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Detecting Cognitive, Functional and Behavioral Response to Donepezil in Alzheimer’s Disease: The Role of Attention Tasks

Clara Vila-Castelar

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DETECTING COGNITIVE, FUNCTIONAL AND BEHAVIORAL RESPONSE TO DONEPEZIL IN ALZHEIMER’S DISEASE: THE ROLE OF ATTENTION TASKS

by

CLARA VILA-CASTELAR, M.A.

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2018
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Clara Vila-Castelar

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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THE CITY UNIVERSITY OF NEW YORK
Abstract

Detecting cognitive, functional and behavioral response to donepezil in Alzheimer’s disease: the role of attention tasks

by

Clara Vila-Castelar

Dissertation Chairperson: Nancy S. Foldi

Introduction: Cholinesterase Inhibitors (ChEIs) used in Alzheimer’s Disease (AD) have modest effects, heterogeneous treatment response, and it has been difficult to detect treatment response. The standard research and clinical outcome measure, the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog) aggregates multiple cognitive domains, and has limited sensitivity. We propose that because acetylcholine is directly linked to the cognitive domain of attention, and ChEIs increase available acetylcholine, measures of attention under high-load conditions could predict long-term cognitive, functional and behavioral response, and thus, unlike global measures, could be sensitive to treatment efficacy.

Method: We conducted a longitudinal, open label donepezil trial assessing twenty-three participants with AD at baseline (T1), 6 weeks (T2) and 6 months (T3). Outcome measures were: a) Computerized measures of attention: Foreperiod Effect, Covert Orienting, and Attentional Blink tasks; b) Cognitive: global (ADAS-Cog), memory (Hopkins Verbal Learning Test–Total Recall), executive function (Delis-Kaplan Executive Functioning Scale- Trail Making Test Condition 4); c) Functional: Lawton-Brody Instrumental Activities of Daily Living (IADL); d) Behavioral: Neuropsychiatric Inventory (NPI). Stepwise hierarchical regression analyses were conducted to assess the contribution of different domains, as well as attention change score T2-
T1, on ADAS-Cog T3-T1 change score. Linear regressions assessed whether measures of attention at T2 predicted IADL and NPI scores.

**Results:** Our findings show that attention measures at 6 weeks (T2) could predict 6-month (T3) global cognitive response to treatment better than any other memory or executive measure. Moreover, change in attention performance from baseline to 6 weeks (T2-T1) similarly predicted cognitive performance at 6 months (T3). Finally, performance on attention at 6 weeks (T2) also predicted instrumental activities of daily living and neuropsychiatric symptoms at six months (T3).

**Conclusion:** Our findings support our hypothesis that measures of attention under high-load conditions are sensitive to donepezil. Performance on these measures predicted long-term cognitive, functional, and behavioral response to ChEIs.
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**Introduction**

Alzheimer’s disease (AD) is the most common cause of dementia in older people. Cholinesterase inhibitors (ChEIs), the foremost pharmacological treatment of AD (Bond et al., 2012), prevent the acetylcholinesterase enzyme from breaking down acetylcholine, leading to increased level and duration of the neurotransmitter in the synapse (Čolović, Krstić, Lazarević-Pašti, Bondžić, & Vasić, 2013). Despite widespread use, significant controversy exists about the usefulness of these medications (Schneider, 2004). Clinical trials have consistently revealed small to modest effect sizes and difficulty in determining what constitutes a clinically meaningful response (Rockwood, 2004; Rockwood, Black, Robillard, & Lussier, 2004). The consensus to treat is that these medications help manage symptoms, but treatment is not without risks, as these medications can cause side effects such as bradykinesia, adverse gastrointestinal responses (e.g., dyspepsia, diarrhea, nausea, vomiting, abdominal pain), or sleep disorders including vivid dreams (Dubois et al., 2015; Lockhart, Mitchell, & Kelly, 2009; Schneider & Farlow, 1995). The lack of a metric to demonstrate an individual’s treatment response compromises the medication’s clinical utility (e.g., when or if to discontinue treatment.) Furthermore, the precise impact on cognitive mechanisms of these medications is not fully understood. Since the inception of ChEIs, the industry-wide efficacy measures are global cognitive screeners (e.g., Alzheimer’s Disease Assessment Scale-Cognitive Subscale, ADAS-Cog), which aggregate multiple cognitive domains. These measures were not designed to target effects of the cholinergic system per se, and thus lack specificity, which, in turn, could explain the modest response rates. We posit that attentional mechanisms mediated by acetylcholine could be more specific, and that such measures could better detect treatment response to inform clinical decisions.
Attention and AD

The National Institute on Aging – Alzheimer’s Associations workgroups characterized AD by impairment of a minimum of two of the following cognitive domains: memory, language, executive function, and visuospatial functions that leads to dysfunction in daily activities (McKhann et al., 2011). While the executive dysfunctions can incorporate “executive attentional deficits” (Stuss & Alexander, 2000), attention can encompass broad functions from simple to more complex demands (e.g., target detection, covert orienting, divided attention, selective attention, etc.) (Petersen & Posner, 2012). As such, attention – as a cognitive domain – has not been conceptualized as a dominant cognitive dysfunction in AD.

Yet, a wide variety of attentional deficits exist in patients with AD (Lawrence & Sahakian, 1995; Perry & Hodges, 1999), including worsening in covert orienting (Parasuraman, Greenwood, Haxby, & Grady, 1992), shifting of attention (Filoteo et al., 1992), dual-task processing (Baddeley, Baddeley, Bucks, & Wilcock, 2001), divided attention (Nebes & Brady, 1989), and choice response time (RT) (Levinoff, Saumier, & Chertkow, 2005; Pirozzolo, Christensen, Ogle, Hansch, & Thompson, 1981). These deficits occur very early in the course of the disease even before other cognitive impairments such as memory, visuospatial and language tasks are manifested (Foldi, Lobasco, & Schaefer, 2002; Grady et al., 1988; Reid et al., 1996; Silveri, Reali, Jenner, & Puopolo, 2007).

Following the model of Kahneman (1973), individuals have a finite amount of attentional capacity, and attentional mechanisms serve to manage or allocate those limited resources. Tasks that are too demanding or “high-load” can be better managed via top-down strategies while low-load tasks can be controlled within the available resources, for which “bottom-up” processing could be sufficient. The attentional deficits in AD could be due to a diminished amount of total...
capacity, or inefficient use of available capacity. Some evidence supports the latter poor allocation of resources, wherein patients fail to draw on top-down mechanisms (Perry & Hodges, 2003). Indeed, this would force patients to rely on less efficient bottom up processing (Foldi, White, & Schaefer, 2005), which in turn slows their speed and increases their errors.

Other relevant measures of attentional functions in AD are inconsistencies in performance (as measured by performance variability) and cognitive fatigue. Differences in latency and accuracy across trials within individuals (referred to as intraindividual variability, IIV) is considered to be a robust and consistent concept (Hultsch, MacDonald, & Dixon, 2002; Rabbitt, Osman, Moore, & Stollery, 2001). Williams and colleagues (2005) studied IIV throughout the lifespan, and found lower inconsistency with increases in age throughout childhood, whereas in mid adulthood, inconsistencies increase. This finding was supported by other studies by Der and Deary (2006) as well as MacDonald and colleagues (2006), who found greater variability in reaction time (RT) as a function of age. Despite the increase in IIV with age, research shows that this effect is exacerbated in individuals with cognitive impairments (Christensen et al., 2005; Dixon et al., 2007; Lövdén, Li, Shing, & Lindenberger, 2007), as well as in patients with mild cognitive impairment (MCI), an intermediate stage of cognitive impairment between normal ageing and dementia (Duchek et al., 2009), and patients with AD (Burton, Strauss, Hultsch, Moll, & Hunter, 2006; Rizzo, Anderson, Dawson, Myers, & Ball, 2000). Interestingly, IIV also predicted subsequent cognitive impairment (Koscik et al., 2016). Given these findings, Gorus, De Raedt, Lambert, Lemper, and Mets (2008) proposed to include IIV as a cognitive marker. Furthermore, MacDonald, Cervenka, Farde, Nyberg, and Bäckman (2009) proposed that rises in IIV associated with increased neural noise might be linked to dysfunctional modulation of acetylcholine and dopamine. This suggests a role of cholinergic
activity in variability differences, and raises the possibility that treatment with ChEIs might reduce IIV.

Fatigue is a common reaction to sustained performance, and in the current study, we operationally defined cognitive fatigued as increased RT over a sustained period (Kluger, Krupp, & Enoka, 2013). Acetylcholine levels are correlated with sustained performance (Passetti, Dalley, O'Connell, Everitt, & Robbins, 2000), and heightened fatigue reduces attentional functions in non-demented older adults (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2011). In addition, sustained attention tasks of increased load and longer task lengths are commonly used to elicit fatigue (Claros-Salinas et al., 2013; Möller, Nygren de Boussard, Oldenburg, & Bartfai, 2014; Neumann et al., 2014; Sandry, Genova, Dobryakova, DeLuca, & Wylie, 2014). To our knowledge, cognitive fatigue has not been investigated in patients with AD. Nevertheless, we believe that the documented attentional deficits observed in patients with AD heighten their susceptibility to cognitive fatigue due to either a diminished amount of total capacity, or inefficient allocation of resources.

**Acetylcholine and Attention**

Acetylcholine has traditionally been linked to cognitive functions in particular learning and memory (Bartus, Dean, Pontecorvo, & Flicker, 1985). Degeneration of the basal forebrain cholinergic system has been linked to cognition in patients at high risk of developing AD (Grothe et al., 2010). Recent studies have focused on the pivotal role that acetylcholine plays as a mediator of attention both in animal and human models. Klinkenberg and Blokland (2010) reviewed the effects of cholinergic activity on behavioral functions in rats and cognition in humans, and concluded that the role of acetylcholine on cognition varies depending on the underlying mechanism examined.
Several animal studies investigated the effects of reduced cholinergic activity achieved through different methods, including cholinergic deafferentation (Newman & McGaughy, 2008), 192-IgC saporin (Dalley et al., 2004), or scopolamine (Davidson & Marrocco, 2000). These animal studies found increased sensitivity to cross-modal distractors during a sustained attention task (Newman & McGaughy, 2008); vigilance decrement and increased impulsive responding under conditions of high attentional load in a choice RT task (Dalley et al., 2004); reduced accuracy, increased RT and omission errors in a 5-choice RT in rats (Robbins et al., 1998); and finally, decreased accuracies, and increased RT in a covert orienting task in rhesus monkeys (Davidson & Marrocco, 2000). In a series of pivotal studies, Sarter, Bruno and colleagues demonstrated a reciprocal relationship between cholinergic availability and attentional performance. Himmelheber, Sarter, and Bruno (2000) used a methodology that allowed measurement of acetylcholine levels in rats in vivo during a task of sustained attention. They found that increase in attentional demands (using distractors) was followed by an increase in acetylcholine levels. Furthermore, Kozak, Bruno, and Sarter (2006) proposed demonstrated increases in acetylcholine efflux in the medial prefrontal cortex during an attentional task and even a greater increase in acetylcholine efflux when attentional function was taxed in demanding conditions.

