Rumination and executive dysfunction: Risk factors for vascular depression

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RUMINATION AND EXECUTIVE DYSFUNCTION: RISK FACTORS FOR VASCULAR DEPRESSION

by

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ABSTRACT

Introduction: The widely-supported vascular depression hypothesis is underspecified with respect to cognitive mechanisms by which high cerebrovascular burden (CVB) and neuropathology relate to depressive symptoms. Integration of the vascular depression hypothesis with the CaR-FA-X model, a framework of affect regulation mechanisms, suggest that Rumination (R) and executive dysfunction (X) may increase due to altered recruitment of the dorsolateral prefrontal cortex resulting from high CVB and underlying neuropathology. This process would contribute to depressive symptomatology among older adults with high CVB. The progression of examined hypotheses included mediation models examining mechanistic relationships between predictors (CVB, DLPFC activation), cognitive correlates (rumination, executive functioning), and affective outcomes (depressive symptoms).

Method: A sample of 52 community-dwelling, stroke-free, individuals over the age of 70, without history of severe mental illness, dementia, or severe cognitive impairment, completed the Ruminative Responses Scale, provided self-reported cerebrovascular burden data (cardiac disease, hypertension, diabetes, high cholesterol), and completed executive function tasks (Stroop, Flanker) while their hemodynamic response was measured using fNIRS. The Geriatric Depression Scale was used to assess depressive symptomatology. Prefrontal cortical recruitment was assessed using functional near-infrared spectroscopy (fNIRS).

Results: A progression of conventional and bootstrapped regression-based models broadly supported relationships between CVB and depressive symptoms, but not between DLPFC activation and depressive symptoms. No mechanistic relationships were found, with respect to analyses testing prospective cognitive mediators.

Conclusions: Primary findings from this study indicate that cerebrovascular burden predicts depressive symptomatology among older adults and is related to a reduction in inhibitory control ability. Further, these findings inform CVB measurement and mental health implications of contrasting approaches to CVB measurement. A primary contribution of this thesis is that results appear to support utilization of fNIRS, a low-cost and accessible neuroimaging paradigm, for the study of lateralized cognition among older adults.

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CHAPTER 1: INTRODUCTION

At the present, the U.S. Census Bureau Population Division (2014) estimates that of the 318.9 million people residing in the United States, 44.7 million are over the age of 65. It is anticipated that this number will double to about 88.5 million older adults by the year 2050 (Shrestha & Heisler, 2011). The projected increase of older adults is not unique to the United States, as the population in the majority of countries shows a similar trend. According to the United Nations, Department of Economic and Social Affairs Population Division (2015), the current world population of 901 million adults 60 years and older is projected to increase to 2.1 billion by 2050. In this population of older adults, depression has been shown as one of the leading causes of physical and mental decline (Blazer, 2003), with 3.0-4.5% of older adults in the United States currently affected by the disorder (Eden, Maslow, Le, & Blazer, 2012). Every year, the incidence of new depression cases is 0.15%, though the incidence and prevalence increase two-fold between the ages of 70-85 years (Krishnan, 2002; Teresi, Abrams, Holmes, Ramirez, & Eimicke, 2001). Additionally, the rate of women affected is two times higher than men.

Risks and Epidemiology of Depression

Major depressive disorder among older adults has been linked to a number of key risk factors common within the aging population. Poor sleep quality, health, perception of health, and prior depression also increase the likelihood of late life depression (Cole & Dendukuri, 2003). The increased rate of depression in women as compared to men may be attributed to the greater number of women who outlive their partner. Rates also differ depending on settings, with about

10-12% of elderly patients within a hospital setting for medical or surgical services reporting depression. This rate is lower in primary-care patients, ranging from to 6-9% (Alexopoulos, 2005; Blazer, 2003). Long-term follow-up studies reported that 23-31% of patients with depression experienced remission, while 44-52% of patients partially recovered and 17-33% experienced a severe chronic course (Beekman et al., 2002).

Late-life depression is also a key prognostic indicator for a variety of adverse health outcomes, such as decreased quality of life (Post, 1962; Saracli et al., 2015), frailty (Paulson & Lichtenberg, 2013b), heart disease (Musselman, Evans, & Nemeroff, 1998), and stroke (Pan, Sun, Okereke, Rexrode, & Hu, 2011) with each outcome often resulting in higher rates of non-suicide mortality (Schulz et al., 2000; Schulz, Drayer, & Rollman, 2002). Suicide risk is also common in the elderly population as cases of suicide mortality are nearly twice as frequent than in the general population, with nearly 80% of these cases experiencing mood disorders (Chan, Chiu, Lam, Wong, & Conwell, 2014). Depression has also been shown to lead to cognitive impairment, mimicking dementia. Termed *pseudodementia*, those with this condition experience memory deficits, executive function deficits, and deficits in speech and language domains; however, cognition typically returns to premorbid functioning following successful treatment of depression (Kang et al., 2014; Kral & Emery, 1989). Older adults also face increased risk of activities of daily living (ADL) impairment due to a greater likelihood of disability (Barry, Allore, Bruce, & Gill, 2009; Bruce, Seeman, Merrill, & Blazer, 1994; Lichtenberg, Gibbons, Nanna, & Blumenthal, 1993).

Vascular Depression

Beyond the previously mentioned risk factors, high cerebrovascular burden (CVB), or burden on the vasculature of the brain, has been distinguished as a significant risk factor for depression in late life. Referred to as "vascular depression," this syndrome consists of cerebrovascular risk factors that "predispose, precipitate, and perpetuate" the development of depressive symptomatology among older adults (Alexopoulos et al., 1997). It has been theorized that vascular depression occurs when CVB induces neurological deterioration in the white matter of the brain, causing white matter hyperintensities (WMH). These WMH interrupt neurological pathways involved with cognitive functions including both emotional regulation and executive functioning. During the early stage of this disease is when depressive symptomatology begins to develop (Paulson & Lichtenberg, 2013a). Factors including hypertension, diabetes, and cardiac disease lead to increased white matter hyperintensities beyond what is expected as a result of typical aging (Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010). A common contributor to cerebrovascular burden is hypertension. Defined as diastolic pressure above 90 mm Hg and systolic blood pressure and above 160 mm Hg (Beevers, 2014; Beevers, Lip, & O'Brien, 2001), consistently high blood pressure has been shown to have deleterious effects on the brain. Similar findings have been demonstrated in older adults with diabetes, where MRI results showed the brains of patients with diabetes were significantly more atrophied. Additionally, diffusion tensor imaging (DTI) showed that patients with diabetes had reduced fractional anisotropy for total white matter and increased mean diffusivity for the bilateral hippocampus, dorsolateral prefrontal cortex (DLPFC), left posterior cingulate, and right putamen, which indicates demyelination and axonal loss (Falvey et al., 2013). Further, MacFall and colleagues (2001) demonstrated that left orbitofrontal cortex lesions, which is associated

with emotion regulation, relate to increased risk of developing depression. Specifically, these effects have been identified in the form of structural damage (Gąsecki, Kwarciany, Nyka, & Narkiewicz, 2013), white matter hyperintensities (Gunning-Dixon & Raz, 2000; Raz, Rodrigue, & Acker, 2003), and vascular dementia (Posner et al., 2002).

The aforementioned irregularities within the brain are not without consequence. Specifically, processing speed and working memory, both of which are related to the prefrontal cortex (PFC), exhibit particularly noticeable impairment (Gąsecki et al., 2013; Raz et al., 2003). It is important to note that the impairment associated with these processes was similar between individuals with untreated hypertension and medically treated hypertension as both experience relatively similar impairment (Raz et al., 2003). Increased WMH have been shown to disrupt processes that rely on executive functioning in older adults (Aizenstein et al., 2002), with deleterious effects on inhibitory control behaviors (Murphy et al., 2007) compared to those with reduced amounts of WMH.

Various neuroimaging studies have shown the limbic-cortical-striatal-pallidal-thalamic circuits (LCSPT) to be associated with emotional regulation and related behaviors (Phillips, Drevets, Rauch, & Lane, 2003). These circuits include the connections between numerous structures within the brain including the orbitomedial prefrontal cortex (OMPFC), amygdala, subiculum, ventromedial striatum, mediodorsal and midline thalamic nuclei and ventral pallidum (Öngür, Ferry, & Price, 2003). Disruptions in the OMPFC network, caused by WMH, have been shown to result in depressive symptoms due to interferences in synaptic transmission (Drevets, Gadde, Krishnan, & Ranga, 2004). The visceromotor network, which is associated with emotional regulation, has also been shown to be disrupted by WMH. (Drevets, Price, & Furey, 2008). Further, disrupted medial prefrontal cortex (MPFC) and limbic structure functioning are

associated with mood-related disturbances such as emotional processing dysregulation, cognitive performance, neurotransmission, autonomic regulation, and neuroendocrine responses (Drevets et al., 2008). Older adults with a greater quantity of hyperintensities tend to exhibit greater numbers of depressive symptoms than those with fewer or no hyperintensities (Coffey, Figiel, Djang, & Weiner, 1990). Likely the consequence of these microvascular changes, disruption in the frontal subcortical white matter results in the expression of depressive symptoms. Compelling evidence for this relationship includes the finding that deep white matter hyperintensities indicate the presence of vascular depression within older populations with a perfect sensitivity of 1.00 and a specificity of .95 (Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008).

Tenants of vascular depression theory are further supported by clinical evidence. Mast and colleagues reported that the presence of two or more cerebrovascular risk factors is associated with significant increases in depressive symptomatology at 18-month follow-up (Mast, Azar, & Murrell, 2005; Mast, Yochim, MacNeil, & Lichtenberg, 2004; Paulson, Bowen, & Lichtenberg, 2014). Longitudinal follow-up supports that finding with additional results showing that patients were five times more likely to exhibit depressive symptoms when two or more cerebrovascular risk factors were present compared to zero or one cerebrovascular risk factor (Mast, Neufeld, MacNeill, & Lichtenberg, 2004). Although these studies present compelling evidence, other findings do not support the vascular depression hypothesis (Lyness et al., 1999).

Functional Near-Infrared Spectroscopy

In recent years the use of fNIRS has become increasingly popular due to many advantages over other neuroimaging methods including affordability, portability, and reduced artifacts due to movement. fNIRS monitors brain activity by measuring changes in oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb), similarly to fMRI (Herrmann, Ehlis, & Fallgatter, 2003). Because near-infrared light ranges between 700-900 nm, it is able to pass through most of the tissue at the scalp and reach the cerebral cortex. When the photons reach the cerebral cortex, chromophores within both O_2Hb and HHb absorb the energy to varying degrees as O_2Hb is slightly paramagnetic, and HHb is highly paramagnetic. That is, HHb absorbs less energy than O_2Hb (Bren, Eisenberg, & Gray, 2015; Pauling & Coryell, 1936). Photons that are not absorbed follow a banana-shaped path and return to the surface of the scalp where they are measured by photoreceptors (Gratton, Maier, Fabiani, Mantulin, & Gratton, 1994). The concentration can then be determined using the modified Beer-Lambert law (Villringer & Chance, 1997). In regards to measurement, fNIRS has been shown to have good temporal resolution within the millisecond range, though spatial accuracy and depth are somewhat limited (Villringer & Chance, 1997).

