# Vasomotor Symptoms and Cognition Among Women Receiving Estrogen Therapy for Breast Cancer

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THESIS

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I would like to dedicate this dissertation to my dad. This milestone could not have been accomplished without his unwavering love and support. Dad, words cannot fully express how thankful I am for all your help throughout this journey. You have been there for me every step of the way, offering support and guidance at every turn. Being able to dedicate this dissertation to you is but a small token of my appreciation and gratitude. Thank you.

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| | |
|---|---|
| ACS | American Cancer Society |
| BTA | Brief Test of Attention |
| CES-D | Center for Epidemiological Studies - Depression Scale |
| Co-STAR | Cognition in the Study of Tamoxifen and Raloxifen |
| CRCI | Cancer-Related Cognitive Impairment |
| CRT | Card Rotations Test |
| CVLT | California Verbal Learning Test |
| DASS | Depression and Anxiety Stress Scale |
| DMN | Default Mode Network |
| DPS | Downloading and Plotting Software |
| DS | Digit Span |
| E2 | Estradiol |
| fMRI | Functional Magnetic Resonance Imaging |
| HF | Hot Flash |
| HT | Hormone Therapy |
| KNDy | Co-expression of Kisspeptin, NKB, and Dynorphine |
| LH | Luteinizing hormone |
| LM | Logical Memory |
| MENQOL | Menopause Specific Qualify of Life |
| MHT | Menopausal Hormone Therapy |
| MMSE | Mini-Mental State Exam |
| mRNA | Messenger Ribonucleic Acid |

## LIST OF ABBREVIATIONS (continued)

| | |
|---|---|
| NCI | National Cancer Institute |
| NKB | Neurokinin B |
| NK3R | Neurokinin B Receptor |
| NSABP | National Surgical Adjuvant Breast and Bowel Project |
| POAH | Preoptic/Anterior Hypothalamus |
| PSQI | Pittsburgh Sleep Quality Index |
| RCT | Randomized Control Trial |
| SERM | Selective Estrogen Receptor Modulator |
| SGB | Stellate Ganglion Blockade |
| SNRI | Selective Serotonin Reuptake Inhibitor |
| SSRI | Serotonin and Norepinephrine Reuptake Inhibitor |
| SWAN | Study of Women's Health Across the Nation |
| VMS | Vasomotor Symptoms |
| WMH | White Matter Hyperintensities |
| WHIMS | Women's Health Initial Memory Study |

## SUMMARY

The ovarian hormones estradiol and progesterone have both organizational and activational effects on the brain. Fluctuations in estrogen lead to alterations in the hippocampus and the prefrontal cortex through changes in dendritic spine density, cerebral blood flow, and connectivity between the two brain regions. Additionally, these fluctuations in estrogen affect memory performance. Decreases in estrogen can also trigger vasomotor symptoms (VMS) (i.e., hot flashes and night sweats). VMS can independently influence memory by triggering cortisol release, altering default mode network connectivity between the hippocampus and other brain regions, adversely affecting cardiovascular function, and/or disrupting sleep. This work in menopause has recently been applied to breast cancer, as women with breast cancer can experience a rapid decrease in estrogen levels from breast cancer treatments, specifically chemotherapy and hormone therapy (HT). These treatments are effective but have been shown to increase VMS and cognitive difficulties. There is considerable interest in lowering the burden of both VMS and cognitive difficulties, as each contributes to decreased quality of life.

Menopausal hormone therapy (MHT) is currently the gold standard for VMS treatment. However, MHT is contraindicated in breast cancer survivors because it may increase the potential for estrogen-dependent cancer cell growth and recurrence. As a result, stellate ganglion blockade (SGB), a procedure in which the stellate ganglion is blocked with local anesthetic, has been used as a potential therapeutic alternative. In healthy women, SGB decreases both VMS that women subjectively report as well as VMS measured physiologically through ambulatory skin conductance monitoring. Moreover, the magnitude of improvement in physiologic VMS was associated with the

magnitude of improvement in verbal memory. This finding raises the possibility that VMS might contribute directly to memory problems. To date, the association between VMS and cognitive impairment among breast cancer survivors has not been explored.

The purpose of the present study was to determine if the effects seen in healthy women generalize to women with breast cancer. Specifically, we evaluated the relationship between VMS and verbal memory performance in midlife women with breast cancer. In Aim 1, we examined the association between VMS (physiologic, as measured by ambulatory monitoring, and subjective, as measured by diary reporting and button presses) and verbal memory performance in breast cancer survivors who report moderate-to-severe VMS. We predicted that a greater number of physiologic, but not subjective, VMS would be associated with worse verbal memory performance. In Aim 2, we examined the effect of SGB intervention for VMS on verbal memory in breast cancer survivors with moderate-to-severe VMS. We predicted that the magnitude of change in VMS following SGB and sham intervention would be related to the magnitude of change in verbal memory performance such that greater improvement in VMS following the intervention would be associated with greater improvement in verbal memory.

# I. SIGNIFICANCE AND BACKGROUND

## A. Breast Cancer

Breast cancer is the most commonly diagnosed cancer among women in the United States. Although breast cancer can affect both men and women, women are disproportionately affected at a ratio of 100:1 (National Cancer Institute [NCI], 2017). Approximately 12.4% of women will develop breast cancer during their lifetime (SEER Cancer Statistics, 2016). The American Cancer Society (ACS) estimated that over 316,000 women will be newly diagnosed with breast cancer in 2018. Approximately 80% of these new cases will be an invasive form of breast cancer, spreading to the surrounding breast tissue. Breast cancer is the second leading cause of death among women with cancer, second only to skin cancer. It is estimated that over 40,600 women in the United States will die this year from breast cancer (ACS, 2017). Currently, there are over 3.3 million people living with a previous breast cancer diagnosis (i.e., survivors) in the United States.

There are a wide range of FDA-approved hormone therapies for the treatment of breast cancer. Treatment options for breast cancer vary greatly depending on disease stage at the time of diagnosis and can include surgery, chemotherapy, radiation therapy, and/ or hormone therapy. Hormone therapy is a specifically targeted treatment approach for those with estrogen receptor- and progesterone receptor-positive breast cancers. Approximately two-thirds of all breast cancers are hormone receptor positive (ACS, 2017). Hormone therapy works by blocking the production of steroid sex

hormones or by disrupting the downstream effects of these hormones that can promote tumor growth.

Tamoxifen is one of the most frequently prescribed hormone therapies for the prevention and treatment of early localized hormone receptor-positive breast cancers among premenopausal women. Tamoxifen is typically prescribed following surgery to decrease the risk of recurrence, including the risk of new cancers forming in the contralateral breast. In breast tissue, tamoxifen acts as an estrogen antagonist by competing with estrogen at receptor binding sites. Tamoxifen also helps prevent the proliferative effects of estrogen on breast tissue.

There are many common side effects associated with breast cancer treatments, particularly chemotherapy and tamoxifen. Side effects may include hair loss, weight loss, nausea, vomiting, sexual problems, fatigue, body image issues, depression, anxiety, vasomotor symptoms (VMS) (i.e., hot flashes and night sweats) and other menopausal symptoms, and changes in cognitive functioning commonly known as “chemo brain” (ACS, 2017; Coates et al., 1983; Kaplan et al., 1992; see Shapiro & Recht, 2001 for review).

Drugs that block ovarian production of estrogen commonly induce premature menopause among breast cancer patients (Khaw, 1992; Quinn, 1991). This is of importance as 21% of women who were diagnosed with breast cancer in the US in 2015 were younger than the average age women start to transition through the menopause (49.5) (ACS, 2016). Premature menopause is accompanied by symptoms that normally occur during the menopausal transition such as ovarian failure, loss in bone mineral density, risk of cardiovascular disease, sexual dysfunction, distress and mood changes,

and VMS (Bruning et al., 1990; Fenlon, 1995; Hunter, 1991; Kaplan, 1992; Lobo, 1991). In fact, the National Surgical Adjuvant Breast and Bowel Project (NSABP) found that the most notable quality of life difference between breast cancer survivors on tamoxifen and on placebo were menopausal symptoms. Specifically, 47.5% of women on tamoxifen reported their hot flashes as “quite a bit” or “extremely” bothersome compared with 28.7% of women on placebo (Fisher et al., 1998). Additional studies have shown that 70-80% of women receiving breast cancer treatment experience VMS (Canney & Hatton, 1994; Hunter et al., 2004). In a study of 113 women who were prescribed tamoxifen within the past five years, 80% reported currently experiencing hot flashes (ranging from 0-140 per week) and 72% reported currently experiencing night sweats (ranging from 0-42 per week) (Hunter et al., 2004).

## B. Vasomotor Symptoms

### 1. Definition and Measurement

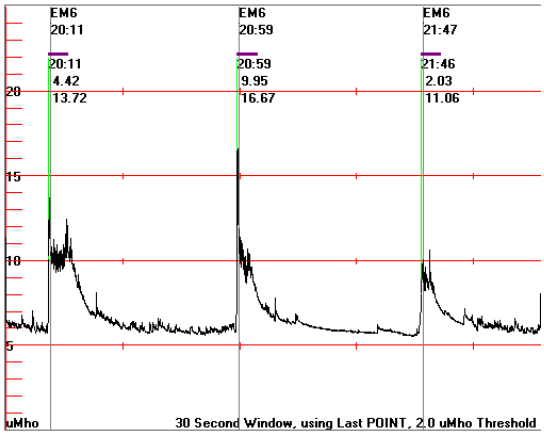
VMS include both daytime hot flashes and night sweats. VMS are characterized by sweating due to peripheral cutaneous vasodilation, and quick, intense feelings of heat usually throughout the neck, chest, face, and upper back (Carpenter et al., 1999; Rance et al., 2013). The start of a hot flash is typically characterized by an increase in skin conductance. Increases in heart rate and peripheral blood flow cause an increase in skin temperature which leads to sweating. The sweating and vasodilation, in turn, result in heat loss and a drop in internal temperature approximately 5-9 minutes following the onset of the VMS (Kronenberg et al., 1984; Tataryn et al.,

1980). VMS can vary in frequency and severity both between individuals and within the same individual over time (Kronenberg, 1990).

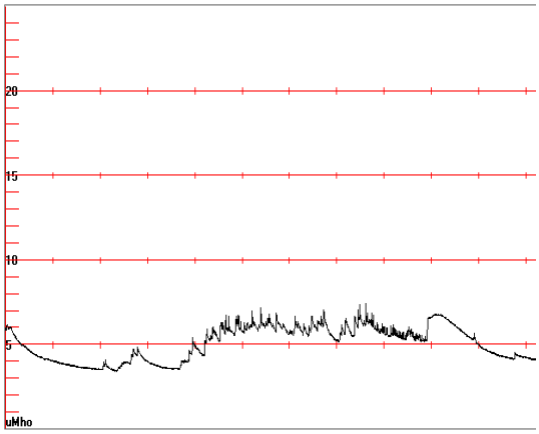
Typically, subjective VMS are measured using self-reported diaries or questionnaires. VMS can also be measured physiologically with skin conductance monitors due to changes in sweating on the skin's surface (Bahr et al., 2014; Freedman, 1989; Sloan et al., 2001). The standard for identifying a physiologically recorded VMS is a 2.0 μMho increase in skin conductance over a 30-second period (Freedman, 1989). These increases are distinct from temperature fluctuations caused by typical sweating. VMS events have a steep rise in skin conductance followed by a slow return to baseline, whereas artifact (usually resulting from the participant sweating in the absence of a VMS) is characterized by rapid fluctuations in skin conductance (see Figure 1). Biolog monitors are highly reliable with up to 95% sensitivity in laboratory settings, have high internal consistency within sessions, and are highly correlated with subjective HFs (hot flashes) in laboratory settings (Carpenter et al., 1999; Freedman, 1989).

Figure 1. Output from the Biolog skin conductance monitor software showing the distinction between hot flashes in the left panel and sweating in the right panel.

Hot Flash




Sweating




The green lines in the left panel represent the monitor's detection of a hot flash exceeding the 2.0 µMho threshold. EM6 indicates an "event marker" where the subject indicated she was experiencing a hot flash. The top number is the time the VMS occurred (i.e., 20:11 for the first VMS) and the second number is the magnitude of the VMS.

The ability to physiologically monitor VMS is critically important because women typically under-report the number of VMS they experience. For example, in a study of 55 breast cancer survivors, the estimated likelihood that a woman reported a physiologic (i.e., monitor-verified) hot flash in the ambulatory setting (i.e., in her daily routine rather than in the lab) was between 36% and 50%. Night sweats were reported between 22% and 42% of the time. The under-reporting of VMS in subjective diaries resulted in missing more than 50% of “severity” and “bother” ratings (Carpenter et al., 2004a). One factor that likely contributes to some of the under-reporting in ambulatory settings is that questionnaires and diaries rely on retrospective recall of the number of VMS whereas physiologic VMS measures do not. However, other factors likely contribute to the under-reporting because studies have found a discordance between physiologic VMS and subjective VMS measured in real time by event markers on ambulatory monitors, a process that does not rely on retrospective recall. In such studies, women detected only 43% of physiologic daytime VMS and 60% of physiologic night sweats (Maki et al., 2008). From a quality of life perspective, it is the degree of bother from subjectively reported VMS that decreases quality of life, and if a hot flash is not detected, it cannot be perceived as bothersome. Only subjective VMS provide information on severity of a VMS; no feature of a physiologic VMS is associated with reports of VMS intensity or distress. Therefore, the simultaneous measurement of VMS, both physiologic and subjective, on ambulatory monitors provides a better account of VMS than does either method alone.

## 2. Neurobiology

Two main brain regions have been linked with VMS: the hypothalamus and the insula. The hypothalamus is the brain region primarily associated with thermoregulation (Dimicco & Zaretsky 2007; Egan et al., 2005; Romanovsky, 2007). Stimulation of the anterior hypothalamus, which includes the preoptic area and anterior nucleus, elicits physiological responses including sweating. Hypothalamic cells constantly monitor blood temperature and initiate physiological changes necessary to maintain homeostasis. Thermosensitive neurons (warm-sensing/cold-sensing POAH [preoptic/anterior hypothalamus]) in the anterior hypothalamus respond to increases in temperature and activate mechanisms that promote heat loss such as cutaneous vasodilation and sweating. These physiological responses are regulated peripherally by cholinergic neurons found in sweat glands (Kazuyuki et al., 1998). Additionally, cells in the posterior hypothalamic nucleus trigger shivering and cutaneous vasoconstriction (conservation of heat) in response to the lowering of blood temperature.

The insula is involved in perception of bodily sensations (Craig et al., 2000). Temperature perception is primarily mediated through the insular cortex. Using functional magnetic resonance imaging (fMRI) during VMS monitoring, Freedman and colleagues (2006) showed significantly greater insular activation during the initial 20 seconds of a hot flash. Additionally, research has shown a significant negative correlation between insular activation and cooling stimulus intensity, highlighting the role of the insula in human thermoregulation (Craig et al., 2000).

## 3. Underlying Mechanisms

Menopause, which typically occurs around the age of 51 in women (Gold

et al., 2001), is characterized by the cessation of ovarian function, resulting in a severe reduction in circulating levels of the ovarian steroids hormones, estradiol (E2) and progesterone (Chakravarti et al., 1976). Previous research has shown that during menopause, decreases in E2 are a contextual factor for VMS, but are not a proximal cause. All women experience menopause, but only 75% of women experience VMS (Gold et al., 2000; Kronenberg,1990). Additionally, E2 levels do not fluctuate immediately before or after a VMS event. Lastly, plasma or serum estrogen levels are not reliably associated with the frequency and severity of VMS (Rannevik et al., 1995). Nevertheless, evidence of estrogen's role in VMS has been established by the therapeutic benefits exogenous estrogen has on VMS (Thurston & Joffe, 2011). Taken together, these studies suggest that estrogen exerts clinic benefits, not directly through estrogen receptors, but indirectly through other neurobiologic mechanisms. In recent years, the proximal events contributing to VMS in the context of low estrogen have been identified as KNDy neurons located in the hypothalamus.

In postmenopausal women, a set of neurons located in the arcuate nucleus of the hypothalamus are enlarged compared with premenopausal women (Abel & Rance 2000; Rance et al., 1990; Sheehan & Kovacs, 1966). This hypertrophy takes place in a specific subpopulation of neurons that show increased expression of neurokinin B (NKB) (Rance & Young 1991). NKB has been linked to VMS in several ways. In a randomized, double-blinded, placebo-controlled, 2-way cross-over study, NKB infusions induced VMS in postmenopausal women (Jayasena et al., 2015). Additionally, estrogen replacement therapy, the gold standard treatment for VMS, reduces NKB mRNA expression (Abel et al., 1999).

NKB receptors are co-localized with kisspeptin, dynorphin, and estrogen receptors on these neurons in the arcuate nucleus (Goodman et al., 2007; Rance, 2009; Rance et al., 2013) and are referred to as KNDy neurons (co-expression of kisspeptin, NKB, and dynorphine) (Lehman et al., 2010). These KNDy neurons are involved in steroid feedback mechanisms and have been implicated in their role in reproductive health and disease (see Lehman et al., 2010 for review).

KNDy neurons influence temperature regulation and subsequent VMS following estrogen withdrawal. Rance and colleagues (2013) performed ovariectomies and selectively ablated KNDy neurons in female rats. Control rats (no ablation) showed an increase in serum LH (luteinizing hormone) following ovariectomy, which returned to intact levels following estrogen treatment. However, rats receiving ablation did not show increases in LH following ovariectomy and serum LH was lower despite estrogen replacement. Furthermore, KNDy neuron ablated rats showed decreases in tail skin temperature and better core temperature control against heat compared with control rats.