In healthy humans, one ChEI (donepezil hydrochloride), led to improvement in complex sustained attention tasks in trained pilots (Yesavage et al., 2002), while inhibition of acetylcholine using scopolamine resulted in selective attention impairments (Furey, Pietrini, Haxby, & Drevets, 2008). Also, Thienel and colleagues (2009) found that administration of scopolamine led to increased RT for conflicting stimulus processes, suggesting that acetylcholine is involved in executive control. A meta-analysis conducted by Heishman, Kleykamp, and
Singleton (2010) concluded that nicotine (a nicotinic acetylcholine receptor agonist) improved alerting and orienting RT. Together, these studies implicate how acetylcholine is involved in attentional processing particularly when the demands of the task are complex or high load. This evidence suggests that if we want to detect effects of cholinergic modulation, we need to incorporate high-load attention measures.

**AD, Attention, and Cholinesterase Inhibitors**

AD is characterized by a deficiency of the cholinergic neurotransmitter with depletion within the pathways of the basal forebrain and throughout the cerebral cortex (Davies & Maloney, 1976), which has been linked to cortical amyloid burden (Teipel et al., 2014). Pharmacotherapy has sought to enhance available acetylcholine by developing agents that inhibit cholinesterase, and one of the earlier pharmacological treatments (donepezil hydrochloride) acted on and inhibited centrally active acetylcholinesterase, which results in increased acetylcholine levels. The efficacy of ChEI was initially demonstrated in large samples (Feldman et al., 2001; Knopman et al., 1996; Rogers, Farlow, Doody, Mohs, & Friedhoff, 1998; Rogers & Friedhoff, 1996), with small effect sizes (Rockwood et al., 2004) and long treatment times (6 months to 1 year) (Rogers, Farlow, et al., 1998; Winblad et al., 2001). Treatment intervals were problematic, as these could confound pharmacological response and disease progression. At best, efficacy was demonstrated by delaying nursing home placement (Geldmacher et al., 2003). Despite expanded use of these drugs, the relationship between attention and acetylcholine has not been well demonstrated in the assessment of ChEI. The small effect sizes of the aforementioned studies may be partially a function of using global outcome measures such as ADAS-Cog (Rosen, Mohs, & Davis, 1984) that obscure the sensitivity to attention and memory with an overall score (Karin et al., 2014; Posner et al., 2013; Raghavan et al., 2013; Wesnes et al., 2010).
Targeted cognitive domains may be better response indicators. In a post-mortem analysis of AD patients, choline acetyltransferase activity correlated with an attention/registration score that was computed grouping Dementia Rating Scale and Mini Mental State Examination items that loaded into a single “attention” latent variable in a factor analysis (e.g., digit span and following commands), wherein higher levels of choline acetyltransferase activity was associated with higher scores (Pappas, Bayley, Bui, Hansen, & Thal, 2000). Moreover, treatment with cholinesterase inhibitors demonstrated attentional and executive control enhancement (Behl et al., 2014; Bentley, Driver, & Dolan, 2008; Bracco, Bessi, Padiglioni, Marini, & Pepeu, 2014; Caramelli et al., 2004; Foster, Drago, Roosa, Campbell, & Witt, 2016). Finally, with respect to functional neuroimaging in patients with AD, ChEI response appears to affect extrastriate and frontoparietal regions involved in attentional function (Bentley et al., 2008). Petrella et al. (2009) showed that after donepezil treatment the placebo group showed decreased cortical activation on the dorsolateral prefrontal, while the donepezil group showed increased activation in the ventrolateral prefrontal cortex. Risacher et al. (2013) demonstrated that donepezil treatment normalized medial temporal lobe activation and improved parietal deactivation. In summary, if attentional function is intrinsically linked to the level of cholinergic activity, it should be used as an outcome measure of ChEI treatment in AD to improve treatment sensitivity.

Our laboratory conducted a study to investigate whether load-dependent attention measures could detect early treatment effects of donepezil hydrochloride in patients newly diagnosed with AD. We posited that if acetylcholine mediates attention (Hasselmo & Sarter, 2011), and increased attentional load taxes the cholinergic system (Himmelheber et al., 2000), (Kozak et al., 2006), then load-dependent attention measures should capture treatment response. Moreover, given their sensitivity, these measures could detect treatment efficacy over a short
treatment period. Confirming our hypotheses, after short-term donepezil treatment (approximately 6 weeks), high-load conditions of three attention measures targeting accuracy, variability, and fatigue detected the drug effects (Vila-Castelar, et al., 2015). Moreover, neither global measures nor any other domain-specific measure of memory, language, visuo-spatial or executive functions could detect treatment response over the same time course. Thus, our current aim is to establish whether these sensitive measures of attention can predict long-term response to ChEIs, as well as functional ability and neuropsychiatric status.

**Cholinesterase Inhibitors and Instrumental Activities of Daily Living**

Functional impairment in the presence of impaired cognition is an essential criterion of an AD diagnosis (McKhann et al., 2011). Detrimental performance on instrumental activities of daily living (IADL), including tasks such as driving or cooking a meal, occurs early in the course of the disease (Bouwens et al., 2007; Giovannetti et al., 2008; Tekin, Fairbanks, O'Connor, Rosenberg, & Cummings, 2002). Decline in functional abilities has been identified as a significant predictor for conversion to MCI (Farias et al., 2017) and AD (Hsiung et al., 2008). And, while the AD diagnosis criteria have undergone changes since its original definition (McKhann et al., 1984; McKhann et al., 2011), functional impairment has always been included.

Several measures have been developed to assess functional impairment. For example, the Clinician’s Interview-Based Impression of Change scale (CIBIC-Plus) (Schneider et al., 1997) assesses functioning in four key areas: general, cognitive, behavioral and activities of daily living. Patients and caregivers rate on a scale from 1-7 relative change with one representing “marked improvement”, seven “marked worsening”, and four “no change”. Lawton and Brody adapted the Physical Self-Maintenance Scale (PSMS) (Lowenthal, 1964) and the Instrumental Activities of Daily Living Scale (IADL) to rate functional independence using a structured
interview (Lawton & Brody, 1969). This scale includes eight items assessing instrumental activities of daily living: ability to use the telephone, shop, prepare food, perform housekeeping, do laundry, use transportation, and handle medications and finances; and six items assessing basic activities of daily living: toileting, feeding, dressing, grooming, locomotion, and bathing. Similar scales include the Disability Assessment for Dementia (Gélinas, Gauthier, McIntyre, & Gauthier, 1999) and the Clinical Dementia Rating Scale (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982), a measure of 6 domains of cognitive and functional performance that include memory, orientation, judgment, problem solving, community affairs, home/hobbies and personal care. The CDR has been used to stage AD progression with a maximum score of five, with higher scores indicating greater functional impairment (Morris et al., 1997).

Cholinesterase inhibitors have been shown to improve functional impairment in patients with mild, moderate, and severe AD, albeit with some mixed results. Winblad et al. (2001) demonstrated gains in IADL performance after one-year of ChEI treatment for individuals with mild to moderate AD. A large body of research demonstrated that ChEIs (including donepezil, galantamine and rivastigmine) slowed the rate of functional decline on daily living performance in patients with mild to severe AD (Burns et al., 1999; Doody, Geldmacher, Gordon, Perdomo, & Pratt, 2001; Feldman et al., 2003; Galasko et al., 1997; Gareri et al., 2014; Gauthier et al., 2008; Grossberg et al., 2013; Hager et al., 2014; Homma et al., 2008; Lopez et al., 2002; Mohs et al., 2001; Nakano et al., 2015; Raskind, Peskind, Wessel, Yuan, & Group, 2000; Richarz, Gaudig, Rettig, & Schauble, 2014; Rogers, Doody, Pratt, & Ieni, 2000; Rogers, Farlow, et al., 1998; Rogers, Doody, Mohs, & Friedhoff, 1998; Tariot et al., 2000; Tariot et al., 2001; Winblad, Kilander, et al., 2006; Zhu et al., 2006). Additionally, ChEIs have been shown to delay nursing
home placement, a proxy that marks significant decline in functional abilities (Feldman et al., 2009; Geldmacher et al., 2003; Howard et al., 2015).

Nevertheless, other studies investigating the effect of ChEIs on functional outcomes in patients with AD were not as conclusive. Black et al. (2007) conducted a 24-week, randomized, double-blind, placebo-controlled donepezil trail, and found that the CIBIC-Plus but not the Alzheimer Disease Cooperative Study–Activities of Daily Living– Severe version detected a treatment effect. While the authors did not address this discrepancy, these findings may be due to the CIBIC-Plus measuring slightly different constructs, or a heightened sensitivity to detect changes in function. Santoro et al. (2010) carried a 36-week, prospective, observational study investigating ChEIs’ efficacy resembling “real practice” settings. Unlike previous studies, ChEIs did not improve or maintain cognitive or functional performance. The differences in sampling and less rigorous procedures of this long-term trial (e.g., lack of randomization, placebo-controlled group) may account for the lack of an effect. Finally, Schneider, Insel, and Weiner (2011) used a cohort study to retroactively investigate the effect of ChEIs on rate of decline in patients with MCI and AD. This study found that MCI and AD patients who were treated with ChEIs declined faster than patients who were not on treatment. Once again, there are important limitations to this study, as it was not a treatment study or a clinical trial, and thus, medication was not assigned randomly or under double-blind procedures.

Global Measures and Treatment Outcomes

The ADAS-Cog (Rosen et al., 1984) has been used as the industry-wide standard for neurocognitive performance during clinical trials for AD. It was developed to assess drug efficacy in AD treatments and it assesses word recall, naming objects and fingers, commands, constructional praxis, ideational praxis, orientation, word recognition, remembering test
instructions, spoken language, word finding, and comprehension. This measure ranges from no impairment (i.e., total score = 0) to severe impairment (i.e., total score = 70), with any scores equal to or above 18 indicating impairment. Despite its widespread use, there are important concerns regarding the psychometric properties of this scale. Karin et al. (2014) compared the psychometric properties of the ADAS-Cog to the Neuropsychological Test Battery (Harrison et al., 2007) detecting change in a donepezil clinical trial with mild to moderate AD patients. Researchers found that the ADAS-Cog demonstrated significant ceiling effects on most of its items, as well as low test-retest reliability. Several other studies have noted concerning limitations of the ADAS-Cog scale such as ceiling effects or low test-retest reliability (Posner et al., 2013; Raghavan et al., 2013; Wesnes et al., 2010).

Numerous ChEI efficacy studies assessed cognition using a global measure, such as the ADAS-Cog or the Mini Mental State Examination (MMSE), in patients with AD yielding mixed findings. Recent studies found that ChEIs improved global cognition and activities of daily living (Gareri et al., 2014; Richarz et al., 2014). Other studies indicated a lack of improvement or maintenance of cognition or function after ChEIs treatment trials (Santoro et al., 2010; Wallin, Wattmo, & Minthon, 2011). While response to ChEIs has been proven to be heterogeneous (Tan et al., 2014), there are also multiple methodological differences that could explain the discrepancies among some of these studies, including drug of choice (Ohta et al., 2017), treatment length, study design, efficacy measures, or sample differences such as age, education, or disease severity. Furthermore, an examination of comprehensive reviews and meta-analyses indicate overall strong evidence supporting the beneficial effect of ChEIs on measures of cognition and/or daily functioning (Deardorff, Feen, & Grossberg, 2015; Di Santo, Prinelli,
Adorni, Caltagirone, & Musicco, 2013; Kobayashi, Ohnishi, Nakagawa, & Yoshizawa, 2015; Tan et al., 2014).

