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Challenge Difficulty and Cardiovascular Responses in Mild Cognitive Impairment

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CHALLENGE DIFFICULTY AND CARDIOVASCULAR RESPONSES IN MILD COGNITIVE IMPAIRMENT

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MEDICAL PSYCHOLOGY

ABSTRACT

This study examined the effect of challenge difficulty on cardiovascular responses in patients with Alzheimer's disease and amnestic mild cognitive impairment. It extended from a model characterizing the determinants and cardiovascular consequences of effort in people confronted with performance challenges. One component of this model holds that ability has the potential to accentuate, attenuate, or have no effect on cardiovascular responses. Specifically, lower ability should accentuate cardiovascular responses so long as performers' view a challenge possible and worthwhile. However, lower ability should attenuate cardiovascular responses when it leads to the perception that a challenge is excessively difficult or impossible. The third outcome is that ability should have no effect on cardiovascular responses when it leaves unaltered the perception that a challenge is excessively difficult or impossible.

The current study extended this analysis to Alzheimer's disease and mild cognitive impairment under the premise that their neuropsychological deficits would affect cardiovascular responses analogously to "lower ability". Cardiovascular responses and performance (accuracy) measures were collected as participants performed cognitive challenges of low, medium, and high difficulty. Participants also rated the subjective difficulty of each challenge. Unfortunately, data collection on the Alzheimer's disease group was discontinued due to low recruitment rate.

Contrary to expectations, challenge difficulty did not significantly influence blood pressure responses in patients with mild cognitive impairment. Controls, however, showed the expected increase in blood pressure responses as challenge difficulty increased. Subjective ratings of challenge difficulty increased across the low, medium, and high difficulty challenges and were comparable between patients with mild cognitive impairment and controls. Accuracy decreased as challenge difficulty increased, and patients with mild cognitive impairment were less accurate than controls.

One tentative interpretation of the results is that patients with mild cognitive impairment can accurately appraise relative differences in challenge difficulty but have problems adjusting their difficulty appraisals to account for their neuropsychological weaknesses, even when their performance suffers. The cardiovascular response data suggest that patients with mild cognitive impairment may not deploy compensatory effort, perhaps because they may not appreciate challenges as more difficult than their cognitively intact counterparts. Other alternative explanations are presented and discussed.

Keywords: Mild cognitive impairment; Alzheimer's disease; Cardiovascular responses; Effort; Challenge difficulty; Ability.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

This study aims to serve as an initial investigation of effort-related cardiovascular (CV) responses in Alzheimer's disease (AD) and its prodromal state, amnestic mild cognitive impairment (MCI) (Petersen et al., 2009). As a novel study, it integrates a wide range of literatures, some of which have not been related to one another previously. The following introduction section attempts to review and integrate these literatures. Given that the reviewed topics are sometimes disparate, readers may at various points feel like they are "losing the forest for the trees." To help assuage this feeling, an overview of the introduction is provided below. It is hoped that this overview facilitates comprehension and can serve as a roadmap should readers begin to feel astray.

The introduction is divided into two main sections. The first section discusses vascular perspectives on AD and leads to a review of CV responses and their relationship to vascular, brain, and cognitive functioning. The purpose of the first section is to provide background information explaining why CV responses may be relevant to AD. Following the first section, topics switch to an unrelated field of study concerned with effort-related CV responses in healthy individuals. The purpose of the second section is to describe and provide evidence for a theoretical framework used to understand and predict effort-related CV responses in healthy individuals. The second section also extends this theoretical framework to include cognitive impairment as a new factor and considers the implications of this extension as applied to AD and MCI. Thus, whereas the first section of the introduction explains why CV responses are of interest (i.e., the study's impe-

tuses), the second section explains why individuals with AD and MCI might exhibit abnormal CV response patterns. Following the second section, the introduction concludes with a formal statement of the study's hypotheses.