In a recent randomized, placebo-controlled, crossover trial, an oral NK3R (NKB receptor) antagonist (MLE4901) was administered to healthy postmenopausal women who were experiencing seven or more daily hot flashes (Prague et al., 2017). Compared with placebo, MLE4901 significantly reduced the total number of weekly hot flashes measured by skin conductance monitoring and hot flash severity, bother, and interference ratings measured by real-time self-report. Additionally, the NK3R antagonist reduced psychosocial and physical symptoms associated with VMS measured by the Menopause Specific Qualify of Life (MENQOL) questionnaire (Prague

et al., 2017). Taken together, these findings add to our understanding about the underlying mechanisms involved in VMS and the potential role KNDy neuron antagonists can have as therapeutic alternatives to estrogen therapy for the treatment of VMS. More fundamentally, the results validate the role of NK3R receptors in the pathophysiology of VMS in women.

### 4. Side Effects and Symptoms

To understand the relationship between VMS and cognitive function, it is important to consider the role of other menopausal symptoms that can co-occur with VMS. VMS are associated with decreased quality of life (Avis et al., 2009; Woods & Mitchell, 2011), depression and anxiety (Bromberger et al., 2007; Freedman, 2000; Freeman et al., 2009), negative health outcomes (Ozkaya et al., 2011; Thurston, et al., 2011), and workplace interference (Woods & Mitchell, 2011). The SWAN (Study of Women's Health across the Nation) demonstrated associations between sleep disturbances and VMS (Kravitz et al., 2003; 2005). Night sweats that cause sleep disruptions are one of the most common complaints of women experiencing VMS (Brown et al., 2009; Kravitz et al., 2008). Sleep disturbances may include difficulties falling asleep, staying asleep, and waking early. Additionally, more frequent VMS are associated with significantly greater sleep disturbances compared with less frequent or no VMS (Kravitz et al., 2008).

### 5. Vasomotor Symptoms and Cognitive Impairment

In addition to VMS, the transition through the menopause is commonly associated with increased self-reported cognitive complaints (Gold et al., 2000; Woods et al., 2000) that correlate with worse performance on verbal memory tests (Drogos et

al., 2013). It is important to note the distinction between physiologically and subjectively measured VMS and cognitive performance. There is a significant relationship between subjectively reported VMS and self-reported cognitive problems (Mitchell & Woods, 2011; Drogos et al., 2013; Schaafsma et al., 2010). However, studies have not found associations between subjectively reported VMS and cognitive performance (Greendale et al., 2010; LeBlanc et al., 2007; Weber et al., 2012). Despite this, the association between physiologically measured VMS and cognitive performance has been demonstrated. Maki and colleagues (2008) examined 29 midlife women with subjectively reported moderate-to-severe VMS. Women were asked to wear an ambulatory VMS monitor, fill out a VMS diary log, and undergo standard cognitive testing. Results showed the total number of physiologic VMS correlated significantly with verbal memory performance whereas subjective diary-reported VMS did not. Additional research has shown that changes in physiologic VMS were significantly negatively correlated with changes in verbal memory performance (Maki et al., 2016), while subjectively reported VMS were not.

Similarly, recent neuroimaging findings reveal associations between physiologic VMS and brain connectivity and white matter. Specifically, Thurston and colleagues (2016) showed that physiologic VMS, not subjective ratings, negatively correlated with verbal memory performance and positively correlated with white matter hyperintensities (WMH) and greater default mode network (DMN) activity, particularly for the DMN connectivity to the hippocampus (Thurston et al., 2015). Verbal memory is critically dependent on hippocampal and prefrontal systems, and deficits in verbal memory have been linked to activity dysregulation in hippocampal and prefrontal-striatal networks

(Haley et al., 2011; Kilpatrick et al., 1997). Although the Thurston et al. (2015) study was the first study to relate VMS to alterations in brain function, there is strong evidence that estrogen influences the function of those regions. The hippocampus and prefrontal cortex have high concentrations of estrogen receptors (Ishunina & Swaab, 2007; Osterlund et al., 2000). Exogenous estrogen can modulate brain activity during verbal memory tests (Maki et al., 2011; Maki & Resnick, 2000; Resnick et al., 1998; Shaywitz et al., 1999) and increase functional connectivity between the prefrontal cortex and hippocampus (Ottowitz et al., 2008).

Cortisol may play a role in the relationship between VMS, cognition, and brain function. The relationship between cortisol and VMS is bidirectional. Increases in the peripheral circulation of cortisol have been observed 20 minutes following a VMS and increases in cortisol can also trigger a VMS (Genazzani et al., 1984; Meldrum et al., 1984). Additionally, increases in cortisol levels have been observed during the late menopausal transition and these women experience more severe VMS compared to women with lower levels of cortisol during this transition (Meldrum et al., 1984; Woods et al., 2006).

## C. Cognitive Function in Breast Cancer Patients: Evidence of Impairment Before Treatment

It is important to note that cancer alone can cause cognitive dysfunction, irrespective of treatment. Ahles and colleagues (2008) assessed cognition among 132 women with breast cancer prior to adjuvant treatment. Results showed that 22% of women with invasive breast cancer demonstrated lower than expected cognitive

performance in domains of verbal ability (reading, vocabulary, and fluency) and verbal memory. Other studies have shown cognitive impairments among breast cancer patients prior to treatment in processing speed, attention, and verbal working memory (Cimprich et al., 2010; Hedayati et al., 2011; Shilling et al., 2005). Hermelink et al. (2007) showed that prior to receiving adjuvant treatment, 56% of breast cancer patients exhibited mild cognitive impairment and 32% of patients showed moderate cognitive impairment. Neuroimaging studies have also shown differences in brain functioning between breast cancer patients and healthy controls prior to adjuvant therapies. These differences include compensatory recruitment of additional working memory/attention circuits during a verbal working memory task (Cimprich et al., 2010; McDonald et al., 2012), increased activity in left inferior frontal cortex during the visuospatial n-back tasks (Scherling et al., 2011), and decreased cerebellar activation during a go/no-go task (Scherling et al., 2012).

## D. Cognitive Function in Breast Cancer Patients: The Role of Chemotherapy and Hormone Therapy

It is important to understand the nature and extent of cancer-related cognitive impairment (CRCI) as it can influence medication adherence, impair quality of life, impact work function, reduce social engagement, and lead to worse cognitive decline in the future (Bradley et al., 2005; Janelsins et al., 2014; Myers, 2012; Reid-Arndt et al., 2009; Wefel et al., 2004). Research on CRCI began to emerge in the mid-1990s (Ahles et al. 2002, Janelsins et al., 2014). However, it was not until Wefel and colleagues (2004) examined both pre- and post-treatment measures of cognitive functioning that

the effects of chemotherapy began to be fully understood. The first published longitudinal investigation of pre- and post-chemotherapy effects on CRCI involved 18 women with breast cancer who were enrolled in a Phase III oncology trial. Women were administered cognitive assessments before the start of chemotherapy (baseline) and approximately six months after baseline. Results showed that 61% of participants demonstrated cognitive decline in one or more aspects of cognitive functioning, specifically learning, attention, and processing speed, following chemotherapy treatment. These results were irrespective of mood or baseline levels of cognitive functioning (Wefel et al., 2004).

Since that time, these results have been replicated. A review by Wefel and Schagen (2012) examined 26 longitudinal studies exploring the effects of chemotherapy as a treatment for breast cancer on cognitive impairment. Of those studies, 69% reported some form of cognitive decline in at least one domain over the course of chemotherapy. The cognitive domains most affected were memory, processing speed, attention, and executive function (Wefel & Schagen, 2012). Furthermore, these cognitive changes can have a late onset following treatment (Wefel et al., 2010) and can persist for up to 20 years following treatment (Koppelmans et al., 2012).

Neuroimaging studies have also shown differences in brain functioning between breast cancer patients and healthy controls following chemotherapy treatment. These studies have assessed brain function one month to five years after chemotherapy and found reduced prefrontal activation during both a card sorting task (Kesler et al., 2011) and verbal encoding task (Kesler et al., 2009), reduced parietal activation during both the Tower of London task and a paired association task (de Ruiter et al., 2011), and

altered network organization and decreased global clustering in areas involved executive control and emotion regulation (Bruno et al., 2012). Similar differences have been demonstrated during memory tasks. Specifically, increased activation in multiple brain regions during verbal recall (Kesler et al., 2009), decreased left frontal lobe activation during a verbal n-back task as early as one month following treatment (McDonald et al., 2012), and reduced local connectivity in areas involved in memory (Bruno et al., 2012).

Research has also demonstrated that tamoxifen alone has negative effects of cognitive functioning. In an exploratory analysis using cognitive data from the Cognition in the study of Tamoxifen and Raloxifen (Co-STAR) and the Women's Health Initial Memory Study (WHIMS), cognitive deficits on the Annual Modified Mini-Mental State exam were worse among those women receiving tamoxifen compared to those women on placebo (Espeland et al., 2010). Previous research has also demonstrated negative effects of cognitive functioning among women taking tamoxifen in combination with chemotherapy. Breast cancer survivors who received both chemotherapy and tamoxifen had significantly worse performance on verbal learning, visual memory, visuospatial domains, and global neurocognitive performance compared with survivors who received chemotherapy alone (Castellon et al., 2004). Similarly, van Dam and colleagues (1998) administered a neurocognitive battery to three groups of women with a history of breast cancer—high-dose chemotherapy plus tamoxifen, standard-dose chemotherapy plus tamoxifen, and women with early stage breast cancer who had not been treated with either chemotherapy or tamoxifen (i.e., controls). Results showed that 32% of women treated with high-dose chemotherapy plus tamoxifen met study-defined criteria of

cognitive impairment compared with 17% and 9% in the standard-dose chemotherapy plus tamoxifen and control groups respectively (van Dam et al., 1998). Additional studies have found significantly worse performance on visual memory, word fluency, visual-spatial ability, processing speed, and verbal memory in women with breast cancer who were prescribed tamoxifen (without chemotherapy) compared with healthy controls (Palmer et al., 2008).

## E. Stellate Ganglion Blockade as an Effective Treatment for Vasomotor Symptoms

Menopausal hormone therapy (MHT) is the gold standard treatment for VMS and can significantly improve symptoms in most women (Kronenberg, 1990; De Villiers et al., 2013). A meta-analysis of double-blind, randomized, placebo-controlled trials of MHT found that compared with placebo, frequency of hot flashes was reduced by 77%. Additionally, there was a significant reduction in the severity of symptoms (MacLennan et al., 2001). However, MHT is not an option for most breast cancer survivors because it can increase the potential for cancer cell growth and recurrence. As a result, researchers have begun to explore potential non-hormonal therapeutic alternatives for VMS among breast cancer survivors. One such alternative is stellate ganglion blockade (SGB) (Lipov et al., 2007; Walega et al., 2014). The stellate ganglion, a sympathetic ganglion (collection of nerves) located in the C6-T2 region of the anterior cervical spine, is commonly blocked with local anesthetics for the treatment of pain. The stellate ganglia act through noradrenergic pathways and provide sympathetic efferents to the upper extremities (i.e., head, neck, and heart). The exact mechanism of action of SGB on VMS is not fully understood, but may involve the interruption of the sympathetic

nervous system, peripheral vasodilation, and modulation of norepinephrine levels in thermoregulatory areas of the brain (Kim et al., 2016; Lipov et al., 2007; Nakase et al., 2004; Walega et al., 2014; Westerhause & Loewy, 2001).

Case report studies and open-label single-arm trials have found that SGB improves VMS. In one such study, 15 women, including five with a history of breast cancer, were treated with SGB and experienced an 80% or greater reduction in VMS during the two weeks following the intervention (Lipov et al., 2007). Similarly, a pilot study in women with breast cancer by Pachman and colleagues (2011) found an initial 60% reduction in VMS in the weeks following SGB and a 44% reduction in VMS frequency 6 weeks following SGB treatment intervention. Similar work has been conducted in breast cancer survivors. In one such pilot study, 13 breast cancer survivors reporting severe VMS were treated with SGB. Total number and intensity of VMS significantly decreased from baseline following the intervention and continued to decline during the 12-week follow-up period, reaching more than an 80% reduction by 12 weeks (Lipov et al., 2008).

In the first randomized controlled trial of SGB, 35 women were randomly assigned to receive either SGB (n=18) or sham-control (saline) injection (n=17) (Walega et al., 2014). Frequency of VMS was measured subjectively by self-reported daily diaries and event markers, and physiologically by ambulatory skin conductance monitors. Results showed a significant reduction of physiologic VMS by 21% in the SGB group compared with the sham-control group 3 months following the intervention. Additionally, the SGB group experienced a 52% reduction in subjectively reported moderate-to-severe VMS and a 38% reduction in VMS intensity compared with the

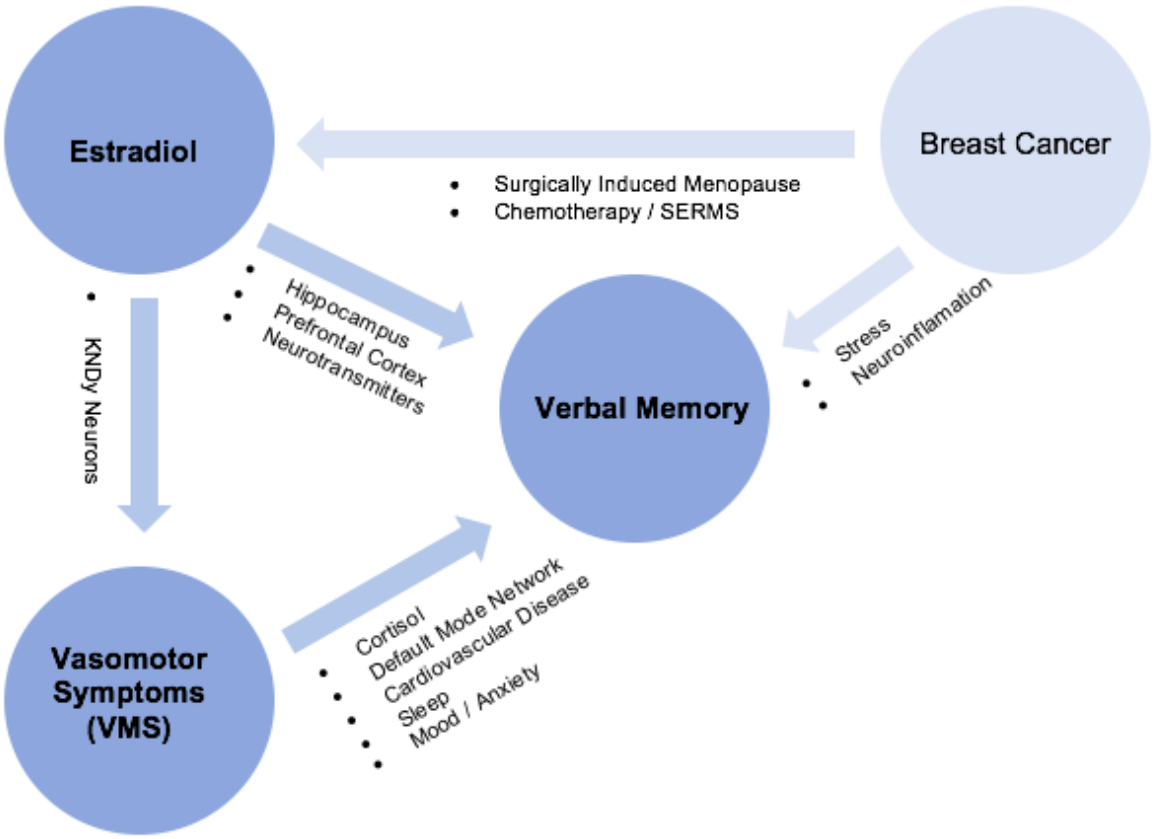
sham-control group (Walega et al., 2014). The purpose of the present study was to expand this to women with a history of breast cancer. We followed the same study design and procedures as in the original RCT (Walega et al., 2014) and expanded on analysis of cognition as a secondary endpoint.

Further evidence of the association between improvement in memory performance and reduction in VMS was demonstrated in a recent nested study by Maki and colleagues (2016). In a sham-controlled SGB pilot intervention study, the effect of SGB on memory function and the relationship between treatment-related decreases in VMS and treatment-related changes in memory performance was examined. From pre- to post-intervention, verbal learning measured by the California Verbal Learning Test (CVLT) significantly improved in the SGB group but not in the sham-control group. Furthermore, observed memory improvement significantly correlated with decreases in total daily VMS, even after controlling for sleep and mood. Consistent with previous studies, changes in self-reported VMS were not correlated with changes in verbal memory performance. Taken together, these results suggest that verbal memory improvement may be directly related to and dependent upon physiologic VMS improvement following SGB intervention. Although a large cognitive battery assessing executive function, attention, concentration, and working memory was administered, the association was specific to verbal memory. This suggests that VMS have a specific relationship with that cognitive domain. More generally, these results further highlight the importance of studying physiologic VMS as it relates to cognitive functioning and support earlier findings of a specific relationship with memory (Maki et al., 2008; Maki et

al., 2016; Thurston et al., 2015).

