood, e) POMS-Tension/Anxiety change from baseline scores, negative change scores indicate improvement in mood and f) POMs-Anger/Hostility change from baseline scores, negative change scores indicate improvement in mood. Treatment groups are distinguished by the following colors: nicotine (black triangles) and placebo (white circles). The grey dashed lines indicate that participants were off patches between Visits 4 and 5. Error bars indicate SE.

Appendix Table 2. Relationship between FACT-Cog Perceived Cognitive Impairment (PCI) and POMS

		Visit 2 POMS-Tension/Anxiety	Visit 2 POMS-Depression	Visit 2 POMS-Anger/Hostility	Visit 2 POMS-Fatigue	Visit 2 POMS-Confusion	Visit 2 POMS-Vigor/Activity	Visit 2 POMS Total Mood Disturbance
Visit 2 (Baseline)								
Visit 2 FACT-Cog PCI Score	Pearson Correlation	-0.053	-0.145	-0.441	-0.397	-0.539	0.196	-0.429
	Sig. (2-tailed)	0.816	0.52	0.04	0.068	0.01	0.381	0.046
	N	22	22	22	22	22	22	22
		Visit 3 POMS-Tension/Anxiety	Visit 3 POMS-Depression	Visit 3 POMS-Anger/Hostility	Visit 3 POMS-Fatigue	Visit 3 POMS-Confusion	Visit 3 POMS-Vigor/Activity	Visit 3 POMS Total Mood Disturbance
Visit 3 (3-Weeks)								
Visit 3 FACT-Cog PCI Score	Pearson Correlation	-0.298	-0.176	-0.108	-0.214	-0.683*	0.291	-0.367
	Sig. (2-tailed)	0.178	0.433	0.632	0.339	0.000461	0.19	0.093
	N	22	22	22	22	22	22	22
		Visit 4 POMS-Tension/Anxiety	Visit 4 POMS-Depression	Visit 4 POMS-Anger/Hostility	Visit 4 POMS-Fatigue	Visit 4 POMS-Confusion	Visit 4 POMS-Vigor/Activity	Visit 4 POMS Total Mood Disturbance
Visit 4 (6-Weeks)								
Visit 4 FACT-Cog PCI Score	Pearson Correlation	-0.276	-0.153	-0.269	-0.073	-0.218	0.281	-0.276
	Sig. (2-tailed)	0.213	0.496	0.225	0.746	0.329	0.205	0.214
	N	22	22	22	22	22	22	22
		Visit 5 POMS-Tension/Anxiety	Visit 5 POMS-Depression	Visit 5 POMS-Anger/Hostility	Visit 5 POMS-Fatigue	Visit 5 POMS-Confusion	Visit 5 POMS-Vigor/Activity	Visit 5 POMS Total Mood Disturbance
Visit 5 (8-Weeks)								
Visit 5 FACT-Cog PCI Score	Pearson Correlation	-0.112	-0.256	-0.023	-0.132	-0.468	0.415	-0.354
	Sig. (2-tailed)	0.621	0.25	0.92	0.557	0.028	0.055	0.106
	N	22	22	22	22	22	22	22

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

Appendix Table 3. Relationship between FACT-Cog Perceived Cognitive Abilities (PCA) and POMS

Visit 2 (Baseline)

		Visit 2 POMS-Tension/Anxiety	Visit 2 POMS-Depression	Visit 2 POMS-Anger/Hostility	Visit 2 POMS-Fatigue	Visit 2 POMS-Confusion	Visit 2 POMS-Vigor/Activity	Visit 2 POMS-TMD
Visit 2 FACT-Cog PCA Score	Pearson Correlation	-0.043	0.114	-0.086	0.14	-0.413	0.161	-0.087
	Sig. (2-tailed)	0.85	0.614	0.704	0.536	0.056	0.475	0.699
	N	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 POMS-Tension/Anxiety	Visit 3 POMS-Depression	Visit 3 POMS-Anger/Hostility	Visit 3 POMS-Fatigue	**Visit 3 POMS-Confusion**	Visit 3 POMS-Vigor/Activity	Visit 3 POMS-TMD
Visit 3 FACT-Cog PCA Score	Pearson Correlation	-0.309	-0.224	-0.289	-0.254	**-.686***	.427	-.464
	Sig. (2-tailed)	0.162	0.316	0.192	0.254	**0.000418**	0.048	0.03
	N	22	22	22	22	**22**	22	22

Visit 4 (6-Weeks)