In studies that utilize fNIRS, differences in activation between patients with depression (MDD) and healthy controls (HC) have been found. In response to threatening or positive stimuli, patients with MDD showed hyperactivation in prefrontal regions including both the middle frontal gyrus, which includes the DLPFC, and the inferior frontal gyrus (Matsubara et al., 2014). Additional research comparing patients with MDD to HC showed that in MDD patients, the level of O_2HB increase in the frontal lobe was significantly lower in comparison to HC during the Halstead-Retain FAS verbal fluency task and the same task using different letters.

When comparing the two groups at baseline, however, no significant differences in activation were present (Herrmann, Ehlis, & Fallgatter, 2004; Noda et al., 2012).

The CaR-FA-X Model

Depressive symptomatology has been identified as significantly and directly impairing to an individual's specific memory recall ability. This change, described as the Overgeneral Autobiographical Memory (OGM) phenomenon, is expressed by the tendency to recall specific memories in a broad or general fashion. Williams and Colleagues (2007) demonstrated that OGM is more prevalent in individuals with depression than those who are not depressed. Further, this phenomenon has been identified as a risk factor for the onset and course of depression. The maintenance of depression is also largely related to the extent of OGM. In a sample of psychiatric inpatients (age range 18-65) beginning treatment with initial scores on the Beck Depression Inventory II indicating severe depression (M = 29.70, SD = 11.00), those with lower rates of OGM were more likely to have fewer depressive symptoms, whereas the quantity of these symptoms remained stable when OGM was high (Hermans et al., 2008).

The mechanisms underlying OGM were partially explained by Conway and Pleydell-Pearce (2000) who described this process as a functional avoidance technique to distance oneself from the effects of discomforting emotional memories. Because this only partially explains the underpinnings of OGM, Conway and Pleydell-Pearce's hypothesis was developed further into a comprehensive model termed the CaR-FA-X Model. This model conceptualizes the OGM as three distinct processes: capture and rumination, functional avoidance, and impaired executive control (Williams et al., 2007).

When in the process of retrieving a memory that encompasses personal concerns or self-representation, attention can remain fixated on the general concept behind the memory instead of retrieving the specific event. In other words, the memory retrieval process becomes *captured* (Ca) and prevents the individual from proceeding beyond the OGM and can trigger rumination (Williams et al., 2007). Rumination (R), which is tied closely to capture, is the attentional focus on one's depressive symptoms and their implications. These negative thought processes are self-focused and repetitive in nature, and have a likelihood to develop into a fixation on general memories (Sutherland & Bryant, 2007). Other findings demonstrate how the manipulation of rumination influences OGM, suggesting that rumination may be a mediating factor or mechanism in the retrieval of overgeneralized memories (Sutherland & Bryant, 2007). When the memory retrieval process is captured, this occurs as an apparent attempt to prevent the recollection of specific memories that may illicit undesired emotional responses (Sumner, 2012).

Functional avoidance (FA), the second mechanism that comprises the CaR-FA-X model, is the process of passively avoiding the retrieval of specific memories to aid in regulation of emotions. Considered an avoidance strategy, it is thought that recalling memories in this more generalized manner reduces the strain brought about by the memory of the specific event itself (Watson, Berntsen, Kuyken, & Watkins, 2013; Williams et al., 2007). Although it is thought to be an avoidance strategy developed to deal with trauma experienced early in life, over time the use of functional avoidance tends to extend to beyond specific traumatic memories to any specific memories as a result of consistent reinforcement (Conway & Pleydell-Pearce, 2000; Sumner, 2012; Williams et al., 2007).

The final mechanism Williams and colleagues (2007) proposed to underlie overgeneralized memories is impaired executive control (X). Executive control is largely

responsible for inhibition (Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001), working memory and information updating (Piolino et al., 2010), selective attention and the ability to maintain attention (Alvarez & Emory, 2006), goal-directed behavior, and verbal proficiency (Sumner, 2012; Sumner et al., 2014). Sumner and colleagues (2014) demonstrated that verbal fluency and brooding, described as analytical rumination, affect the degree of specificity of a given memory based on whether the individual had a history of major depressive disorder. Those with a history of major depressive disorder engaged in more brooding, although autobiographical memory specificity increases as well. In a collaborative effort, the aforementioned processes facilitate the retrieval of specific memories. Further, a disruption in any one CaR-FA-X process increases the likelihood that the intended specific memory will not be located, resulting in the recollection of an overgeneralized memory instead.

Primary Goals

Obvious parallels exist between the CaR-FA-X literature and the vascular depression literature. Both lines of study examine mechanisms by which depressive symptoms emerge and are sustained, and both address the connection between executive functions and depression. Despite these obvious parallels, they coexist as unconcatenated distinct research domains. The present synthesis suggests a broader theoretical framework may relate these areas of work. With (a) CVB resulting in the development of white matter hyperintensities, and (b) frontostriatal white matter implicated in mood regulation as well as executive functioning behaviors including inhibitory control, deficiencies in these processes may lead to a dysregulation of the mechanisms described in the CaR-FA-X model. From this broad theoretical framework, several testable hypotheses emerge. CVB will predict depressive symptomatology, decreases in specific aspects of executive functioning such as inhibitory functioning, increased rumination, and OGM in

adults 70 years of age and older. Further, inhibitory functioning will predict rumination, while both inhibition functioning and rumination will also predict depression.

Hypotheses

The goal of this thesis was to examine the relationships among inhibitory functioning, rumination, depression and neurovascular response in older adults with cerebrovascular burden.

Hypothesis 1:

1a) Within adults over the age of 70 years, high CVB will predict depressive symptomatology, decreased executive functioning, and increased rumination.

Hypothesis 2:

2a) Hemodynamic response, reflecting the magnitude of DLPFC and orbitofrontal pole oxygenated and deoxygenated hemoglobin during inhibitory control tasks, will positively predict depression.

2b) Hemodynamic response, as characterized in the prior hypothesis, will positively predict executive functioning.

2c) The relationship between hemodynamic response and depression will be mediated by executive functioning.

Hypothesis 3:

3a) Hemodynamic response will positively predict depression.

3b) Hemodynamic response will positively predict rumination.

3c) The relationship between hemodynamic response and depression will be mediated by rumination.

CHAPTER 2: METHODS

Participants

The current study recruited 52 participants over 70 years of age from the Learning Institute For Elders (LIFE) group at the University of Central Florida (UCF), as well as from the surrounding community. A direct analogue of the proposed research could not be identified in the extant literature, though a conceptually similar study examining the relationships between rumination, depression, and size of the DLPFC was used to estimate sample size required for the proposed research (Wang et al., 2015). Based on reported Wang et al.'s (2015) findings, a sample size of 32 was necessary to provide an 80% probability of identifying an indirect effect with r^2=.16. Selected participants were drawn from the larger Vascular Aging Study. Selected participants included those who are self-reportedly right-hand dominant, have normal or corrected to normal vision, speak English as a native language, have no reported developmental or neurological disorders, no history of head trauma or cerebrovascular events, and are not currently taking medications (narcotic, sedatives, anti-epileptic) that may interfere with cognitive ability. Additionally, the Telephone Interview for Cognitive Status (TICS) was used to rule out the presence of moderate to severe dementia. Participants provided informed consent in accordance with the procedures of the University of Central Florida Institutional Review Board.

Measures

A participant questionnaire was used to collect demographic information including age, gender, ethnicity, race, and socioeconomic status. Additionally, participants were asked questions regarding activities of daily living (ADLs), self-rated quality of sleep and sleep habits. The cerebrovascular burden of each participant was measured using self-reported diabetes, chest

problems cardiac disease, and high cholesterol. A composite score for self-reported cerebrovascular burden was then calculated by summing the CVB self-report responses and converting the total into a z-score.

Telephone Interview for Cognitive Status-Modified (TICS-M): This 11 item test is slightly modified from the older TICS measure is an interview designed for assessing an individual's levels of orientation, language, registration, memory, spelling, and calculation in person or by telephone (Brandt, Spencer, & Folstein, 1987). The maximum possible score is 35, with scores below 11 suggesting clinically significant cognitive impairment. The TICS has high test–retest reliability and is generally sensitive to cognitive impairment (Desmond, Tatemichi, & Hanzawa, 1994). Modeled after the Mini Mental State Examination (MMS), and containing two questions from the MMS, TICS scores are highly correlated with MMS scores (.94) Additionally, TICS has a sensitivity is 94% and specificity of 100%. Test-retest reliability over a six-week period was reported at .97, and intraclass correlation coefficient was .99. (Brandt et al., 1987).

Geriatric Depression Scale (GDS): This 30-item scale requires participants to indicate their level of depressive symptomatology by responding 'yes' or 'no' to each question. The GDS has an alpha coefficient of 0.92, as well as a sensitivity of 84.2% and a specificity of 72.7% for major depressive disorder among older adults when the cutoff score is 11 (Lach, Chang, & Edwards, 2010).

Ruminative Responses Scale (RRS): This 22-items scale evaluates the degree to which an individual engages in ruminative thinking. Each item of this scale can be rated one of four items, ranging from 1 (Almost Never) to 4 (Almost Always). Overall, this task has demonstrated an alpha coefficient of 0.90, test-retest reliability of 0.67 over a one-year period, and acceptable

convergent and predictive validity (Gonzalez, Nolen-Hoeksema, & Treynor, 2003; Nolen-Hoeksema, Larson, & Grayson, 1999).

Wide Range Achievement Test IV: Reading Test (WRAT IV): The Reading Recognition subtest of the Wide Range Achievement Test, Fourth edition (Dell, Harrold, & Dell, 2008) includes identifying letters and correctly pronouncing a series of words. The reading subtest of the WRAT IV has a reported internal consistency ranging from .92 to .98. The reliability of the measure is also supported by the alternate form coefficient at .95, and alternate-form reliability at .88. In terms of validity, the WRAT IV has been shown to correlate from low to moderate with Wechsler Scales of Intelligence between full-scale IQ and subtest scores ranging from .57 (for spelling) and .72 (for reading).

The Neuropsychological Assessment Battery: Executive Functions Module (NAB): The Executive Functions module consists of Mazes, Judgment, Word Categories, and Word Generation. The Mazes task, a timed planning task, requires participants to complete a series of mazes from start to finish without lifting their pencil from the paper, and it has an alpha coefficient of .78 in adults between the ages 70-97 years (White & Stern, 2003). Judgment consists of 10 daily activity judgment questions pertaining to home safety, health, and medical issues, and has an alpha coefficient of .45 within the same age range. In the Word Categories task, participants are given photographs and information about six people, and are asked to create different two-group categories based on that information. Average inter-rater reliability for this task was .97. This primary function if Word Categories is to measure concept formation, cognitive response sets, mental flexibility, and generativity. For the Word Generation subtest, participants are given two minutes to create as many three-letter words from a list of letters presented. Letters cannot be used twice within the same word, and they must not be proper

nouns. Word Generation is used as a measure of verbal fluency and generativity. This task has an alpha coefficient of .64. Overall, this module has a moderately high correlation with the WAIS-III comprehension subtest, as well as acceptable overall reliability with alpha coefficients ranging from .43 to .64, and the generalizability coefficient is .83.