While most ChEI efficacy trials included both measures of global cognition and function, very few articles have directly addressed the relationship between global cognition and functional outcome in AD. For instance, Wlodarczyk, Brodaty, and Hawthorne (2004) investigated the link between cognitive functioning and quality of life. These researchers found a correlation between scores on MMSE and quality of life scale as reported by patient and caregiver. This study exemplifies the link between perceived functioning level and measures of global cognition. Baum, Edwards, Yonan, and Storandt (1996) found that functional behavior was correlated with performance on a neuropsychological battery, while no single test was identified to explain more variance in a sample of patients with AD and controls. Similarly, Nadler, Richardson, Malloy, Marran, and Brinson (1993) found that the Dementia Rating Scale predicted ADLs performance in a psychogeriatric sample. In addition, Liu-Seifert et al. (2015) demonstrated that cognitive decline predicted later functional impairment. Supporting these findings, Wattmo, Wallin, Londos, and Minthon (2010) conducted a ChEI trial and found that lower global cognitive abilities at baseline, as measured by the MMSE, were a risk factor for nursing home placement.

**Domain-Specific Cognitive Domains and Functional Outcomes**

The gold standard efficacy measure, the ADAS-Cog, aggregates performance of all cognitive domains into a global score, which might not capture the effects of treatment on discrete cognitive scores. Thus, specific domains may be more closely linked to functional outcome; however, no general consensus has addressed the relationship between cognitive domains and instrumental activities of daily living (IADL).
Several studies investigated the relationship between executive function and IADL performance in older adults and patients with AD yielding mixed results. Mahurin, DeBettignies, and Pirozzolo (1991) found that an ADL scale, the Structured Assessment of Independent Living Skills, correlated highly with visuospatial abilities, attention, and visual memory in a sample of AD and controls. Similarly, Benedict, Goldstein, Dobraski, and Tannenhaus (1997) found that a task performance ADL measure correlated with measures of visuospatial and executive function in a geriatric sample, even after controlling for premorbid IQ and mood state. Brown, Devanand, Liu, and Caccappolo (2011) investigated the relation between memory and functional outcome in patients with MCI and AD and found an inverse relationship between the magnitude of functional impairment and performance on auditory and verbal memory tasks.

Attentional deficits are a hallmark symptom early in the course of AD (Perry & Hodges, 1999). Moreover, attention has been closely linked to executive function, exemplified by the concept of executive attention, coined by Stuss and Alexander (2000). Baddeley et al. (2001) referred to this mechanism as the ability to allocate attentional resources when task demands shift. Stoeckel et al. (2013) found that a measure of attention (Dementia Rating Scale – Attention) was associated with financial ability performance in patients with mild AD, and two separate studies linked visual perceptual functions to IADL status (Glosser et al., 2002; Jefferson, Barakat, Giovannetti, Paul, & Glosser, 2006). Other studies corroborated the link between IADLs and executive function both in patients with MCI and AD (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Boyle et al., 2003; Cahn-Weiner, Boyle, & Malloy, 2002; Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000; Hall, Vo, Johnson, Barber, & O'Bryant, 2011; Marshall et al., 2011; Monaci & Morris, 2012; Pillai, Bonner-Jackson, Walker, Mourany, & Cummings, 2014). More recently, Mayo et al. (2013) found that IADL performance
predicted scores on the CDR judgment/problem Solving subscale. Miloyan, Razani, Larco, Avila, and Chung (2013) found that the digit span backwards, but not forward score, was the best predictor of daily function abilities.

In contrast, a recent study conducted by Lee et al. (2015) demonstrated attentional improvements after galantamine treatment, but no significant association between changes in attention and activities of daily living or cognition. Thus, given the relationship between functional outcome and neuropsychological performance (Brown et al., 2011; Lee et al., 2015; Marshall et al., 2011; Mayo et al., 2013; Miloyan et al., 2013; Monaci & Morris, 2012; Stoeckel et al., 2013), determining the magnitude to which cholinergic system based impairments affect functional outcome performance would be extremely beneficial in elucidating the neurobiological correlates of functional impairment.

**Cholinesterase Inhibitors and Neuropsychiatric Function**

Other key contributors to the clinical presentation in AD are neuropsychiatric symptoms, often referred as behavioral and psychological symptoms’ of dementia (BPSD) (Finkel, 1996). BPSD may include irritability, apathy, delusions, hallucinations, and depression (Lyketsos et al., 2000), and are present in approximately 85% of patients with MCI (Apostolova & Cummings, 2007; Rozzini et al., 2007), and 60-90% of patients with AD (Cummings et al., 2016). Importantly, behavioral symptoms led to greater degree of caregiver burden (Rouch et al., 2014), premature institutionalization, and lower quality of life (Cerejeira, Lagarto, & Mukaetova-Ladinska, 2012) and may also predict faster decline in patients with MCI (Palmer et al., 2007; Teng, Lu, & Cummings, 2007), and cognitively normal patients (Burke, Maramaldi, Cadet, & Kukull, 2016; Masters, Morris, & Roe, 2015). The Neuropsychiatric Inventory (NPI) assesses frequency and severity of psychiatric and behavioral symptomatology (Cummings et al., 1994)
and is deemed an effective tool to measure treatment outcome in dementia (Nowrangi, Lyketsos, & Rosenberg, 2015).

Neuropsychiatric symptoms have been linked to imbalances in neurotransmitters (e.g., serotonin, dopamine, acetylcholine, noradrenaline, glutamate, and e-aminobutyric acid) (Pinto, Lanctôt, & Herrmann, 2011). Specifically, in patients with AD, cholinergic deficiency affecting the limbic system, frontal lobe, temporal regions and other relevant projections have been associated with the presence of apathy, agitation, aggression, and psychosis among others (Cummings & Back, 1998; Francis, Ramírez, & Lai, 2010; Lanari, Amenta, Silvestrelli, Tomassoni, & Parnetti, 2006; Lemstra, Eikelenboom, & van Gool, 2003). Moreover, Van Dalen, Caan, van Gool, and Richard (2016) recently demonstrated that lower fractional anisotropy and higher mean diffusivity (proxys of degeneration) in the nucleus basalis of Meynert cortical pathway were associated with specific neuropsychiatric symptoms.

ChEIs can improve neuropsychiatric symptoms in patients with AD after varied treatment intervals of 12 weeks (Gareri et al., 2014; Gauthier, Juby, Dalziel, Réhel, & Schecter, 2010; Holmes et al., 2004; Matthews, Korbey, Wilkinson, & Rowden, 2000; Nakano et al., 2015; Richarz et al., 2014; Rosenblatt, Gao, Mackell, & Richardson, 2010; Yang & Kwak, 2016), 24 weeks (Carrasco, Agüera, Gil, Moriñigo, & Leon, 2011; Cummings, Schneider, Tariot, Graham, & Group, 2006; Feldman et al., 2001; Feldman et al., 2005; Gauthier et al., 2002; Rogers, Farlow, et al., 1998; Waldemar et al., 2011) or even longer intervals (Cumbo & Ligori, 2014; Santoro et al., 2010). Using shorter treatment intervals, Cummings, McRae, Zhang, and Donepezil-Sertraline Study Group (2006) corroborated these findings after only 8 weeks of donepezil treatment.
Despite the numerous studies suggesting the effect of ChEIs on neuropsychiatric function, a few studies showed mixed results. Tariot et al. (2001) did not find group differences on the NPI after donepezil treatment in patients with AD who were living on a nursing home setting. However, treatment did improve agitation/aggression symptoms. These findings may be explained by the characteristics of the sample, which included older patients, who were more medically complex, and had more severe AD than those in other studies. In addition, participants were also on concomitant psychotropic medications. Winblad, Wimo, et al. (2006) did not find an effect of 12-month donepezil treatment on NPI scores in patients with mild-to-moderate AD; similarly, Black et al. (2007) found no significant NPI score differences between patients with AD treated with donepezil for 6 months and those in the placebo group. A recent meta-analysis conducted by Kobayashi et al. (2015) compared the effect of different ChEIs on patients with mild-to-moderate AD, and did not find an effect of treatment on neuropsychiatric symptoms. Differences in results may be due to differences in ChEI selection or dosage, treatment intervals, as well as disease severity.

To date, no study has explored how functioning in specific cognitive domains relate to neuropsychiatric symptoms in patients with AD. Several hypotheses delineated the mechanisms linking treatment improvements in attention, cognitive function, and neuropsychiatric symptoms. Lemstra et al. (2003) proposed that cholinergic deficiency presents with attention deficits that contribute to neuropsychiatric symptoms. Alternatively, Brousseau, Rourke, and Burke (2007) hypothesized that ChEIs improve neuropsychiatric symptoms, which in turn improve attention capacities that result in enhanced cognitive functioning. The paucity of literature studying the mechanisms underlying treatment effects on cognitive domains and neuropsychiatric symptoms, motivated the current study to enhance our understanding the value of ChEIs.
In summary, the degree to which the ADAS-Cog captures cognitive and functional changes in AD, and how neurocognitive performance contributes to neuropsychiatric function in AD remain unclear. Thus, future studies are needed to clarify the effect of ChEIs on neuropsychiatric symptoms, and given the importance of mitigating psychiatric symptoms, it would be valuable to predict which patients will best benefit from ChEI treatment. The goal of this study is to investigate whether measures of demanding attention tasks could predict long-term neuropsychiatric response to donepezil treatment.

**Selection of attentional measures**

Given the documented attentional deficits seen in patients with AD including slower RT (Levinoff et al., 2005; Pirozzolo et al., 1981), higher inconsistency (Burton et al., 2006), reduced cueing effect in covert orienting (Parasuraman et al., 1992), and less efficient top-down abilities (Perry & Hodges, 2003), and based on our previous results where high-load attention measures detected an early response to donepezil, we selected attention measures of accuracy, variability, and fatigue under conditions of increased load.

Accuracy was measured using the Attentional Blink paradigm (Duncan, Ward, & Shapiro, 1994), which occurs when stimuli are presented in rapid succession, and resources used for processing and identifying the first stimulus can prevent or impair accurate processing of the succeeding stimulus. A common Attentional Blink paradigm is the rapid serial visual presentation paradigm, in which two targets (typically alphanumeric characters of letters or numbers) are placed among a stream of stimuli (Raymond, Shapiro, & Arnell, 1992). Given prior instructions, the participant is informed of which impending target to search. The Attentional Blink phenomenon is measured by the accuracy of the second target after varying SOAs, with lower accuracy after the shorter SOA (e.g., SOAs below 350ms).
There is evidence that age affects the duration of the Attentional Blink. Older adults take longer to recover resources and are only able to identify the second target when it is after a longer interval (i.e., greater blink duration), compared to younger adults who can recover from the Attentional Blink in a shorter period (Georgiou-Karistianis et al., 2007; Lahar, Isaak, & McArthur, 2001). There is evidence of reduced executive attentional control in aging and specifically decline in top-down processing. Perry and Hodges (2003) examined Attentional Blink in MCI using a variation of the classic rapid serial visual presentation paradigm. In brief, their experimental apparatus involved varying the time between targets as opposed to number of distracters. They found that MCI subjects had worse accuracy (i.e. greater Attentional Blink magnitude) at short intervals compared to healthy older adult controls. Our experimental procedure was modeled after Perry and Hodges (2003) to allow us to investigate the effects of ‘top-down’ processing in AD. The task is simplified to accommodate patients’ limitations, yet captures the blink effect in the context by instructing the participants what item to attend to (a letter or a number) pre- and post-treatment. The current study will expand our previous work investigating the effect of AD in the Attentional Blink (Ly, 2013) by investigating whether this task is able to predict long-term response to cholinesterase inhibitors.