		Visit 4 POMS-Tension/Anxiety	Visit 4 POMS-Depression	Visit 4 POMS-Anger/Hostility	Visit 4 POMS-Fatigue	Visit 4 POMS-Confusion	Visit 4 POMS-Vigor/Activity	Visit 4 POMS-TMD
Visit 4 FACT-Cog PCA Score	Pearson Correlation	-0.062	-0.272	-0.15	-0.039	-.465	0.331	-0.268
	Sig. (2-tailed)	0.784	0.221	0.504	0.864	0.029	0.133	0.228
	N	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 POMS-Tension/Anxiety	Visit 5 POMS-Depression	Visit 5 POMS-Anger/Hostility	Visit 5 POMS-Fatigue	Visit 5 POMS-Confusion	Visit 5 POMS-Vigor/Activity	Visit 5 POMS-TMD
Visit 5 FACT-Cog PCA Score	Pearson Correlation	0.048	-.443	0.082	-.440	-0.368	.611	-.486
	Sig. (2-tailed)	0.832	0.039	0.715	0.04	0.092	0.003	0.022
	N	22	22	22	22	22	22	22

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

Appendix Table 4. Relationship between FACT-Cog Quality of Life (QOL) and POMS

Visit 2 (Baseline)

		Visit 2 POMS-Tension/Anxiety	Visit 2 POMS-Depression	Visit 2 POMS-Anger/Hostility	Visit 2 POMS-Fatigue	Visit 2 POMS-Confusion	Visit 2 POMS-Vigor/Activity	Visit 2 POMS-TMD
Visit 2 FACT-Cog QOL Score	Pearson Correlation	-0.014	-0.059	-0.107	-0.276	-.570	0.272	-0.34
	Sig. (2-tailed)	0.952	0.794	0.634	0.213	0.006	0.22	0.122
	N	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 POMS-Tension/Anxiety	Visit 3 POMS-Depression	Visit 3 POMS-Anger/Hostility	Visit 3 POMS-Fatigue	Visit 3 POMS-Confusion	Visit 3 POMS-Vigor/Activity	Visit 3 POMS-TMD
Visit 3 FACT-Cog QOL Score	Pearson Correlation	-0.325	-0.21	-0.145	-0.255	-.538	.427	-0.416
	Sig. (2-tailed)	0.141	0.348	0.521	0.252	0.01	0.047	0.054
	N	22	22	22	22	22	22	22

Visit 4 (6-Weeks)

		Visit 4 POMS-Tension/Anxiety	Visit 4 POMS-Depression	Visit 4 POMS-Anger/Hostility	Visit 4 POMS-Fatigue	Visit 4 POMS-Confusion	Visit 4 POMS-Vigor/Activity	Visit 4 POMS-TMD
Visit 4 FACT-Cog QOL Score	Pearson Correlation	-0.066	-.471	-0.33	-0.183	-0.25	0.127	-0.264
	Sig. (2-tailed)	0.771	0.027	0.134	0.414	0.261	0.575	0.235
	N	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 POMS-Tension/Anxiety	Visit 5 POMS-Depression	Visit 5 POMS-Anger/Hostility	Visit 5 POMS-Fatigue	Visit 5 POMS-Confusion	Visit 5 POMS-Vigor/Activity	Visit 5 POMS-TMD
Visit 5 FACT-Cog QOL Score	Pearson Correlation	-0.094	-0.179	-0.049	-0.345	-.495	.569	-.463
	Sig. (2-tailed)	0.676	0.425	0.827	0.116	0.019	0.006	0.03
	N	22	22	22	22	22	22	22

Bonferroni corrected at 0.05 level

Appendix Table 5. Relationship between FACT-Cog Comments from Others (CFO) and POMS

Visit 2 (Baseline)

		Visit 2 POMS-Tension/Anxiety	Visit 2 POMS-Depression	Visit 2 POMS-Anger/Hostility	Visit 2 POMS-Fatigue	Visit 2 POMS-Confusion	Visit 2 POMS-Vigor/Activity	Visit 2 POMS-TMD
Visit 2 FACT-Cog CFO Score	Pearson Correlation	-.622	-.437	-.569	-0.148	-.486	-0.196	-0.38
	Sig. (2-tailed)	0.002	0.042	0.006	0.51	0.022	0.381	0.081
	N	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 POMS-Tension/Anxiety	Visit 3 POMS-Depression	Visit 3 POMS-Anger/Hostility	Visit 3 POMS-Fatigue	Visit 3 POMS-Confusion	Visit 3 POMS-Vigor/Activity	Visit 3 POMS-TMD
Visit 3 FACT-Cog CFO Score	Pearson Correlation	-0.367	0.024	-0.164	-0.1	-0.374	-0.04	-0.149
	Sig. (2-tailed)	0.093	0.917	0.467	0.658	0.087	0.86	0.508
	N	22	22	22	22	22	22	22

Visit 4 (6-Weeks)