Halstead-Retain Neuropsychological Test Battery: *Trail Making Test* (TMT) is designed to evaluate neuropsychological functioning and condition of the brain and the nervous system. The test is intended for individuals 15 years and older and is administered as Part A and Part B. For Part A, participants are asked to draw lines connecting consecutively numbered circles on a worksheet. Part B asks that the subject connect consecutively numbered and lettered circles by alternating between the numbers and letters. The test-retest reliability is adequate for Part A, ranging from .36 to .79, and Part B, ranging from .44 to .89. In addition, inter-rater reliability was .94 for Part A, and .90 for Part B (Reitan, 1958).

Autobiographical Memory Test (AMT) measures the degree of specificity to which an individual recalls autobiographical memories based on single-word prompts. Participants are prompted to recall an event that a specific cue reminds them of, and then asked to rate the vividness of the memory on a scale from 1 to 5 and the pleasantness of the memory on a scale from 1 to 5. The alpha coefficient for the AMT is 0.77 (Griffith et al., 2009).

Functional Near-Infrared Spectroscopy (fNIRS) is a non-invasive imaging technology designed to evaluate oxygen levels and changes in the prefrontal cortex through the use of near infrared light and sensors that are applied to the head of the research subject. Neural responses in PFC will be measured using a functional Near-Infrared Spectroscopy (fNIR) system. fNIRS is a brain imaging technology similar to fMRI, as it measures the blood oxygenation level dependent (BOLD) signal. This occurs by measuring the changes in oxygenation levels of tissue within the

cortex. A 22 optode system with 8 sources and 8 detectors designed by NIRx Medical Technologies, LLC (the NIRSport 88 system) will be used. Participants wear a LED-based sensor cap, which is connected to the fNIRS device. The sensor cap contains optode connection points, and ultrasound gel is applied to the interior of the connection points to increase signal strength. Though the fNIRS is capable of measuring the majority of the cortex, the activity of specific regions of interest that will be spatially localized include dorsolateral PFC (Brodmann Areas 9 & 46), anterior PFC (BA 10), and part of inferior frontal gyrus (BA 45). The use of functional near infrared spectroscopy (fNIRS) allows the ratio of O_2Hb to blood volume within the brain to be measured by using light in the near-infrared range between 700 nm and 900 nm to measure physiological changes within the optical composition of these tissues (Bunce, Izzetoglu, Izzetoglu, Onaral, & Pourrezaei, 2006). Using fNIRS during executive functioning tasks, Prakash and colleagues (2009) and Zysset and colleagues (2007) revealed that older adults demonstrate large increases in activation during the interference condition within the left dorsolateral prefrontal cortex (DLPFC), or Brodmann's Areas (BA) 6 and 9 and in the left inferior frontal gyrus (BA 6). While connected to fNIRS, participants will complete tasks including the Flanker task and Stroop test programmed using the software E-Prime 2.0 Professional.

Flanker Task: This measure of inhibitory control includes a control condition and an experimental condition. All participants are administered both conditions. While completing the control condition, the participants will be asked to respond to the directionality of a single large bold arrow by pressing the corresponding keyboard key. If the arrow is pointing to the left, the participant would respond by pressing the 'D' key with their left index finger. If the arrow is pointing to the right, the participant would respond by pressing the 'K' key with their right index

finger. While completing the experimental condition, participants' attention will be directed towards a series of five arrows presented on a computer screen. The participant is asked to press a button indicating the direction of the center arrow (left or right). Some trials will present arrows pointed in congruent directions (e.g. <<<<<). In other trials, peripheral arrows will point in the contradictory direction (e.g. <<><<). This task is alternated in brief blocks with a control task in which the respondent is asked to judge the direction of a single arrow with no distractor stimuli. Instructions are presented on screen and are self-paced. After reading the instructions, a fixation cross appears for 20000ms before the practice trial begins. The practice block consists of 14 trials (7 control and 7 experimental stimuli) each appearing for 5000ms each with a 1000ms fixation cross in between. Feedback consisting of correct, incorrect, or no response is also provided following each practice stimuli. Once the practice block has been completed, the control and experimental blocks follow. There are four control blocks and four experimental blocks, with each block beginning with a 20000ms fixation cross to allow the BOLD signal to stabilize. Control (Figure 1) and experimental (Figure 2) blocks are composed of 12 trials, with each trial presenting for 3000ms and a 1000ms fixation cross between each trial.

Stroop Test: This task consists of four counterbalanced conditions. In the Block A, participants must respond to the color of the text shown by pressing the corresponding key. For this condition, the target text is "******" and can appear as the color red, green, or blue. In the Block B, participants must respond by responding to the word being presented. There are three potential targets, red, green, and blue. All targets in this condition are presented as black text. In the Block C, red, green, and blue are possible target words, and each word presented is colored congruently (e.g. the word red colored red). Finally, in Block D red, green, and blue are possible target words, but two-thirds of the targets are colored incongruently (e.g. the word red colored

green) and one-third of the targets are congruent with participants responding to the text. The four blocks are counterbalanced, and each block begins with self-paced instructions. Following the instructions, there is a practice specific to the type of trials that will be shown in that block. Each practice trial is shown for 5000ms each, with feedback and a 1000ms fixation cross between each trial. A 20000ms fixation cross is shown prior to the experimental trials beginning. Blocks A, B, and C consists of 24 trials lasting 3000ms each, with a 1000ms fixation cross between each trial while Block D consists of 36 trials (Figure 3).

Procedure

Individuals who responded to the study advertisement were contacted initially over the telephone, at which point they completed a brief screening questionnaire as well as the TICS-M to determine eligibility for the study. Those who were eligible were then scheduled to come to the UCF psychology clinic for testing. Once a participant arrived for the testing session, the consent form was explained, including that $20 compensation for participating would be given at the completion of the session, and any questions the participant had were clarified. Further, if the participant met criteria for the fNIRS portion of the session, they were offered an opportunity to complete that portion of the testing and explained that an additional $10 would be provided for this component. Thus, participants included in the proposed research that included the fNIRS component all received $30 compensation for their participation.

After completing the consent process, the participant was asked a range of questions that comprise numerous measures, including demographic information, the GDS as a measure of depression, and RRS as a measure of rumination. The participant then completed the WRAT-IV Reading subtest, a measure of word reading typically interpreted as a gross indicator of

premorbid intellectual functioning, the executive functions module of the NAB and TMT as measures of executive functioning, and then the AMT as a measure of memory specificity. Physiological data such as height, weight, and blood pressure, were also collected. The final portion of testing included two measures of executive functioning, the Stroop and Flanker tasks, using the E-Prime. If the participant agreed to the fNIRS portion of the testing, the tasks were completed while connected to the fNIRS device. Those who did not meet eligibility requirements or preferred not to be connected to the fNRIS device completed the tasks outside of the fNIRS device. Finally, each participant was thanked for participating and compensated accordingly.

Statistical Methods

Examination of primary hypotheses required considerable data preparation. To include executive functioning in the models, a composite score was calculated by converting the reaction time of each experimental condition of the executive functioning tasks (TMT-B, Stroop, and Flanker) into a Z-score, and then summing standardized scores across executive functioning measures to allow for the creation of a composite variable. Similarly, a composite variable representing cerebrovascular burden was generated by summing values reflecting self-reported endorsement of diabetes, hypertension, cardiac disease, or history of cerebrovascular events. Continuous variables were also converted to full-sample z-scores.

FNIRS data were analyzed using NIRSLab in conjunction with SPM12. The approach of NIRSLab uses a general linear model-based method along with atlas-based mapping of the brain to reflect the data accurately. Data representing neurovascular activation was generated during administration of the Flanker and Stroop tasks described above, as these tasks are designed to require inhibitory control. Based on the block design described above, fNIRS-measured O_2Hb

and HHb produced a series of values representing response to task demands associated with the inhibitory control condition. The values from channels 1, 2, and 3 were averaged and the values from channels 20, 21, and 22 were averaged to produce values representing fNIRS-measured O_2Hb and HHb for each participant's LDLPFC and RDLPFC respectively.

To examine the data based on this study's aims and hypotheses, mediation analyses were bootstrapped with bias-correction as described by Efron & Tibshirani (1986). Bootstrapping, which draws a specified number of observations with replacement from the original data, requires a minimum of 32 participants to achieve a power of 0.8. This study drew 5,000 observations (Fritz & MacKinnon, 2007) from the original sample (N = 52) through resampling and replacement. An additional advantage of bootstrapping is that this analytic method does not require the assumptions of normality and homogeneity to be met by the sample. Mediation models were completed using the Process add-on to SPSS 22, which include preconfigured variations of moderation and mediation models (Hayes, 2017). Model 4 of Process, the simple mediation model, was used to address each specific aim of this study. Each model was completed twice, once including the LDLPFC and once including the RDLPFC. In model A of *Figure 4*, the total effect represents the relationship between LDLPFC and RDLPFC O_2Hb and depression (pathway c) prior to examining whether the latent variable for executive functioning serves as a significant mediator of the relationship. Direct effects represent the regression coefficients across model A for O_2Hb and EF (pathway a), and also EF predicting depression after controlling for O_2Hb (pathway b). The direct effect of O_2Hb predicting depression after controlling for the potential mediation of EF and/or rumination is considered as a separate effect (pathway c').

In model B of *Figure 4*, the total effect represents the relationship between LDLPFC and RDLPFC O_2Hb and depression (pathway c) prior to examining whether rumination serves as a significant mediator of the relationship. Direct effects represent the regression coefficients across model B for O_2Hb and rumination (pathway a), and also EF and rumination predicting depression after controlling for O_2Hb (pathway b). The direct effect of O_2Hb predicting depression after controlling for the potential mediation of EF and/or rumination will also be considered as a separate effect (pathway c'). Indirect effects will be examined by accounting for the residual difference of the magnitude between the direct effect of O_2Hb, depression, and the inclusion of each mediating variable, EF and rumination respectively.

Finally, to calculate effect ratios, the indirect effect was divided by the total effect. Doing so provided an estimated proportion for each significant total effect due to the mediating paths.