Intra-individual variability (IIV) measures inconsistencies in performance, which we evaluated using trial-to-trial fluctuations of RT. Higher IIV has been documented in patients with MCI (Troyer, Vandermorris, & Murphy, 2016) and AD compared to healthy controls (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000), and was explained not only by depleted white matter integrity (Jackson, Balota, Duchek, & Head, 2012), but also increased neural noise due to dysfunctional modulation of acetylcholine (MacDonald, Cervenka, Farde, Nyberg, & Bäckman, 2009). Phillips et al. (2013) has already concluded that higher cognitive demands
increased IIV in response latency tasks in both MCI and AD, and Gorus et al. (2007) also demonstrated reduced IIV after 8 weeks galantamine treatment in AD. Therefore, we hypothesized that treatment with donepezil should reduce IIV of attention tasks, particularly the demanding, short interval conditions.

Fatigue is a common reaction to sustained performance, and in the current study, we operationally defined cognitive fatigue as increased RT over a sustained period (Kluger, Krupp, & Enoka, 2013). Acetylcholine levels are correlated with sustained performance (Passetti, Dalley, O'Connell, Everitt, & Robbins, 2000), and heightened fatigue reduces attentional functions in non-demented older adults (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2011). In addition, sustained attention tasks of increased load and longer task lengths are commonly used to elicit fatigue (Claros-Salinas et al., 2013; Möller, Nygren de Boussard, Oldenburg, & Bartfai, 2014; Neumann et al., 2014; Sandry, Genova, Dobryakova, DeLuca, & Wylie, 2014). To our knowledge, no previous research has investigated cognitive fatigue in patients with AD, and we posited that the attentional and cholinergic deficits observed in patients with AD would heighten their susceptibility to cognitive fatigue, and this, in turn could improve with donepezil treatment.

In summary, we proposed that high-load attention measures targeting accuracy, variability and fatigue should be sensitive indicators of cognitive, functional and behavioral response after 6 weeks and 6 months of donepezil treatment.

**Study aims and hypotheses**

**Aim 1. Attention vs Other domains.** To document which cognitive domains (i.e., attention, memory, and executive function) best account for treatment response at six months (T3). We hypothesize that performance on attention tasks under high load conditions, after only 6 weeks of
treatment (T2), would predict 6-month response to donepezil on ADAS-Cog performance (as the industry-standard measure) (T3-T1).

**Aim 2. Early response.** To determine whether an attentional change seen in patients early in the treatment course predicts drug response. It is hypothesized that change in attention measured between baseline and 6 weeks (T2-T1) will predict 6-month response to donepezil on ADAS-Cog performance (T3-T1).

**Aim 3. IADLs.** Given the contribution of attention and executive function to activities of daily living, our aim is to examine whether early performance on demanding measures of attention could predict functional impairment after 6 months of treatment. It is hypothesized that performance on attention tasks under high load conditions, after only 6 weeks of treatment (T2), would predict 6-month treatment response on instrumental activities of daily living (T3).

**Aim 4. Neuropsychiatric Status.** This is an exploratory aim to determine whether early performance on demanding measures of attention could predict psychological and behavioral functioning after 6 months of treatment. It is hypothesized that performance on attention tasks under high load conditions after only 6 weeks of treatment (T2), would predict 6-month treatment response on neuropsychiatric function (T3).

**Method**

The study was approved by the Institutional Review Boards of the City University of New York, Queens College, Queens, NY, and Winthrop-University Hospital, Stony Brook School of Medicine, Mineola, NY. Written consents were obtained from each participant and next of kin. This study is reported following the 2010 Consolidated Standards of Reporting Trials (CONSORT) guidelines (Begg et al., 1996), and is registered in ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT03073876).
Participants

Twenty-five individuals were recruited through the Memory and Cognitive Disorders Center at Winthrop-University Hospital over the course of approximately 2 years. Patients were referred from other psychologists, geriatricians, internists, and psychiatrists. Patients were recruited after they were newly diagnosed with AD, based on full medical, neuropsychological, neuroradiological (MRI) assessment, and consensus of the neuropsychologist, geriatrician and/or neurologist and radiologist. Inclusion criteria were the National Institute on Aging – Alzheimer’s Associations workgroups diagnostic criteria for AD (McKhann et al., 1984; McKhann et al., 2011) and MMSE (Folstein, Folstein, & McHugh, 1975) score >15 to ensure ability to perform experimental attention tasks. Participants could participate with concurrent therapy of nonsteroidal anti-inflammatory drugs, Vitamin E, or antidepressants. Exclusion criteria were other dementia diagnoses of Parkinson’s disease (PD), Lewy Body dementia (LBD), Normal Pressure Hydrocephalus (NPH), fronto-temporal dementia (FTD), or prominent cerebral vascular accident, prior or current use of cholinesterase inhibitors, use of memantine hydrochloride, and concurrent anticholinergic treatment for non-dementia disorders (e.g., tolterodine or oxybutynin). One participant in the Drug group did not receive allocated intervention due to unrelated medical complications. Two participants in the Placebo group were lost to follow-up, one due to complaints of side effects, and another one moved away. One participant’s 6-weeks (T2) data on neuropsychological measures was lost, and one participant did not complete the second block of the Foreperiod Effect Task at T2. These participants are excluded from the related analyses. Therefore, the final sample included 21 participants.

Demographic characteristics (including age, years of education, and gender), as well as baseline performance on global measures of cognition (MMSE; DRS; ADAS-Cog cognitive
subscale), estimated premorbid skills (NART: National Adult Reading Test (Nelson, 1982)) and measures of functional and mood assessment are described in Table 1.

**Procedure**

We conducted a longitudinal, randomized, double-blind placebo-controlled trial (See Figure 1). In the first arm of the study, all participants were: (1) tested at baseline (T1); (2) randomized into two groups, Drug (n=12, 5mg donepezil hydrochloride, Aricept) or Placebo (n=11, gelatin capsules); and (3) retested after approximately 6 weeks (T2; Average = 46 days). This interval was selected to ensure that testing occurred after steady-state was reached (Rogers, Cooper, et al., 1998). After T2 assessment, the treatment assignment was unblinded, and placebo patients began treatment. During the second arm of the study, all patients were treated open label and retested after 6 months of treatment. Randomization, preparation, and treatment were managed by the pharmacy director of the hospital site. Donepezil hydrochloride, a ChEI, was chosen for this protocol because an effective dose can be achieved early in the course of treatment (Rogers, Cooper, et al., 1998); it requires only once-daily administration and a single dose titration step from 5mg to the dose of 10 mg. Participant caregivers were informed that unblinding would occur only after completion of the T2 session. Study participation was indicated in patient’s medical chart, and the study could be halted and unblinded in case of medical necessity.

Potential participants were clinically screened to meet inclusion criteria listed above, and MMSE and CDR were reviewed. Once met, written informed consent was obtained. Participants were administered neuropsychological tests and attention tasks in a standard sequence designed to avoid task interference. Attention, global, and domain-specific measures were administered at
each time point in an order to avoid interference among tasks. Participants received $30 after each session lasting approximately 2½ hours.

Computerized attention tasks were conducted in a well-lit room, on a 2.01 GHz, 960 MB RAM PC computer, and a 13½” flat screen monitor with a refresh rate of 75 Hz. that was connected to a mount and an Ergodex® keypad with one key positioned in the center of the pad. After participants were seated within comfortable range of the keypad, the monitors were adjusted to 50 cm from the participant, and vertically and horizontally centered at each participant’s line of vision. Participants were instructed not to deviate from that position throughout the experiment, and their head placement was continually monitored. The global and domain-specific cognitive measures were administered in a quiet and well-lit room.

**Measures**

**Global Measures**

The following measures were selected to assess global cognitive function.

a. The Dementia Rating Scale-2 (DRS: Mattis, 1988) is a widely used scale targeting subdomains of attention, initiation-perseveration, construction, conceptualization, and memory with a total maximum score of 144. The test’s total score is used to assess level of cognitive deficit for individuals with dementia, and subscales have been used to describe profiles within patient populations (Vitaliano, Breen, Albert, Russo, & Prinz, 1984).

b. Mini-Mental State Examination (MMSE: Folstein, et al., 1975). This 30-item screening test includes brief assessments of memory, language, praxis, and orientation and has been used extensively in clinical AD research.
c. The Alzheimer Disease Assessment Scale-Cognitive Section (ADAS-Cog: Rosen et al., 1984). This cognitive test was originally designed as a measure of drug efficacy and includes tests of memory, language, praxis, and visuospatial function to generate a maximum score of 70.

d. Geriatric Depression Scale (GDS: Yesavage et al., 1982) depression scale specifically designed for older adults (DV: Global score= max. 30).

e. Clinical Dementia Rating (CDR: Hughes et al., 1982) is used to assess clinical staging of dementia through a semi-structured interviews with the patient and informant to rate the patient’s cognitive abilities in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. (DV: Global Score= max. 5).

Domain-Specific Cognitive measures

The following measures were selected to target specific cognitive domains.

1. **Attention**: Longest Digit Span Forward and Backward – Wechsler Memory Scale III (LDSF, LDSB) (Wechsler, 1997) recorded the longest digit span forward and backward (DV: LDSF = max. 9, and LDSB = max. 8).

2. **Memory**: Hopkins Verbal Learning Test- Revised (HVLT-R) (Brandt, 1991) is a list-learning task that creates scores for Total Recall across three learning trials, delayed recall, and delayed recognition. Raw scores of each measure were used in analyses (DV: Total Recall = max. 30; Delayed Recall = max. 30; and Recognition = max. 20).

3. **Language**: Fluency was adopted to assess speed of verbal generativity and included Letter fluency (FAS) (Benton, 1967) and Category Fluency (animals, fruits, and vegetables) (Newcombe, 1969) using mean scores for each task across 3 minutes. NART (Nelson, 1982) serves as a premorbid reading level and language function.
4. **Executive Function:** Trail Making Test (Delis-Kaplan Executive Function System; DKEFS-TMT) (Delis, Kaplan, & Kramer, 2001) Condition-4 measuring ability to switch set (number-letters); measure used was total error types, including omission, sequencing, and set-loss errors.

5. **Visuospatial function:** Visual Form Discrimination (Benton, Sivan, des Hamsher, Varney, & Spreen, 1994) assessing matching and visual recognition using total score (Maximum = 32).

6. **Motor Speed:** Trail Making Test (DKEFS-TMT) Condition 5 measured speeded motor skills (DV: Completion time in sec).

**Functional Outcome Measures**

The following measures were selected to assess functional impairment, psychological and behavioral symptoms.