To date this line of work has not been examined in women with breast cancer, despite evidence of impairment in verbal memory in that population. There is considerable interest in lowering the burden of both VMS and cognitive difficulties, as each contributes to decreased quality of life among breast cancer survivors (Fisher et al., 1998; Woods & Mitchell, 2011). This investigation aimed to evaluate the relationship between VMS (physiologic, as measured by ambulatory monitoring, and subjective, as measured by diary reporting and button presses) and verbal memory performance in midlife women with breast cancer with moderate-to-severe VMS in a sham-controlled clinical trial of SGB (see Figure 2). We first predicted that, consistent with previous work by Maki and colleagues (2008), a greater number of physiologic, but not subjective VMS will be correlated with worse verbal memory performance at baseline. Second, we predicted that the magnitude of change in VMS following SGB and sham intervention will be related to the magnitude of change in verbal memory such that greater improvement in VMS following the intervention would be associated with greater improvement in verbal memory.

Figure 2. Conceptual model of the relationship between Estradiol, Vasomotor Symptoms, and Verbal Memory.



## II. STATEMENT OF AIMS AND HYPOTHESIS

The primary purpose of the project was to evaluate the relationship between VMS and verbal memory performance in midlife women with breast cancer and moderate-to-severe VMS.

**General Hypothesis:** VMS will be negatively associated with verbal memory performance in midlife women with breast cancer.

**Aim 1:** To examine the association between VMS (physiologic and subjective) and verbal memory performance in breast cancer survivors with moderate-to-severe VMS.

**Hypothesis 1a:** A greater number of physiologic VMS will be significantly associated with worse verbal memory performance at baseline.

**Hypothesis 1b:** The total number of subjective VMS will not be significantly associated with verbal memory performance at baseline.

**Aim 2:** To examine the effect of a SGB intervention for VMS on verbal memory in breast cancer survivors with moderate-to-severe VMS.

**Hypothesis 2a:** The magnitude of decrease in physiologic VMS following SGB and sham intervention will be related to the magnitude of improvement in verbal memory performance.

**Hypothesis 2b:** The magnitude of decrease in physiologic VMS following SGB and sham intervention will not be related to any other cognitive domain.

## III. METHODS

The proposed investigation and informed consent documents were approved by the Institutional Review Boards of Northwestern Medicine and the University of Illinois at Chicago.

### A. Participants

Participants provided written informed consent before any study procedures and were compensated for their time and effort. Women 30 to 75 years of age currently using tamoxifen, aromatase inhibitors, or SERMs (selective estrogen receptor modulator) for a breast cancer indication for at least six months, reporting moderate-to-very severe VMS (defined as ≥ 28 reported VMS per week) and willing to undergo fluoroscopy-guided SGB or sham intervention were recruited for this study. Participants were recruited from flyers at Northwestern Medicine, physician-provider letters and referrals, and internet advertisements. Participants were confirmed to have ≥ 28 VMS per week as measured by self-report on paper diaries completed for a minimum of two weeks prior to enrollment in the present study. Exclusion criteria included: acute illness/infection; conditions that prohibit SGB or sham-control intervention (e.g., anatomic abnormalities of the anterior neck or cervical spine; cardiac/pulmonary issues; allergic reactions or contraindications to a local anesthetic or contrast dye; coagulopathy or bleeding disorder); use of medication in the past two months that can impact VMS (e.g., use of MHT or contraceptives, SSRIs, SNRIs); conditions or disorders affecting cognitive test performance (e.g., dementia/mild cognitive impairment; traumatic brain

injury; stroke; alcohol/substance use; English as a second language; inability to write, speak, or read in English); scores of ≥ 21 on depression subscale of the Depression Anxiety and Stress Scale (DASS) (Lovibond & Lovibond, 1995); scores of ≥ 15 on the anxiety subscale on the DASS; a Mini-Mental State Exam (MMSE) score of ≤ 28; and any conditions that may affect sleep quality.

## B. General Procedures

Participants reported to Northwestern Medical Center for a total of four visits. During Visit 1, after the participant reviewed and signed informed consent, information pertaining to basic demographic information and medical history was collected. Participants were asked to maintain a daily paper diary of their VMS, recording the time, severity, and bother ratings of each VMS on a scale of “0” to “10”. They were asked to do this for a minimum of two weeks prior to the first study visit to determine eligibility. At the end of two weeks, a member of the research team contacted the participant via phone to ask how many weekly VMS they reported. If they qualified based on the total number of VMS (≥ 28 per week), they were scheduled to return to the research office for placement of the VMS monitor, questionnaire completion, and cognitive testing procedures.

Visit 2 occurred 2-3 weeks following Visit 1. During this visit, participants completed a cognitive test battery and were asked to complete a series of questionnaires. Participants were fitted with a hot flash monitor and actiwatch which they wore for 24 hours. Visit 2 lasted approximately 2-2.5 hours.

Visit 3 occurred 4-5 weeks following Visit 1. During this visit, the stellate ganglion blockade injection procedure was performed. Participants were interviewed to assess health status and a brief physical exam was performed by the injectionist. Once determined eligible for the SGB, participants were randomized to receive either active SGB injection or a sham-control injection.

Visit 4 occurred three months following the injection procedure (Visit 3). At this visit, the same procedures that were administered during Visit 2 (cognitive test battery [with parallel test forms where applicable] and questionnaires) were administered. Participants again were placed with a VMS and actiwatch which they wore for 24 hours. Participants were compensated for parking and were paid $200.00 by check at study completion for their time and effort.

## C. Outcome Measures

Participants were administered a standardized cognitive battery which took approximately 1.5-2 hours to complete. At each session, they met one-on-one with a research assistant trained in administration of the cognitive test battery used in this study. The cognitive test battery was adapted from the test battery used in the pilot trial of SGB in healthy women (Maki et al., 2016). Parallel versions of the cognitive tests were used where applicable to limit carry-over effects.

### 1. Primary Cognitive Outcomes

Based on findings from previous reports, the primary cognitive outcomes for the present study were in the cognitive domain of verbal memory and included Logical Memory (LM) and the CVLT (Maki et al., 2008).

*Logical Memory Subtest of the Wechsler Memory Scale-Revised (WMS-R/LM-R) (Wechsler, 1981):* This is a test of both immediate and delayed recall of a short story. Participants were read a brief story containing 25 discreet units of information. Participants were instructed that they would have to recall as much of the story as possible immediately following the reading (immediate recall) and again 15 minutes later (delayed recall). Total scores ranged from 0 to 25 on both the immediate and delayed recall.

*California Verbal Learning Test (CVLT) (Delis et al., 1987):* The CVLT is a 16-item list learning test used to measure verbal episodic learning and memory during immediate, short-, and long-delay recall trials. A target list (list A) of 16 words belonging to four sematic categories (i.e., vegetables, ways of traveling, desserts, office supplies) was read aloud five times. The order of the words was randomized so that words from the same semantic category were not presented consecutively. After each presentation, the participant was asked to recall as many of the words as they could remember (verbal learning maximum score = 80). Next, a 16-word interference list (list B) was read aloud one time and participants were asked to recall words *only* from list B (not list A). Participants were then asked to recall the original word list (list A) (short-delay recall: max score = 16). Following a 20-minute delay, participants were then asked to recall the original word list (long-delay recall: max score = 16). Outcomes included total verbal learning, short-delay recall, and long-delay recall.

**2. <u>Secondary Cognitive Outcomes</u>**

Secondary cognitive outcomes were included to evaluate the specificity of

the relationship between VMS and verbal memory (Hypothesis 2b). These outcomes included Card Rotations Test (CRT), Letter Fluency, Semantic Fluency, Digit Span (DS) Forward and Backward, Brief Test of Attention (BTA) Letters and Numbers, and the Finding A's Test.

*Card Rotations (Wilson et al., 1975):* This is a timed paper-and-pencil test of visuospatial ability. In each trial, participants were given three minutes to view a target line drawing of a geometric figure and eight alternative line drawings which represented either a two- or three-dimensional rotation of the target figure. Participants were instructed to mark the box beside "S" for same which representations of the target are a rotation and mark the box beside "D" for different for those which are mirror-image representations of the target figure. The outcome measure was the total number of correctly identified responses minus the number of incorrectly identified responses across both trials with a maximum possible score of 160.

*Letter Fluency (Benton, 1968):* This is a test of verbal fluency. Participants were given one minute to generate as many words as possible which begin with a particular letter (i.e., P, W [baseline] C, L [3-month]). Participants were instructed to avoid saying proper nouns or to use the same word with multiple endings (e.g., dance, danced, and dancing). The outcome measure was the total number of words produced across two 60-second trials.

*Semantic Fluency (Kertesz, 1982; Mattis, 1988):* This is a test of categorical fluency. Participants were given one minute to generate as many words as possible that belong to a category (i.e., animals, things at a supermarket). The outcome measure was the total number of words produced across two 60-second trials.

*Digit Span Forward and Backward (Wechsler, 1981):* This is a test of both attention and working memory. During the Digit Span Forward test, the examiner read a series of number strings to the participant, who was instructed to repeat the series back to the examiner. In Digit Span Backwards, the participant was read a string of numbers, and was asked to repeat the series in reverse order. The outcome measures were the number of trials correctly completed for the forward and backward trials, respectively.

*Brief Test of Attention (Schretlen et al., 1996):* This is a test of auditory attention. The examiner read aloud a series of letters and numbers (e.g., 5-H-T). For one block of 10 trials, participants were told to track and report the number of letters presented, and in the other block of trials they were told to track and report the number of numbers presented. Difficulty increased as the series of numbers and letters increased from 4 to 18 items across the 10 trials. The outcome measure was the total number of correct responses.

*Finding A's (Ekstrom et al., 1976):* This is a test of visuoperceptual speed and attention. Participants were shown five columns of words on a sheet of paper. Participants were instructed to cross out the five words in each column that contain the letter 'A' as quickly

and accurately as possible within two minutes. The outcome measure was the total number of correct responses.

Data were scored and entered independently by two trained staff members into the database. Staff members were blinded to treatment assignment. Discrepancies were resolved by the two independent coders reviewing the raw data and reaching an agreement.

**3. Questionnaires**

Since mood (depression and anxiety) are common side effects of premature menopause and have been shown to be significant predictors of cognition, these questionnaires were included to control for mood in our statistical model.

*The Center for Epidemiological Studies - Depression Scale (CES-D) (Radloff, 1977):* The CES-D is a self-administered 20-item questionnaire measuring depressive symptoms over the past week. A score of ≥ 16 is considered probable depression. The questionnaire was administered on a Likert-like scale with participants endorsing each symptom occurring “never or rarely” (score of 0) to “most or all of the time” (score of 3).

*Depression Anxiety and Stress Scale (DASS) (Lovibond & Lovibond, 1995):* The DASS is a 42-item questionnaire including three self-report scales measuring negative emotional states of depression, anxiety, and stress. Participants were asked to use a 4-point Likert scale ranging from 0 to 3 to indicate the extent to which they have experienced each state over the past week.

### 4. Vasomotor Symptom Monitoring

The primary outcomes were the frequency of total VMS reported by daily diaries and button presses (subjective) and the frequency of VMS measured by ambulatory skin conductance monitors (physiologic). Following baseline cognitive testing, participants were fitted with an ambulatory sternal skin conductance monitor (Biolog Model 3991 x/2-HFI; Biolog Model 3991 x/2-SCL) which they were instructed to wear for 24 hours. Two skin conductance electrodes were applied to the participant's sternum by adhesive electrode pads (UFI, 1081-HFD) using 0.05 M potassium chloride Unibase/glycol paste. The monitor was placed in a small pouch that participants could wear on a belt or over their shoulder. A minimum of 18 hours of recorded VMS data was required for the session to be considered valid.

Participants were also asked to maintain a diary reporting time of VMS, magnitude of severity and bother, and whether the VMS occurred during sleep or waking hours. Participants were instructed to record the time, severity, and bother ratings of each hot flash or night sweat using the following definitions: “severity” refers to the intensity of the hot flash, “bother” refers to the discomfort of distress caused by the hot flash. Both severity and bother were rated on a scale from 0-10 where “0” indicated very mild and “10” indicated very severe.

Physiologic (i.e., > 2.0 μmho increase in 20 seconds) and subjective (button press) VMS were recorded according to standard procedures (Freedman, 1989). Participants were instructed to press a button, an event marker, on the Biolog monitor whenever they felt that they were experiencing a VMS. These events were time stamped on the Biolog output data to record the time of the subjective VMS (see Figure

1).

The monitor sampled 12-bit skin conductance data at 1 Hz (once per second) from electrodes connected to the monitor by a 0.5 constant voltage circuit. Raw VMS data was stored in internal memory and when recording was complete, the Biolog interface Box connected the 3991x Biolog to a serial port on the PC. Downloading and Plotting Software (DPS) was used to download recorded data on a PC host computer. Time series of skin conductance data in μmho units was shown in a time-based graphical display showing both subjective VMS (event markers) and physiologic VMS using specialized software (DPS V.1.5, UFI; FlashTrax V2.1, UFI) (see Figure 1). Raw VMS data was analyzed by two trained data coders and automated computer software. According to standard procedures, once a physiologic VMS was coded, no other VMS was coded for the next 15 minutes (Carpenter et al., 1999). Data was scored and entered independently into the database. Coders were blinded to randomization group assignment. Coder discrepancies were resolved prior to analysis.

Frequency of physiologic and subjective VMS during both sleep and wake hours were scored based on reports in the diary logs of the time participants went to bed and woke up. Primary outcome measures were total physiologic and subjective VMS in a 24-hour period, during waking hours, and during sleeping hours. The following types of VMS were coded for the present study: true positive, false negative, and false positive. A true positive was defined as a VMS that was both reported by the participant and recorded on the monitor within a five-minute timespan. True positives could be subjectively confirmed by the participant either through diary reporting or event markers. False negatives were defined as a physiologic VMS event that was not subjectively

reported within five minutes of the physiological event. False positive were defined as a subjective VMS that was not recorded on the monitor within five minutes of the subjective VMS. Primary outcomes were total number of physiologic VMS (i.e., true positives and false negatives) recoded while awake, asleep, and the total number (awake + asleep).

**a. Vasomotor Sensitivity**

Sensitivity was calculated for VMS data by dividing the total number of true-positive VMS (i.e., physiologically determined VMS that were subjectively reported) by the sum of the total number of physiologic VMS (i.e., true positives and false negatives).

**5. Sleep Monitoring**

Sleep disturbances commonly co-occur with night sweats and are a significant predictor of cognition. We included both subjectively measured sleep and objectively measured sleep monitoring as outcome variables to control for sleep in our statistical model.

*Modified Pittsburgh Sleep Quality Index (PSQI) (Buysse et al.,1989):* This is a self-report questionnaire that measures sleep quality, including the latency to fall asleep, sleep duration, and sleep disturbances. Items were combined to form seven "component" scores, each with a range of 0-3. In all cases, a score of "0" indicated no difficulty, while a score of "3" indicated severe difficulty. A global sleep score was calculated by summing all the component scores (range 0-21), with higher scores indicating greater sleep disturbance (Buysse et al., 1989).

*Objective Sleep Quality:* Objective sleep quality was measured by wrist actigraphy. The Spectrum Plus Actiwatch and Actiwatch Score (Minimitter, Philips Respironics) are small, lightweight, waterproof accelerometers, worn like a wrist watch with a piezoelectric beam to detect all three axes of movement. The acceleration/deceleration signal was digitized by an analog to digital converter and numerically integrated over a pre-programmed epoch interval. The monitors were programmed for start time and data collection interval. Data were retrieved for analysis via a PC interface and scoring software provided with the accelerometer. This allowed for scoring: 1) total sleep time (the hours/night spent sleeping while in bed); 2) frequency and duration of awakenings after sleep onset (sleep onset is determined by the Actiware scoring algorithm which compares activity counts for each epoch and those surrounding it to a threshold value); and 3) sleep efficiency (percent of time in bed spent sleeping). The recording also allowed quantification of sleep latency (number of minutes to fall asleep) and daytime inactivity/napping. Scoring of actigraph data with standardized computer algorithms is reliable and valid relative to polysomnography (Philips Actiware 6.0.9) (Cole et al., 1992; Sadeh et al., 1994). The actigraph watch was worn on the non-dominant wrist during the same hours as the VMS monitor for a period of 24 hours. Sleep variables were calculated for the night.

## D. Randomization

A computer-generated 1:1 block randomization scheme was used to determine whether participants received either a sham injection with saline or SGB injection with bupivacaine. Prior to the injection procedure, the injectionist revealed the participant

number and injection assignment which was sealed in an opaque envelope. Randomization assignment was kept under lock and key. Participants and all other study personnel, including those who performed follow-up evaluations, were blinded to group assignment. The injectionist did not have access to VMS, cognitive, or questionnaire data until the conclusion of the study.

## E. Stellate Ganglion Blockade Intervention

Prior to injection, participants were interviewed to assess health status and a brief physical exam was performed. Participants were then randomized into one of two groups. One group received the active study intervention (stellate ganglion blockade injection with local anesthetic or numbing medication) and the other received a sham-control intervention involving a saline injection in the superficial tissues of the right side of the neck in the region just below the skin layer.

Before the procedure, a 20-g angiocatheter was placed in the left hand/arm for peripheral intravenous access as a safety precaution. An oxygen monitor, temperature monitor, and blood pressure cuff was placed on the right hand. Participants were positioned supine in cervical extension**.** The anterior neck was swabbed with chlorhexidine to clean the skin, and sterile equipment and technique was used for the entire of the procedure.