CHAPTER 3: RESULTS

Demographics

The total sample consisted of 52 participants, which had an average age of 76.40 (*SD* = 4.60), was largely female (63.46%), and predominantly White/Caucasian (90.39%). The sample was well-educated (*M* = 16.46, *SD* = 2.94 years) with an interquartile income range of $42,500.00 and a median income of $62,500.00. Approximately 12% of the sample had GDS scores that fell above the cutoff score of 11. The mean number of endorsed comorbidities (high blood pressure, problems with heart and circulation, chest problems, and problems with diabetes) was 1.02 (*SD* = 1.20). A subset of 33 participants completed the fNIRS protocol, which generated data on hemodynamic response during executive functioning tasks described below. Demographically those individuals were similar to those from the full sample as illustrated in *Table 1*.

Cognitive Performance

Inhibitory control was evaluated based on total reaction time in milliseconds for correct trials only with complete Flanker, Stroop, and Trails B data for 45 participants (see *Figure* 5 for participant allocation). Reaction time on Flanker task hard blocks (*M* = 1,035.40, *SD* = 238.10), Stroop incongruent block (*M* = 1,354.20, *SD* = 258.70), and Trails B (*M* = 94.61, *SD* = 35.87) were used to create a Z-score for each task, and a composite score representing inhibitory control was created by adding together the three z-scores.

Paired samples t-tests showed significant differences between Flanker easy and hard condition accuracy ($t(44) = -2.19$, $p = .033$) and reaction time ($t(44) = 15.34$, $p < .001$) as well as Stroop color (easy) and incongruent (hard) condition accuracy ($t(44) = -2.36$, $p = .022$) and

reaction time ($t(44) = 9.38$, $p < .001$). Significant differences were not observed when comparing oxygenated blood flow during the Flanker easy and hard conditions or the Stroop easy and hard conditions, and deoxygenated blood flow also did not differ significantly between the conditions.

To examine whether oxygenated or deoxygenated blood flow related to task performance, a series of linear regressions were conducted. Results indicated that oxygenated blood flow in the RDLFPC during the Flanker easy condition predicted accuracy during that condition ($\beta = -.41$, t (31) = -2.48, $p = .019$; F (1, 31) = 6.16, $p = .019$), with an R^2 of .166. Results also indicated that deoxygenated blood flow in the LDLPFC during the Stroop incongruent (hard) condition predicted both accuracy ($\beta = -.40$, t (31) = -2.31, $p = .029$; F (1, 31) = 5.33, $p = .029$, $R^2 = .160$), and reaction time ($\beta = .52$, t (31) = 3.25, $p = .003$; F (1, 31) = 10.55, $p = .003$, $R^2 = .274$) during that condition. These results support the rationale for the proposed hypotheses, as findings suggest a relationship between blood flow and task performance.

Cerebrovascular Burden

Hypotheses that high cerebrovascular burden would predict depressive symptomatology, decreased executive functioning, and increased rumination (*hypothesis 1*) were examined using a progression of regression analyses. Results indicated that self-reported CVB predicted depressive symptomatology ($\beta = .29$, t (51) = 2.18, $p = .034$), but did not predict executive functioning ($\beta = -.61$, $t(45) = -1.61$, $p = .069$), or rumination ($\beta = .19$, $t(51) = 1.40$, $p = .168$). Given that CVB predicted depressive symptomatology, previous findings indicating an effect of CVB on blood flow, and the relationship between hemodynamic response and cognitive performance, this indicates further support for the proposed mediation models.

Mediation: fNIRS, Executive Functioning, and Depression

The remaining hypotheses were tested using a subset of 31 participants from the sample who completed the functional near-infrared spectroscopy (fNIRS) portion of testing. To examine the hypothesis that fNIRS hemodynamic response of the DLPFC during inhibitory control tasks would positively predict depression (*hypothesis 2a*), executive functioning reaction time (*hypothesis 2b*) and that the relationship between hemodynamic response and depression would be mediated by executive functioning (*hypothesis 2c*), mediation analyses were conducted using Model 4 in Process (Hayes, 2017). Models were run eight times, first with oxygenated blood flow in the RDLPFC during the Flanker task, oxygenated blood flow in the LDLPFC during the Flanker task, oxygenated blood flow in the RDLPFC during the Stroop task, and with oxygenated blood flow in the LDLPFC during the Stroop task. These models were then run again, but examining deoxygenated blood flow instead. Results of the mediation, which can also be found in Tables 2 and 3, indicated that depressive symptomatology was not predicted by oxy-Hb in the RDLPFC during Flanker (β = -2657.79, *SE* = 1790.35, p = .148), oxy-Hb did not predict executive functioning (β = -6385.93, *SE* = 4149.03, p = .134), and executive functioning did not mediate the relationship between oxy-Hb and depression (β = -3296.57, *SE* = 1839.96, p = .084). Similarly, LDLPFC oxy-Hb during Flanker did not predict depressive symptomatology (β = -1986.46, *SE* = 2582.24, p = .448), or executive functioning (β = -5868.66, *SE* = 5962.90, p = .333), and executive functioning did not mediate the relationship between LDLPCF oxy-Hb flow and depression (β = -2427.71, *SE* = 2627.92, p = .363).

Results of the mediation indicated that depressive symptomatology was not predicted by oxy-Hb in the RDLPFC during Stroop (β = 19.05, *SE* = 85.70, p = .826), oxy-Hb did not predict executive functioning (β = -275.95, *SE* = 185.99, p = .149), and executive functioning did not

mediate the relationship between oxy-Hb and depression (β = 7.38, *SE* = 90.25, *p* = .936). Similarly, LDLPFC oxygenated blood flow during Stroop did not predict depressive symptomatology (β = -262.03, *SE* = 3225.09, *p* = .936), or executive functioning (β = -9799.79, *SE* = 7023.51, *p* = .174), and executive functioning did not mediate the relationship between LDLPCF oxy-Hb and depression (β = -744.19, *SE* = 3376.97, *p* = .827).

To examine the hypothesis that oxygenated hemodynamic response of the DLPFC during inhibitory control tasks would positively predict depression (*hypothesis 3a*), rumination (*hypothesis 3b*) and that the relationship between oxy-Hb and depression would be mediated by rumination (*hypothesis 3c*), mediation analyses using Model 4 in Process (Hayes, 2017) were also used. As with the previous hypotheses, all models were run for the RDLPFC and LDLPFC for both the Flanker and Stroop tasks. Results of the mediation indicated that depressive symptomatology was not predicted by Flanker oxy-Hb in the RDLPFC (β = -1,611.04, *SE* = 1,610.80, *p* = .325), oxy-Hb did not predict rumination (β = -1,812.24, *SE* = 1,965.39, *p* = .364), and rumination did not mediate the relationship between oxy-Hb and depression (β = -919.52, *SE* = 1,468.87, *p* = .536). Similarly, LDLPFC oxygenated blood flow did not predict depressive symptomatology (β = -1,835.07, *SE* = 1,779.50, *p* = .310), or rumination (β = -1,474.32, *SE* = 2,186.99, *p* = .505), and rumination did not mediate the relationship between LDLPCF oxy-Hb and depression (β = -1,270.89, *SE* = 1,608.04, *p* = .436).

Similarly, results of the mediation indicated that depressive symptomatology was not predicted by oxy-Hb in the RDLPFC during the Stroop task (β = 32.13, *SE* = 80.82, *p* = .694), oxy-Hb did not predict rumination (β = 43.56, *SE* = 99.96, *p* = .666), and rumination did not mediate the relationship between oxy-Hb and depression (β = 15.71, *SE* = 72.99, *p* = .831). Similarly, LDLPFC oxy-Hb did not predict depressive symptomatology (β = 853.60, *SE* =

2219.02, p = .703), or rumination (β = 94.17, SE = 2753.08, p = .973), and rumination did not mediate the relationship between LDLPCF oxy-Hb and depression (β = 817.90, SE = 1992.99, p = .685).

The previously described analyses were also run for deoxygenated blood flow as well. Results for HHb followed a similar pattern to those reported for models including O_2Hb and can be found in Tables 4 and 5.

In addition to these analyses, recent findings (Diamond, 2013; Nigg, 2000; Sánchez-Cubillo et al., 2009) suggested that auxiliary analyses were indicated, and therefore a number of post-hoc tests were run examining Stroop and Flanker performance separately instead of as part of a composite score for inhibitory control. Similarly to the previous analyses, hemodynamic response in the RDLPFC and LDLPFC were examined separately to determine if there was a mediating effect of either Stroop or Flanker correct trial reaction time (RT) on the relationship between hemodynamic response and depression. Mediation analyses using Model 4 in Process (Hayes, 2017) were used, and results indicated that depressive symptomatology was not predicted by oxy-Hb in the RDLPFC during Flanker (β = -1,570.02, SE = 1,578.81, p = .328), oxy-Hb did not predict Flanker RT (β = 200.03, SE = 2,087.32, p = . 924), and Flanker RT did not mediate the relationship between oxy-Hb and depression (β = -1,611.04, SE = 1,610.80, p = .325). Similarly, LDLPFC oxy-Hb during Flanker did not predict depression (β = -1,525.23, SE = 1,766.41, p = .395), oxy-Hb did not predict Flanker RT (β = 1,609.45, SE = 2,290.37, p = .488), and Flanker RT did not mediate the relationship between oxy-Hb and depression (β = -1,835.07, SE = 1,779.50, p = .310)

Further analyses indicated that depressive symptomatology was not predicted by hemodynamic response in the RDLPFC during Stroop (β = 17.36, SE = 92.42, p = .852), oxy-Hb

did not predict Stroop RT (β = -158.20, *SE* = 85.69, p = .075), and Stroop RT did not mediate the relationship between oxy-Hb and depression (β = 19.05, *SE* = 85.70, p = .826). Similarly, LDLPFC hemodynamic response during Stroop did not predict depression (β = -460.07, *SE* = 3,502.06, p = .897), oxy-Hb did not predict Stroop RT (β = -6,291.64, *SE* = 3199.13, p = .059), and Stroop RT did not mediate the relationship between oxy-Hb and depression (β = -262.03, *SE* = 3225.08, p = .936)

Correlation: Cerebrovascular Burden, CaR-FA-X, and fNIRS

Finally, a bivariate correlation analysis was conducted to evaluate how the variables included in these analyses (e.g., self-reported CVB, CaR-FA-X, fNIRS) are related. Results can be found in Table 7, and indicate that self-reported CVB was positively correlated with depression (r = .29, p = .03), and Flanker RT (r = .35, p = .01), and depression correlated positively with rumination (r = .63, p < .001). In regard to executive functioning, the easy (color) condition of the Stroop correlated positively with the Flanker easy RT (r = .45, p = .002), RT on the hard (incongruent) condition of the Stroop (r = .59, p < .001), RT on the hard condition of the Flanker (r = .38, p = .009), Trail Making Test B (TMTB) time (r = .52, p < .001), fNIRS O_2Hb activation in the RDLPFC on the hard Flanker condition (r = .39, p = .025), and negatively correlated with accuracy on the easy condition of Stroop (r = -.43, p = .002). RT on the easy condition of the Flanker was positively correlated with both the hard Flanker RT (r = .86, p < .001), and TMTB time (r = .35, p = .01).