Cardiovascular and Cerebrovascular Pathology in AD

The Vascular Hypothesis of AD

Historically, research on AD has primarily focused on the amyloid cascade hypothesis, which maintains that "the accumulation of amyloid protein, as determined by its generation versus clearance in the brain, is the primary driver of AD-related pathogenesis, including neurofibrillary tangle formation, synapse loss, and neuronal cell death" (Tanzi & Bertram, 2005, p. 545). Over the last two decades, the amyloid cascade hypothesis has garnered a large body of support, primarily from genetics and biological studies. While these studies are beyond the scope of the current study, it is worth noting that the treatment implication of the amyloid cascade hypothesis is that AD treatments should aim to "curb the production of amyloid or accelerate [its] clearance and degradation [from the brain]" (Tanzi & Bertram, 2005, p. 552).

Although it is the predominant view, the amyloid cascade hypothesis is not without critics. Evidence most commonly cited against it includes the poor association between amyloid burden in the brain and severity of dementia, and the presence of significant amounts of amyloid in cognitively intact individuals (Castellani et al., 2009). An additional critique is evidence suggesting a vascular contribution to AD. Review of consortium data has shown that "more than 30% of AD cases exhibit cerebrovascular neuropathology" and that "about one third of patients diagnosed with vascular dementia will

have AD-type pathology at autopsy" (Kalaria & Ballard, 1999, p.115). These findings have led to the idea that AD and vascular dementia fall on opposite ends of a continuum, with AD-related neuropathology and vascular-related neuropathology acting additively or synergistically in a large percentage of probable AD cases (Castellani et al., 2009).

One alternative to the amyloid cascade hypothesis that accounts for presence of mixed pathology in AD is the vascular hypothesis, first proposed by de la Torre and Mussivand (1993). Contrary to the amyloid cascade hypothesis, the vascular hypothesis maintains that the root cause of AD neurodegeneration is years or decades of chronically reduced blood flow to the brain. It also holds that amyloid plaques and neurofibrillary tangles are byproducts of chronic blood flow reductions and, as byproducts, do not play a central role in AD neurodegeneration. The treatment implication of the vascular hypothesis can be contrasted against that of the amyloid cascade hypothesis. Whereas the amyloid cascade hypothesis targets amyloid reduction to cure AD, the vascular hypothesis targets vascular risk factors in the years prior to clinical manifestation of AD in hope of preventing AD (de la Torre, 2010).

The proposed mechanism of AD neurodegeneration under the vascular hypothesis is called the "critically attained threshold of cerebral hypoperfusion" (CATCH) (de la Torre, 2009). The overall idea is that CATCH occurs due to the combined effect of age-related reductions in cerebral blood flow, which have been estimated to decrease by 21% between the age of 22 and 60 (Leenders et al., 1990), and reductions in cerebral blood flow related to clinical or subclinical CV or cerebrovascular disease. For example, CATCH may result from aging plus a local or global disruption in cerebral blood flow, as is the case in cardiac arrest or ischemic stroke. Alternatively, CATCH may result from

aging plus an insidious dwindling in cerebral blood flow secondary to non-fatal carotid artery stenosis or cardiac disease. Other factors presumed to contribute to CATCH include genetics, lifestyle, diet, and gender. Once reached, CATCH is hypothesized to result in cerebromicrovascular changes that cause an energy crisis in the brain. In turn, this energy crisis leads to neurono-glial dysfunction and, eventually, neuronal death. This cascade of events is proposed to occur first in ischemic-sensitive brain areas (e.g., the medial temporal lobe) before moving on to more ischemic-resistant brain areas with continued reductions in cerebral blood flow (e.g., lateral temporal lobe, neocortex and occipital cortex). In this way, the vascular hypothesis accounts the selective medial temporal atrophy and memory impairment characteristic of the earlier stages of AD and the more widespread cortical atrophy and broader cognitive impairment characteristic of the later stages of AD (de la Torre, 2005).