		Visit 4 POMS-Tension/Anxiety	Visit 4 POMS-Depression	Visit 4 POMS-Anger/Hostility	Visit 4 POMS-Fatigue	Visit 4 POMS-Confusion	Visit 4 POMS-Vigor/Activity	Visit 4 POMS-TMD
Visit 4 FACT-Cog CFO Score	Pearson Correlation	-0.066	0.092	0.024	0.102	-0.124	-.424	0.151
	Sig. (2-tailed)	0.771	0.684	0.915	0.65	0.583	0.049	0.502
	N	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 POMS-Tension/Anxiety	Visit 5 POMS-Depression	Visit 5 POMS-Anger/Hostility	Visit 5 POMS-Fatigue	Visit 5 POMS-Confusion	Visit 5 POMS-Vigor/Activity	Visit 5 POM - TMD
Visit 5 FACT-Cog CFO Score	Pearson Correlation	0.238	0.11	0.175	-0.12	0.014	-0.069	0.092
	Sig. (2-tailed)	0.285	0.625	0.436	0.593	0.95	0.762	0.685
	N	22	22	22	22	22	22	22

Bonferroni corrected at 0.05 level

Appendix Table 6. Relationship between FACT-Cog Total Score and POMS

Visit 2 (Baseline)

		Visit 2 POMS-Tension/Anxiety	Visit 2 POMS-Depression	Visit 2 POMS-Anger/Hostility	Visit 2 POMS-Fatigue	Visit 2 POMS-Confusion	Visit 2 POMS-Vigor/Activity	Visit 2 POMS-TMD
Visit 2 FACT-Cog Total Score	Pearson Correlation	-0.114	-0.137	-0.412	-0.32	-.620	0.2	-.424
	Sig. (2-tailed)	0.614	0.544	0.057	0.147	0.002	0.373	0.049
	N	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 POMS-Tension/Anxiety	Visit 3 POMS-Depression	Visit 3 POMS-Anger/Hostility	Visit 3 POMS-Fatigue	**Visit 3 POMS-Confusion**	Visit 3 POMS-Vigor/Activity	Visit 3 POMS-TMD
Visit 3 FACT-Cog Total Score	Pearson Correlation	-0.371	-0.207	-0.201	-0.261	**-.752***	0.374	-.451
	Sig. (2-tailed)	0.089	0.356	0.369	0.241	**0.000148**	0.087	0.035
	N	22	22	22	22	**22**	22	22

Visit 4 (6-Weeks)

		Visit 4 POMS-Tension/Anxiety	Visit 4 POMS-Depression	Visit 4 POMS-Anger/Hostility	Visit 4 POMS-Fatigue	Visit 4 POMS-Confusion	Visit 4 POMS-Vigor/Activity	Visit 4 POM-TMD
Visit 4 FACT-Cog Total Score	Pearson Correlation	-0.229	-0.28	-0.294	-0.082	-0.393	0.282	-0.316
	Sig. (2-tailed)	0.305	0.206	0.184	0.716	0.07	0.203	0.152
	N	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 POMS-Tension/Anxiety	Visit 5 POMS-Depression	Visit 5 POMS-Anger/Hostility	Visit 5 POMS-Fatigue	Visit 5 POMS-Confusion	Visit 5 POMS-Vigor/Activity	Visit 5 POMS-TMD
Visit 5 FACT-Cog Total Score	Pearson Correlation	-0.035	-0.329	0.029	-0.305	-.477	.545	-.444
	Sig. (2-tailed)	0.878	0.135	0.897	0.168	0.025	0.009	0.038
	N	22	22	22	22	22	22	22

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

Appendix Table 7. Relationship between FACT-Cog Perceived Cognitive Impairment (PCI) and Cognitive Performance Measures

Visit 2 (Baseline)

		Visit 2 CPT RT SE/ ISI	Visit 2 CFF Ascending Mean	Visit 2 CFF Descending Mean	Visit 2 CRT Recognition Time Median (ms)	Visit 2 CRT Motor Time Median (ms)	Visit 2 CRT Total RT (ms)	Visit 2 ID Task (Speed)	Visit 2 Detection Task (Speed)	Visit 2 Two Back (Accuracy)	Visit 2 Set Shifting (Errors)	Visit 2 Groton Maze Total (Errors)
Visit 2 FACT-Cog PCI Score	*r*	0.317	0.267	0.073	-0.164	-0.229	-0.225	-0.107	-0.1	-0.161	-0.199	-0.191
	Sig. (2-tailed)	0.151	0.23	0.746	0.466	0.305	0.315	0.637	0.657	0.474	0.376	0.393
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 CPT RT SE/ ISI	Visit 3 CFF Ascending Mean	Visit 3 CFF Descending Mean	Visit 3 CRT Recognition Time Median (ms)	Visit 3 CRT Motor Time Median (ms)	Visit 3 CRT Total RT (ms)	Visit 3 ID Task (Speed)	Visit 3 Detection Task (Speed)	Visit 3 Two Back (Accuracy)	Visit 3 Set Shifting (Errors)	Visit 3 Groton Maze Total (Errors)
Visit 3 FACT-Cog PCI Score	*r*	-0.397	-0.127	0.02	-0.146	0.248	0.126	-0.097	0.197	-0.083	-0.422	-0.557
	Sig. (2-tailed)	0.067	0.573	0.931	0.518	0.265	0.578	0.667	0.379	0.712	0.051	0.007
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 4 (6-Weeks)