Stroop RT on the hard (incongruent) condition was positively correlated with TMTB (r = .36, p = .01), fNIRS HHb activation in the LDLPFC on the hard (incongruent) Stroop condition (r = .52, p = .003), fNIRS activation in the RDLPFC on the hard condition of the Flanker task (r

= .44, p = .01), and negatively correlated with accuracy during the Stroop hard (incongruent) condition (r = -.31, p = .03). TMTB time was negatively correlated with accuracy on the easy (color) condition of the Stroop (r = -.37, p = .011) and fNIRS HHb activation in the LDLPFC on the hard condition of the Flanker task (r = -.37, p = .036). It was also positively correlated with fNIRS O_2Hb activation in the LDLPFC during the Stroop task (r = .40, p = .025), with O_2Hb activation in the RDLPFC during the hard condition of the Flanker task (r = .40, p = .021), and with fNIRS HHb activation in the LDLPFC on the Stroop task (r = .51, p = .003)

Accuracy on the Stroop easy (color) condition of the task was negatively correlated with fNIRS HHb activation in the LDLPFC (r = .42, p = .020), while accuracy on the Stroop hard (incongruent) condition was negatively correlated with fNIRS HHb activation in the LDLPFC. Accuracy on the Flanker easy condition, however, was negatively correlated with fNIRS O_2Hb activation in the LDLPFC during the easy condition of the Flanker (r = -.41, p = .019) as well as during the hard condition in both the LDLPFC (r = -.40, p = .022) and RDLPFC. (r = -.38, p = .029).

CHAPTER 4: DISCUSSION

Primary findings from this study partially supported initial hypotheses and are consistent with recent findings from a subset of the sample used in the current study. Self-reported cerebrovascular burden predicted depressive symptomatology, though executive functioning and rumination did not. The hypothesis that executive functioning mediated the relationship between hemodynamic response-assessed measures of prefrontal recruitment during executive functioning tasks and depression was not supported. Similarly, the hypothesis that rumination mediated the relationship between hemodynamic response and depression was not supported.

Ancillary analyses, however, indicated a number of relationships that support initial hypotheses and may inform future research, though these analyses should be interpreted with caution due to the number of comparisons run and therefore increased potential for family-wise error. Among older adults in this sample, high CVB related to slower response times on measures of inhibitory control. This is consistent with previous research suggesting that among older adults, higher CVB negatively affects executive functioning performance (Mast et al., 2008; Mast, Yochim, et al., 2004; Raz et al., 2003). It is important to note that as described previously self-reported CVB instead of physiological indicators of CVB were used in these analyses and when physiological indicators were used, they did not predict depressive symptomatology. One possible explanation for this occurrence is that a number of the physiological indicators of CVB (e.g., heart rate, blood pressure, blood oxygenation) are health conditions that can be treated. As these health conditions are more state-like, whether they fall within normal ranges or not can be dependent on medication adherence and whether the participant has taken the medication the day of testing. Many participants whose physiological indicators of CVB fell within normal limits also endorsed some of the self-reported indicators of

CVB and also reported taking medication to control the previously described health conditions. It is possible that other physiological indicators of CVB that were not measured as a part of this study, such as intima-media thickness or arterial stiffness, may be better indicators of vascular health that could be comparable to those that are self-reported.

Executive functioning RT was also correlated with O_2Hb fNIRS response in the RDLPFC and HHb fNIRS response in the LDLPFC. Further, negative relationships were found between executive functioning accuracy and LDLPFC and RDLPFC O_2Hb and HHb. These findings are consistent with and extend work by Laguë-Beauvais and colleagues (2013) who found recruitment and lateralization differences between younger (19 – 36 years) and older (59 – 69 years) adults on inhibitory control tasks. Although what they considered as older adults was much younger than the older adults enrolled in the present study, our results indicate that the dispersion of activation during inhibitory control tasks continues to occur as well. The consistency between the patterns of hemodynamic response suggests that fNIRS could be a viable option for use with the older adult population. The fNIRS device is much less expensive than other neuroimaging modalities, easier to maintain, and ferrous metals (e.g., pacemakers, dental implants) do not affect the quality of the signal, and as such may be more accessible in clinical settings. Although this seems promising, follow-up work is needed to ensure that measurement of the hemodynamic response is comparable to that of other modalities, such as fMRI.

Despite null findings for a portion of the proposed hypotheses, this project accomplished the goal of connecting clinically-defined vascular burden (Mast, Neufeld, et al., 2004; Mast, Yochim, et al., 2004; Paulson et al., 2014) with the increased endorsement of depressive symptomatology. Further, this study provides key information that further supports the CaR-FA-

X model, in that the proposed link between CVB and rumination has been demonstrated. In combination with other emerging research (Herrera, 2017), these findings do support the conceptual integration of the vascular depression hypothesis with the CaR-FA-X model. Further work along these lines may lead to the refinement of existing psychotherapies, such as reminiscence therapy, that employ reminiscence of specific memories as a therapeutic device. Additionally, such findings may contribute to identification of emerging psychotherapeutic interventions. A third possibility is that particular treatments may be uniquely suited to varying depression presentations (ruminative, dysexecutive, etc.).

In combination with other emerging work, these results also inform our understanding of CVB measurement and mental health implications of contrasting approaches to CVB measurement. Past treatment of self-report and physiological CVB measures has resulted in conflicting findings throughout the literature. Results of this thesis suggest that future research should include both physiological and self-report CVB measures to help us better understand these differences. This concept was demonstrated in the current study when examining other aspects of the CaR-FA-X model. Specifically, cerebrovascular burden was found to map onto rumination when using self-reported measures but not physiological measures. This approach was also supported by recent emerging research that showed self-reported CVB was a stronger predictor of depressive symptomology and even autobiographical memory then physiological CVB (James, Brush, Herrera, & Paulson, 2018).

Because fNIRS has not been used commonly to date with older adults, the extent to which CVB and aging may potentially interfere with measurement accuracy is unknown. We know from studies employing MRI that cortical thickness is reduced in the presence of both CVB (Leritz et al., 2011) and healthy aging (Raz et al., 2010). Given these changes in thickness

coupled with the limited penetration depth of fNIRS, the question of impact on blood flow detection is warranted and requires validation within an older adult population. Future studies could employ simultaneous fMRI and fNIRS paradigms to compare signal detection between the two modalities. Doing so would potentially promote use of fNIRS for the clinical identification and characterization of vascular neuropathology without the need for MRI, which, given its cost and inaccessibility for reasons discussed previously, would provide significant benefit to this population. Further, it would allow for the identification of novel neuropsychiatric intervention targets. As it was mentioned previously, it is possible that indicators of CVB may also influence the degree to which O_2Hb and HHb are detected. One such factor not examined during the course of this study was arterial stiffness, though it has been demonstrated as another predictive indicator of cardiovascular health beyond that of even other physiological measures (Hansen et al., 2006). Because there are currently no medications that increase arterial flexibility (Quinn, Tomlinson, & Cockcroft, 2012), it is likely that arterial stiffness would be representative of its actual current state and remain relatively consistent across measurements. As such, future research could incorporate the use of an Arteriograph as a physiological measure to identify CVB and potentially determine whether arterial stiffness affects blood flow detection.

Limitations

A potential limitation to the current study was the conceptualization of inhibitory control. In the current study, inhibitory control was represented by a composite variable that included the reaction time on the Stroop Test, Flanker, and Trail Making Test B. Although these tasks have generally been described as executive control tasks, they may be measuring different aspects of executive control. Specifically, the Stroop Test has been described as an interference control task

instead of an inhibitory control task (Nigg, 2000), while the Flanker and TMTB tasks have been described as requiring inhibitory control over selective attention (Diamond, 2013; Sánchez-Cubillo et al., 2009). This may be an important distinction to make when examining executive dysfunction in vascular depression, as Friedman and Miyake (2004) have demonstrated that the ability to stop unwanted intrusive thoughts relies significantly on interference control instead of inhibitory control. This may also in part be due to the Stroop Test's incorporation of the verbal executive component while the Flanker and TMTB include either little or no verbal engagement. Despite the strong correlations between each task, the subtle distinction between these tasks may suggest that not only do these tasks not represent inhibitory control well and that interference control should be considered separately from inhibitory control when examining vascular depression.

Another limitation was that the sample included in this study might not be representative of the older adult population. Despite recruitment being open to the community, the current sample included many participants who achieved high levels education, remain both physically and mentally active, and engage with the community on a regular basis. As such, minorities were generally underrepresented in the sample. Another additional factor that was not accounted for was participant medication use, as medications that may have had an effect on depressive or cardiovascular symptomatology were not taken into account.

In addition, another variable that was not included in the current study but has been demonstrated as an influential factor likely preceding the CaR-FA-X model is sleep. Recent emerging work suggests that sleep quality predicts both rumination and depression, and these relationships are moderated by inhibitory control (Brush et al., 2018). As such, including sleep in

the CaR-FA-X model may be imperative to understand the mechanisms underlying vascular depression in older adults.

Implications and Directions for Future Research

Findings of this study indicate support for two aspects of the CaR-FA-X model, rumination and executive control, as mechanisms largely responsible for the development of vascular depression in older adults. The current study not only further elucidated the role of various cognitive constructs in the development of depression and addressed some important measurement issues that will facilitate research on these constructs. This work also began to demonstrate the potential usefulness of fNRIS as a means of measuring differences in the hemodynamic response related to depression instead of costly and highly restrictive fMRI.

Future research should address previously described limitations such as recruiting a more diverse sample to allow for better generalization, examine these mechanisms in clinical groups as well as within a younger adult population, and include additional executive functioning measures that test interference control to more accurately assess its role in developing depression.

Further research contributing to the understanding of vascular depression and the clinical use of fNIRS will allow for the development of targeted and cost-effective treatments for late-life depression.