For active SGB, a right-sided SGB was performed. Using a low dose x-ray machine (fluoroscopy machine) to help guide the injection, the C6 vertebra was identified and the skin overlying the tubercle will be anesthetized using 2mL of 1% lidocaine. A 22 gauge 1.5-inch needle was placed to contact the anterolateral portion of

the C6 vertebra and then retracted 1-2mm and secured. Contrast material (iopamidol 1-2 mL) was injected to confirm contrast dye spread in the prevertebral fascial plane and to rule out intravascular or intrathecal dye spread. 0.5% bupivacaine (5 mL) was injected and the needle was removed. For sham injections, an identical technique was used with the same auditory, tactile, and visual cues, except the needle was placed in the superficial tissues of the anterior neck. Preservative-free saline (5 mL) was injected and the needle was then removed. Participants were monitored in a reclining position for at least 30 minutes following the injection procedure to assess potential adverse effects. Vital signs were measured every five minutes during the recovery phase. Presence of a Horner's sign such as miosis, ptosis, and anhidrosis will be recorded to validate successful SGB. These procedures are consistent with previous studies of SGB intervention performed by our group (Walega et al., 2014).

# IV. STATISTICAL ANALYSIS

## A. Vasomotor Symptoms and Verbal Memory Performance

### 1. Aim I

Descriptive statistics for each cognitive outcome were examined to ensure completeness of the data, check normality of the distribution, identify any outliers (i.e., values > 3 SD above or below the mean). Statistical outliers that were not deemed to be valid measures of performance were removed from analysis (Tabachnick & Fidell, 2001). Missing cognitive and questionnaire data was handled by mean substitution for each individuals' score on the specific subscale. Missing VMS data were handled as follows. If an individual had less than 24 hours of recorded VMS data (but greater than 18 hours), the missing data was estimated separately for daytime and nighttime VMS because the average number of hourly VMS is generally higher during daytime than night time hours (Maki et al., 2008). The total number of day time HFs was estimated by calculating the average number of HF per hour and then multiplying that average by total number of awake hours. The same calculation was used for night sweats using total sleep hours. Definitions of effect sizes for correlational analyses were based on Cohen, 1988, using *r* values of 0.1, 0.3, and 0.5 (small, medium, and large respectively).

Correlations were used to evaluate Aim 1, the association between VMS (physiologic [true positives and false negatives] and subjective) and verbal memory performance. Pearson's correlations were conducted to examine the unadjusted relationship between total physiologic and subjective VMS (waking and sleeping hours)

and verbal memory performance (immediate and delayed total LM score, total learning, short-delay recall, and long-delay recall on the CVLT). Significance was set at $p < 0.05$. If significant correlations were found, Pearson's correlations were then conducted to evaluated the specific breakdown by time of day (i.e., VMS during waking hours and while asleep). Significance was set at $p < 0.05$.

A series of stepwise regression analyses were then conducted to examine the extent to which VMS accounted for verbal memory performance when other significant predictors of cognition such as age, mood (CES-D and DASS), and sleep quality (global PSQI and actiwatch sleep data) were included in the model. Follow-up regression analyses were conducted using any variable that also correlated with that verbal memory outcome to determine whether any significant correlation between VMS and verbal memory remained significant. All statistical analyses were conducted using SPSS statistical software (version 22.0 for Windows, SPSS, Chicago, IL). Significance was set at $p < 0.05$.

**2. <u>Aim II</u>**

Baseline differences between treatment conditions were analyzed using chi-square tests for categorical variables and t-tests for continuous variables. Pearson correlations were conducted to assess the association between changes in VMS (physiologic [true positives and false negatives] and subjective) and changes in cognitive performance. Partial correlations were used to examine if any significant associations remained significant after controlling for covariates (i.e. mood and sleep) that correlate with the primary dependent measures. A series of random intercept, mixed-effects regressions were used to assess changes in cognitive performance over

time as a function of treatment condition. Independent predictors included Treatment Condition (sham-control vs. active SGB), a 3-month dummy variable (vs. baseline), and their interaction. These analyses were consistent with previous methods used in RCTs of SGB for the treatment of VMS (Walega et al., 2014). Significance was set at $p < 0.05$ for VMS and primary verbal memory outcome measures. Significance was set at $p < 0.01$ for secondary memory outcome measures.

### 3. Power Analysis

Power for analyzing the primary outcome of physiologic VMS was calculated based on the prior SGB pilot study (Walega et al., 2014) using PASS (Power Analysis and Sample Size) software and is based on a mixed design with one between-subjects factor (Treatment: placebo, active treatment) and one within subjects factor (Time: baseline, post-treatment) and a Geisser-Greenhouse Corrected F-Test with 5% significance level. For the power calculations, we assumed mean differences for the sham-control group (M = 19.18 at baseline, M = 20.35 post-treatment), standard deviations (SD = 9.51 at baseline, SD = 9.89 post-treatment), and test-retest reliability (0.90) based on unpublished data from a recently completed clinical trial in women with moderate-to-severe VMS. We anticipated that the active treatment should confer a minimum “clinically significant” benefit of 25%, that is, that active treatments will attenuate the number of physiologic VMS by 25%. For example, if we are underestimating the difference in group means by 50% and the true difference is 50% greater than observed by our pilot data (i.e., k = 1.50 rather than k = 1.00), we could achieve power of 80% to test the two-way interaction between Treatment and Time with

a sample size of 10 per group. Specifically, based on our pilot data we could achieve 80% power to test the Treatment x Time interaction with a sample of 20 per group.

# V. RESULTS

## A. Characteristics of the Participants

A total of 45 participants were recruited for the present study. Three of the 45 recruited participants did not have valid physiologic VMS data (i.e., two due to the use of expired gel, one due to loose electrodes), three did not have valid cognitive data (i.e., one had prior knowledge of the cognitive tests, one opted out of cognition testing, and one was English as a second language), four did not qualify based on inclusion criteria, and one refused to participate. Therefore, 11 women were excluded from the present analysis (see Figure 3). Participants ranged in age from 35 to 73 years (mean = 52.56). 61.8% had a college degree or better. 73.5% of the participants were White; 23.5% of the participants were Black. Table I shows demographic data, MMSE scores, mood scales, sleep quality, and physiologic and subjective VMS (total, awake, sleep) for the 34 participants included in the present study. Table II shows primary cognitive outcomes (CVLT, LM test) and secondary cognitive outcomes (CRT, Verbal Fluency, Finding A's, DS, BTA). There were no statistical outliers on any cognitive or VMS outcome variable (i.e., none ± 3 SD from the mean).

Figure 3. Consort Diagram

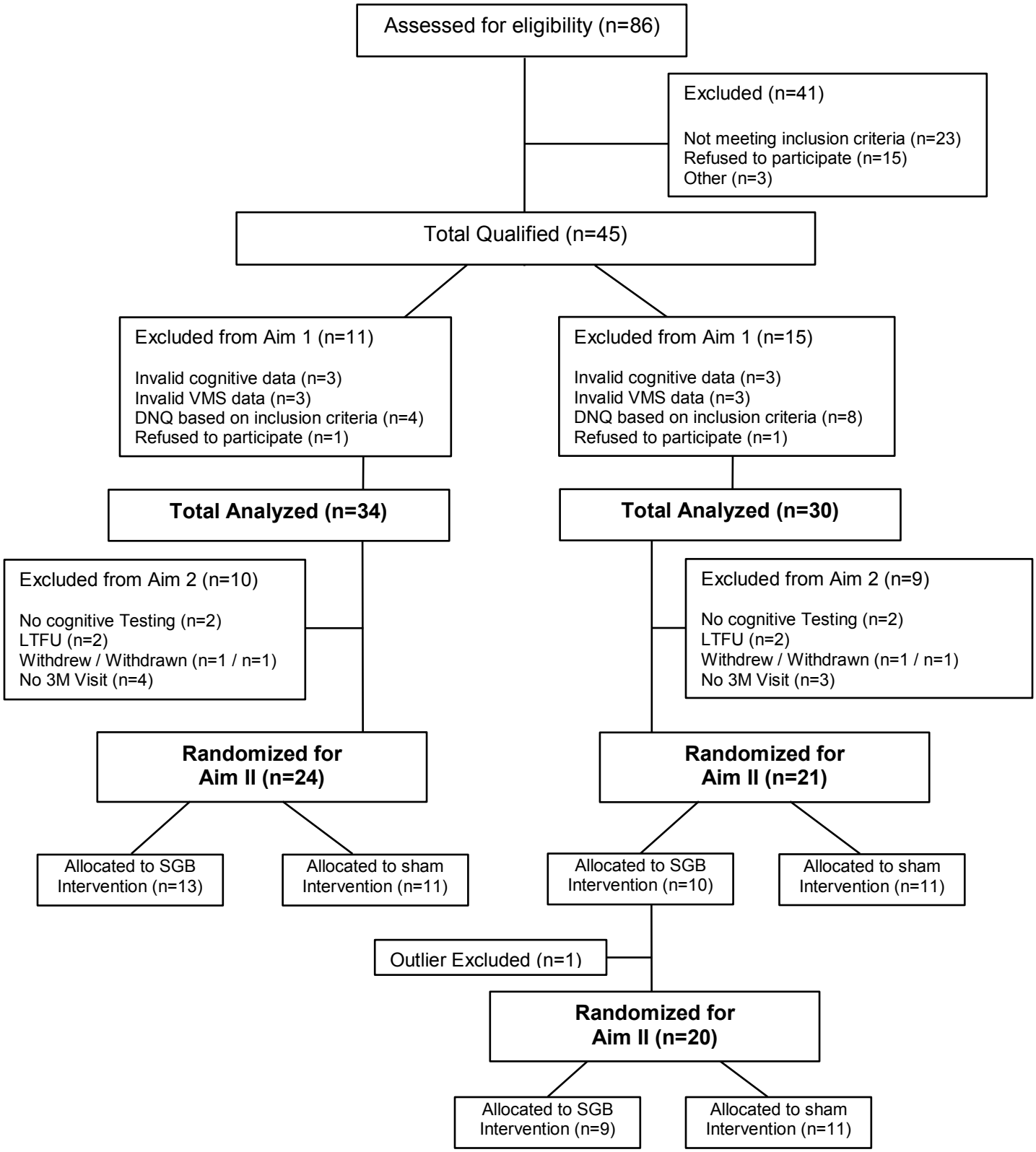


TABLE I. Demographic and clinical characteristics at baseline of the complete sample (N=34) of women who met eligibility criteria for VMS based on subjective reporting as well on a of the subsample (n=30) of women who met eligibility criteria based on physiologic monitoring.

| ***Met eligibility criteria for VMS based on:*** | **Subjective Reporting (N = 34)** | **Physiologic Reporting (n = 30)** |
|---|---|---|
| Age, M (SD) | 52.56 (8.98) | 52.67 (8.92) |
| Education, n (%) | | |
| HS degree | 3 (8.80) | 2 (6.70) |
| Some college | 10 (29.40) | 10 (33.30) |
| College degree | 14 (41.20) | 12 (40.00) |
| Post-graduate degree | 7 (20.60) | 6 (20.00) |
| Race, n (%) | | |
| Black | 8 (23.50) | 8 (26.70) |
| White | 25 (73.50) | 21 (70.00) |
| Asian | 1 (2.90) | 1 (3.30) |
| MMSE, M (SD) | 29.06 (1.56) | 28.93 (1.64) |
| **Mood Scales, M (SD)** | | |
| CES-D$^{\alpha}$ | 12.88 (10.72) | 12.97 (10.80) |
| *DASS* | | |
| Anxiety | 8.29 (6.76) | 8.17 (6.69) |
| Depression | 5.24 (5.61) | 5.17 (5.32) |
| Stress | 10.94 (10.30) | 10.27 (9.60) |
| **Sleep, M (SD)** | | |
| Global PSQI Score$^{\beta}$ | 10.64 (3.45) | 10.57 (3.58) |
| *Actigraphy* | | |
| Total Sleep Time (min.) | 379.54 (102.53) | 379.38 (105.53) |
| Sleep Efficiency (%) | 80.76 (11.71) | 80.23 (11.95) |
| **Vasomotor Symptoms (Daily Count), M (SD)** | | |
| Total Physiologic | 18.09 (11.56) | 20.30 (10.44) |
| Total Subjective | 7.35 (5.80) | 6.47 (5.40) |

**Note.** Groups were comparable on all measures.
MMSE = Mini-Mental State Exam; CES-D = Center for Epidemiologic Studies Depression Scale; DASS = Depression Anxiety Stress Scales; PSQI = Pittsburgh Sleep Quality Index.
$^{\alpha}$ Scores ≥ 16 points is considered depressed.
$^{\beta}$ Scores range from 0-21 with 21 indicating worse sleep.

TABLE II. Primary and secondary cognitive outcomes at baseline in the complete sample (N=34) of women who met eligibility criteria for VMS based on subjective reporting as well on a of the subsample (n=30) of women who met eligibility criteria based on physiologic monitoring.

| ***Met eligibility criteria for VMS based on:*** | **Subjective Reporting (N = 34)** | **Physiologic Reporting (n = 30)** |
|---|---|---|
| **Primary Cognitive Outcomes, M (SD)** | | |
| *CVLT* | | |
| Total (across 5 trials) | 52.00 (12.32) | 53.07 (12.09) |
| Short-delay free recall | 11.26 (3.60) | 11.37 (3.53) |
| Long-delay free recall | 11.97 (3.33) | 12.17 (3.29) |
| Total Clustering | 11.91 (5.10) | 12.20 (4.99) |
| *Logical Memory Test* | | |
| Immediate total score | 14.82 (4.20) | 14.57 (4.16) |
| Delayed total score | 13.88 (4.41) | 13.67 (4.41) |
| **Secondary Cognitive Outcomes, M (SD)** | | |
| Card Rotations Test (N = 33 / 29) | 73.03 (33.72) | 71.93 (33.58) |
| *Verbal Fluency* | | |
| Letter Fluency | 27.00 (8.23) | 27.80 (7.89) |
| Semantic Fluency | 49.24 (11.77) | 49.33 (11.65) |
| Finding A's | 27.97 (8.43) | 27.63 (8.47) |
| *Digit Span Test* | | |
| Forward | 9.00 (2.95) | 9.13 (3.00) |
| Backward | 7.26 (2.41) | 7.27 (2.43) |
| Brief Test of Attention | 16.71 (3.01) | 16.73 (3.14) |

**Note.** Groups were comparable on all outcomes.

CVLT = California Verbal Learning Test.

## 1. Vasomotor Symptoms (N=34)

Two of the 24 women had less than 24 hours of recorded VMS data (22 and 20.5 hours). Missing VMS data was estimated and prorated used the procedures outlined above. A total of 250 subjective VMS were reported and 615.05 physiologic VMS were recorded for the 34 participants. The mean number of subjective and physiologic VMS per day were 7.35 (SD = 5.80; range 0-23) and 18.09 (SD = 11.56; range 0-46), respectively. The mean number of subjective VMS during waking hours was 5.79 (SD = 4.60; range 0-17); mean number of subjective VMS during sleeping hours was 1.56 (SD = 2.27; range 0-10). Mean number of physiologic VMS during waking hours was 13.52 (SD = 8.86; range 0-41); mean number of physiologic VMS during sleeping hours was 4.57 (SD = 4.56; range 0-17) (see Table I).

Women typically under-report the number of VMS they experience (Carpenter et al., 2004b; Maki et al., 2008). To examine this phenomenon, mean sensitivity – defined as the number of physiologic VMS subjectively detected – was calculated. The mean sensitivity during a 24-hour monitoring period was 44.81%, indicating that physiologic VMS was under-reported by 55.19%. The mean sensitivity during waking hours was 54.03%, indicating that physiologic daytime VMS was under-reported by 45.07%. The mean sensitivity during sleeping hours was 23.08%, indicating that physiologic nighttime VMS was under-reported by 76.92%. Mean sensitivity data are presented in Figure 4 and Figure 5.

Figure 4. Mean sensitivity (percentage of VMS correctly reported) during waking hours, sleeping hours, and overall.