		Visit 4 CPT RT SE/ ISI	Visit 4 CFF Ascending Mean	Visit 4 CFF Descending Mean	Visit 4 CRT Recognition Time Median (ms)	Visit 4 CRT Motor Time Median (ms)	Visit 4 CRT Total RT (ms)	Visit 4 ID Task (Speed)	Visit 4 Detection Task (Speed)	Visit 4 Two Back (Accuracy)	Visit 4 Set Shifting (Errors)	Visit 4 Groton Maze Total (Errors)
Visit 4 FACT-Cog PCI Score	*r*	0.169	0.143	0.146	-0.168	0.238	0.067	-0.203	0.157	-0.017	-0.164	-0.282
	Sig. (2-tailed)	0.451	0.524	0.517	0.454	0.285	0.768	0.366	0.486	0.94	0.467	0.203
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 CPT RT SE/ ISI	Visit 5 CFF Ascending Mean	Visit 5 CFF Descending Mean	Visit 5 CRT Recognition Time Median (ms)	Visit 5 CRT Motor Time Median (ms)	Visit 5 CRT Total RT (ms)	Visit 5 ID Task (Speed)	Visit 5 Detection Task (Speed)	Visit 5 Two Back (Accuracy)	Visit 5 Set Shifting (Errors)	Visit 5 Groton Maze Total (Errors)
Visit 5 FACT-Cog PCI Score	*r*	-0.105	-0.011	-0.159	-0.354	0.166	-0.09	0.133	-0.165	0.283	0.019	-0.401
	Sig. (2-tailed)	0.641	0.962	0.481	0.106	0.461	0.69	0.555	0.464	0.201	0.932	0.064
	N	22	22	22	22	22	22	22	22	22	22	22

CPT: Continuous Performance Task, CFF: Critical Flicker Fusion Task, CRT: Choice Reaction Time Task, ID Task: Identification Task
Bonferroni Corrected at 0.05 level

Appendix Table 8. Relationship between FACT-Cog Perceived Cognitive Abilities (PCA) and Cognitive Performance Measures

Visit 2 (Baseline)

		Visit 2 CPT RT SE/ ISI	Visit 2 CFF Ascending Mean	Visit 2 CFF Descending Mean	Visit 2 CRT Recognition Time Median (ms)	Visit 2 CRT Motor Time Median (ms)	Visit 2 CRT Total RT (ms)	Visit 2 ID Task (Speed)	Visit 2 Detection Task (Speed)	Visit 2 Two Back (Accuracy)	Visit 2 Set Shifting (Errors)	Visit 2 Groton Maze Total (Errors)
Visit 2 FACT-Cog PCA Score	*r*	-0.096	0.226	-0.121	-0.344	-0.163	-0.269	-0.331	-0.035	-0.256	-0.186	-0.208
	Sig. (2-tailed)	0.669	0.313	0.593	0.117	0.469	0.226	0.132	0.876	0.25	0.407	0.354
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 CPT RT SE/ ISI	Visit 3 CFF Ascending Mean	Visit 3 CFF Descending Mean	Visit 3 CRT Recognition Time Median (ms)	Visit 3 CRT Motor Time Median (ms)	Visit 3 CRT Total RT (ms)	Visit 3 ID Task (Speed)	Visit 3 Detection Task (Speed)	Visit 3 Two Back (Accuracy)	Visit 3 Set Shifting (Errors)	Visit 3 Groton Maze Total (Errors)
Visit 3 FACT-Cog PCA Score	*r*	-0.449	0.021	0.169	-0.217	0.245	0.096	0.042	0.157	0.096	-0.29	-0.406
	Sig. (2-tailed)	0.036	0.927	0.453	0.332	0.273	0.672	0.852	0.486	0.669	0.19	0.061
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 4 (6-Weeks)