A) **IADL:** A modified version (Giovannetti, Libon, Buxbaum, & Schwartz, 2002) of the Lawton-Brody Instrumental Activities of Daily Living Scale (Lawton & Brody, 1969) was used. This consisted of a structured interview with the individual’s primary caregiver. This scale consisted of 8 items with a three-point rating scale for each and were aggregated in a global score (0 = independence, 1 = assistance, 2 = dependence; max.= 16; with higher scores indicating worsening of functioning).

B) **Neuropsychiatric Behavior.** The NPI (Cummings et al., 1994) was used to assess psychiatric and behavioral symptomatology, in addition to caregiver distress. This measure consisted of a structured interview with the individual’s primary caregiver. This scale consisted of 12 items with a three-point rating scale for behavior frequency and a four-point rating scale for behavior severity in generating a global score for patient behavior (NPI Frequency (3) X Severity (4) max. = 144; higher scores indicating worsening of functioning). Each of the 12 items are also rated on a five-point scale for caregiver distress (e.g., “how emotionally
distressing do you find this behavior; NPI Caregiver Distress max. = 60; higher scores indicating worsening of functioning).

**Attentional measures**

To address our hypotheses, different types of attentional mechanisms were assessed using three attention tasks: the Foreperiod Effect, The Covert Orienting, and the Attentional Blink task. These tasks have been previously piloted or used in participants with AD. Moreover, all participants completed a set of practice trials to ensure comprehension of the task instructions.

a) **The Foreperiod Effect** (See Figure 2) *(Van Dyk et al., 2015)* measured processing speed, variability, and fatigue. Median RT measured detection of a consecutive centrally placed asterisk, presented at six randomized variable intervals (SOA: 350, 500, 650, 800, 1100, and 1400ms), with ten trials at each interval generating 60 trials. High load was defined as the two shortest SOAs (350ms and 500ms). Database management included deletion of the first trial (necessary to elicit the Foreperiod Effect), anticipatory trials (RT < 100ms), erroneous button click responses, and missed responses (total 4% trials). Intra-individual variability was measured as the standard deviation of RT at each SOA. The task was administered at the beginning (Block 1) and end of each testing session (Block 2). Fatigue was defined by comparing overall median RT (across all SOAs) at each block.

b) **The Covert Orienting Task** (See Figure 3) measured orienting and fatigue. We measured the RT to detect a target following an exogenous spatial cue in the same visual field (valid), opposite field (invalid), or in both fields (neutral) (Posner, 1980). High load was defined as RT after an invalid cue. Participants fixated on a central red cross throughout each trial, and responded with a button press to the target (‘X’). The cue-target intervals were set at 250ms or catch trials at 850ms. A total of 170 trials (18% catch, 12% neutral, 12% invalid, 58% valid)
were randomly presented over 5 sequential blocks each containing 34 trials. Prior to aggregating
the data, catch trials were removed. Orienting was assessed using median RT to valid, invalid,
and neutral cues across blocks. Fatigue was assessed comparing overall median RT across
orienting cues between Block 1 and Block 5.

c) **The Attentional Blink Task** (See Figure 4) (Perry & Hodges, 2003) measured top-
down accuracy under increasing levels of temporal load. Prior to any task administration,
individualized stimulus duration was established such that each participant obtained ≥ 85%
accuracy identifying a single alphanumeric character (Ly, 2013). The task consisted of two
random stimuli sequentially presented to the right or left of a fixation point – one number (i.e., 2,
3, 5, 6, or 9) and one letter (i.e., A, D, E, N, or R). Each stimulus was immediately followed by a
mask, and the interstimulus interval varied randomly (SOA: 133, 266, 399, 532, or 655ms). The
blink occurs between 250-500ms (Theeuwes, Godijn, & Pratt, 2004), and we defined high load
as SOAs 266ms and 399ms. Eighty trials were administered with the top-down instruction to
target the second item. Instructions equally divided trials to ‘report the letter’ or ‘report the
number’, which was counter-balanced. Verbal responses were recorded by the examiner.
Accuracy of the second stimulus presented at each SOA was used as the dependent variable.

**Analyses**

**Aim 1. Attention vs Other domains.** To document which cognitive domains best account
for treatment response at six months, a stepwise hierarchical multiple regression will be
conducted. A change score will be created by subtracting the total score on the ADAS-Cog total
score at T1 (baseline) from ADAS-Cog at T3 (after 6-months of treatment). Performance after 6
weeks of treatment (T2) will be predictor variables, and ADAS-cog T3-T1 difference scores
serve as the dependent variable. DRS will be entered first in to the regression to control for disease severity, followed by attention, memory, and executive function. The R-squared change will evaluate the unique variance contributed by attention to ADAS-cog without the contribution of the remaining domains.

**Aim 2. Early response.** To determine whether an attentional change seen in patients early in the treatment course predicts 6-month drug response, a stepwise hierarchical regression analysis will be conducted with change score of attention variables (T2-T1) used as the predictor variables, and ADAS-cog score (difference T3-T1) used as the dependent variable.

**Aim 3. IADLs.** If attention measures are determined to best account for treatment response, we propose that performance on these measures after 6 weeks of treatment could predict 6-month functional impairment. Several linear regressions will be conducted: 1) predicting activities of daily living scores at T3 using performance on attention tasks under high-load conditions at T2 as independent variables; 2) assessing the predictive power of the model including only significant predictors identified in Analysis 1.

**Aim 4. Neuropsychiatric Status.** To determine whether performance on demanding measures of attention at after 6 weeks of treatment could predict psychological and behavioral functioning after 6 months of treatment, several linear regressions will be conducted: 1) predicting neuropsychiatric function at T3 using performance on attention tasks under high-load conditions at T2 as independent variables; 2) assessing the predictive power of the model including only significant predictors identified in Analysis 1.
Results

Descriptive measures are reported in Table 1. Frequency of IADL and NPI symptoms at baseline are reported in Table 2 and 3 respectively. We standardized all variables by creating z scores prior to conducting the analyses.

Aim 1

Our first aim tested the hypothesis that performance on attention tasks under high load conditions after 6-weeks treatment with donepezil would predict 6-month treatment response as measured by the ADAS-Cog (T3-T1).

Assumptions of the model were assessed and there was no evidence of multicollinearity (bivariate correlations r > .9; see Table 4) or serial correlations between errors (Durbin-Watson = 2.24). Mahalanobis distance and leverage values were within normal limits. One participant had a slightly elevated Cook’s distance value and standardized df Fit, however, there were no multivariate residuals over ± 3 standard deviations. Thus, given the small sample size, we decided to retain this individual for analysis.

Results from the stepwise hierarchical multiple regression indicated that supporting our hypothesis, accuracy variables significantly contributed to the variance of ADAS-Cog T3-T1 after controlling for disease severity (see Table 5). Specifically, increases in accuracy at T2 AB-SOA 399ms resulted in maintenance of ADAS-Cog scores after treatment (Table 7). No other variable contributed to the variance beyond the effect of accuracy. Of note, the regression model was a significant fit of the overall data at Step 2- Accuracy, and Step 3 –Variability, although not at Step 4- Fatigue (Table 6) (See Figure 6).
**Aim 2**

To address our second hypothesis that an early attentional change seen in patients after 6 weeks of treatment with donepezil predicts 6-month drug response, we conducted a stepwise multiple regression.

Assumptions of the model were assessed and we found no evidence of multicollinearity (bivariate correlations $r > .9$; see Table 8) or serial correlations between errors (Durbin-Watson = 2.51). Mahalanobis distance and leverage values were within normal limits. One participant had a slightly elevated Cook’s distance value and standardized df Fit; however, there were no multivariate residuals over ± 3 standard deviations. Thus again, given the small sample size, we decided to retain this individual for analysis.

Consistent with our hypothesis, results from the stepwise hierarchical multiple regression indicated that changes in accuracy after 6 weeks of treatment significantly contributed to ADAS-Cog change score (T3-T1) (see Table 9). Maintenance of accuracy on the AB-SOA 399ms at 6 weeks compared to baseline predicted maintenance of ADAS-Cog scores after 6 months of treatment (Table 11). A regression model including all attention change score variables significantly fit the overall data (Table 10) (See Figure 7).

**Aim 3**

Our third hypothesis predicted that performance on demanding measures of attention after 6 weeks of treatment would predict functional impairment after 6 months. We conducted two linear regressions. Analysis 1 predicted 6-month Instrumental Activities of Daily Living scores using performance on attention tasks under high-load conditions after 6 weeks of treatment as independent variables (Accuracy: AB-SOA 266 and 399ms; Variability: Foreperiod Effect-SOA 350ms; Fatigue: Foreperiod Effect and Covert Orienting). Analysis 2 assessed the
predictive power of the model including only significant predictors identified in Analysis 1. First, linear regression revealed that Accuracy at the AB SOA-266ms ($\beta = -.48, p = .02$) predicted IADL scores after 6 months of treatment (Table 12). Second, linear regression revealed that a model only with this significant predictor (Accuracy: AB SOA 266ms,) accounted for 30% of the variability in IADL scores after 6 months of treatment ($p = .03$) (See Figure 8).

**Aim 4**

The fourth aim proposed that performance of high-load measures of attention after 6 weeks of treatment could predict neuropsychiatric function (NPI) after 6 months of treatment. We conducted two linear regressions. The first analysis predicted 6-month NPI scores using 6-week performance on attention tasks under high-load conditions as independent variables (Accuracy: AB-SOA 266 and 399ms; Variability: Foreperiod Effect-SOA 350ms; Fatigue: Foreperiod Effect and Covert Orienting). The linear regression revealed that Accuracy at the AB-SOA 266ms ($\beta = -.60, p = .02$), and Variability ($\beta = .48, p = .02$) significantly predicted NPI scores after 6 months of treatment (Table 13). The second analysis assessed the predictive power of the model including those predictors identified as significant in Analysis 1. The linear regression revealed that the model with two significant predictors (Accuracy: AB-SOA 266ms, Variability: Foreperiod Effect-SOA 350ms) accounted for 31% of the variability in NPI scores after 6 months of treatment ($p = .03$) (See Figure 9 and 10).

**Discussion**

While cholinesterase inhibitors (ChEIs) remain the first line of treatment for Alzheimer’s disease (AD) (Di Santo et al., 2013; Tan et al., 2014), there is still uncertainty regarding their degree of cognitive benefit (Bond et al., 2012; Deardorff et al., 2015; Kobayashi et al., 2015).
The ADAS-Cog remains the primary cognitive outcome measure of drug efficacy, but this measure assesses performance on multiple cognitive domains and thus limits detection of potential cognitive changes of treatment (Cano et al., 2010). Our previous study was designed to demonstrate that we can improve sensitivity to treatment based on the known direct link between the attention domain and acetylcholine (Hasselmo & Sarter, 2011): as ChEIs increase available acetylcholine, we hypothesized a) that demanding attention tasks would better detect treatment response than other cognitive domain or a global cognitive measure, and b) that attention tasks would detect treatment response within a short time period. The study supported these hypotheses, showing that the attention measures of accuracy, variability, and fatigue under high-load conditions, not only detected the drug effects, but also did so after only approximately 6 weeks of donepezil treatment. Importantly, neither global measure (ADAS-Cog) nor any other domain-specific measure of memory, language, visuo-spatial or executive functions could detect a treatment response over the same time course. The findings of this first study (Vila-Castellar, 2015) supported that targeted specific neuropsychological measures directly associated with the underlying pharmacological mechanism of donepezil is a more appropriate and sensitive measure of drug efficacy.