APPENDIX A: TABLES

Table 1: *Demographic Data*

Variable	Mean (SD) or % (Unless indicated otherwise)	
	(*N* = 52)	**(*N* = 33)**
Age	76.40 (4.60)	77.19 (4.38)
Gender (Female)	63.46%	67.70%
Race		
White	90.39%	90.30%
Hispanic/Latino	7.69%	6.50%
Native American	1.92%	3.20%
Education Level (Years)	16.46 (2.94)	16.07 (2.42)
Income (*Interquartile Range*)ǂ	$42,500.00	$45,000.00
Marital Status		
Married	55.77%	48.40%
Divorced	17.31%	22.60%
Widowed	26.92%	29.00%
Employment Status		
Employed Part-Time	5.77%	
Retired	94.23%	100.00%
Handedness (Right)	92.31%	93.50%
Number of People in Household		
One - I live alone	36.54%	38.70%
Two	61.54%	58.10%
Five	1.92%	3.20%
Depressive Symptomatology (GDS)	6.23 (4.10)	5.97 (3.30)
Heart rate	71.67 (13.71)	74.00 (15.76)
Oxygen Saturation	95.02 (5.43)	93.70 (5.57)
Systolic Blood Pressure	134.77 (16.63)	134.23 (18.38)
Diastolic Blood Pressure	71.58 (10.05)	68.87 (9.02)
Self-Reported Health Complaintsǂǂ		
High Blood Pressure	40.39%	45.16%
Heart and Circulation Problems	19.23%	22.58%
Chest Problems	9.62%	16.12%
Diabetes	19.23%	22.58%

ǂ Income Amount in U.S. Dollars
ǂǂ Health Complaints During the Past Year

Table 2: *Regression Results for the Mediation of the Effect of Oxy-Hb on Depression by Executive Functioning*

Model	Estimate	*SE*	*p*
O_2Hb Flanker RDLPFC fNIRS → Depression (c)	-2657.79	1790.35	.148
O_2Hb Flanker RDLPFC fNIRS → ExF (a)	-6385.93	4149.03	.134
ExF → Depression (b)	-.10	.08	.210
O_2Hb Flanker RDLPFC fNIRS → Depression (c')	-3296.57	1839.96	.084
O_2Hb Flanker LDLPFC fNIRS → Depression (c)	-1986.46	2582.24	.448
O_2Hb Flanker LDLPFC fNIRS → ExF (a)	-5868.66	5962.90	.333
ExF → Depression (b)	-.08	.08	.350
O_2Hb Flanker LDLPFC fNIRS → Depression (c')	-2427.71	2627.92	.363
O_2Hb Stroop RDLPFC fNIRS → Depression (c)	19.05	85.70	.826
O_2Hb Stroop RDLPFC fNIRS → ExF (a)	-275.95	185.99	.149
ExF → Depression (b)	-.04	.09	.636
O_2Hb Stroop RDLPFC fNIRS → Depression (c')	7.38	90.25	.936
O_2Hb Stroop LDLPFC fNIRS → Depression (c)	-262.03	3225.09	.936
O_2Hb Stroop LDLPFC fNIRS → ExF (a)	-9799.79	7023.51	.174
ExF → Depression (b)	-.05	.09	.580
O_2Hb Stroop LDLPFC fNIRS → Depression (c')	-744.19	3376.97	.827

*p< .05; ** p <.01; *** p <.001

Table 3: *Regression Results for the Mediation of the Effect of Oxy-Hb on Depression by Rumination*

Model	Estimate	*SE*	*p*
O_2Hb Flanker RDLPFC fNIRS → Depression (c)	-1611.04	1610.80	.325
O_2Hb Flanker RDLPFC fNIRS → Rum (a)	-1812.24	1965.39	.363
Rum → Depression (b)	.38	.13	.007**
O_2Hb Flanker RDLPFC fNIRS → Depression (c')	-919.52	1468.87	.536
O_2Hb Flanker LDLPFC fNIRS → Depression (c)	-1835.07	1779.50	.310
O_2Hb Flanker LDLPFC fNIRS → Rum (a)	-1474.32	2186.99	.505
Rum → Depression (b)	.38	.13	.007**
O_2Hb Flanker LDLPFC fNIRS → Depression (c')	-1270.89	1608.04	.436
O_2Hb Stroop RDLPFC fNIRS → Depression (c)	32.13	80.82	.694
O_2Hb Stroop RDLPFC fNIRS → Rum (a)	43.56	99.96	.666
Rum → Depression (b)	.38	.14	.009**
O_2Hb Stroop RDLPFC fNIRS → Depression (c')	15.71	72.99	.831
O_2Hb Stroop LDLPFC fNIRS → Depression (c)	853.60	2219.02	.703
O_2Hb Stroop LDLPFC fNIRS → Rum (a)	94.17	2753.08	.973
Rum → Depression (b)	.38	.13	.009**
O_2Hb Stroop LDLPFC fNIRS → Depression (c')	817.90	1992.99	.685

*p< .05; ** p <.01; *** p <.001

Table 4: *Regression Results for the Mediation of the Effect of Deoxy-Hb on Depression by Executive Functioning*

Model	Estimate	*SE*	*p*
HHb Flanker RDLPFC fNIRS → Depression (c)	-2080.78	2337.97	.381
HHb Flanker RDLPFC fNIRS → ExF (a)	-6690.60	5365.96	.222
ExF → Depression (b)	-.08	.08	.313
HHb Flanker RDLPFC fNIRS → Depression (c')	-2626.67	2395.64	.282
HHb Flanker LDLPFC fNIRS → Depression (c)	-2944.16	6074.52	.631
HHb Flanker LDLPFC fNIRS → ExF (a)	-8427.20	14084.77	.554
ExF → Depression (b)	-.07	.08	.403
HHb Flanker LDLPFC fNIRS → Depression (c')	-3510.14	6139.30	.572
HHb Stroop RDLPFC fNIRS → Depression (c)	61.41	126.42	.630
HHb Stroop RDLPFC fNIRS → ExF (a)	-209.74	283.13	.465
ExF → Depression (b)	-.04	.08	.649
HHb Stroop RDLPFC fNIRS → Depression (c')	53.15	129.49	.685
HHb Stroop LDLPFC fNIRS → Depression (c)	-1965.99	4627.33	.674
HHb Stroop LDLPFC fNIRS → ExF (a)	-18494.10	9852.47	.071
ExF → Depression (b)	-.06	.09	.486
HHb Stroop LDLPFC fNIRS → Depression (c')	-3135.02	4954.46	.532

*p< .05; ** p <.01; *** p <.001

Table 5: *Regression Results for the Mediation of the Effect of Deoxy-Hb on Depression by Rumination*

Model	Estimate	*SE*	*p*
HHb Flanker RDLPFC fNIRS → Depression (c)	-1436.87	2221.31	.523
HHb Flanker RDLPFC fNIRS → Rum (a)	-1405.69	2710.37	.607
Rum → Depression (b)	.39	.13	.006**
HHb Flanker RDLPFC fNIRS → Depression (c')	-889.09	1995.04	.659
HHb Flanker LDLPFC fNIRS → Depression (c)	-1674.35	2086.38	.428
HHb Flanker LDLPFC fNIRS → Rum (a)	-8.71	2565.92	.997
Rum → Depression (b)	.40	.13	.005**
HHb Flanker LDLPFC fNIRS → Depression (c')	-1670.91	1853.72	.375
HHb Stroop RDLPFC fNIRS → Depression (c)	73.92	122.36	.551
HHb Stroop RDLPFC fNIRS → Rum (a)	108.35	151.04	.479
Rum → Depression (b)	.37	.14	.010**
HHb Stroop RDLPFC fNIRS → Depression (c')	33.39	111.43	.767
HHb Stroop LDLPFC fNIRS → Depression (c)	737.26	2068.17	.724
HHb Stroop LDLPFC fNIRS → Rum (a)	-1030.00	2557.91	.690
Rum → Depression (b)	.39	.13	.008**
HHb Stroop LDLPFC fNIRS → Depression (c')	1134.38	1855.23	.546

*p< .05; ** p <.01; *** p <.001

Table 6: *Bivariate Correlation Analysis of CaR-FA-X Components and Oxy-Hb*

	CVB-SR	GDS	RRS	Stroop Easy RT	Flanker Easy RT	Stroop Hard RT	Flanker Hard RT	TMTB RT	Stroop Easy Acc	Flanker Easy Acc	Stroop Hard Acc	Flanker Hard Acc	Left DLPFC Oxy Stroop Hard	Right DLPFC Oxy Stroop Hard	Left DLPFC Oxy Stroop Easy	Right DLPFC Oxy Stroop Easy	Left DLPFC Oxy Flanker Easy	Right DLPFC Oxy Flanker Easy	Left DLPFC Oxy Flanker Hard
CVB-SR	-																		
GDS	**.29***	-																	
RRS	.19	**.63*****	-																
Stroop Easy RT	.22	**.29***	.26	-															
Flanker Easy RT	.25	.12	.22	**.45****	-														
Stroop Hard RT	.10	.12	.14	**.59*****	.24	-													
Flanker Hard RT	**.35***	.09	.19	**.38****	**.86*****	.20	-												
TMTB RT	.12	.07	.12	**.52*****	**.35***	**.36***	.23	-											
Stroop Easy Acc	.13	.10	.09	**-.43****	-.25	-.18	-.18	**-.39***	-										
Flanker Easy Acc	-.11	.05	.12	-.02	.24	-.11	.28	-.16	.09	-									
Stroop Hard Acc	-.01	.09	.21	-.20	-.20	**-.31***	-.20	-.27	.05	-.04	-								
Flanker Hard Acc	.02	-.01	-.05	-.25	-.13	-.07	-.01	-.25	-.09	-.06	.10	-							
Left DLPFC Oxy Stroop Hard	-.02	.07	.01	.26	.11	.20	.18	**.40***	.21	-.06	-.08	-.01	-						
Right DLPFC Oxy Stroop Hard	.21	.07	.08	.33	.13	.32	.11	.28	-.13	-.06	-.10	-.06	.22	-					
Left DLPFC Oxy Stroop Easy	-.23	.07	.15	.18	-.22	.03	-.19	-.21	-.03	.08	.09	.08	.27	.08	-				
Right DLPFC Oxy Stroop Easy	.03	.06	.07	.23	-.19	.21	-.20	-.14	-.02	-.01	.04	.00	-.09	.42*	**.55****	-			
Left DLPFC Oxy Flanker Easy	.01	-.30	-.10	-.25	-.06	-.04	-.19	.02	-.02	**-.41***	-.25	.06	-.35	-.34	-.16	-.14	-		
Right DLPFC Oxy Flanker Easy	-.28	-.19	-.23	-.13	-.07	-.05	-.16	.02	-.04	-.10	.02	.11	.01	**.71*****	-.07	-.14	.28	-	
Left DLPFC Oxy Flanker Hard	.05	-.18	-.12	-.07	-.14	.23	-.12	-.21	.13	**-.40***	-.31	.04	**-.41***	**-.37***	-.11	.05	**.62*****	.07	-
Right DLPFC Oxy Flanker Hard	-.08	-.18	-.16	**.39***	-.02	**.44***	-.08	**.40***	-.02	**-.38***	-.08	.05	**.49****	**.47****	.01	**.36***	-.20	.12	-.10