		Visit 4 CPT RT SE/ ISI	Visit 4 CFF Ascending Mean	Visit 4 CFF Descending Mean	Visit 4 CRT Recognition Time Median (ms)	Visit 4 CRT Motor Time Median (ms)	Visit 4 CRT Total RT (ms)	Visit 4 ID Task (Speed)	Visit 4 Detection Task (Speed)	Visit 4 Two Back (Accuracy)	Visit 4 Set Shifting (Errors)	Visit 4 Groton Maze Total (Errors)
Visit 4 FACT-Cog PCA Score	*r*	-0.195	0.529	0.316	-0.439	-0.025	-0.297	0.054	0.218	0.115	0.029	0.089
	Sig. (2-tailed)	0.384	0.011	0.152	0.041	0.911	0.18	0.812	0.33	0.609	0.9	0.695
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 CPT RT SE/ ISI	Visit 5 CFF Ascending Mean	Visit 5 CFF Descending Mean	Visit 5 CRT Recognition Time Median (ms)	Visit 5 CRT Motor Time Median (ms)	Visit 5 CRT Total RT (ms)	Visit 5 ID Task (Speed)	Visit 5 Detection Task (Speed)	Visit 5 Two Back (Accuracy)	Visit 5 Set Shifting (Errors)	Visit 5 Groton Maze Total (Errors)
Visit 5 FACT-Cog PCA Score	*r*	-0.412	-0.097	-0.096	-0.304	-0.172	-0.326	-0.209	-.470	0.075	-0.021	0.111
	Sig. (2-tailed)	0.057	0.669	0.67	0.169	0.444	0.138	0.349	0.027	0.741	0.928	0.622
	N	22	22	22	22	22	22	22	22	22	22	22

CPT: Continuous Performance Task, CFF: Critical Flicker Fusion Task, CRT: Choice Reaction Time Task, ID Task: Identification Task
Bonferroni Corrected at 0.05 level

Appendix Table 9. Relationship between FACT-Cog Quality of life (QOL) and Cognitive Performance Measures

Visit 2 (Baseline)

		Visit 2 CPT RT SE/ ISI	Visit 2 CFF Ascending Mean	Visit 2 CFF Descending Mean	Visit 2 CRT Recognition Time Median (ms)	Visit 2 CRT Motor Time Median (ms)	Visit 2 CRT Total RT (ms)	Visit 2 ID Task (Speed)	Visit 2 Detection Task (Speed)	Visit 2 Two Back (Accuracy)	Visit 2 Set Shifting (Errors)	Visit 2 Groton Maze Total (Errors)
Visit 2 FACT-Cog QOL Score	*r*	0.023	0.347	0.204	-0.343	-0.426	-0.432	-0.392	-0.338	-0.171	-0.035	-0.037
	Sig. (2-tailed)	0.918	0.113	0.362	0.118	0.048	0.045	0.071	0.125	0.446	0.877	0.87
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 CPT RT SE/ ISI	Visit 3 CFF Ascending Mean	Visit 3 CFF Descending Mean	Visit 3 CRT Recognition Time Median (ms)	Visit 3 CRT Motor Time Median (ms)	Visit 3 CRT Total RT (ms)	Visit 3 ID Task (Speed)	Visit 3 Detection Task (Speed)	Visit 3 Two Back (Accuracy)	Visit 3 Set Shifting (Errors)	Visit 3 Groton Maze Total (Errors)
Visit 3 FACT-Cog QOL Score	*r*	-0.403	-0.274	-0.178	-0.035	0.085	0.016	0.007	-0.015	0.018	-0.062	-0.276
	Sig. (2-tailed)	0.063	0.217	0.429	0.877	0.707	0.943	0.975	0.946	0.937	0.783	0.214
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 4 (6-Weeks)

		Visit 4 CPT RT SE/ ISI	Visit 4 CFF Ascending Mean	Visit 4 CFF Descending Mean	Visit 4 CRT Recognition Time Median (ms)	Visit 4 CRT Motor Time Median (ms)	Visit 4 CRT Total RT (ms)	Visit 4 ID Task (Speed)	Visit 4 Detection Task (Speed)	Visit 4 Two Back (Accuracy)	Visit 4 Set Shifting (Errors)	Visit 4 Groton Maze Total (Errors)
Visit 4 FACT-Cog QOL Score	*r*	0.272	0.22	-0.042	-0.364	-0.07	-0.228	0.207	0.195	0.304	0.109	0.245
	Sig. (2-tailed)	0.221	0.325	0.853	0.096	0.758	0.308	0.356	0.384	0.169	0.629	0.273
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 CPT RT SE/ ISI	Visit 5 CFF Ascending Mean	Visit 5 CFF Descending Mean	Visit 5 CRT Recognition Time Median (ms)	Visit 5 CRT Motor Time Median (ms)	Visit 5 CRT Total RT (ms)	Visit 5 ID Task (Speed)	Visit 5 Detection Task (Speed)	Visit 5 Two Back (Accuracy)	Visit 5 Set Shifting (Errors)	Visit 5 Groton Maze Total (Errors)
Visit 5 FACT-Cog QOL Score	*r*	-0.256	-0.19	-0.119	-0.285	0.035	-0.149	0.087	-0.213	0.183	0.194	0.089
	Sig. (2-tailed)	0.249	0.397	0.599	0.198	0.876	0.508	0.702	0.341	0.416	0.387	0.693
	N	22	22	22	22	22	22	22	22	22	22	22