For the current study, we sought to identify whether the short-term attention response measures that detected subtle cognitive change, could predict treatment cognitive response at later disease stages, and whether they would be predictive of associated with functional and neuropsychiatric outcomes. Thus, the current study hypothesized that the attention measures that detected short-term treatment could predict long-term cognitive, functional and behavioral response to ChEIs. Our results supported these predictions, namely that high-load attention performance after 6 weeks is a significant predictor of response to ChEIs after long-term
treatment. We demonstrated that: 1) attention measures at T2 – compared to any other cognitive domain – predicted treatment response as measured by change on the standard metric of the ADAS-Cog after 6 months of treatment (T1-T3); 2) the degree of attentional response to treatment between T1 and T2 predicted long-term drug response (T1-T3); 3) attention measures predicted performance on instrumental activities of daily living, and 4) attention measures predicted neuropsychiatric status at T3.

**Aim 1**

First, we previously demonstrated that demanding measures of attention selectively responded to treatment after only 6 weeks (T1-T2) (Vila-Castelar, 2015), and hypothesized that this performance would anticipate a positive treatment response as measured by the standard ADAS-Cog change (T1-T3), and would do so better than other cognitive domains of memory and executive function. Supporting our hypothesis, attention accounted for a significant proportion of variance in ADAS-Cog T3-T1 change score after controlling for disease severity.

Among the attention tasks tested, the top-down processing of the Attentional Blink prevailed over other attention variables, where increased accuracy on the short demanding interval of SOA 399ms predicted maintenance of ADAS-Cog scores at 6 months. Moreover, measures of memory (HVLT-R Total Recall) and executive function (DKEFS Trail Making Test – Condition 4) did not contribute to the prediction of ADAS-Cog change score (T3-T1) beyond the effect of attention measures.

Attention functions are the basis for other cognitive function such as memory and executive function (Brousseau et al., 2007; Lemstra et al., 2003; Perry & Hodges, 1999), and thus deficits in attention may impact other domains. One interpretation of this may be that attention function could be providing a key contribution to overall cognition, suggesting that
improved attention resulting from ChEIs could result in improvement or maintenance of global cognition. Thus, the specific high load measures of attention could serve as predictors of global response to ChEIs in AD.

**Aim 2**

Much of the research suggests that ChEIs have modest effects and individual treatment response is heterogeneous (Tan et al., 2014). Therefore, it is clinically relevant to investigate which response patterns best identify salient predictors. Previous literature identified several variables that modulate treatment response, including age, disease severity, level of education, cognitive profile, genetics, and structural and functional changes, such as acetylcholine network degeneration (Boccardi et al., 2016; Droogsma et al., 2015; Lee et al., 2015; Mayo et al., 2013; Miloyan et al., 2013; Mossello et al., 2004; Stoeckel et al., 2013). Additionally, studies by Miranda et al. (2015) and Calabria, Geroldi, Lussignoli, Sabbatini, and Zanetti (2009) investigated the association between short-term and long-term response to ChEI therapy, and revealed that individuals considered responders to ChEIs, show improvements early in the course of treatment (e.g., after 3 months) using the Mini Mental State Examination. In contrast, several studies (Boccardi et al., 2016; Droogsma et al., 2015; Lee et al., 2015) could not demonstrate that an initial response, as measured by Mini Mental State Examination or attention tasks, was associated with long-term response. On interpretation of these discrepancies among studies is that the course of treatment may be heterogeneous and/or influenced by factors such as age, disease severity, or rate of decline among others.

We therefore sought to identify which neuropsychological measures were best predictors of treatment response, and proposed that given the strong link between attention measures and cholinergic activity, early changes in attention performance would be the most sensitive
predictor of long-term cognitive response. Supporting our hypothesis, we found that change scores in attention measures of accuracy, variability, and fatigue from T1-T2 predicted 6-month global response to treatment as measured by the ADAS-Cog change score between T1-T3. The stepwise hierarchical regression analysis demonstrated that accuracy variables, entered first in the model, predicted ADAS-Cog change score, while measures of variability and fatigue could not. Of interest, while accuracy of the Attentional Blink at SOA 399ms was initially a significant predictor (Step 1 and 2), this effect dissipated in the final model. We believe that this may be due to a lack of power to detect an effect given the number of variables and few data points in the model. Nevertheless, the overall model with all attention variables (i.e., accuracy, variability, and fatigue) remained a good fit of the data.

These findings support the previous studies suggesting that we should be able to identify treatment responders early in the treatment course (Calabria et al., 2009; Miranda et al., 2015; Mossello et al., 2004). Our study corroborates that attention changes in demanding measures of accuracy and variability are sensitive to short-term cholinergic augmentation. Moreover, attention changes after 6 weeks of treatment are predictive of future overall cognitive response, and this is yet further support that the cognitive mechanism underlying cholinergic treatment response is linked to attention. We add to the literature, showing that more targeted measures were able to not only detect performance change after only 6 weeks, but also predict long-term response. This information can be of important clinical utility and can guide clinical treatment decisions as well as of cost-effectiveness.

**Aim 3**

Several studies (Glosser et al., 2002; Jefferson et al., 2006; Mayo et al., 2013; Miloyan et al., 2013; Stoeckel et al., 2013) have demonstrated an association between attention and
executive function and IADL skills in patients with AD. However, the relationship between specific attention networks and IADLs in the context of ChEI treatment has been less explored. We thus proposed that performance on selected demanding measures of attention would be able to predict functional impairment after 6 months of treatment. Our hypothesis was supported, wherein higher accuracy and lower variability on attention measures after 6 weeks of treatment predicted better 6-month IADL skills.

Our results contradict those of Lee et al. (2015), who found that early changes in simple and choice RT measures were not associated with functional outcomes as measured by an instrumental activities of daily living scale. We believe that the discrepancy in results may be due to the difference in the measures they selected. While they used simple and choice RT tasks, our measures were able to capture performance under high-load conditions. Our laboratory previously demonstrated that attention networks are differentially responsive to ChEIs treatment, and only demanding measures under high-load conditions targeting accuracy, fatigue and variability detected a treatment effect, suggesting higher sensitivity of these measures (Vila-Castelar, 2015). By contrast, Lee et al. (2015) selected shorter assessment intervals compared to our study (4 weeks and 3 months versus 6 weeks and 6 months), and perhaps a longer interval would have increased the magnitude of their effect.

In summary, this study refines our understanding of the mechanisms that may underlie IADL function. We not only corroborate that demanding aspects of attention contribute to better performance or preservation of IADL skills, but also suggest that these measures could be used as valid predictors of long-term functional outcome in the context of ChEIs therapy.
Aim 4

Behavioral and psychiatric symptoms of dementia are associated with caregiver burden, lower quality of life (Cohen et al., 1993), and higher institutionalization of patients with AD (Cerejeira et al., 2012). Neuropsychiatric symptoms have been linked to the cholinergic deficiency (Cummings & Back, 1998; Lemstra et al., 2003) and improved with ChEI therapy (Cummings et al., 2016). However, no study to date investigated the role of specific cognitive domains and neuropsychiatric symptoms, although several theories have pointed to attention function (Brousseau et al., 2007; Lemstra et al., 2003). Therefore, our last aim was to clarify how cognitive performance contributes to neuropsychiatric function in the treatment with ChEIs. Given the strong link between neuropsychiatric symptoms and cholinergic activity, and how acetylcholine mediates attention, we proposed that better early performance on demanding measures of attention could predict neuropsychiatric status after 6 months of treatment. This hypothesis was supported, wherein higher accuracy and lower variability measures after 6-weeks of treatment predicted improved neuropsychiatric response after 6-months treatment.

To our knowledge, this is the first study that specifically linked attention performance to neuropsychiatric symptoms. These findings suggest that cholinergic activity is, at least in part, a neurobiological underpinning of neuropsychiatric function. There are different mechanisms that can explain our findings. First, given the common mechanism between attention and neuropsychiatric function, ameliorating the cholinergic depletion with ChEI therapy might have broad-spectrum effects improving both attention function and neuropsychiatric symptoms. It is also likely that the effect of attention on global cognition in turn, impacts neuropsychiatric status. Alternatively, Brousseau et al. (2007) proposed that reduction of neuropsychiatric symptoms results in improved attention. Thus, we propose that measures of attention sensitive to
cholinergic augmentation could be used as a valid measure to predict subsequent neuropsychiatric response.

**Limitations**

This study had several limitations. First, our study had a small sample, in part due to patients and families’ reluctance to participate in the placebo intervention of the first arm of the study. While a larger sample would have increased power, we were, nonetheless, still able detect treatment effects to support the notion that appropriate attentional measures can detect subtle cognitive changes in smaller samples. Furthermore, our sample was not ethnically diverse and educational attainment of the participants was relatively high. Future studies should aim to increase minority participation to ensure generalizability. We chose donepezil hydrochloride as the treatment for this study, although other common drugs sued are galantamine hydrobromide and rivastigmine. These differ from donepezil in that they have slightly modified post-synaptic receptor response (Čolović et al., 2013), which could impact the cognitive effect of treatment. Lastly, in an effort to control for neuropharmacological availability of the cholinesterase inhibitor in all participants, dosing throughout the 6 months of the study remained at 5mg without titrating to larger doses. Future studies could investigate whether larger dosing may have larger or different benefits.

**Conclusions**

In summary, this study investigated cognitive predictors of response to ChEIs. We found that early performance on selected measures of attention under high-load conditions were predictive of long-term cognitive, functional, and behavioral performance. These findings
corroborate the link between cholinergic activity and attention, particularly under high-load conditions (Himmelheber et al., 2000; Kozak et al., 2006), and further our understanding of the mechanisms by which ChEIs help maintain cognition and functional abilities. We believe that individuals with AD have limited attention resources and/or inefficient strategies to allocate available attention resources, and that ChEIs precisely ameliorate these deficits. Thus, attention measures capturing high-load demands are highly sensitive to ChEIs treatment effects.

To our knowledge, this is the first study linking neuropsychiatric symptoms and attentional performance. Our findings suggest that cholinergic activity is associated to the behavioral disturbances characteristic of AD. While the specific mechanisms remain largely unknown, future studies including imaging techniques may explain how cholinergic degeneration in specific areas manifest in behavioral disturbances to ultimately inform treatment options.

These findings also expand our understanding of the relationship between neuropathological degeneration and cognition in AD. As the field strives to develop a deeper understanding of the pathophysiological progression of AD, these findings can in turn promote research aimed at clarifying how acetylcholine depletion relates to other biomarkers to understand the pathogenesis and temporal course of cognitive decline in AD.