*p< .05; ** p <.01; *** p <.001

Table 7: *Bivariate Correlation Analysis of CaR-FA-X Components and Deoxy-Hb*

	CVB-SR	GDS	RRS	Stroop Easy RT	Flanker Easy RT	Stroop Hard RT	Flanker Hard RT	TMTB RT	Stroop Easy Acc	Flanker Easy Acc	Stroop Hard Acc	Flanker Hard Acc	Left DLPFC Deoxy Stroop Hard	Right DLPFC Deoxy Stroop Hard	Left DLPFC Deoxy Stroop Easy	Right DLPFC Deoxy Stroop Easy	Left DLPFC Deoxy Flanker Easy	Right DLPFC Deoxy Flanker Easy	Left DLPFC Deoxy Flanker Hard
CVB-SR	-																		
GDS	**.29***	-																	
RRS	.19	**.63*****	-																
Stroop Easy RT	.22	**.29***	.26	-															
Flanker Easy RT	.25	.12	.22	**.45****	-														
Stroop Hard RT	.10	.12	.14	**.59*****	.24	-													
Flanker Hard RT	**.35***	.09	.19	**.38****	**.86*****	.20	-												
TMTB RT	.12	.07	.12	**.52*****	**.35***	**.36***	.23	-											
Stroop Easy Acc	.13	.10	.09	**-.43****	-.25	-.18	-.18	**-.39***	-										
Flanker Easy Acc	-.11	.05	.12	-.02	.24	-.11	.28	-.16	.09	-									
Stroop Hard Acc	-.01	.09	.21	-.20	-.20	**-.31***	-.20	-.27	.05	-.04	-								
Flanker Hard Acc	.02	-.01	-.05	-.25	-.13	-.07	-.01	-.25	-.09	-.06	.10	-							
Left DLPFC Oxy Stroop Hard	.05	-.19	.02	-.23	-.22	.16	-.25	-.16	-.30	-.31	-.27	.08	-						
Right DLPFC Deoxy Stroop Hard	-.26	-.12	-.16	-.03	.02	.09	-.07	-.02	-.08	-.02	.02	.09	.07	-					
Left DLPFC Deoxy Stroop Easy	.20	-.14	-.00	-.21	-.21	.15	-.12	**-.37***	.15	-.11	-.18	-.05	**.77*****	-.03	-				
Right DLPFC Deoxy Stroop Easy	-.128	-.12	-.09	.22	.15	.24	.02	.21	.14	.06	.02	.02	-.27	**.73*****	-.23	-			
Left DLPFC Deoxy Flanker Easy	-.27	.10	.15	.19	-.14	.00	-.13	-.08	-.01	.12	.08	.08	-.25	-.05	-.30	.10	-		
Right DLPFC Deoxy Flanker Easy	-.12	.01	-.06	.13	-.16	.05	-.21	-.01	.05	.04	.07	-.01	.15	**.51****	.15	**.61*****	.27	-	
Left DLPFC Deoxy Flanker Hard	-.15	.07	-.08	.36	.23	**.52****	.15	**.51****	**-.42***	-.12	**-.40***	.04	**-.55*****	.05	**-.84*****	.25	.23	-.21	-
Right DLPFC Deoxy Flanker Hard	.25	.11	.13	.22	.05	.15	.09	.20	-.14	-.08	-.10	-.07	-.07	**-.88*****	-.10	-.44	.11	-.32	.20

*p< .05; ** p <.01; *** p <.001

APPENDIX B: FIGURES

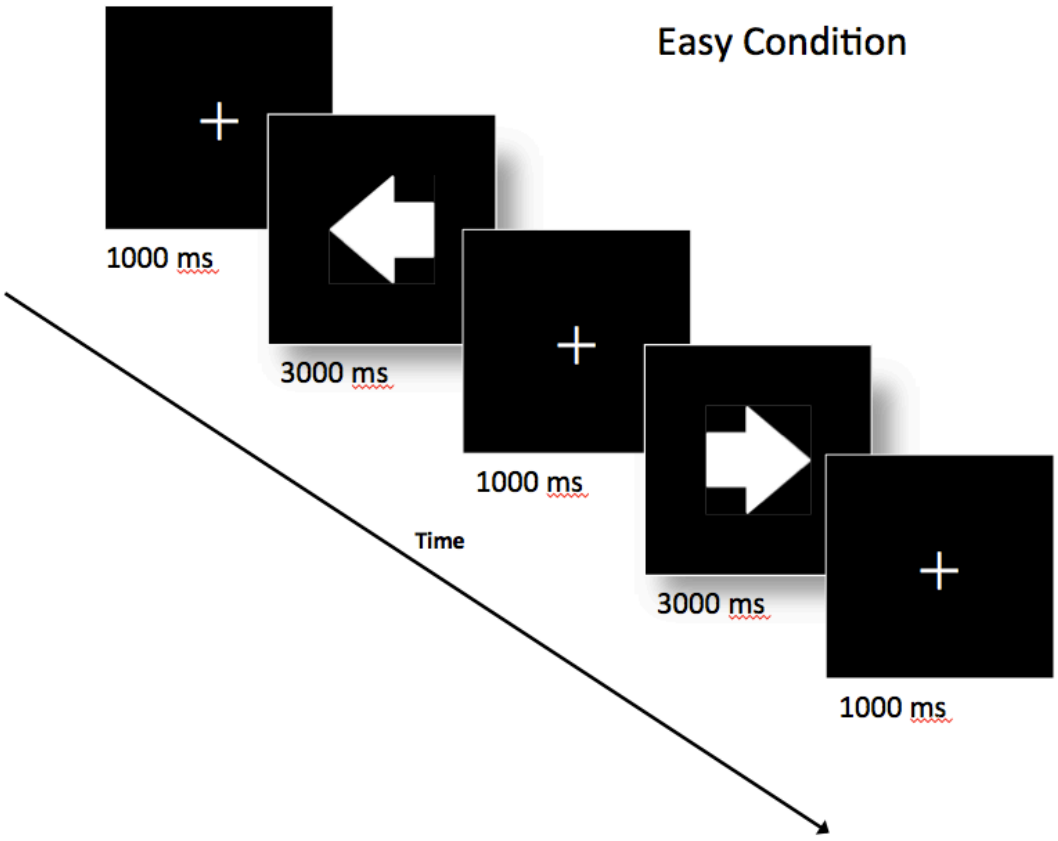

Figure 1: ***Summary of the Flanker easy condition paradigm***

The figure presents an example of a left and right trial. The directionality of each trial is random, and participants report the direction the arrow is pointing via keyboard button press ('D' if pointing left, 'K' if pointing right). The time listed below each picture indicates the duration the stimulus or fixation is on screen. Each block consists of 12 trials is followed by a 20000ms fixation cross before proceeding to the experimental condition.

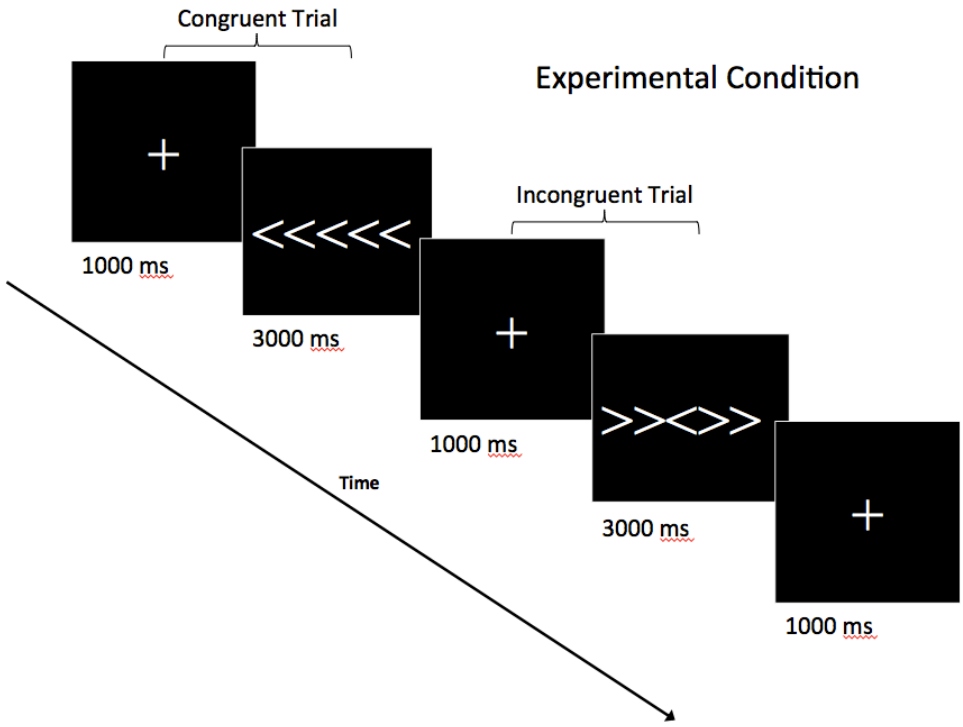

Figure 2: ***Summary of the Flanker experimental condition paradigm.***

The figure presents an example of a congruent and incongruent trial. The directionality of each trial is random, and participants report the direction the arrow is pointing via keyboard button press ('D' if pointing left, 'K' if pointing right). The time listed below each picture indicates the duration the stimulus or fixation is on screen. Each block consists of 12 trials is followed by a 20000ms fixation cross before proceeding to the easy condition.

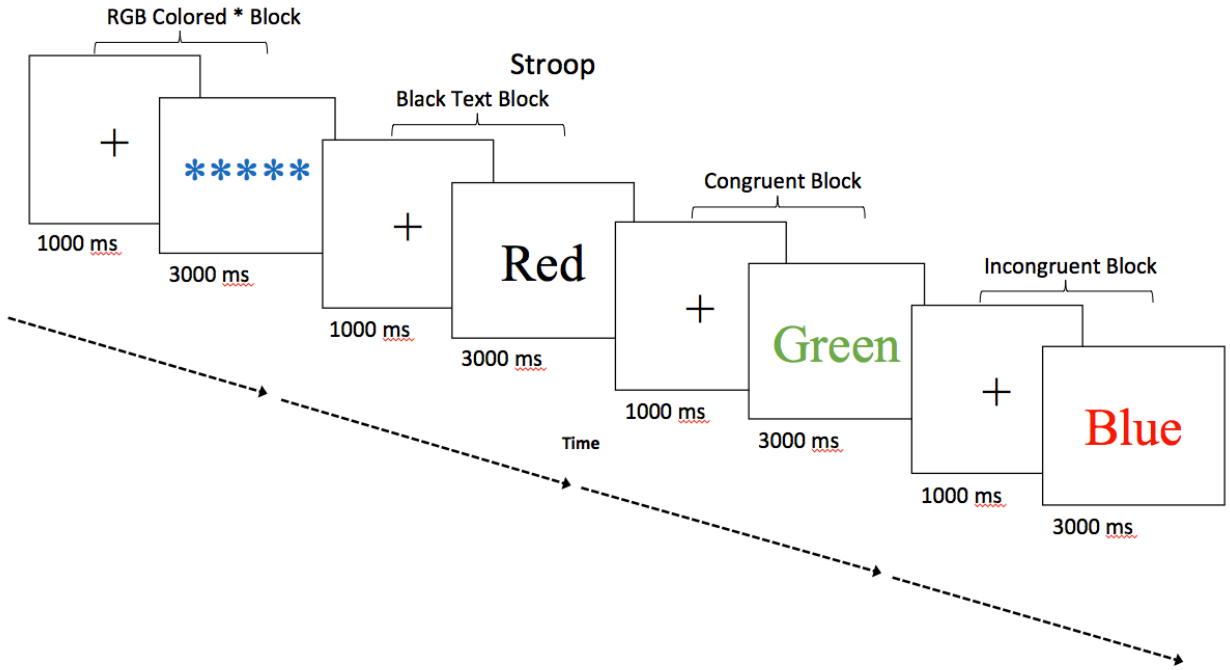

Figure 3: ***Summary of the Stroop paradigm.***

The figure presents an example of the four different blocks. The presentation of each block is counterbalanced, and participants are instructed to report either the color of the text or what the text says via keyboard button press ('8' if Red, '9' if Green, or '0' if Blue). The time listed below each picture indicates the duration the stimulus or fixation is on screen. The incongruent block consists of 36 trials, while the other three blocks consists of 24 trials. Prior to the start of every block, a 20000ms fixation cross is presented.