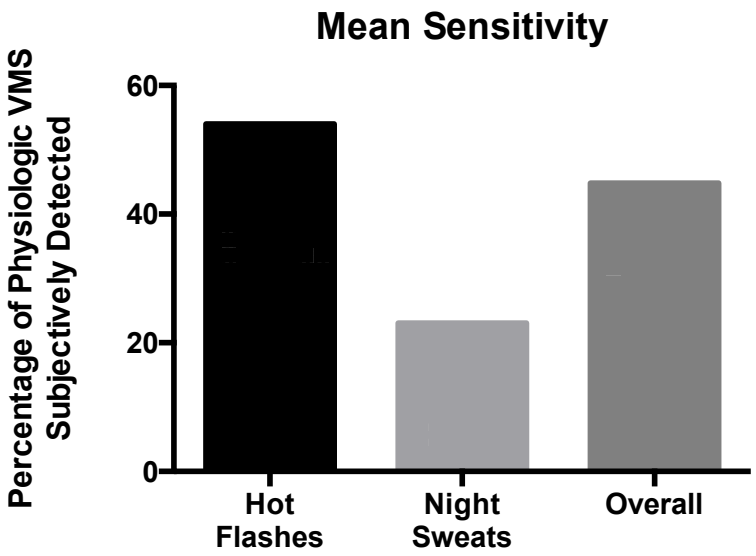
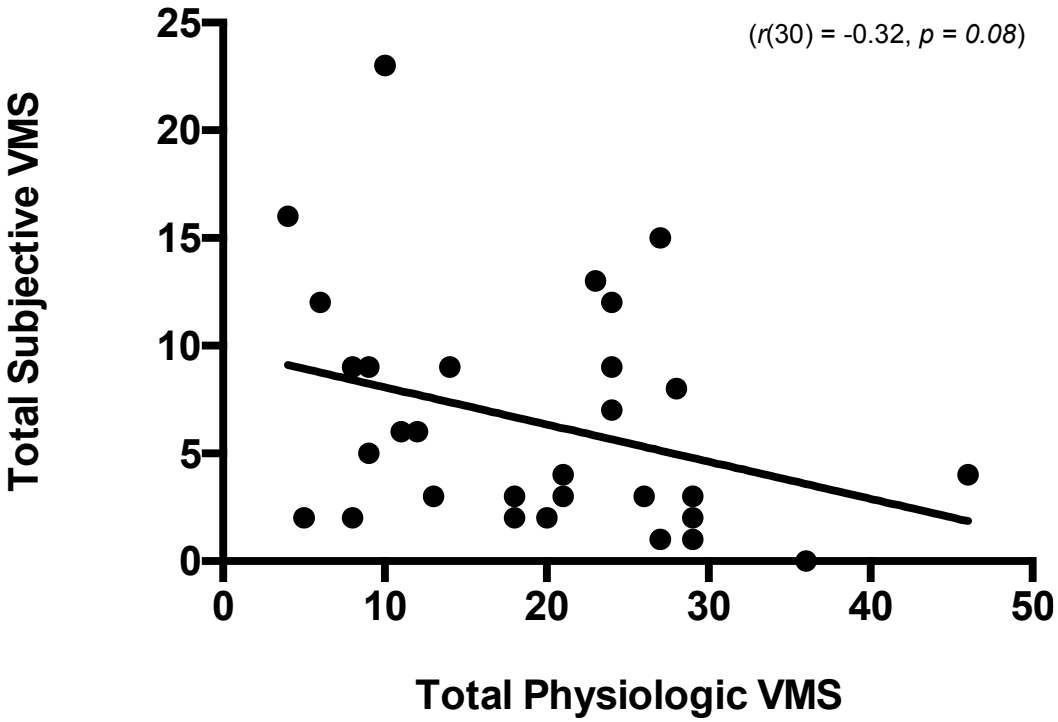


Figure 5. Relationship between total physiologic VMS and total subjective VMS at baseline.



## B. Aim I

Aim I was to examine the association between VMS (physiologic and subjective) and verbal memory performance in breast cancer survivors with moderate-to-severe VMS. Correlations were examined both on the complete sample (N=34) of women who met eligibility criteria for VMS based on subjective reporting (i.e. $\geq$ 4 VMS per day [ $\geq$ 28 per week] based on diary/event monitoring) as well on a subsample of 30 women who met eligibility criteria (i.e. $\geq$ 4 VMS per day [ $\geq$ 28 per week]) based on physiologic monitoring (see Figure 3). The subsample of 30 women were comparable to the 34 women who met eligibility based on subjective reporting on all demographic measures and clinical characteristics (see Table I and II). Data for each group will be presented in turn.

### 1. Sample Meeting Subjective Vasomotor Symptoms Eligibility Criteria (N=34)

Total Physiologic VMS did not correlate with any outcomes on the California Verbal Learning Test (CVLT) or the Logical Memory Test (immediate, delayed). Similarly, total subjective VMS did not correlate with any of the verbal memory outcomes (see Table III).

TABLE III. Correlation coefficients for total physiologic and total subjective VMS data across verbal memory outcomes at baseline.

| **Met eligibility criteria for VMS based on:** | **Subjective Reporting N = 34** | | **Physiologic Reporting n = 30** | |
|---|---|---|---|---|
| | **Physiologic Total VMS** | **Subjective Total VMS** | **Physiologic Total VMS** | **Subjective Total VMS** |
| **Primary Cognitive Outcomes, *r* (*p*)** | | | | |
| ***CVLT*** | | | | |
| Total (across 5 trials) | -0.14 (0.42) | 0.13 (0.47) | -0.35 (0.06) | 0.26 (0.17) |
| Short-delay free recall | -0.28 (0.12) | 0.17 (0.34) | -0.41 (0.03)* | 0.19 (0.33) |
| Long-delay free recall | -0.23 (0.20) | 0.14 (0.44) | -0.39 (0.03)* | 0.20 (0.28) |
| Total Clustering | -0.21 (0.24) | 0.21 (0.24) | -0.37 (0.04)* | 0.27 (0.15) |
| ***Logical Memory Test*** | | | | |
| Immediate total score | -0.20 (0.27) | 0.06 (0.76) | -0.15 (0.43) | -0.01 (0.98) |
| Delayed total score | -0.23 (0.19) | -0.04 (0.84) | -0.21 (0.27) | -0.10 (0.60) |

**Note:** * $p < 0.05$.

A series of stepwise regression analyses were conducted to assess the extent to which VMS accounted for memory performance when other variables that are typically significant predictors of cognition in the literature, such as sociodemographic characteristics (age), mood (CES-D and DASS), and sleep quality (global PSQI and actiwatch sleep data) were included in the model. For CVLT (total learning, short-delay free recall, long-delay free recall) and LM outcome measures (immediate and delayed recall), no variable entered the model and neither total physiologic or subjective VMS were significant predictors of verbal memory performance.

### 2. Subsample Meeting Physiologic Vasomotor Symptom Eligibility Criteria (n=30)

Total number of physiologic VMS significantly correlated with CVLT short-delay free recall, ($r(30) = -0.41$, $p < 0.05$), CVLT long-delay free recall, ($r(30) = -0.42$, $p < 0.05$), and CVLT total clustering ($r(30) = -0.39$, $p < 0.05$) (see Figures 6, 7, and 8 respectively), and showed a trend for CVLT total learning, ($r(30) = -0.35$, $p = 0.06$). These results show that increased physiological VMS were associated with worse performance on CVLT outcome measures. When analyzed by breakdown of time of day, neither physiologic daytime VMS or physiologic nighttime VMS correlated with any outcome measures on the CVLT. Total physiologic VMS did not significantly correlate with either outcome measure on the Logical Memory Test (immediate or delayed). Total subjective VMS did not significantly correlate with any of the verbal memory outcome measures (see Table III).

Figure 6. Relationship between CVLT short-delay free recall and total physiologic VMS at baseline.

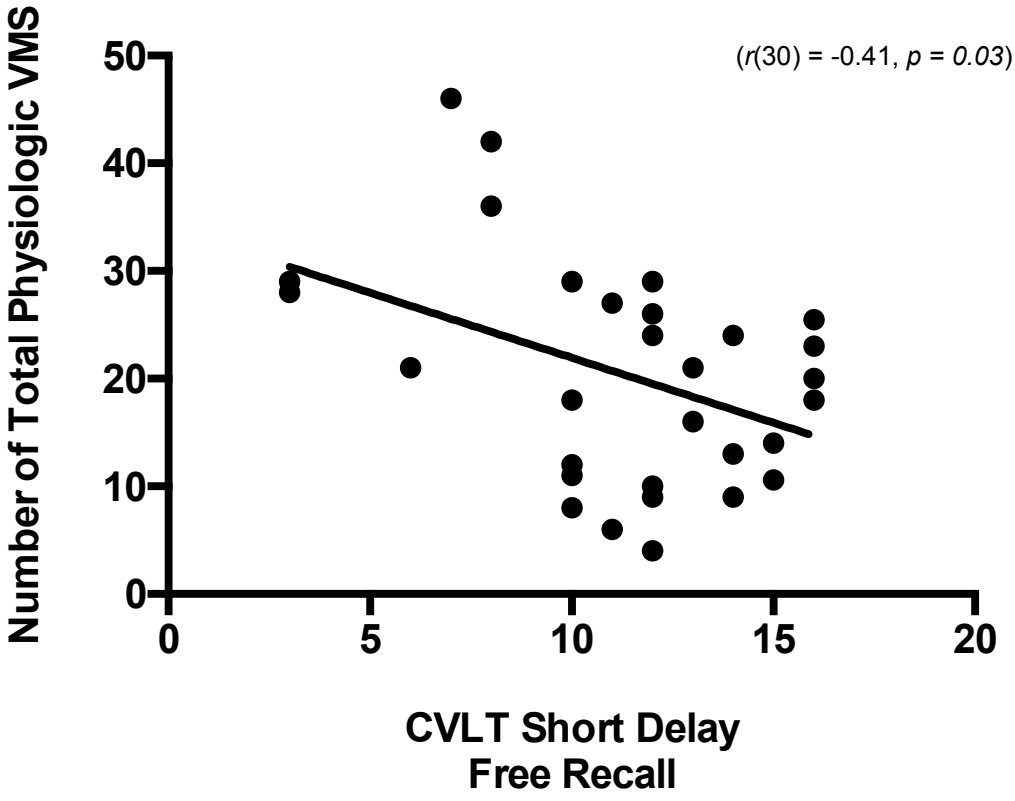


Figure 7. Relationship between CVLT long-delay free recall and total physiologic VMS at baseline.

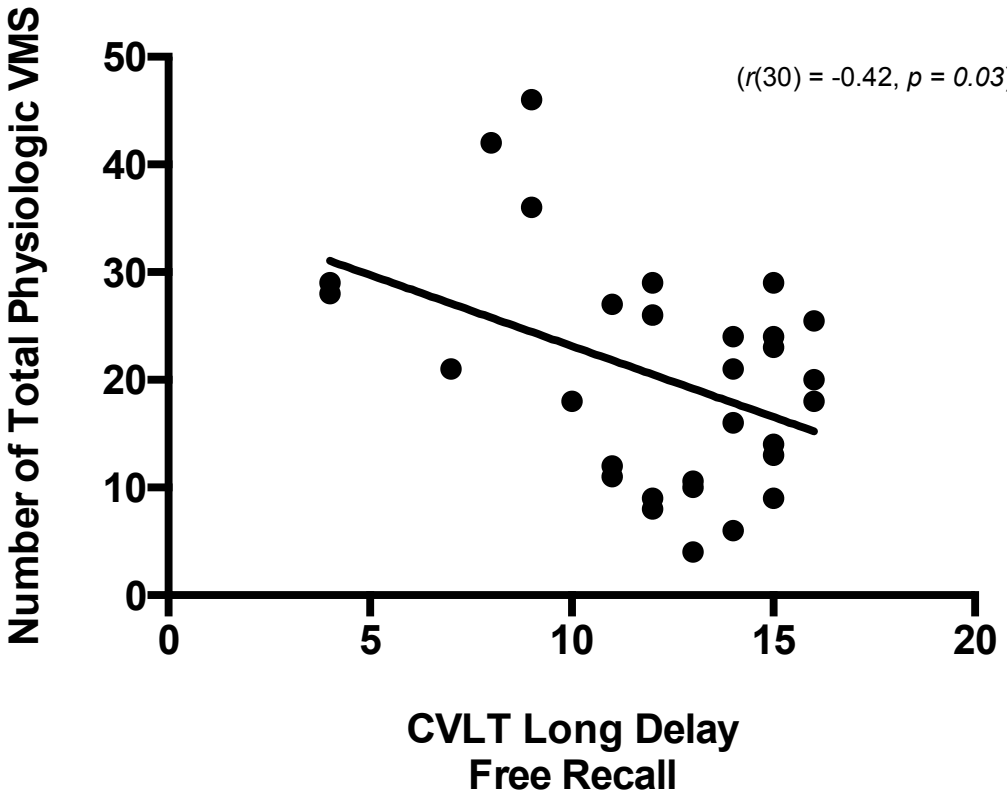
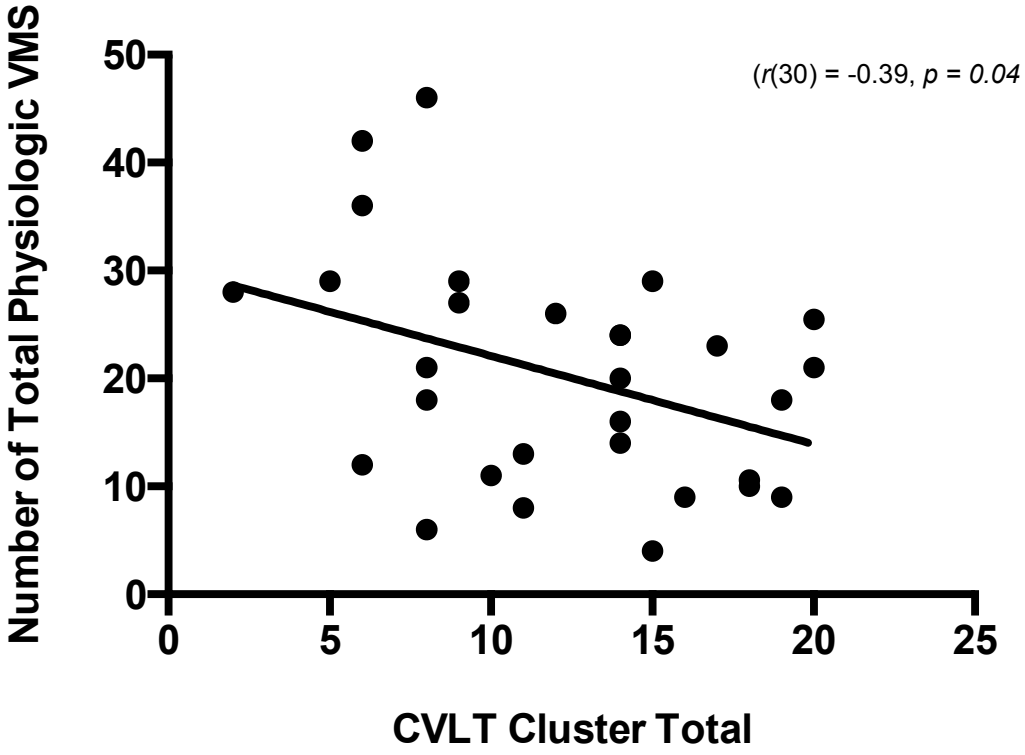


Figure 8. Relationship between CVLT total clustering and total physiologic VMS at baseline.



A series of stepwise regression analyses were conducted to assess the extent to which total physiologic VMS accounted for memory performance when other variables that are typically significant predictors of cognition in the literature, such as demographic information (age), mood (CES-D and DASS), and sleep quality (global PSQI and actiwatch sleep data) were included in the model. No other variable entered the model, and total physiologic VMS remained a significant predictor of performance on all three CVLT outcomes (short-delay free recall [B = -0.14, β = -0.41, SE = 3.28, $p < 0.05$]), (long-delay free recall [B = -0.13, β = -0.39, SE = 3.08, $p < 0.05$]), and (total clustering [B = -0.18, β = -0.37, SE = 4.71, $p < 0.05$]).

**3. Secondary Cognitive Outcomes**

Neither total physiologic VMS nor total subjective VMS correlated significantly with any of secondary cognitive outcomes (*ps* > 0.01).

## C. Aim II

Aim II examined the effect of SGB intervention for VMS on verbal memory performance in breast cancer survivors with moderate-to-severe VMS. Of the 34 participants with valid baseline data, 24 received either SGB or sham injection and had valid 3-month post-injection data. Of the 10 women who did not receive an injection or have valid 3-month post injection data, 4 had not yet been scheduled for their 3-month visit, 1 withdrew from the study, 2 did not complete cognitive testing procedures (1 due to medication change, 1 due to sedation from the injection procedure), 1 was discontinued due to non-compliance with diary-reporting, and 2 were lost to follow up.

There was one statistical outlier (i.e., < 3 SD from the mean) on the difference score (i.e., change from baseline to 3-months) on CVLT long-delay free recall. Correlations were examined on the complete sample of women who met eligibility criteria for VMS based on subjective reporting (Group 1) (n=24), on a subsample of women who met eligibility criteria based on physiologic monitoring (Group 2) (n=21), and on a subsample with the outlier removed (Group 3) (n=20) (see Figure 3). Table IV shows demographic and clinical characteristics (MMSE scores, mood scales, sleep quality, and physiologic and subjective VMS) at baseline for the three groups. All three subsamples of women were comparable on demographic and clinical measures (see Table IV). Data for each group will be presented in turn.