Vascular-related Risk Factors of AD

The most compelling evidence favoring the vascular hypothesis or, more broadly, some type of vascular connection to AD comes from independent epidemiological studies. These studies have identified over 20 vascular-related risk factors for AD, ranging from brain-related risk factors (e.g., ischemic stroke, silent stroke) to heart-related risk factors (e.g., congestive heart failure, coronary artery disease, atrial fibrillation, aortic and mitral valve prolapse) to peripheral risk factors (e.g., high serum cholesterol, diabetes mellitus II) (de la Torre, 2009). Markers of preclinical vascular disease (e.g., carotid artery wall thickness, plaque in the carotid arteries) also have been shown to increase AD risk (Hofman et al., 1997; Newman et al., 2005). Most of these vascular risk factors have been associated with vascular-related neuropathology (e.g., subclinical stroke and white

matter disease), AD-related neuropathology (e.g., amyloid plaques and neurofibrillary tangles), poorer cognitive functioning, and accelerated cognitive decline (Obrien, 2006; Romero et al., 2009; Skoog & Gustafson, 2006; Qiu et al., 2004). The magnitude of risk associated with vascular factors appears to be independent of and comparable to or greater than the magnitude of risk associated with apolipoprotein E status (a genetic risk factor) (Kivipelto et al., 2001).

Yet another important attribute of vascular risk factors, particularly with regard to intervention, is that their presence at midlife confers risk of AD at late-life. That is, vascular risk factors appear years or decades prior to the clinical manifestation of AD (Rosano & Newman, 2006). Case in point, multiple studies have found that midlife hypertension increases the likelihood of AD 25 to 30 years later (Freitag et al., 2006; Kivipelto et al., 2001; Launer et al., 2000). These studies have also found that treated hypertension confers less risk than untreated hypertension, thus providing preliminary evidence that vascular-related AD risk can be reduced with appropriate (midlife) treatment of vascular pathology (Skoog & Gustafson, 2006).

CV Responses: A Potential Measure of Interest in AD

CV responses – defined as the magnitude of an individual's hemodynamic response to behavioral stressors (Treiber et al., 2003) – have not been previously investigated in relation to AD but hold promise as important measures. Similar to the vascular risk factors referenced above, CV responses to mental and physical challenges have been associated with poorer cerebrovascular functioning, brain integrity, and cognitive functioning. Specifically, exaggerated CV responses have been associated with carotid artery wall thickness, increased risk of future stroke, silent brain infarcts, periventricular and

deep white matter hyperintensities, and poorer cognitive functioning, including poorer memory functioning (Bellelli, Pezzini, Bianchetti, Trabucchi, 2002; Brown et al., 2009; Everson et al., 2001; Kamarck et al., 1997; Perman & Lachman, 2009; Waldstein et al., 2004; Waldstein et al., 2005). In addition, exaggerated CV responses have been associated with preclinical and clinical CV disease at long-term follow-up (>10 years), including hypertension, left ventricular mass (a strong predictor of future CV disease morbidity and mortality), and perhaps coronary heart disease (Kapuku et al., 1999; Kasagi, 1995; Keys et al., 1971; Manuck et al., 1992; Menkes et al., 1989; Wood, Sheps, Elveback, & Schirger, 1984).

Together, these studies suggest that CV responses may confer AD risk directly, e.g., by altering cerebrovascular functioning, brain integrity, and cognition. They also suggest that CV responses may confer AD risk indirectly, e.g., by promoting the development of preclinical and clinical CV disease states that are established risk factors of AD (e.g., hypertension). Yet another possibility is that CV responses serve as a marker of abnormalities in associated but independent physiological systems that confer AD risk, including the hypothalamic-pituitary-adrenocortical axis and metabolic and immune systems (Wendell et al., 2009).

Summary

A large body of evidence supports a connection between vascular functioning and AD. However, the mechanism or mechanisms linking vascular functioning to AD have not been adequately demonstrated and the vascular hypothesis in particular remains controversial. Other candidate mechanisms linking vascular functioning and AD include

metabolic dysfunction, inflammatory processes, and/or shared genetic factors (Elias et al., 2001; Stampfer, 2006; Wendell et al., 2009).