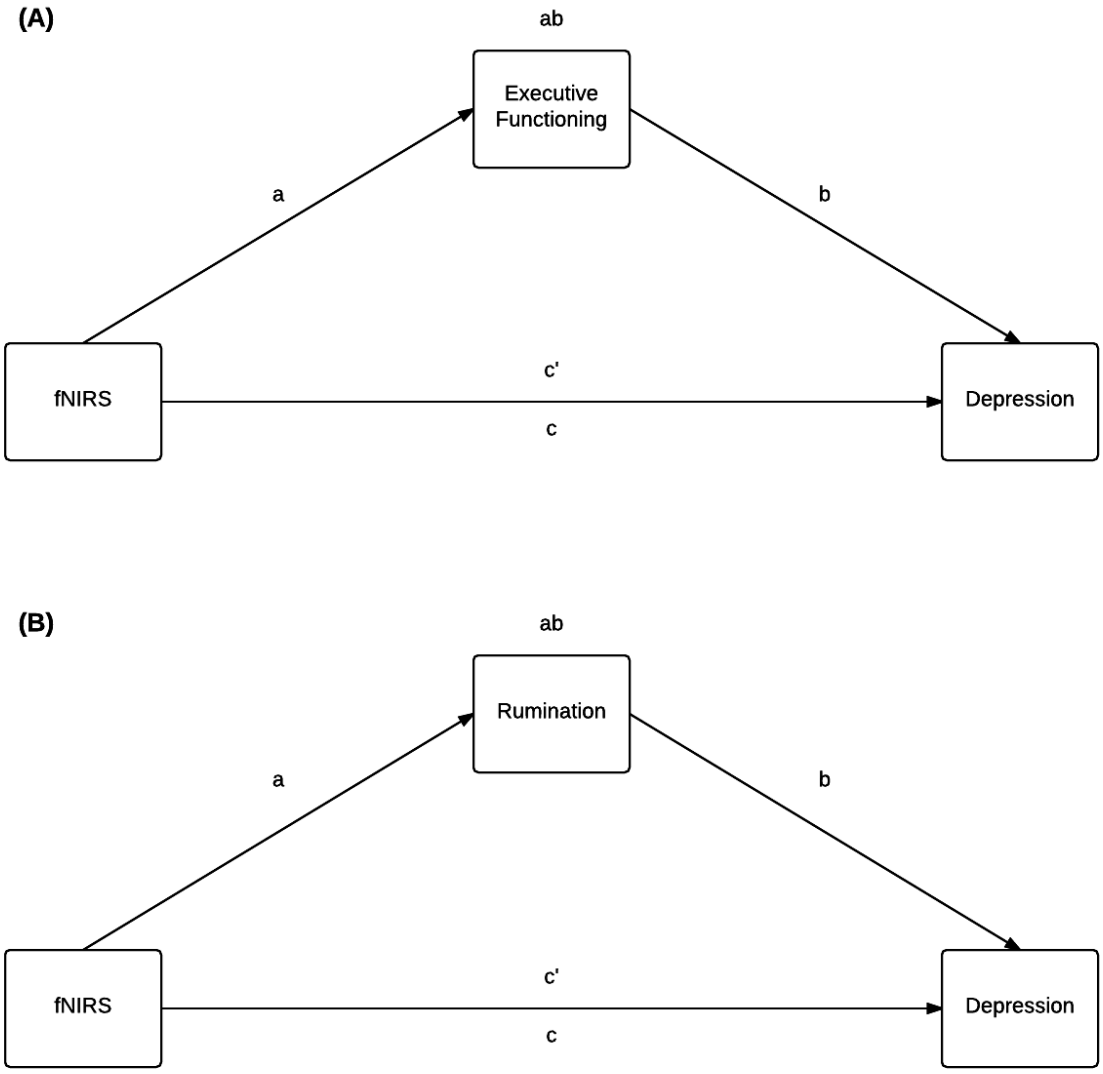

Figure 4: *Hypothesized mediation effects of executive function (inhibitory control) on the relationship between fNIRS response (O2Hb and HHb) and depression (Model A), and hypothesized mediation effects of rumination on the relationship between hemodynamic response and depression (Model B).*

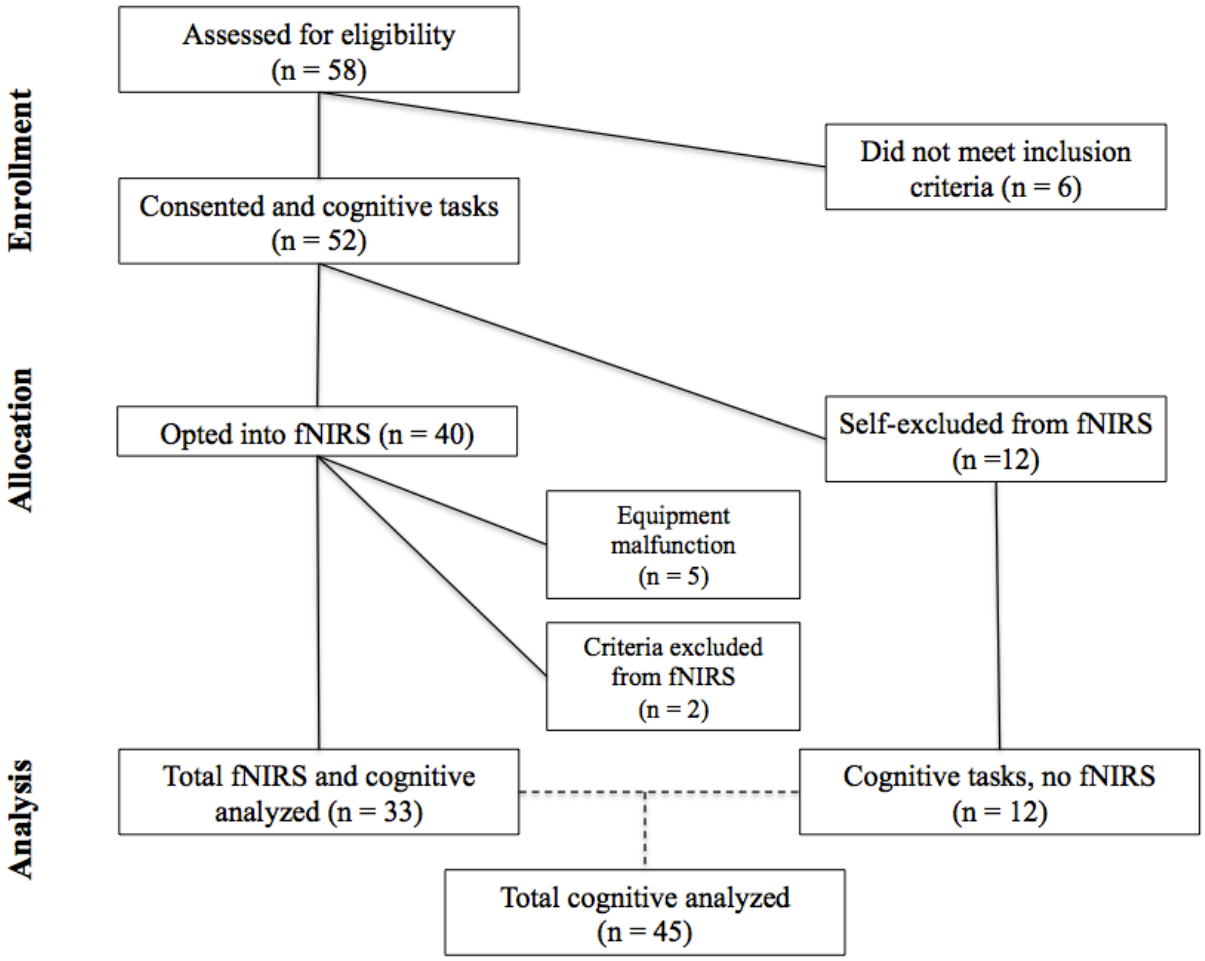

Figure 5: *Consort diagram depicting participant inclusion.*

APPENDIX C: APPROVAL LETTER

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Human Research

From: **UCF Institutional Review Board #1**
FWA00000351, IRB00001138

To: **Daniel Lee Paulson** and Co-PIs: **David Brush & Manuel Herrera Legon**

Date: **January 05, 2017**

Dear Researcher:

On 01/05/2017 the IRB approved the following human participant research until 01/04/2018 inclusive:

Type of Review:	IRB Continuing Review Application Form Expedited Review
Project Title:	UCF Vascular Aging Study
Investigator:	Daniel Lee Paulson
IRB Number:	SBE-15-11791
Funding Agency:	College of Sciences, Learning Institute for Elders at UCF
Grant Title:	
Research ID:	N/A

The scientific merit of the research was considered during the IRB review. The Continuing Review Application must be submitted 30days prior to the expiration date for studies that were previously expedited, and 60 days prior to the expiration date for research that was previously reviewed at a convened meeting. Do not make changes to the study (i.e., protocol, methodology, consent form, personnel, site, etc.) before obtaining IRB approval. A Modification Form **cannot** be used to extend the approval period of a study. All forms may be completed and submitted online at https://iris.research.ucf.edu .

If continuing review approval is not granted before the expiration date of 01/04/2018, approval of this research expires on that date. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

Use of the approved, stamped consent document(s) is required. The new form supersedes all previous versions, which are now invalid for further use. Only approved investigators (or other approved key study personnel) may solicit consent for research participation. Participants or their representatives must receive a signed and dated copy of the consent form(s).

All data, including signed consent forms if applicable, must be retained and secured per protocol for a minimum of five years (six if HIPAA applies) past the completion of this research. Any links to the identification of participants should be maintained and secured per protocol. Additional requirements may be imposed by your funding agency, your department, or other entities. Access to data is limited to authorized individuals listed as key study personnel.

In the conduct of this research, you are responsible to follow the requirements of the Investigator Manual.

On behalf of Sophia Dziegielewski, Ph.D., L.C.S.W., UCF IRB Chair, this letter is signed by:

Kamille Chap

Signature applied by Kamille Chaparro on 01/05/2017 04:52:12 PM EST

IRB Coordinator

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