TABLE IV. Demographic and clinical characteristics at baseline of women with valid 3-month data. Table includes Group 1 (n=24), Group 2 (n=21), and Group 3 (n=20).

| | **Group 1 n = 24** | **Group 2 n = 21** | **Group 3 n = 20** |
|---|---|---|---|
| Age, M (SD) | 51.79 (8.91) | 52.48 (9.130 | 52.30 (9.33) |
| Education, n (%) | | | |
| HS degree | 2 (8.30) | 1 (4.80) | 1 (5.00) |
| Some college | 8 (33.30) | 8 (38.10) | 8 (40.00) |
| College degree | 11 (45.80) | 9 (42.90) | 8 (40.00) |
| Post-graduate degree | 3 (12.50) | 3 (14.30) | 3 (15.00) |
| Race, n (%) | | | |
| Black | 5 (20.80) | 5 (23.80) | 4 (20.00) |
| White | 18 (75.00) | 15 (71.40) | 15 (75.00) |
| Asian | 1 (4.20) | 1 (4.80) | 1 (5.00) |
| MMSE, M (SD) | 29.29 (1.49) | 29.19 (1.57) | 29.15 (1.60) |
| **Mood Scales, M (SD)** | | | |
| CES-D | 13.38 (11.99) | 13.24 (12.14) | 11.65 (9.97) |
| *DASS* | | | |
| Anxiety | 8.67 (7.20) | 8.33 (7.09) | 7.75 (6.74) |
| Depression | 4.96 (5.71) | 4.81 (5.15) | 4.25 (4.59) |
| Stress | 11.25 (10.81) | 10.19 (9.68) | 9.35 (9.12) |
| **Sleep, M (SD)** | | | |
| Global PSQI Score | 11.00 (3.36) | 11.05 (3.49) | 10.95 (3.55) |
| *Actigraphy* | | | |
| Total Sleep Time (min.) | 381.52 (82.50) | 387.60 (84.99) | 384.23 (85.75) |
| Sleep Efficiency (%) | 81.07 (9.40) | 80.45 (9.10) | 80.02 (9.12) |
| **Vasomotor Symptoms (Daily Count), M (SD)** | | | |
| Total Physiologic | 17.79 (10.43) | 20.10 (8.96) | 19.90 (9.14) |
| Total Subjective | 7.04 (6.30) | 5.95 (5.71) | 5.90 (5.86) |

**Note.** Groups were comparable on all measures.

### 1. Complete Sample Based on Subjective Vasomotor Symptom Eligibility (n=24) Group 1

#### a. Differences by Treatment Group

There were no treatment group differences on sociodemographic variables, sleep quality variables, mood scales, cognitive outcomes, or VMS outcomes (see Table V). Pair-sample t-tests were conducted to examine the difference between VMS from baseline to 3-months post-injection. There were no significant differences in either total physiologic or total subjective VMS from baseline to 3-month post-injection ($p = 0.77$ and $p = 0.10$ respectively).

TABLE V. Demographic and clinical characteristics by treatment group at baseline for group 1 with valid 3-month data.

| | Treatment Group 1 (n=24) | | |
|---|---|---|---|
| | **SGB (n=13)** | **Sham-control (n=11)** | **p-value** |
| Age, M (SD) | 49.92 (6.13) | 54.00 (11.29) | 0.27 |
| Education, n (%) | | | 0.24 |
| HS degree | 1 (7.70) | 1 (9.10) | |
| Some college | 5 (38.50) | 3 (27.30) | |
| College degree | 7 (53.80) | 4 (36.40) | |
| Post-graduate degree | 0 (0.00) | 3 (27.30) | |
| Race, n (%) | | | 0.53 |
| Black | 2 (15.40) | 3 (27.30) | |
| White | 10 (76.90) | 8 (72.70) | |
| Asian | 1 (7.70) | 0 (0.00) | |
| MMSE, M (SD) | 29.23 (1.92) | 29.36 (0.81) | 0.83 |
| **Mood Scales, M (SD)** | | | |
| CES-D | 13.85 (12.71) | 12.82 (11.65) | 0.84 |
| *DASS* | | | |
| Anxiety | 8.69 (7.35) | 8.64 (7.37) | 0.99 |
| Depression | 5.08 (6.21) | 4.82 (5.36) | 0.92 |
| Stress | 11.38 (11.74) | 11.09 (10.16) | 0.95 |
| **Sleep, M (SD)** | | | |
| Global PSQI | 10.67 (3.94) | 11.36 (2.73) | 0.63 |
| *Actigraphy* | | | |
| Total Sleep Time (min.) | 399.62 (60.77) | 360.14 (101.47) | 0.25 |
| Sleep Efficiency (%) | 84.42 (8.22) | 77.11 (9.50) | 0.06* |
| **Vasomotor Symptoms (Daily Count), M (SD)** | | | |
| Total Physiologic | 18.31 (13.69) | 19.55 (7.45) | 0.78 |
| Total Subjective | 8.54 (5.57) | 5.27 (5.57) | 0.17 |

**Note.** Groups were comparable on all outcomes.

* *p < 0.10.*

### b. Magnitude of Change Correlations

A series of raw correlations were conducted to examine magnitude of change in VMS with the magnitude of change in cognitive performance over time. For cognitive data, change scores were calculated by subtracting baseline scores from 3-month scores (i.e., higher values referred to improved performance following SGB). For VMS data, change scores were calculated by subtracting 3-month scores from baseline scores (i.e., higher values referred to improved VMS symptoms following SGB). There were no significant changes from baseline to the 3-month post-injection assessment between total physiologically measured VMS or any of the primary verbal memory outcomes (see Table VI).

TABLE VI. Correlation coefficients for the magnitude of change in physiologic and subjective VMS data and change in cognitive performance over time.

| | Group 1 n = 24 | | Group 2 n = 21 | | Group 3 n = 20 | |
|---|---|---|---|---|---|---|
| **Primary Cognitive Outcomes, *r* (*p*)** | **Physiologic Total VMS** | **Subjective Total VMS** | **Physiologic Total VMS** | **Subjective Total VMS** | **Physiologic Total VMS** | **Subjective Total VMS** |
| ***CVLT*** | | | | | | |
| Total (across 5 trials) | -0.15 (0.48) | -0.15 (0.49) | -0.19 (0.42) | -0.33 (0.14) | -0.25 (0.28) | -0.44 (0.05)* |
| Short-delay free recall | 0.02 (0.94) | 0.01 (0.97) | 0.17 (0.95) | -0.06 (0.79) | -0.02 (0.93) | -0.13 (0.57) |
| Long-delay free recall | 0.30 (0.16) | -0.02 (0.91) | 0.31 (0.18) | -0.13 (0.57) | 0.36 (0.12) | -0.29 (0.21) |
| ***Logical Memory Test*** | | | | | | |
| Immediate total score | -0.03 (0.90) | 0.23 (0.29) | -0.64 (0.78) | 0.21 (0.37) | -0.09 (0.70) | 0.18 (0.44) |
| Delayed total score | 0.07 (0.75) | 0.19 (0.39) | 0.05 (0.84) | 0.14 (0.54) | 0.03 (0.90) | 0.12 (0.61) |

**Note.** *$p = 0.05$.

Significant changes were found on baseline to the 3-month post-injection assessment between the magnitude of change of total subjective VMS with the magnitude of change on BTA total ($r(24) = 0.53$, $p < 0.01$). These data indicate that decreases in the number of total subjective VMS from baseline to 3-month post injection were associated with improvements on the BTA (during that time frame). No other significant correlations were found between total subjective VMS or any other cognitive outcome measure.

**c. Mixed-Effects Regressions**

A series of random intercept, mixed-effects regressions were used to assess changes in cognitive performance over time as a function of treatment condition. Independent predictors included Treatment Condition (sham-control vs. active SGB), a 3-month dummy variable (vs. baseline), and their interaction. There were no significant reductions from baseline to the 3-month post-injection assessment in the SGB intervention group or in the sham-control group on either total physiologically or total subjectively measured VMS (*ps* > 0.05) (see Table VII). Table VIII shows changes in primary cognitive outcome measures from baseline to 3-months post injection in the SGB and sham-control groups. Results show that there were no significant improvements from baseline to the 3-month post-injection assessment in the SGB intervention group or in the sham-control group on any of the primary cognitive outcome measures (*ps* > 0.05). The SGB intervention group showed a trending improvement on CVLT total learning ($B = 3.77$, $SE = 2.02$, $p = 0.08$). There was a trending interaction between treatment group and time for CVLT total learning ($p = 0.07$).

TABLE VII. Estimated means (SE) and estimate change scores over time for the physiologic VMS outcomes and objective sleep outcomes in active SGB and sham-control groups for Group 1 with valid 3-month data.

| | Group 1 (n=24) | | | | | | Differential Mean Change between Groups | |
|---|---|---|---|---|---|---|---|---|
| | SGB (n=13) | | | Sham-Control (n=11) | | | | |
| **Vasomotor Symptoms (Daily Count)** | **Baseline B (SE)** | **Post B (SE)** | **Change B (SE)** | **Baseline B (SE)** | **Post B (SE)** | **Change B (SE)** | **B (SE)** | **p-value** |
| *Physiologic (via monitor)* | | | | | | | | |
| Total | 18.31 (3.71) | 20.62 (3.71) | 2.31 (3.52) | 19.55 (4.03) | 16.18 (4.03) | -3.36 (3.82) | 5.67 (5.19) | 0.29 |
| Awake | 12.08 (2.64) | 13.85 (2.64) | 1.77 (2.48) | 15.18 (2.87) | 12.36 (2.87) | -2.82 (2.70) | 4.59 (3.67) | 0.22 |
| Sleep | 6.23 (1.47) | 6.78 (1.47) | 0.54 (1.57) | 4.36 (1.60) | 3.82 (1.60) | -0.55 (1.71) | 1.08 (2.32) | 0.65 |
| Subjective Total | 8.54 (1.54) | 6.46 (1.54) | -2.08 (1.36) | 5.27 (1.68) | 4.00 (1.68) | -1.27 (1.48) | -0.80 (2.01) | 0.69 |

TABLE VIII. Estimated means (SE) and estimate change scores over time for the verbal memory (primary) outcomes in active SGB and sham-control groups for Group 1 with valid 3-month data.

| | Group 1 (n=24) | | | | | | Differential Mean Change between Groups | |
|---|---|---|---|---|---|---|---|---|
| | SGB (n=13) | | | Sham-Control (n=11) | | | | |
| **Test** | **Baseline B (SE)** | **Post B (SE)** | **Change B (SE)** | **Baseline B (SE)** | **Post B (SE)** | **Change B (SE)** | **B (SE)** | **p-value** |
| ***CVLT*** | | | | | | | | |
| Total Learning | 51.53 (3.40) | 55.31 (3.40) | 3.77 (2.02) | 49.36 (3.69) | 47.30 (3.69) | -2.00 (2.19) | 5.77 (2.98) | 0.07* |
| Short-delay Free Recall | 11.62 (0.98) | 12.08 (0.98) | 0.46 (0.55) | 10.00 (1.06) | 10.00 (1.06) | 0.00 (0.59) | 0.46 (0.81) | 0.57 |
| Long-delay Free Recall | 12.46 (0.92) | 12.69 (0.92) | 0.23 (0.75) | 10.55 (1.00) | 10.91 (1.00) | 0.36 (0.82) | -0.13 (1.12) | 0.91 |
| ***Logical Memory*** | | | | | | | | |
| Immediate | 15.31 (1.16) | 14.31 (1.16) | -1.00 (1.18) | 14.27 (1.26) | 13.73 (1.26) | -0.55 (1.29) | -0.45 (1.75) | 0.80 |
| Delayed | 14.54 (1.16) | 12.69 (1.16) | -1.90 (1.14) | 13.09 (1.27) | 12.55 (1.27) | -0.55 (1.13) | -1.30 (1.53) | 0.41 |

**Note.** * $p < 0.10$.

Results showed a significant improvement in CRT total score following the SGB intervention ($B$ = 14.78, $SE$ = 4.91, $p < 0.01$). The sham-control group showed a trending improvement on this CRT total score ($p$ = 0.04). However, there was no significant interaction between treatment group and time for CRT total score ($p$ = 0.68). There were no other significant improvements from baseline to the 3-month post-injection assessment in the SGB intervention group or in the sham-control group on any of the other secondary cognitive outcome measures ($ps > 0.01$).

**d. Correlations Stratified by Treatment Group**

A series of correlations were conducted to examine changes in VMS with changes in cognitive performance stratified by treatment group.

**i. Sham-Control Group**

Among the sham-control group, decreases in total physiologic VMS from baseline to 3-months following injection significantly correlated with improvements in CVLT long-delay free recall ($r(11) = 0.70$, $p < 0.05$). Subsequent analyses revealed that decreases in physiologic VMS while awake also significantly correlated with improvement in CVLT long-delay free recall ($r(11) = 0.71$, $p < 0.05$). No correlations were found between physiologic VMS while asleep and CVLT long-delay free recall ($p = 0.21$).

Increases in total subjective VMS significantly correlated with improvements on CVLT total learning from baseline to 3-months following injection ($r(11) = -0.63$, $p < 0.05$). No other significant correlations were found between physiologic or subjective VMS on any other cognitive outcome measure.

#### ii. Stellate Ganglion Blockade Intervention Group

Among the SGB intervention group, no significant correlations were found between total physiologic or subjective VMS on any primary cognitive outcome measure (*ps* > 0.05) or secondary cognitive outcome measure (*ps* > 0.01).

### 2. Subsample Based on Physiologic Vasomotor Symptom Eligibility (n=21) Group 2

#### a. Differences by Treatment Group

There were no treatment group differences on sociodemographic variables, sleep quality variables, mood scales, cognitive outcomes, or VMS outcomes. Pair-sample t-tests were conducted to examine the difference between reported VMS from baseline to 3-months post-injection. There were no significant differences in either total physiologic or total subjective VMS from baseline to 3-month post-injection ($p$ = 0.77 and $p$ = 0.21 respectively).

#### b. Magnitude of Change Correlations

A series of raw correlations were conducted to examine magnitude of change in VMS with the magnitude of change in cognitive performance over time. There were no significant changes from baseline to the 3-month post-injection assessment between total physiologically measured VMS or any of the verbal memory outcomes (see Table VI). The magnitude of change of total subjective VMS correlated significantly with the magnitude of change on BTA total ($r(21) = 0.57$, $p < 0.01$), indicating that decreases in the number of total subjective VMS from baseline to 3-month post injection were associated with improvements on the BTA during that time.

No other significant correlations were found between total subjective VMS or any other cognitive outcome measure.

### c. Mixed-Effects Regressions

A series of random intercept, mixed-effects regressions were used to assess changes in cognitive performance over time as a function of treatment condition. Independent predictors included Treatment Condition (sham-control vs. active SGB), a 3-month dummy variable (vs. baseline), and their interaction. There were no significant reductions from baseline to the 3-month post-injection assessment in the SGB intervention group or in the sham-control group on total physiologically measured VMS or total subjectively measured VMS. Results show that there were no significant improvements from baseline to the 3-month post-injection assessment in the SGB intervention group or in the sham-control group on any of the primary cognitive outcome measures (*p*s > 0.05). Results showed a significant improvement in CRT total score following the SGB intervention (*B* = 17.30, *SE* = 5.66, *p < 0.01).* The sham-control group showed a trending improvement on this primary outcome (*p* = 0.04) There was no significant interaction between treatment group and time for CRT total score (*p* = 0.48). There were no other significant improvements from baseline to the 3-month post-injection assessment in the SGB intervention group or in the sham-control group on any of the other secondary cognitive outcome measures (*p*s > 0.01).

### d. Correlations Stratified by Treatment Group

A series of correlations were conducted to examine changes in VMS with changes in cognitive performance stratified by treatment group.

#### i. Sham-Control Group

The sham-control group (n=11) for Group 2 (n=21) is the same as with Group 1 (n=24). Therefore, correlations are the same as noted above.

#### ii. Stellate Ganglion Blockade Intervention Group

Among the SGB intervention group, decreases in total subjective reported VMS were significantly correlated with improvements in BTA total score from baseline to 3-months following injection ($r(10) = 0.742$, $p = 0.01$).

### 3. Subsample Based on Physiologic Vasomotor Symptom Eligibility Excluding Outlier (n=20) Group 3

#### a. Differences by Treatment Group

There were no treatment group differences on sociodemographic variables, sleep quality variables, mood scales, cognitive outcomes, or VMS outcomes. Pair-sample t-tests were conducted to examine the difference between reported VMS from baseline to 3-months post-injection. There was no significant difference in either total physiologic or total subjective VMS from baseline to 3-month post-injection ($p = 0.83$ and $p = 0.20$ respectively).

#### b. Magnitude of Change Correlations

A series of raw correlations were conducted to examine magnitude of change in VMS with the magnitude of change in cognitive performance over time. There were no significant changes from baseline to the 3-month post-injection assessment between total physiologically measured VMS or any of the verbal memory outcomes (see Table VI). The magnitude of change of total subjective VMS correlated significantly with the magnitude of change on BTA total ($r(20) = 0.61$, $p < 0.01$), indicating that

decreases in the number of total subjective VMS from baseline to 3-month post injection were associated with improvements on the BTA. There was a trend for the magnitude of change of total subjective VMS and the magnitude of change on CVLT total (r(20) = -0.44, $p$ = 0.05). No other significant correlations were found between total subjective VMS or any other cognitive outcome measure.

**c. Mixed-Effects Regressions**

A series of random intercept, mixed-effects regressions were used to assess changes in cognitive performance over time as a function of treatment condition. Independent predictors included Treatment Condition (sham-control vs. active SGB), a 3-month dummy variable (vs. baseline), and their interaction. Results showed a significant improvement in CVLT total learning following the SGB intervention ($B$ = 4.22, $SE$ = 1.97, $p$ < 0.05*).* The sham-control group did not show a significant improvement on this primary outcome measure ($p$ = 0.28). Additionally, there was a significant interaction between treatment group and time for CVLT total learning ($p$ < 0.05). There were no other significant improvements from baseline to the 3-month post-injection assessment in the SGB intervention group or in the sham-control group on any of the other primary cognitive outcome measures (see Table IX).