Lastly, these findings have important clinical implications to establish evidence-based guidelines to discontinuation of ChEIs. If we can determine which patients are responding after approximately 6 weeks of treatment, we could better predict subsequent outcome, potential adverse side effects, and ease financial decision-making needs towards improved patient care. Therefore, future research should explore the clinical assessment implications in the context of treatment evaluation. Moreover, demanding attention tasks have been proven to be sensitive to
subtle cognitive changes and are great candidates to detect response to ChEIs, even early in the disease process. As such, these measures could be applied in the study of pre-dementia conditions including MCI, where assessment of cognitive changes are particularly challenging.
Figures

Figure 1. Diagram of procedures.
Figure 2. Foreperiod Effect task. Visual depiction of the Foreperiod Effect Task. Presentation times of the target occur at randomized intervals (SOAs).
Figure 3. Covert Orienting task. Visual depiction of the Covert Orienting task. Presentation of the target ‘X’ is preceded by a cue.
Figure 4. Attentional Blink task. Visual depiction of the Attentional Blink task. Time in between the masking of the first stimulus and the presentation of the second stimulus is referred to as SOA. S1 = Stimulus 1; S2 = Stimulus 2.
**Figure 5. Aims and Analyses.** Diagram describing study aims and corresponding analyses.
**Figure 6. Partial Regression plot.** Aim 1: Accuracy on the Attentional Blink SOA 399ms at T2 predicts ADAS-Cog change score (T3-T1).
**Figure 7. Partial Regression plot.** Aim 2: Accuracy at T2 AB SOA 399ms predicts ADAS-Cog change score (T3-T1).
Figure 8. Regression plot. Aim 3: Accuracy at T2 AB SOA 266ms predicts IADLs at T3.
Figure 9. Partial Regression plot. Aim 4: Accuracy at T2 AB SOA 266ms predicts NPI scores at T3.
Figure 10. Partial Regression plot. Aim 4: Variability at T2 predicts NPI scores at T3.
### Table 1. Baseline sample demographics

<table>
<thead>
<tr>
<th></th>
<th>SAMPLE (n = 21)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>80.29</td>
<td>6.08</td>
</tr>
<tr>
<td>Gender</td>
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<td></td>
</tr>
<tr>
<td>Education (years)</td>
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<td>4.23</td>
</tr>
<tr>
<td>MMSE</td>
<td>24.90</td>
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</tr>
<tr>
<td>DRS</td>
<td>122.95</td>
<td>9.99</td>
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<tr>
<td>CDR</td>
<td>.86</td>
<td>.36</td>
</tr>
<tr>
<td>GDS</td>
<td>6.81</td>
<td>5.47</td>
</tr>
</tbody>
</table>

**Note.** Mini-Mental State Examination (MMSE); Dementia Rating Scale (DRS); Clinical Dementia Rating Scale (CDR); Geriatric Depression Scale (GDS); Standard Deviation (SD).
Table 2. Baseline NPI frequency

<table>
<thead>
<tr>
<th>Baseline NPI Symptoms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>24</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>9</td>
</tr>
<tr>
<td>Agitation/Aggression</td>
<td>43</td>
</tr>
<tr>
<td>Depression</td>
<td>29</td>
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<tr>
<td>Anxiety</td>
<td>14</td>
</tr>
<tr>
<td>Elation</td>
<td>19</td>
</tr>
<tr>
<td>Apathy</td>
<td>38</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>24</td>
</tr>
<tr>
<td>Irritability</td>
<td>24</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>14</td>
</tr>
<tr>
<td>Sleep and Nighttime</td>
<td>38</td>
</tr>
<tr>
<td>Appetite and eating changes</td>
<td>43</td>
</tr>
</tbody>
</table>

*Note.* Neuropsychiatric Inventory (NPI). Frequency of Neuropsychiatric Inventory symptoms at baseline.
Table 3. Baseline IADL skills

<table>
<thead>
<tr>
<th>Baseline IADL</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to use the phone</td>
<td>52</td>
</tr>
<tr>
<td>Shopping</td>
<td>62</td>
</tr>
<tr>
<td>Food preparation</td>
<td>57</td>
</tr>
<tr>
<td>Housekeeping</td>
<td>52</td>
</tr>
<tr>
<td>Laundry</td>
<td>48</td>
</tr>
<tr>
<td>Mode of transportation</td>
<td>57</td>
</tr>
<tr>
<td>Responsibility for medications</td>
<td>67</td>
</tr>
<tr>
<td>Ability to handle finances</td>
<td>48</td>
</tr>
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</table>

*Note.* Instrumental Activities of Daily Living (IADL). Assistance required completing IADLs at baseline.
<table>
<thead>
<tr>
<th>ADAS-Cog Change (T3-T1)</th>
<th>ADAS-Cog Change</th>
<th>Baseline DRS</th>
<th>AB SOA 399</th>
<th>AB SOA 266</th>
<th>Variability</th>
<th>Fatigue Covert</th>
<th>Fatigue Foreperio d</th>
<th>HVLT</th>
<th>D-KEI Cond.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog Change (T3-T1)</td>
<td>1.00</td>
<td>.31</td>
<td>-.57*</td>
<td>-.21</td>
<td>-.05</td>
<td>.02</td>
<td>-.31</td>
<td>.11</td>
<td>.32</td>
</tr>
<tr>
<td>Baseline DRS</td>
<td>.31</td>
<td>1.00</td>
<td>-.13</td>
<td>.21</td>
<td>-.72*</td>
<td>-.15</td>
<td>-.18</td>
<td>.28</td>
<td>.06*</td>
</tr>
<tr>
<td>T2 Accuracy – AB SOA 399ms</td>
<td>-.57*</td>
<td>-.13</td>
<td>1.00</td>
<td>.58*</td>
<td>.05</td>
<td>-.12</td>
<td>-.12</td>
<td>-.25</td>
<td>-.06</td>
</tr>
<tr>
<td>T2 Accuracy – AB SOA 266ms</td>
<td>-.21</td>
<td>.21</td>
<td>.58*</td>
<td>1.00</td>
<td>-.26</td>
<td>-.05</td>
<td>-.29</td>
<td>.00</td>
<td>.07</td>
</tr>
<tr>
<td>T2 Variability - Foreperiod Task</td>
<td>-.05</td>
<td>-.72*</td>
<td>.05</td>
<td>-.26</td>
<td>1.00</td>
<td>-.10</td>
<td>-.01</td>
<td>-.38*</td>
<td>-.47*</td>
</tr>
<tr>
<td>T2 Fatigue-Covert Orienting</td>
<td>.02</td>
<td>-.15</td>
<td>-.12</td>
<td>-.05</td>
<td>-.10</td>
<td>1.00</td>
<td>-.02</td>
<td>.03</td>
<td>.23</td>
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<tr>
<td>T2 Fatigue-Foreperiod Effect</td>
<td>-.31</td>
<td>-.18</td>
<td>-.12</td>
<td>-.29</td>
<td>-.01</td>
<td>-.02</td>
<td>1.00</td>
<td>.13</td>
<td>-.15</td>
</tr>
<tr>
<td>T2 HVLT Recall</td>
<td>.11</td>
<td>.28*</td>
<td>.25</td>
<td>.00</td>
<td>-.38*</td>
<td>.03</td>
<td>.13</td>
<td>1.00</td>
<td>.04*</td>
</tr>
<tr>
<td>T2 D-KEFS Cond. 4</td>
<td>.32</td>
<td>.59*</td>
<td>-.06</td>
<td>.07</td>
<td>-.47*</td>
<td>.23</td>
<td>-.15</td>
<td>.04*</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Note.** Alzheimer’s Disease Assessment Scale- Cognitive (ADAS-Cog); Dementia Rating Scale (DRS); Attentional Blink task (AB); Stimulus onset asynchrony (SOA); Hopkins Verbal Learning Test – total delayed recall; Delis-Kaplan Executive Function System- Condition 4 (D-KEFS Cond. 4). Correlations among attention, memory, and executive function variables at T2 included in the stepwise hierarchical regression. ‘ADAS-Cog’ change score represents difference from baseline (before treatment) to 6 months. Statistics reported are Pearson’s correlations. (*) indicates $p \leq 0.05$. 
Table 5. Regression model summary. Variables at T2 predict ADAS-Cog T3-T1.

<table>
<thead>
<tr>
<th>Steps</th>
<th>Statistics</th>
</tr>
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<tr>
<td></td>
<td>R² Change</td>
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<tr>
<td>Baseline DRS</td>
<td>.10</td>
</tr>
<tr>
<td>T2 Accuracy</td>
<td>.29</td>
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<tr>
<td>T2 Variability</td>
<td>.06</td>
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<tr>
<td>T2 Fatigue</td>
<td>.08</td>
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<td>T2 Memory</td>
<td>.07</td>
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<tr>
<td>T2 Executive Function</td>
<td>.03</td>
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</table>

*Note.* Dementia Rating Scale (DRS). Statistics at each step of the hierarchical stepwise multiple regression. Step 1: Baseline DRS; Step 2: T2 Accuracy (Attentional Blink SOA 266 and 399ms); Step 3: T2 Variability (Foreperiod Effect-SOA 350ms); Step 4: T2 Fatigue (Foreperiod Effect and Covert Orienting); Step 5: T2 Memory (HVLT Recall); and Step 6: T2 Executive Function (D-KEFS Condition 4). Statistics reported: R Square Change (R² Change), F-ratio Change (F Change); Degrees of Freedom (df); Significance Level (p); (*) indicates p<0.05.
Table 6. Stepwise Multiple Regression ANOVA Summary.

<table>
<thead>
<tr>
<th>Model</th>
<th>SS_M</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Regression</td>
<td>1.89</td>
<td>1</td>
<td>1.89</td>
<td>1.94</td>
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<tr>
<td></td>
<td>Residual</td>
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<td>18</td>
<td>.97</td>
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</tr>
<tr>
<td></td>
<td>Total</td>
<td>19.36</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Regression</td>
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<td>3</td>
<td>2.48</td>
<td>3.33</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>3</td>
<td>Regression</td>
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<td>2.98</td>
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<tr>
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<td></td>
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<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Regression</td>
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<td>2.38</td>
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<td>.71</td>
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<tr>
<td>5</td>
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<td>.77</td>
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<td></td>
<td>Total</td>
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<td>19</td>
<td></td>
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<tr>
<td>6</td>
<td>Regression</td>
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<td>1.76</td>
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<tr>
<td></td>
<td>Residual</td>
<td>8.48</td>
<td>11</td>
<td>.77</td>
<td></td>
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<tr>
<td></td>
<td>Total</td>
<td>19.36</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Statistics at each step of the regression assessing the predicting power of each domain. Statistics reported: Sum of Squares (SS_M); Degrees of Freedom (df) Mean Sum of Squares (MS), F-ratio (F); significance value (p); (*) indicates p ≤ 0.05.
Table 7. Stepwise Multiple Regression. *T2 predictors of ADAS-Cog T3-T1.*