CPT: Continuous Performance Task, CFF: Critical Flicker Fusion Task, CRT: Choice Reaction Time Task, ID Task: Identification Task
Bonferroni Corrected at 0.05 level

Appendix Table 10. Relationship between FACT-Cog Comments from Others (CFO) and Cognitive Performance Measures

Visit 2 (Baseline)

		Visit 2 CPT RT SE/ ISI	Visit 2 CFF Ascending Mean	Visit 2 CFF Descending Mean	Visit 2 CRT Recognition Time Median (ms)	Visit 2 CRT Motor Time Median (ms)	Visit 2 CRT Total RT (ms)	Visit 2 ID Task (Speed)	Visit 2 Detection Task (Speed)	Visit 2 Two Back (Accuracy)	Visit 2 Set Shifting (Errors)	Visit 2 Groton Maze Total (Errors)
Visit 2 FACT-Cog CFO Score	*r*	0.225	0.057	0.311	0.364	0.248	0.328	0.184	0.248	-0.298	-0.512	0.079
	Sig. (2-tailed)	0.315	0.802	0.159	0.096	0.265	0.136	0.413	0.267	0.179	0.015	0.725
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 CPT RT SE/ ISI	Visit 3 CFF Ascending Mean	Visit 3 CFF Descending Mean	Visit 3 CRT Recognition Time Median (ms)	Visit 3 CRT Motor Time Median (ms)	Visit 3 CRT Total RT (ms)	Visit 3 ID Task (Speed)	Visit 3 Detection Task (Speed)	Visit 3 Two Back (Accuracy)	Visit 3 Set Shifting (Errors)	Visit 3 Groton Maze Total (Errors)
Visit 3 FACT-Cog CFO Score	*r*	-0.226	0.065	0.302	0.056	0.147	0.155	0.1	0.188	-0.067	-0.601	-0.412
	Sig. (2-tailed)	0.311	0.772	0.172	0.806	0.514	0.49	0.658	0.402	0.766	0.003	0.057
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 4 (6-Weeks)

		Visit 4 CPT RT SE/ ISI	Visit 4 CFF Ascending Mean	Visit 4 CFF Descending Mean	Visit 4 CRT Recognition Time Median (ms)	Visit 4 CRT Motor Time Median (ms)	Visit 4 CRT Total RT (ms)	Visit 4 ID Task (Speed)	Visit 4 Detection Task (Speed)	Visit 4 Two Back (Accuracy)	Visit 4 Set Shifting (Errors)	Visit 4 Groton Maze Total (Errors)
Visit 4 FACT-Cog CFO Score	*r*	0.045	0.193	.490	0.194	0.139	0.162	0.375	0.44	-0.205	-0.245	-0.233
	Sig. (2-tailed)	0.844	0.389	0.02	0.388	0.537	0.47	0.085	0.041	0.36	0.273	0.297
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 CPT RT SE/ ISI	Visit 5 CFF Ascending Mean	Visit 5 CFF Descending Mean	Visit 5 CRT Recognition Time Median (ms)	Visit 5 CRT Motor Time Median (ms)	Visit 5 CRT Total RT (ms)	Visit 5 ID Task (Speed)	Visit 5 Detection Task (Speed)	Visit 5 Two Back (Accuracy)	Visit 5 Set Shifting (Errors)	Visit 5 Groton Maze Total (Errors)
Visit 5 FACT-Cog CFO Score	*r*	0.154	-0.209	-0.19	-0.115	-0.052	-0.087	0.155	-0.1	-0.078	-0.171	-0.46
	Sig. (2-tailed)	0.493	0.351	0.397	0.61	0.817	0.701	0.491	0.658	0.731	0.447	0.031
	N	22	22	22	22	22	22	22	22	22	22	22

CPT: Continuous Performance Task, CFF: Critical Flicker Fusion Task, CRT: Choice Reaction Time Task, ID Task: Identification Task
Bonferroni Corrected at 0.05 level

Appendix Table 11. Relationship between FACT-Cog Total Score and Cognitive Performance Measures

Visit 2 (Baseline)

		Visit 2 CPT RT SE/ ISI	Visit 2 CFF Ascending Mean	Visit 2 CFF Descending Mean	Visit 2 CRT Recognition Time Median (ms)	Visit 2 CRT Motor Time Median (ms)	Visit 2 CRT Total RT (ms)	Visit 2 ID Task (Speed)	Visit 2 Detection Task (Speed)	Visit 2 Two Back (Accuracy)	Visit 2 Set Shifting (Errors)	Visit 2 Groton Maze Total (Errors)
Visit 2 FACT-Cog Total Score	*r*	0.235	0.303	0.096	-0.208	-0.245	-0.256	-0.192	-0.112	-0.228	-0.24	-0.177
	Sig. (2-tailed)	0.292	0.171	0.67	0.352	0.271	0.25	0.392	0.621	0.308	0.283	0.43
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 3 (3-Weeks)