CV responses have not been previously examined in relation to AD but hold promise as a contributing factor. Reasons for this are at least twofold. One reason is that exaggerated CV responses have been associated with poorer vascular functioning, brain integrity, and cognitive functioning, as described above. The second reason is based on a theoretical framework used to understand and predict effort-related CV responses in healthy individuals. This theoretical framework suggests that individuals with AD and its prodromal state, amnestic MCI, may show abnormal CV responses as a consequence of their cognitive impairment. In the next section, this theoretical framework is presented and extended to AD and MCI.

The Determinants and CV Consequences of Effort

For over a decade, the chief aim of Rex Wright's laboratory has been the development of a model that characterizes the determinants and cardiovascular consequences of effort. This work is premised on the integration of Paul Obrist's active coping hypothesis (Obrist, 1981) and Jack Brehm's motivation intensity analysis (Brehm & Self, 1989). Below, Obrist's and Brehm's contributions are briefly reviewed in conceptual terms, first separately and then together in Wright's integrative model. Following this, some exemplary studies examining effort-related CV responses in healthy populations are summarized and synthesized. Wright's integrative model is then extended to cognitive impairment, first in general terms and then in the context of AD and MCI. The introduction concludes with a statement of the study's hypotheses.

Obrist's Active Coping Hypothesis: Linking Effort with CV Responses

Of Paul Obrist's multiple seminal contributions, central to the current study is his research linking effort with CV responses. This work demonstrated that people manifest CV adjustments that cannot be explained somatically when they are provided the chance to attain a desired outcome or avoid an undesired one by meeting some performance standard. Specifically, Obrist found that study participants evinced stronger CV responses under conditions that, intuitively, would seem conducive to effortful, active coping. In addition, he showed that the CV responses participants evinced appeared largely, if not exclusively, due to sympathetic nervous system stimulation. Obrist accordingly concluded that sympathetic nervous system, specifically beta-adrenergic, influence on the heart and vasculature varies with effort, with increasingly greater effort yielding increasingly pronounced sympathetically-mediated CV responses. This came to be known as Obrist's active coping hypothesis (Obrist, 1981).

Brehm's Motivation Intensity Theory: A Framework for Predicting Effort

In a line of research independent from Obrist's active coping hypothesis, Jack Brehm and colleagues' developed motivation intensity analysis, a theoretical framework that predicts the determinants and expenditure of effort in instrumental behavior (i.e., behavior aimed at achieving a desired outcome) (Brehm & Self, 1989; Ford & Brehm, 1987). Central to motivation intensity analysis is the assumption that effort follows a law of conservation. That is, effort is assumed to be a valued resource that performers expend only when it yields a return (i.e., a benefit) that exceeds its value. Effort is also assumed to be expended by performers only to the degree that it is needed. Together, these assumptions challenge the intuitive notion that effort varies as a simple function of suc-

cess importance, with people trying more when much is at stake and trying less when little is at stake. They suggest, instead, that effort should be determined by what can, will, and must be done to meet a performance challenge. So long as success is viewed as both possible (i.e., within a performer's capabilities) and worthwhile (i.e., worth the effort investment), then effort should correspond to the perceived difficulty of the challenge. By contrast, when success is viewed as excessively difficult (i.e., exceeds the amount of effort a performer is willing to expend, given the benefit of success) or impossible (i.e., beyond a performer's capabilities), then effort should be low. Thus, effort should bear a non-monotonic relation to challenge difficulty, first rising at lower levels of difficulty and then falling abruptly as difficulty increases, with the fall occurring where challenge demand exceeds what performers can or will do.