<table>
<thead>
<tr>
<th>Statistics</th>
<th>b</th>
<th>SE B</th>
<th>β</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline DRS</td>
<td>.15</td>
<td>.37</td>
<td>.16</td>
<td>.41</td>
<td>.69</td>
</tr>
<tr>
<td>T2 Accuracy – AB SOA 399ms</td>
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<td>.28</td>
<td>-.63</td>
<td>-2.31</td>
<td>.04*</td>
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<td>T2 Accuracy – AB SOA 266ms</td>
<td>.09</td>
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<td>.09</td>
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<td>.75</td>
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<td>T2 Variability- Foreperiod Effect</td>
<td>.27</td>
<td>.35</td>
<td>.26</td>
<td>.78</td>
<td>.45</td>
</tr>
<tr>
<td>T2 Fatigue – Covert Orienting</td>
<td>-.09</td>
<td>.30</td>
<td>-.07</td>
<td>-.31</td>
<td>.76</td>
</tr>
<tr>
<td>T2 Fatigue – Foreperiod Effect</td>
<td>-.32</td>
<td>.23</td>
<td>-.30</td>
<td>-1.35</td>
<td>.20</td>
</tr>
<tr>
<td>T2 HVLT-R Total Recall</td>
<td>.04</td>
<td>.22</td>
<td>.04</td>
<td>.16</td>
<td>.87</td>
</tr>
<tr>
<td>T2 D-KEFS Condition 4</td>
<td>.29</td>
<td>.29</td>
<td>.28</td>
<td>.98</td>
<td>.35</td>
</tr>
</tbody>
</table>

*Note.* Dementia Rating Scale (DRS); Attentional Blink task (AB); Stimulus onset asynchrony (SOA); Hopkins Verbal Learning Test – total delayed recall; Delis-Kaplan Executive Function System- Condition 4 (D-KEFS Cond. 4). This table reflects the contribution of each variable at the last step of the model. Statistics reported: Beta (B); Standard Error of Beta (SE B); Standardized Beta (β); T test (t); significance value (p); (*) indicates \( p \leq 0.05 \).
Table 8. Correlations among attention change score variables (T2-T1)

<table>
<thead>
<tr>
<th>Model Variables</th>
<th>ADAS-Cog Change (T3-T1)</th>
<th>Δ AB SOA 399 (T2-T1)</th>
<th>Δ AB SOA 266 (T2-T1)</th>
<th>Δ Variability- Foreperiod Effect (T2-T1)</th>
<th>Δ Fatigue- Covert Orienting (T2-T1)</th>
<th>Δ Fatigue- Foreperiod Effect (T2-T1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog Change (T3-T1)</td>
<td>1.00</td>
<td>-.57*</td>
<td>-.28</td>
<td>.31</td>
<td>-.41*</td>
<td>-.50*</td>
</tr>
<tr>
<td>Δ Accuracy – AB SOA 399ms (T2-T1)</td>
<td>-.57*</td>
<td>1.00</td>
<td>.49*</td>
<td>-.18</td>
<td>.09</td>
<td>.44*</td>
</tr>
<tr>
<td>Δ Accuracy – AB SOA 266ms (T2-T1)</td>
<td>-.28</td>
<td>.49*</td>
<td>1.00</td>
<td>-.03</td>
<td>-.10</td>
<td>-.10</td>
</tr>
<tr>
<td>Δ Variability- Foreperiod Effect (T2-T1)</td>
<td>.31</td>
<td>-.18</td>
<td>-.03</td>
<td>1.00</td>
<td>.06</td>
<td>-.11</td>
</tr>
<tr>
<td>Δ Fatigue- Covert Orienting (T2-T1)</td>
<td>-.41*</td>
<td>.09</td>
<td>-.10</td>
<td>.06</td>
<td>1.00</td>
<td>.28</td>
</tr>
<tr>
<td>Δ Fatigue- Foreperiod Effect (T2-T1)</td>
<td>-.50*</td>
<td>.44*</td>
<td>-.10</td>
<td>-.11</td>
<td>.28</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Note. Delta change score (Δ); Alzheimer’s Disease Assessment Scale- Cognitive Change score T3-T1 (ADAS-Cog); Attentional Blink task (AB); Stimulus onset asynchrony (SOA); Hopkins Verbal Learning Test – total delayed recall; Delis-Kaplan Executive Function System- Condition 4 (D-KEFS Cond. 4). ‘ADAS-Cog’ change score represents difference from baseline (before treatment) to 6 months. Statistics reported are Pearson’s correlations. (*) indicates $p \leq 0.05$. 
Table 9. Regression model summary

<table>
<thead>
<tr>
<th>Steps</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$ Change</td>
</tr>
<tr>
<td>Accuracy T2-T1</td>
<td>.32</td>
</tr>
<tr>
<td>Variability T2-T1</td>
<td>.05</td>
</tr>
<tr>
<td>Fatigue T2-T1</td>
<td>.20</td>
</tr>
</tbody>
</table>

Note. Attention change score variables (T2-T1) predict ADAS-Cog T3-T1. Statistics at each step of the hierarchical stepwise multiple regression. Step 1: Accuracy T2-T1 (AB-SOA 266 and 399); Step 2: Variability T2-T1 (Foreperiod Effect-SOA 350ms); Step 3: Fatigue T2-T1 (Foreperiod Effect and Covert Orienting). Statistics reported: R Square Change ($R^2$ Change), F-ratio Change (F Change); Degrees of Freedom (df); Significance Level ($p$); (*) indicates $p<0.05$. 
Table 10. Stepwise Multiple Regression ANOVA Summary

<table>
<thead>
<tr>
<th>Steps</th>
<th>SS_M</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.24</td>
<td>2</td>
<td>3.12</td>
<td>4.05</td>
<td>.04*</td>
</tr>
<tr>
<td>Regression</td>
<td>6.24</td>
<td>2</td>
<td>3.12</td>
<td>4.05</td>
<td>.04*</td>
</tr>
<tr>
<td>Residual</td>
<td>13.12</td>
<td>17</td>
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<td>Total</td>
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<td>19</td>
<td></td>
<td></td>
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</tr>
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<td>2</td>
<td>7.14</td>
<td>3</td>
<td>2.38</td>
<td>3.12</td>
<td>.06</td>
</tr>
<tr>
<td>Regression</td>
<td>7.14</td>
<td>3</td>
<td>2.38</td>
<td>3.12</td>
<td>.06</td>
</tr>
<tr>
<td>Residual</td>
<td>12.22</td>
<td>16</td>
<td>.76</td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>19.36</td>
<td>19</td>
<td></td>
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<td></td>
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<td>10.99</td>
<td>5</td>
<td>2.20</td>
<td>3.67</td>
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<tr>
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<td>5</td>
<td>2.20</td>
<td>3.67</td>
<td>.02*</td>
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<tr>
<td>Residual</td>
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<td>14</td>
<td>.60</td>
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<tr>
<td>Total</td>
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<td>19</td>
<td></td>
<td></td>
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</table>

Note. Statistics at each step of the regression assessing the predicting power of attention change score variables (T2-T1). Statistics reported: Sum of Squares (SSM), Degrees of Freedom (df), Mean Sum of Squares (MS), F-ration (F); significance value (p); (*) indicates p ≤ 0.05.
Table 11. Stepwise Multiple Regression Model Coefficients

<table>
<thead>
<tr>
<th>Step</th>
<th>Δ AB SOA 399</th>
<th>Δ AB SOA 266</th>
<th>Δ AB SOA 399</th>
<th>Δ AB SOA 266</th>
<th>Δ Foreperiod Variability</th>
<th>Δ Foreperiod Effect</th>
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<tbody>
<tr>
<td>1</td>
<td>-.55</td>
<td>-.01</td>
<td>-.51</td>
<td>-.02</td>
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<tr>
<td></td>
<td>SE B</td>
<td>SE B</td>
<td>SE B</td>
<td>SE B</td>
<td>SE B</td>
<td>SE B</td>
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<tr>
<td></td>
<td>.22</td>
<td>.22</td>
<td>.23</td>
<td>.22</td>
<td>.22</td>
<td>.19</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>β</td>
<td>β</td>
<td>β</td>
<td>β</td>
<td>β</td>
</tr>
<tr>
<td></td>
<td>-.56</td>
<td>-.01</td>
<td>-.52</td>
<td>-.03</td>
<td>.22</td>
<td>-.34</td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>t</td>
</tr>
<tr>
<td></td>
<td>-2.46</td>
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<td>-2.23</td>
<td>-1.11</td>
<td>1.08</td>
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<tr>
<td></td>
<td>p</td>
<td>p</td>
<td>p</td>
<td>p</td>
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<td>p</td>
</tr>
<tr>
<td></td>
<td>.02*</td>
<td>.04*</td>
<td>.91</td>
<td>.91</td>
<td>.29</td>
<td>.09</td>
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</table>

Note. Delta change score (Δ); Attentional Blink task (AB); Stimulus onset asynchrony (SOA). The table reflects the contribution of each variable at the last step of the model. Statistics reported: Beta (B); Standard Error of Beta (SE B); Standardized Beta (β); significance value (p); (*) indicates p ≤ 0.05.
Table 12. Attention measures at T2 predict Instrumental Activities of Daily Living scores

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>S.E.</th>
<th>β</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 Accuracy – AB SOA 399ms</td>
<td>.02</td>
<td>.04</td>
<td>.13</td>
<td>.53</td>
<td>.60</td>
</tr>
<tr>
<td>T2 Accuracy – AB SOA 266ms</td>
<td>-.48</td>
<td>.19</td>
<td>-.48</td>
<td>-2.47</td>
<td>.02*</td>
</tr>
<tr>
<td>T2 Variability – Foreperiod Effect</td>
<td>.04</td>
<td>.02</td>
<td>.38</td>
<td>1.85</td>
<td>.08</td>
</tr>
<tr>
<td>T2 Fatigue – Foreperiod Effect</td>
<td>.02</td>
<td>.01</td>
<td>.38</td>
<td>1.8</td>
<td>.09</td>
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<tr>
<td>T2 Fatigue – Covert Orienting</td>
<td>.02</td>
<td>.03</td>
<td>.15</td>
<td>.68</td>
<td>.50</td>
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</table>

*Note.* Analysis 1- Linear regression model coefficients. Statistics reported: Beta (B); Standard Error of Beta (S.E.); Standardized Beta (β); significance value (p); (*) indicates $p \leq 0.05$. 
Table 13. Attention measures at T2 predict Neuropsychiatric Inventory scores

<table>
<thead>
<tr>
<th>Variables</th>
<th>$B$</th>
<th>S.E.</th>
<th>$\beta$</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 Accuracy – AB SOA 399ms</td>
<td>.21</td>
<td>.15</td>
<td>.33</td>
<td>1.39</td>
<td>.18</td>
</tr>
<tr>
<td>T2 Accuracy – AB SOA 266ms</td>
<td>-.27</td>
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<td>-.59</td>
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<td>.02*</td>
</tr>
<tr>
<td>T2 Variability – Foreperiod Effect</td>
<td>.18</td>
<td>.07</td>
<td>.48</td>
<td>2.44</td>
<td>.02*</td>
</tr>
<tr>
<td>T2 Fatigue – Foreperiod Effect</td>
<td>.01</td>
<td>.04</td>
<td>.06</td>
<td>.26</td>
<td>.80</td>
</tr>
<tr>
<td>T2 Fatigue – Covert Orienting</td>
<td>-.01</td>
<td>.10</td>
<td>-.2</td>
<td>-0.7</td>
<td>.94</td>
</tr>
</tbody>
</table>

Note. Analysis 1- Linear regression model coefficients. Statistics reported: Beta ($B$); Standard Error of Beta (SE $B$); Standardized Beta ($\beta$); significance value ($p$); (*) indicates $p \leq 0.05$. 
References


following 192 IgG–saporin-induced lesions of the medial prefrontal cortex. Cerebral Cortex, 14(8), 922-932.