		Visit 3 CPT RT SE/ ISI	Visit 3 CFF Ascending Mean	Visit 3 CFF Descending Mean	Visit 3 CRT Recognition Time Median (ms)	Visit 3 CRT Motor Time Median (ms)	Visit 3 CRT Total RT (ms)	Visit 3 ID Task (Speed)	Visit 3 Detection Task (Speed)	Visit 3 Two Back (Accuracy)	Visit 3 Set Shifting (Errors)	Visit 3 Groton Maze Total (Errors)
Visit 3 FACT-Cog Total Score	*r*	-0.47	-0.104	0.074	-0.154	0.254	0.125	-0.028	0.184	-0.021	-0.42	-0.548
	Sig. (2-tailed)	0.027	0.646	0.744	0.494	0.253	0.58	0.901	0.412	0.927	0.052	0.008
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 4 (6-Weeks)

		Visit 4 CPT RT SE/ ISI	Visit 4 CFF Ascending Mean	Visit 4 CFF Descending Mean	Visit 4 CRT Recognition Time Median (ms)	Visit 4 CRT Motor Time Median (ms)	Visit 4 CRT Total RT (ms)	Visit 4 ID Task (Speed)	Visit 4 Detection Task (Speed)	Visit 4 Two Back (Accuracy)	Visit 4 Set Shifting (Errors)	Visit 4 Groton Maze Total (Errors)
Visit 4 FACT-Cog Total Score	*r*	0.088	0.374	0.288	-0.325	0.158	-0.091	-0.023	0.289	0.055	-0.115	-0.146
	Sig. (2-tailed)	0.698	0.087	0.194	0.14	0.484	0.687	0.918	0.193	0.808	0.61	0.517
	N	22	22	22	22	22	22	22	22	22	22	22

Visit 5 (8-Weeks)

		Visit 5 CPT RT SE/ ISI	Visit 5 CFF Ascending Mean	Visit 5 CFF Descending Mean	Visit 5 CRT Recognition Time Median (ms)	Visit 5 CRT Motor Time Median (ms)	Visit 5 CRT Total RT (ms)	Visit 5 ID Task (Speed)	Visit 5 Detection Task (Speed)	Visit 5 Two Back (Accuracy)	Visit 5 Set Shifting (Errors)	Visit 5 Groton Maze Total (Errors)
Visit 5 FACT-Cog Total Score	*r*	-0.237	-0.092	-0.163	-0.372	0.029	-0.206	0.025	-0.314	0.21	0.014	-0.221
	Sig. (2-tailed)	0.287	0.685	0.469	0.089	0.897	0.357	0.913	0.154	0.349	0.951	0.323
	N	22	22	22	22	22	22	22	22	22	22	22

CPT: Continuous Performance Task, CFF: Critical Flicker Fusion Task, CRT: Choice Reaction Time Task, ID Task: Identification Task
Bonferroni Corrected at 0.05 level

Appendix Table 12. Descriptive and ANOVA Results for Endocrine Therapy Status

		N	Mean	Std. Deviation	Std. Error	ANOVA Result
CCI Score	Not on Endocrine Therapy	10	0.406	0.165	0.052	F(1,22) = 1.391, p= 0.251
	On Endocrine Therapy	14	0.475	0.11906	0.03182	
BDI	Not on Endocrine Therapy	10	3.900	3.695	1.169	F(1,22) = 1.273, p= 0.271
	On Endocrine Therapy	14	5.640	3.754	1.003	
MSC Score	Not on Endocrine Therapy	10	23.000	15.026	4.752	F(1,22) = 2.024, p= 0.169
	On Endocrine Therapy	14	31.360	13.579	3.629	
CRT Median Processing Time	Not on Endocrine Therapy	10	481.450	107.652	34.042	F(1,22) = 0.484, p= 0.494
	On Endocrine Therapy	14	456.821	65.935	17.622	

CCI: Cognitive Complaint Index, BDI: Beck Depression Inventory, MSC: Menopause Symptom Checklist; CRT: Choice Reaction Time Task

Appendix Table 13. Descriptive and ANOVA Results for Menopausal Status Prior to Chemotherapy