TABLE IX. Estimated means (SE) and estimate change scores over time for the verbal memory (primary) outcomes in active SGB and sham-control groups for Group 3 with valid 3-month data.

| | Group 3 (n=20) | | | | | | Differential Mean Change between Groups | |
|---|---|---|---|---|---|---|---|---|
| | SGB (n=9) | | | Sham-Control (n=11) | | | | |
| Test | Baseline B (SE) | Post B (SE) | Change B (SE) | Baseline B (SE) | Post B (SE) | Change B (SE) | B (SE) | p-value |
| ***CVLT*** | | | | | | | | |
| Total Learning | 52.67 (4.17) | 56.89 (4.17) | 4.22 (1.97) | 49.36 (3.77) | 47.30 (3.77) | -2.00 (1.78) | 6.22 (2.65) | 0.03* |
| Short-delay Free Recall | 11.56 (1.17) | 12.56 (1.17) | 1.00 (0.58) | 10.00 (1.06) | 10.00 (1.06) | 0.00 (0.52) | 1.00 (0.78) | 0.22 |
| Long-delay Free Recall | 12.78 (1.06) | 13.44 (1.06) | 0.67 (0.67) | 10.55 (0.96) | 10.91 (0.96) | 0.36 (0.61) | 0.30 (0.90) | 0.74 |
| ***Logical Memory*** | | | | | | | | |
| Immediate | 14.78 (1.43) | 14.89 (1.43) | 0.11 (1.26) | 14.27 (1.29) | 13.73 (1.29) | -0.55 (1.14) | 0.66 (1.69) | 0.70 |
| Delayed | 14.44 (1.42) | 12.89 (1.42) | -1.56 (1.21) | 13.09 (1.29) | 12.55 (1.29) | -0.55 (1.09) | -1.01 (1.63) | 0.54 |

**Note.** * $p < 0.05$.

Results showed a significant improvement in CRT total score following the SGB intervention (*B* = 17, *SE* = 6.13, *p = 0.01).* The sham-control group showed a trending improvement on this primary outcome (*p* = 0.05). There was no significant interaction between treatment group and time for CRT total score (*p* = 0.53). There were no other significant improvements from baseline to the 3-month post-injection assessment in the SGB intervention group or in the sham-control group on any of the other secondary cognitive outcome measures.

**d. Correlations Stratified by Treatment Group**

A series of correlations were conducted to examine changes in VMS with changes in cognitive performance stratified by treatment group.

**i. Sham-Control Group**

The sham-control group (n=11) for Group 3 (n=20) is the same as with Group 1 (n=24). Therefore, correlations are the same as noted above.

**ii. Stellate Ganglion Blockade Intervention Group**

Among the SGB intervention group, decreases in total subjectively reported VMS were significantly correlated with improvements in BTA total score from baseline to 3-months following injection ($r(9) = 0.80$, $p < 0.01$).

# VI. DISCUSSION

The primary aim of the study was to evaluate the relationship between VMS and verbal memory performance in midlife women with breast cancer who exhibited moderate-to-severe VMS. More generally, the present study aimed to determine if VMS are modifiable risk factors for cognitive impairment among women with a history of breast cancer. Previous studies have shown an association between increased number of physiologic VMS and worse verbal memory performance (Maki et al., 2008). The relationship between VMS and verbal memory performance among women with breast cancer has yet to be explored, even though women with breast cancer have more severe VMS (Canney and Hatton, 1994; Hunter et al., 2004).

## A. Aim I

Our first aim was to examine the association between VMS (physiologic and subjective) and verbal memory performance in breast cancer survivors with moderate-to-severe VMS. Our hypothesis was that a greater number of physiologic, but not subjective, VMS would be significantly associated with worse verbal memory performance at baseline. Previous studies have demonstrated the association between verbal memory and physiologic, but not subjectively measured VMS performance (Maki et al., 2008; 2016). In the present study, two measures of verbal memory performance were used: the CVLT and LM. Our hypothesis was confirmed. Specifically, physiologic VMS significantly correlated with CVLT short-delay free recall, CVLT long-delay free recall, CVLT total clustering, and was trending with CVLT total learning. Of note, these

findings were based on those women who met the initial criterion for physiological recorded, not subjectively reported VMS. Consistent with previous research, total number of subjective VMS did not significantly correlate with any of the verbal memory outcomes (Greendale et al., 2010; LeBlanc et al., 2007; Maki et al., 2008; Weber et al., 2012). There were no significant correlations between VMS, physiologic or subjective, on either LM outcomes among women who experienced the required number of physiologic VMS for study inclusion (i.e., n=30).

Women in the present study under-reported the total number of physiologically-measured VMS. Day-time hot flashes were under-reported by 45%; night sweats were under-reported by 78%. This magnitude of nighttime under-reporting of is higher than in previous studies among women with a history of breast cancer. For example, Carpenter and colleagues found that women with a history of breast cancer missed 36%-50% of hot flashes and 22%-42% of night sweats as captured by ambulatory monitoring (Carpenter et al., 2004b). Although the reason is unknown, one possible explanation may be due to sleep. Women in the present study reported an average global PSQI score above 10 (indicating very poor sleep). A score of five or greater has been previously established as a cutoff for poor sleep quality and high sleep disturbance (Buysse et al., 1989). It may be that that these baseline poor levels of sleep quality were so disruptive that they overshadowed the ability to subjectively detect VMS. Of note, Carpenter et al. (2004b) did not report PSQI scores so direct comparisons to that study are not possible. These results highlight the importance of utilizing physiologically

monitored VMS as a measure of VMS in studies examining the cognitive correlates of VMS.

Two measures of verbal memory, the CLVT and LM, were used. Only measures on the CVLT were related to physiologic VMS. Although these two measures are commonly thought to be interchangeable as measures of verbal memory, there are important differences between the two tasks. To measure total learning and immediate recall, the CVLT is presented five times as a 16-item word list covering four semantic categories. By contrast, LM is presented once as a structured story with 25 discrete units of information. The delay times for the CVLT and LM were 20 minutes and 15 minutes respectively. The CVLT and LM evoke different aspects of verbal memory and can be influenced by other aspects of cognition (e.g., attention, encoding). Numerous studies have found differential performance on these two memory tasks (Brooks et al., 2006; Rabin et al., 2009; Silva et al., 2012; Tremont et al., 2010). Previous reports have shown list-learning tasks like the CVLT rely more on executive functioning (Alexander et al., 2003; Tremont et al., 2000) whereas story memory tasks like the LM are more sensitive to temporal lobe dysfunction (Ragland et al., 2000). This may be due to the CVLT requiring more strategic encoding and organization (Vanderploeg et al., 1994) compared with the LM which provides more contextual cues (Brooks et al., 2006). The present study found an association between CVLT total clustering and total physiologic VMS. CVLT total clustering is a measure of strategic encoding. These results provide further evidence that the differences found were due to executive function performance.

The lack of a relationship between LM and physiologic VMS in our study contrasts with previous reports from our group. Specifically, Maki and colleagues (2008)

found significant associations between LM delayed, not CVLT outcomes, and total physiologic VMS. One possible explanation may be due to the task itself. Maki et al., (2008) used a three-trial version of the CVLT, whereas the present study used a five-trial version, which may be more sensitive than the three-trial version. Another possible explanation for this discrepancy could be due to the different populations enrolled in these studies. All women in the present study had a history of breast cancer, whereas the previous study by Maki et al. (2008) enrolled healthy, menopausal women. Of note, 10 of the 30 women in the present study were taking tamoxifen. Schilder and colleagues (2009) administered a verbal memory test to 80 women with breast cancer taking tamoxifen and 120 healthy controls. Results showed that being on tamoxifen for one year was associated with worse performance on verbal memory and executive functioning tasks. fMRI studies have shown that women with a history of breast cancer and treatment with chemotherapy have reduced prefrontal activation during executive function tasks (de Ruiter et al., 2011). Pre-existing impairments on executive functioning tasks may help explain why subjects in the present study showed significant impairments on the CVLT, an executive functioning task requiring encoding and organization, compared with Maki et al. (2008) where no such differences were found.

### 1. Physiologic and Subjective Vasomotor Symptoms

Consistent with previous reports (Maki et al., 2008), the present study found physiologic VMS, not subjective VMS, significantly correlated with verbal memory outcomes. These results suggest that it is physiologic VMS that independently influences memory performance. VMS can independently influence memory by triggering cortisol release, altering default mode network connectivity between the

hippocampus and other brain regions, adversely affecting cardiovascular function, and/or disrupting sleep (Genazzani et al., 1984; Meldrum et al., 1984; Thurston et al., 2015; 2016). Research has also shown that both high doses of exogenous (Kirschbaum et al., 1996; Newcomer et al., 1999) and endogenous cortisol (Segerstrom et al., 2016) decrease memory performance. Taken together, these findings indicate that cortisol may be involved in mediating the relationship between VMS and cognitive functioning. Future studies should aim to explore the relationship between cortisol levels and VMS monitoring.

### 2. Sleep

Sleep disruptions caused by night sweats are one of the most common complaints associated with VMS (Brown et al., 2009; Kravitz et al., 2008). The present study examined objective sleep measures to further understand the association between VMS and memory performance, and whether or not sleep may account for any relationship between VMS and cognition. Global subjective sleep, as measured by the PSQI (Buysse et al., 1989), was computed for each participant. A score of five or greater has been previously established as a cutoff for poor sleep quality and high sleep disturbance (Buysse et al., 1989). In the present study, every participant had a global sleep score greater than five. In fact, these women had an average global sleep score of 10.57 (SD = 3.58), which indicates extremely poor sleep quality. The mean total sleep time measured by actigraphy was 379.54 minutes (SD = 102.95).

The present study did not reveal any significant associations between any subjective or objective sleep variables with any of the primary cognitive outcomes. The women in the present study had severe sleep disturbances, but those disturbances did

not associate with verbal memory performance. Similarly, no associations between sleep outcome measures and physiologic and subjective VMS were found. It is worth noting that in the subset of women who met eligibility criteria for physiologic VMS, total physiologic VMS remained a significant predictor of performance on all three CVLT outcomes after controlling for both subjectively reported and objectively measured sleep outcomes. This finding indicates that there may be more of a direct relationship between VMS and verbal memory performance that is not due to sleep disturbance.

Previous studies examining the association between sleep outcomes and physiologic VMS have found mixed results. Some studies have shown associations between sleep disturbances and VMS (Brown et al., 2009; Kravitz et al., 2003; 2008). However, other studies failed to find significant associations between subjective sleep variables and physiologically monitored VMS (Freedman and Roehrs, 2004; Thurston et al., 2006; 2012; de Zambotti et al., 2014). One possible explanation for the lack of association found in the present study may be because women with a history of breast cancer typically report worse sleep quality compared to women with other types of cancer and women without a history of breast cancer (Carpenter et al., 2004a; Davidson et al., 2002; Savard et al., 2001). For example, Otte and colleagues examined sleep-wake disturbances among 246 breast cancer survivors and 246 aged-matched women without a history of breast cancer. Results showed significantly higher PSQI global scores among breast cancer survivors compared with controls (Otte et al., 2010). The poor baseline level of sleep quality among our sample might minimize the incremental

impact of additional sleep disturbances due to night sweats, resulting in the lack of association found in the present study.

A second possible explanation comes from a recent work by Savard et al. (2013) who studied 56 women diagnosed breast cancer. The study sought to examine the relationship between sleep disturbances and physiologic VMS. Women were fitted with ambulatory sternal skin conductance and polysomnography devices which they wore for 24 hours. Results showed that it was the duration of onset and the duration of the total night sweats that contributed to worse sleep efficiency, rather than the total number of night sweats per se. These night sweat duration characteristics were not measured in the present study. Future studies should aim to explore duration specific characteristics of night sweats to further unpack this complex relationship.

## B. Aim II

Our second aim examined the effects of SGB intervention for VMS on verbal memory in breast cancer survivors with moderate-to-severe VMS. Previous open-label trials have shown that SGB intervention reduced frequency of VMS in women both with a history of breast cancer (Lipov et al., 2008; Pachman et al., 2011). Additionally, a sham-controlled trial showed greater reductions with SGB versus sham intervention in women without a history of breast cancer (Walega et al., 2014). Previous research has shown that the reduction in VMS resulted in improved verbal performance (Maki et al., 2016).

Our hypothesis was that the magnitude of decrease in physiologic VMS following SGB and sham intervention will be related to the magnitude of improvement in verbal

memory performance. Our hypothesis was not confirmed. Specifically, SGB intervention did not lead to a reduction in physiologically or subjectively reported VMS. Despite this lack of improvement in VMS frequency, the present study did find verbal memory improvements among the SGB intervention Group 3 and trending improvements among the SGB intervention Group 1. This improved verbal memory performance, despite the lack of reduction in physiologically or subjectively reported VMS is not consistent with previous reports examining the effects of SGB on women with moderate-to-severe VMS. Previous reports examining the effects of SGB on verbal memory all have first demonstrated a reduction in the number of VMS following SGB intervention. For example, in a sham-controlled SGB pilot intervention among 40 postmenopausal women, Walega and colleagues (2014) found that the total number of physiologically measured VMS was significantly reduced from baseline to the 3-month assessment in the SGB group (M = 7.21, 5.74), but not in the sham-control group (M = 5.60, 6.24). This reduction in VMS following SGB intervention has also been demonstrated among women with a history of breast cancer (Lipov et al., 2008; Pachman et al., 2011). Maki et al. 2016, demonstrated that this reduction in VMS following SGB intervention resulted in improvements on verbal memory. This study adds to previous findings that SGB intervention improves verbal memory performance. The present study differs in terms of the role VMS plays in this relationship. This inconsistency may be due to the small sample size and lack of power in the present study compared with previous studies. For example, Maki et al. 2016, enrolled 36 women compared with the 24, 21, and 20 women enrolled in the present study.

A second possible explanation for the lack of observed reduction in both total physiologic and total subjective VMS following SGB intervention may be due to differences in SGB intervention, VMS monitoring, and VMS frequency found in our sample. For example, Lipov et al. (2008) showed a reduction in VMS among women with a history of breast cancer following SGB intervention. However, unlike the present study, eight of the 13 women enrolled in that study received two SGB injections prior to post-injection cognitive testing. It is possible that a second SGB injection is necessary to improve VMS among this particular population.

A third difference between previous research on women with a history of breast cancer and the present study is that previous studies only evaluated subjectively measured VMS (Lipov et al., 2008; Pachman et al., 2011). By contrast, the present study evaluated both physiologically recorded and subjectively reported VMS. As noted previously, it is critically important to be able to evaluate physiologically recorded VMS as women consistency under-report the number of VMS they experience.

Lastly, women in the two open-label trials mentioned above reported on average 11.34 and 10.1 subjective VMS per day with reductions to 7.13 and 5.4 following SGB intervention. By contrast, women in the present study reported 6.47 subjective VMS per day, which is similar to the post-treatment values reported in the two-open label trials. It may be that the lack of observed reduction in VMS following the SGB intervention was due to the low baseline number of subjectively reported VMS in the present study compared with previous open-label trials.

In all three sample size groups, the present study found significant improvements in CRT total score among the SGB intervention group and with trending improvements

among the sham-control group at the 3-month assessment compared with baseline. These results are consistent with previous reports from our group showing improved CRT performance over time (Maki et al., 2016). A likely explanation for these finding may be due to known practice effects on mental rotations tests (Casey & Brabeck, 1989; Hampson, 1990; Peters et al., 1995). Future studies should explore the use of alternative versions to rule out whether these findings are in fact due to practice effects.

Results for Group 1 (n=24) showed a trend for improvement in CVLT total learning following SGB intervention and a trending interaction between treatment group and time for CVLT total learning. Group 2 (n=21*)* did not show any significant improvements on any primary verbal memory outcome measures following SGB intervention. Group 3 (n=20) showed a significant improvement in CVLT total learning following SGB intervention. Additionally, there was a significant interaction between treatment group and time for CVLT total learning ($p < 0.05$) in Group 3. This improvement in CVLT total learning following SGB intervention in Groups 1 and 3 is consistent with previous work from our lab (Maki et al., 2016). However, unlike Maki et al. (2016), the present study did not find any decreases in physiologically observed VMS following SGB intervention. This is an important distinction highlighting the direct impact of SGB intervention, not necessarily VMS, on verbal memory improvement. The findings in the present study are consistent with previous research demonstrating cognitive improvements following SGB intervention, irrespective of VMS. For example, Mulvaney et al. (2015) found that among 11 combat veterans with PTSD, SGB intervention significantly improved performance on four different cognitive domains. Of note, results also showed a reduction in PTSD symptoms. It is therefore unclear

whether these cognitive improvements were due solely to the effects of SGB intervention or due to the effects of reduced PTSD symptoms (Mulvaney et al., 2015). Future studies should aim to explore the direct effects of SGB intervention on memory performance among healthy controls to rule out potential confounding effects.

Taken together with the findings from Aim 1, this study raises the question more broadly of the underlying mechanisms associated with VMS and verbal memory. It is thought that VMS leads to sleep disturbances, and that these sleep disturbances in turn are associated with worse verbal memory performance. However, the results from the present study demonstrate that this was in fact not the case. The present study showed that VMS was directly associated with verbal memory performance outcomes, irrespective of sleep. This demonstrates that VMS may be a direct modifiable risk factor for verbal memory performance. Additionally, results showed that SGB intervention had a direct effect on verbal memory performance, irrespective of changes in VMS. Additional studies with increased sample sizes are needed to rule out the effects of statistical power on the ability to detect a main effect of SGB on VMS among this population.