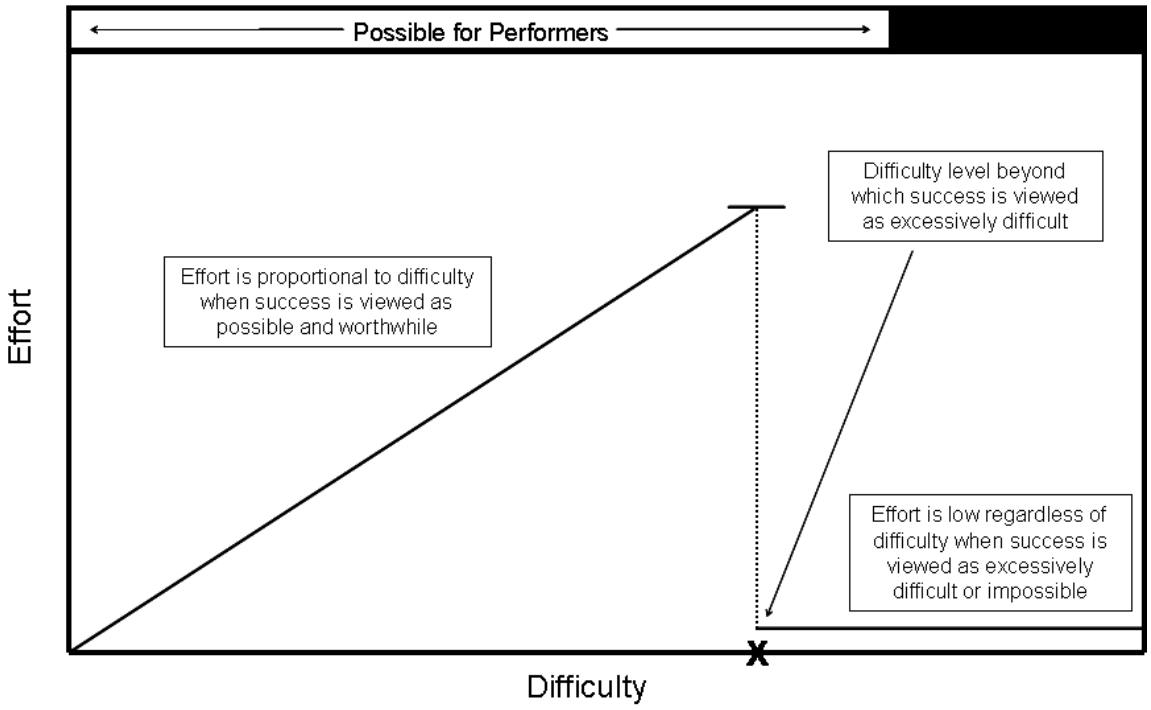

Figure 1: Effort as a function of challenge difficulty.

The proximal determinant of effort in Brehm's motivation intensity analysis is the performer's subjective (personal) appraisal of difficulty with respect to the challenge at hand. Theoretically, difficulty appraisals should be determined in part by the characteristic features of the challenge, that is, the degree of objective demand. However, they also should be determined in part by the performance capacity (i.e., ability) of the person performing the challenge. To illustrate this point, consider the hypothetical difficulty appraisals of a graduate student (low ability) versus those of a tenured senior research scientist (high ability) when asked to write a scientific manuscript for publication. It seems reasonable to expect that the graduate student would appraise this challenge as more difficult than the senior research scientist on the basis that the ability of the graduate student is much less than the ability of the senior research scientist. Thus, generally speaking, it follows that difficulty appraisals should be inversely proportional to ability, with lower ability corresponding to higher difficulty appraisals. In addition, it follows that ability should play a separate (though conceptually related) role from the characteristic features of the challenge (i.e., objective demand) in determining performers' appraisal of difficulty.

The independent role that ability should play in determining effort can be illustrated figuratively by depicting challenge difficulty along the X-axis of a graph and then drawing separate effort functions for performers with relatively low- and high-ability (see Figure 2 on next page).