		N	Mean	Std. Deviation	Std. Error	ANOVA Result
CCI Score	Post-menopausal	11	0.464	0.116	0.035	F(1,22) = 0.309, p= 0.584
	Pre-menopausal	13	0.431	0.161	0.044	
BDI	Post-menopausal	11	4.64	3.749	1.130	F(1,22) = 0.109, p= 0.744
	Pre-menopausal	13	5.15	3.891	1.079	
MSC Score	Post-menopausal	11	28.360	17.282	5.211	F(1,22) = 0.022, p= 0.883
	Pre-menopausal	13	27.460	12.400	3.439	
CRT Median Processing Time	Post-menopausal	11	493.636	111.335	33.568	F(1,22) = 2.099, p= 0.161
	Pre-menopausal	13	444.615	46.619	12.929	

CCI: Cognitive Complaint Index, BDI: Beck Depression Inventory, MSC: Menopause Symptom Checklist; CRT: Choice Reaction Time Task

Appendix Table 14. CFF and SRT Descriptive and ANOVA Results

		N	Mean	Std. Dev	Std. Error	Minimum	Maximum	ANOVA Result
CFF Ascending Mean	maSCD+	16	36.875	4.71	1.17	28.5	45.3	F (2,57) = 1.486, p = 0.235
	maSCD-	20	35.745	5.56	1.24	26.5	48.2	
	pCRCI	24	34.15	4.70	0.96	24	42.6	
CFF Descending Mean	maSCD+	16	36.43	6.27	1.56	26.3	46.2	F (2,57) = 0.559, p = 0.575
	maSCD-	20	38.13	4.09	0.91	30.4	44.1	
	pCRCI	24	36.64	5.50	1.12	25.7	50	
SRT Total Recall 5 Trials	maSCD+	16	41.38	14.32	3.58	0	60	F (2,60) = 1.318, p = 0.275
	maSCD-	23	46.91	10.36	2.16	27	68	
	pCRCI	24	42.25	11.57	2.36	6	65	
SRT Total Recall 8 Trials	maSCD+	16	74.81	16.063	4.01	49	102	F (2,60) = 1.159, p = 0.321
	maSCD-	23	82.17	16.80	3.50	46	116	
	pCRCI	24	80.63	13.16	2.68	53	113	
SRT Total Consistency 5 Trials	maSCD+	16	19.75	9.93	2.48	4	38	F (2,60) = 0.238, p = 0.789
	maSCD-	23	21.96	11.47	2.39	2	49	
	pCRCI	24	20.42	9.71	1.98	6	43	
SRT Total Consistency 8 Trials	maSCD+	16	38.44	19.90	4.97	6	72	F (2,60) = 1.117, p = 0.334
	maSCD-	23	46.17	22.87	4.76	2	97	
	pCRCI	24	47.71	16.90	3.45	21	89	
SRT Total Recall Failure 5 Trials	maSCD+	16	11.5	6.91	1.73	1	23	F (2,60) = 2.232, p = 0.116
	maSCD-	23	9.3	8.91	1.85	-11	25	
	pCRCI	24	14.08	7.07	1.44	1	32	
SRT Total Recall Failure 8 Trials	maSCD+	16	15.38	9.99	2.49	2	31	F (2,60) = 1.051, p = 0.356
	maSCD-	23	12.13	10.80	2.25	-11	36	
	pCRCI	24	16.25	9.47	1.93	1	40	
SRT Delayed Recall	maSCD+	16	9.5	2.09	0.52	6	13	F (2,60) = 0.523, p = 0.595
	maSCD-	23	10.26	2.37	0.49	6	15	
	pCRCI	24	9.54	3.38	0.69	4	16	

CFF: Critical Flicker Fusion Task, SRT: Selective Reminding Task

Appendix Table 15. Correlation Results for Behavioral and Cognitive Outcome Measures

		CCI Score	Age	BDI	MSC Score	CRT Median Recognition Time
CCI Score	Pearson Correlation	1	-0.004	.502**	.597**	.355**
	Sig. (2-tailed)		0.976	.000	.000	0.005
	N	63	63	63	63	60
Age	Pearson Correlation	-0.004	1	-0.003	-0.105	0.153
	Sig. (2-tailed)	0.976		0.981	0.413	0.244
	N	63	63	63	63	60
BDI	Pearson Correlation	.502**	-0.003	1	.583**	0.108
	Sig. (2-tailed)	.000	0.981		0	0.411
	N	63	63	63	63	60
MSC Score	Pearson Correlation	.597**	-0.105	.583**	1	0.165
	Sig. (2-tailed)	.000	0.413	.000		0.209
	N	63	63	63	63	60
CRT Median Recognition Time	Pearson Correlation	.355**	0.153	0.108	0.165	1
	Sig. (2-tailed)	0.005	0.244	0.411	0.209	
	N	60	60	60	60	60

CCI: Cognitive Complaint Index, BDI: Beck Depression Inventory, MSC: Menopause Symptom Checklist, CRT: Choice Reaction Time Task

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

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

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