VMS are quite common among women transitioning through menopause, effecting approximately 75% of menopausal women (Gold et al., 2000; Kronenberg, 1990). Menopause is characterized by cessation of ovarian function leading to a severe reduction in circulating levels of ovarian steroids hormones (Chakravarti et al., 1976). MHT is currently the gold standard for VMS treatment. MHT reduces VMS, which in turn improves verbal memory performance among healthy menopausal women. Exogenous estrogen has therapeutic benefits not only on VMS (Thurston & Joffe, 2011), but also on

verbal memory performance (Maki et al., 2011; Maki & Resnick, 2000; Resnick et al., 1998; Shaywitz et al., 1999). Future studies should examine how reductions in VMS following MHT treatment improve memory in midlife women.

MHT is contraindicated in breast cancer survivors because it may increase the potential for estrogen-dependent cancer cell growth and recurrence. It is clinically important to find alternatives to MHT for women with histories of breast cancer. In the present study, SGB intervention in Group 3 women improved verbal memory performance, irrespective of reductions in VMS. This is an important finding, specifically for women with breast cancer. SGB intervention may be an alternative therapeutic to improve verbal memory performance among women with a history of breast cancer. This finding raises the broader question of whether there is an alternative way to improve verbal memory performance, irrespective of changes in VMS. Future studies should aim to identify some of the potential contributing factors to worse verbal memory performance, outside of VMS.

Several limitations should be considered. A primary limitation of the present study is that the sample size is small and we were underpowered for the Aim 2 analyses. The study is currently on-going. Final sample sizes may be large enough to detect associations that were not found in this preliminary analysis.

A second limitation is the lack of consideration of potential breast cancer disease characteristic variability within the sample. For example, Couzi et al. (1995) found that early onset diagnosis was related to significantly increased severity of VMS. Similarly, Ahles and colleagues (2008) observed a differential impact on cognitive performance among women with invasive versus non-invasive breast cancer. These breast cancer

variability factors may very well play a role in VMS and cognitive outcome studies and should be explored further.

A third potential limitation of the study is that we did not gather data on previous medication history. For example, previous research has demonstrated that chemotherapy and other medication regimens differentially impact cognitive performance among women with a history of breast cancer (Espeland et al., 2010; Schilder et al, 2009; Wefel et al., 2004; Wefel & Schagen, 2012). More large-scale studies are needed to be able to examine the differences between different treatment medication effects on cognitive performance. Future studies should aim at controlling for previous chemotherapy histories as a way to understand the trajectory of cognitive decline among these women.

## C. Conclusion

The purpose of the present study was to examine the relationship between VMS and verbal memory performance in midlife women with breast cancer and moderate-to-severe VMS. We found that physiologic VMS significantly correlated with verbal memory outcomes and subjective VMS did not. Women with higher frequency of physiologic VMS performed worse on verbal memory outcomes. The study also examined effect of SGB intervention for VMS on verbal memory in breast cancer survivors with moderate-to-severe VMS. We failed find any significant decrease in frequency of VMS following the 3-month SGB or sham-control intervention. However, the present study did find significant improvements on verbal memory performance. Previous research has demonstrated a relationship between VMS and cognitive

functioning. Our results extend on that work. However, to our knowledge, this is the first study exploring this relationship among women with a history of breast cancer. Additional research is needed to further unpack the relationship between VMS and cognitive functioning in this population.

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de Zambotti, M., Colrain, I. M., Javitz, H. S., & Baker, F. C. (2014). Magnitude of the impact of hot flashes on sleep in perimenopausal women. *Fertility and sterility*, *102*(6), 1708-1715.

# VIII. VITA

## Jessica S. Fogel, M.S.

College of Liberal Arts and Sciences, Department of Psychology
Behavioral Neuroscience Program
University of Illinois at Chicago

EDUCATION

| | |
|---|---|
| Fall 2015-Present | University of Illinois at Chicago<br>Ph.D. Candidate, College of Liberal Arts and Sciences<br>Department of Psychology<br>Behavioral Neuroscience Program<br>Advisor: Pauline M. Maki, Ph.D. |
| Fall 2013-Summer 2015 | University of Kentucky<br>M.S., Behavioral Neuroscience and Psychopharmacology<br>Thesis Title: Effects of Repeated Cue Exposure on Cannabis Craving<br>Advisor: Joshua A. Lile, Ph.D. |
| Fall 2004-Spring 2008 | University of Michigan<br>B.A., Psychology |

RESEARCH EXPERIENCES

| | |
|---|---|
| August 2015-Present | Graduate Research Assistant<br>Feinberg School of Medicine<br>Northwestern University |
| August 2015-July 2017 | Graduate Research Assistant<br>Department of Psychiatry<br>Rush University Medical Center |
| August 2013-May 2015 | Graduate Research Assistant<br>Residential Research Facility<br>University of Kentucky |
| May 2010-June 2013 | Research Assistant<br>Substance Use Research Center<br>New York State Psychiatric Institute<br>Columbia University Medical Center |
| October 2008-May 2010 | Research Associate<br>Ethics Department<br>Saint Vincent's Catholic Medical Center |
| January 2008-June 2008 | Data Management Lab Assistant<br>Addiction Research Center<br>University of Michigan |

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|---|---|
| September 2007-<br>December 2007 | Research Assistant<br>Department of Clinical and Developmental Psychology<br>University of Michigan |
| September 2007-<br>December 2007 | Research Assistant<br>Department of Cultural and Social Psychology<br>University of Michigan |

ADVISING ACTIVITIES

Undergraduate Students

| | |
|---|---|
| Mariana Reyes | Fall 2016 – Spring 2018<br>Honors College Capstone Project<br>University of Illinois Chicago |
| Agnieszka Cisak | Summer 2016 – Fall 2017<br>University of Illinois Chicago |
| Hira Choudry | Fall 2016, Spring 2017<br>Honors College Capstone Project<br>University of Illinois Chicago |
| Annesti Elmasri | Summer 2016, Fall 2016<br>Honors College Capstone Project<br>University of Illinois Chicago |
| Jordan Krawczyk | Spring 2016, Summer 2016<br>University of Illinois Chicago |
| Tyler Delong | Spring 2015<br>BIO 395: Independent Work in Biology<br>University of Kentucky College of Arts and Sciences |
| Inna Malyuk, B.A. | Summer 2014<br>University of Kentucky<br>Summer Training in Alcohol Research<br>Center for Drug Abuse Research Translation |

PROFESSIONAL ACTIVITIES AND PROFESSIONAL DEVELOPMENT

Memberships

| | |
|---|---|
| Joined 2017 | International Cannabinoid Research Society |
| Joined 2013 | College on Problems of Drug Dependence |

**Awards**

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|---|---|
| 2017 | Center for Research on Women and Gender<br>UIC Women's Health Research Day Annual Meeting<br>First Place Poster Presentation |
| 2014 | Women and Gender Junior Investigator Travel Award<br>College on Problems of Drug Dependence Annual Meeting<br>San Juan, Puerto Rico |

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|---|---|
| 2014-2015 | National Institute on Drug Abuse Predoctoral Training Fellowship<br>Department of Behavioral Science, University of Kentucky College of Medicine |
| 2013-2014 | Graduate Dean's Scholarship<br>Department of Behavioral Science, University of Kentucky College of Medicine |

Journal Peer Review
Drug and Alcohol Dependence
Journal of International Neuropsychology Society

INVITED SPEAKING ENGAGEMENTS

| | |
|---|---|
| 2018 | Effects of a Stellate Ganglion Block on Vasomotor Symptoms in Women Receiving Anti-Estrogen Therapy for Breast Cancer<br>Psychology Department Cross Program Conference<br>University of Illinois, Chicago |
| 2017 | Addiction and cognition in HIV-infected, substance abusing women<br>Association of Neuropsychology Students in Training Seminar Series<br>University of Illinois, Chicago |
| 2017 | Effects of Sex and HIV serostatus on spatial learning and memory among substance users<br>Psychiatric Institute and Center for Alcohol Research in Epigenetics Neuroscience Seminar Series<br>University of Illinois, Chicago |
| 2015 | Effects of environmental cues on cannabis craving<br>NIDA T32 Training Symposium<br>University of Kentucky |

RESEARCH & INTELLECTUAL CONTRIBUTIONS
**Publications**
Peer-Reviewed Original Research in Scientific Journals

6. Martin EM, Keutmann MK, **Fogel JS**, Maki PM, Gonzalez R, Vassileva J, Rubin LH, Hardy D (2018) Verbal and spatial working memory among drug-using HIV-infected men and women. *Journal of Neurovirology, In submission.*

5. **Fogel J**, Rubin LH, Maki P, Keutmann MK, Gonzalez R, Vassileva J, Marin EM (2017) Effects of sex and HIV serostatus on spatial navigational learning and memory among cocaine users. *Journal of Neurovirology,* 23: 855-863.

4. **Fogel JS**, Kelly TH, Westgate PM, Lile JA (2016) Sex differences in the subjective effects of oral $\Delta^9$-THC in cannabis users. *Pharmacology, Biochemistry, and Behavior,* 52: 44-5. *doi: 10.1016/j.pbb.2016.01.007.*

3. Jansen LA, **Fogel JS**, Brubaker M (2013) Experimental philosophy, clinical intentions, and evaluative judgment. *Cambridge Quarterly Journal of Health Care Ethics*, 22: 126-135. PMID: 23507175.

2. Jansen LA, Appelbaum PS, Klein WK, Weinstein ND, Cook W, **Fogel JS**, Sulmasy DP (2011) Unrealistic optimism in early-phase oncology trials. *IRB: Ethics and Human Research*, 33: 1-8. PMID: 21314034.

1. Jansen LA, **Fogel JS** (2010) Ascribing intentions in clinical decision-making. *Journal of Medical Ethics*, 36: 2-6. PMID: 20026685.

Book Chapters

Lile JA, **Fogel JS**, Kelly TH (2017) The role of $\gamma$-aminobutyric acid in the interoceptive effects of oral $\Delta^9$-tetrahydrocannabinol in humans. In: Preedy VR, (ed), The Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment. London: Academic Press

**Abstract Presentations**

National/International

23. Martin EM, Gonzalez R, **Fogel J**, Vassileva J, Bechara A (2019). Double dissociation of HIV and SUD effects on tasks dependent on striatal integrity. Oral presentation. Problems of Drug Dependence 2019: College on Problems of Drug Dependence 81$^{th}$ Annual Scientific Meeting. San Antonio, TX

22. **Fogel JS,** Cisak A, Bark JS, Kilic E, Dowty S, Maki PM (2018). Effects of Vasomotor Symptoms on Cognition Among Women Receiving Estrogen Therapy for Breast Cancer. Poster Presentation. UIC Department of Psychiatry Annual Research Forum. Chicago, IL

21. Bark JS, **Fogel JS,** Kilic E, Dowty S, Horwitz R, Maki PM (2018). Night Sweats, Sleep, and Cognition in Breast Cancer Survivors: A Contributor to “Brain Fog”? Poster Presentation. UIC Department of Psychiatry Annual Research Forum. Chicago, IL

20. Martin EM, Maki P, **Fogel J**, Gonzalez R, Rubin LH, Keutmann MK, Hardy D (2018). Verbal and spatial working memory among drug-using HIV-infected men and women. Poster Presentation. International Society for Neurovirology 15th Annual Symposium and 24th Scientific Conference of the Society on Neuroimmune Pharmacology. Chicago, IL

19. Reyes M, **Fogel JS**, Cisak A, Kilic E, Maki PM (2018) The association between depression and cognition among women with breast cancer. UIC Spring Student Research Forum. Chicago, Illinois

18. **Fogel JS**, Rubin LH, Maki P, Keutmann MK, Gonzalez R, Vassileva J, Marin EM (2017). Effects of sex and HIV serostatus on spatial navigational learning and memory among cocaine users. Poster Presentation. UIC Women’s Health Research Day. Chicago, Illinois

17. Chouhdry H, **Fogel JS**, Pezley L, Dowty S, Maki PM (2017). The Effects of Pregnancy Intention on Perinatal Depression. Poster Presentation. UIC Spring Student Research Forum. Chicago, Illinois

16. Elmasri A, **Fogel JS**, Pezley L, Dowty S, Maki PM (2016). Association between anxiety and gestational diabetes among racial and ethnic minorities. Poster presentation. UIC Honors College Fall Research Symposium. Chicago, Illinois

15. **Fogel JS**, Kelly T, Harvanko A, Lile J (2015). Effects of repeated cue exposure on cannabis craving. Poster presentation. Problems of Drug Dependence 2015: College on Problems of Drug Dependence 77th Annual Scientific Meeting. Phoenix, Arizona

14. Harvanko AM, Martin CM, **Fogel JS**, Lile JA, Kelly TH (2015) A comparison of the behavioral effects of electronic and tobacco cigarettes following 24-hr tobacco deprivation. Poster presentation. Problems of Drug Dependence 2015: College on Problems of Drug Dependence 77th Annual Scientific Meeting. Phoenix, Arizona

13. Harvanko AM, Martin CM, **Fogel JS**, Lile JA, Kelly TH (2015) The abuse liability of electronic cigarettes as a function of nicotine dose. Poster presentation. American Psychological Association 123th Annual Scientific Meeting, Division 28 Psychopharmacology and Substance Abuse Poster Session and NIDA/NIAA/APA (Divisions 28 and 50) Early Career Investigators Poster Session and Social Hour. Toronto, Canada

12. Harvanko AM, Martin CM, **Fogel JS**, Lile JA, Kelly TH (2015) A comparison of the self-reported effects of electronic and conventional cigarettes. Poster presentation. University of Kentucky Clinical and Translational Research Spring Conference 2015. Lexington, KY

11. **Fogel JS**, Kelly T, Charnigo R, Harvanko A, Lile J (2014) Predictors of the response to oral $\Delta^9$-THC in regular cannabis users: Focus on sex differences. Poster presentation. Problems of Drug Dependence 2014: College on Problems of Drug Dependence 76th Annual Scientific Meeting. San Juan, Puerto Rico

10. **Fogel JS**, Kelly T, Charnigo R, Harvanko A, Lile J (2014) Sex differences in subjective and physiological responses to oral $\Delta^9$-THC in regular cannabis users. Poster presentation. University of Kentucky Clinical and Translational Research Spring Conference 2014. Lexington, KY

9. Lile J, Kelly T, Stoops W, **Fogel JS**, Harvanko A, Charnigo R, Hays L (2014) Cannabis self-administration in the laboratory and use in the natural environment during outpatient tiagabine maintenance. Poster presentation. Problems of Drug Dependence 2014: College on Problems of Drug Dependence 76th Annual Scientific Meeting. San Juan, Puerto Rico

8. Harvanko AM, Martin CM, Charnigo RJ, **Fogel JS**, Lile JA, Kelly TH (2014) Predicting the effects of d-amphetamine using measures of sensation seeking and impulsivity. Poster presentation. Problems of Drug Dependence 2014: College on Problems of Drug Dependence 76th Annual Scientific Meeting. San Juan, Puerto Rico

7. Harvanko AM, Martin CM, Charnigo RJ, **Fogel JS**, Lile JA, Kelly TH (2014) The relationship between sensation seeking and impulsivity on d-amphetamine taking behavior. Poster presentation. University of Kentucky Clinical and Translational Research Spring Conference 2014. Lexington, KY

6. Kelly TH, Anderson A, Jenkins S, Harvanko A, Martin CA, **Fogel JS**, Joseph J, Lile JA (2014) d-Amphetamine effects and monetary incentive delay task performance: an fMRI study. Poster presentation. Problems of Drug Dependence 2014: College on Problems of Drug Dependence 76th Annual Scientific Meeting. San Juan, Puerto Rico

5. Sullivan MA, Manubay JM, Vosburg SK, Jones JD, Cooper ZD, **Fogel JS**, Davidson JW, Comer SD (2013) Buprenorphine/naloxone for the treatment of prescription opioid abuse and chronic pain. Poster presentation. Problems of Drug Dependence 2013: College on Problems of Drug Dependence 75th Annual Scientific Meeting. San Diego, CA

4. Manubay JM, Davidson JW, Vosburg SK, Jones JD, Cooper ZD, **Fogel JS**, Comer SD, Sullivan MA (2013) Sex differences among opioid-abusing chronic pain patients in a clinical trial. Poster presentation. Problems of Drug Dependence 2013: College on Problems of Drug Dependence 75th Annual Scientific Meeting. San Diego, CA

3. Mogali S, Askalsky P, **Fogel JS**, Madera G, Jones JD, Sullivan MA, Manubay JM, Comer SD (2013) The effects of minocycline on oxycodone-induced responses. Podium presentation. Experimental Biology 2013. Boston, MA

2. Comer SD, Bisaga A, Jones JD, Mogali S, Manubay JM, Sullivan MA, Vosburg SK, Cooper ZD, Roux P, **Fogel JS**, Shiffrin L (2012) Relationship between reactivity to heroin-related cues, heroin craving, and heroin self-administration in buprenorphine-maintained heroin abusers. Poster presentation. American College of Neuropsychopharmacology 2012. Hollywood, FL

1. Manubay JM, Vosburg SK, Comer SD, Jones JD, Cooper ZD, **Fogel JS**, Sullivan MA (2011) Sex differences in patients with chronic pain and prescription opioid abuse during buprenorphine/naloxone maintenance. Poster presentation. Problems of Drug Dependence 2011: College on Problems of Drug Dependence 73rd Annual Scientific Meeting. Hollywood, FL

**Sponsored Research Funding**

*Principal Investigator*

Active

Title: Effects of Environmental Cues on Cannabis Craving
PI: Jessica Fogel (faculty mentor: Joshua Lile, Ph.D.)
Source: Department of Behavioral Science, University of Kentucky College of Medicine
Duration: 02/12/14-06/30/14
Total Award: $3,120