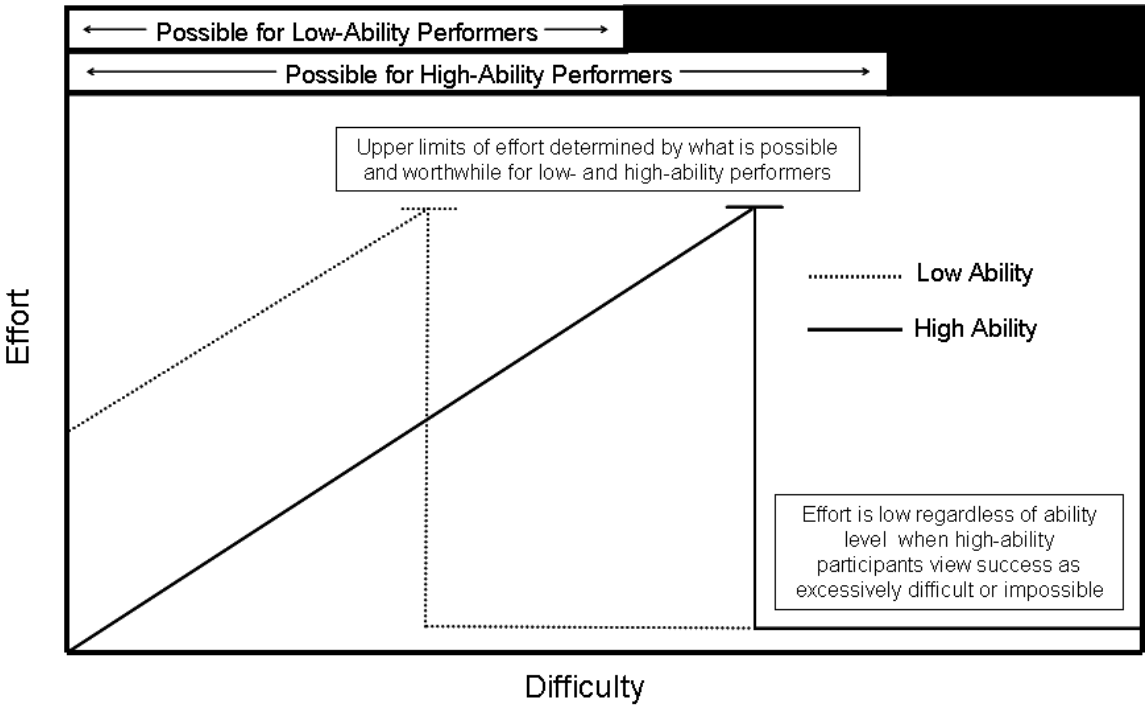

Figure 2: Effort as a function of ability and challenge difficulty.

Such a depiction highlights several theoretical points:

1. Effort should be greater for low- than high-ability performers so long as low-ability performers perceive success as both possible and worthwhile. The reason is that low-ability performers should find these challenges more difficult than high-ability performers and thus have to exert compensatory effort in order to achieve success.
2. Low-ability performers should withhold effort at a lower difficulty level than should high-ability performers, creating a window within which effort is lower for low- than high-ability performers. The reason for this converse relationship is that, within this window, low-ability performers should perceive

the challenge as excessively difficult or impossible, whereas high-ability performers should continue to perceive the challenge as possible and worthwhile.

3. Effort should be weak for both low- and high-ability groups under conditions where success calls for more effort than high-ability performers can or will do. Thus, at the highest difficulty levels, effort should be low regardless of ability, as even high-ability performers should perceive the challenge as excessively difficulty or impossible.

A theoretical point implicit in this analysis is that ability effects on effort should be moderated by success importance, that is, the magnitude of the benefit associated with good performance (i.e., what is at stake). Where performers view success as possible, their decision of whether or not to try should depend on their assessment of whether success benefit will outweigh success cost of effort. If they believe that benefit is greater, then they should try in proportion to their perception of difficulty. On the other hand, if they believe that cost greater, then they should withhold effort. Synthesizing these points, it follows that so long as low- and high-ability performers view success as possible, the point at which performers withhold effort should be determined by success importance, with lower importance appraisals yielding drop points at lower levels of difficulty and higher importance appraisals yielding later drop points at higher levels of difficulty (see Figure 3 on next page). These importance effects on effort were recently illustrated empirically (Stewart, Wright, Hui, & Simmons, 2009).

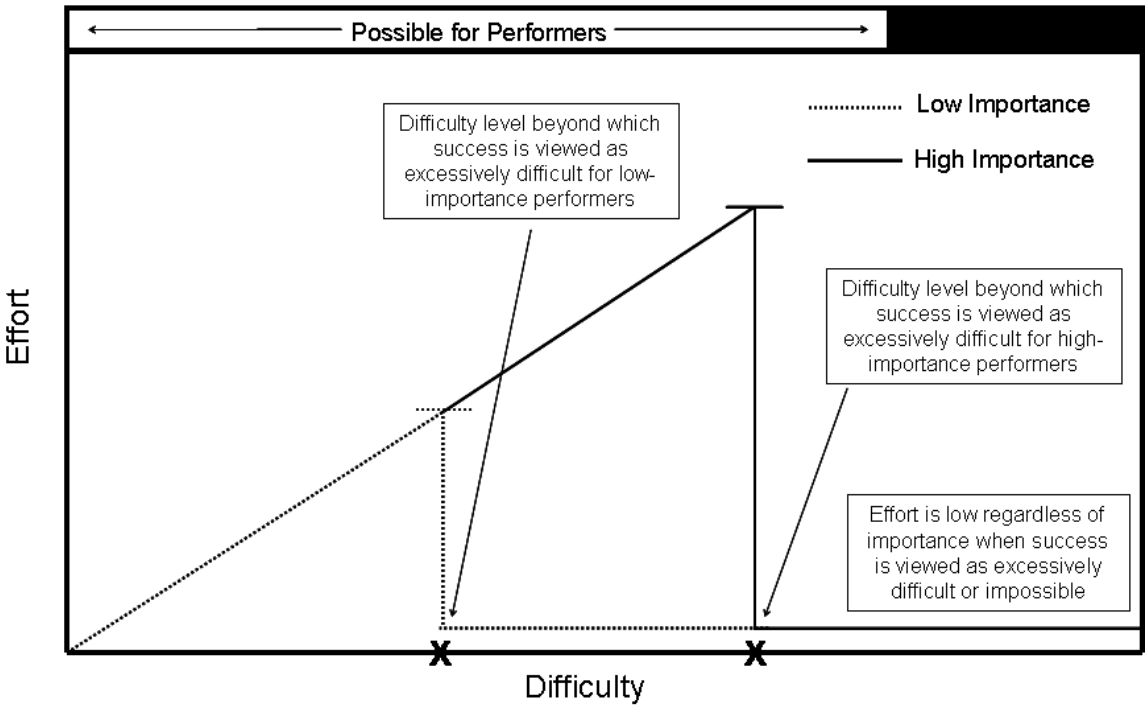

Figure 3: Effort as a function of difficulty and as moderated by success importance.

Wright's Integrative Model, Part I: Conceptual Framework

Wright's integrative model melds Obrist's active coping hypothesis with Brehm's motivational intensity analysis on the basis that both concern the deployment of effort in instrumental behavior (Wright & Kirby, 2001). Whereas motivational intensity analysis describes the factors determining whether or not and how much effort performers will deploy when facing a challenge (i.e., the determinants of effort), active coping hypothesis links the expenditure of effort to sympathetically-mediated CV responses (i.e., the consequence of effort). In integrating these two ideas, Wright's model proposes that sympathetically-mediated CV responses in instrumental behavior should follow the effort predictions of motivation intensity analysis (Wright & Kirby, 2001) (see Figure 4 on next page).

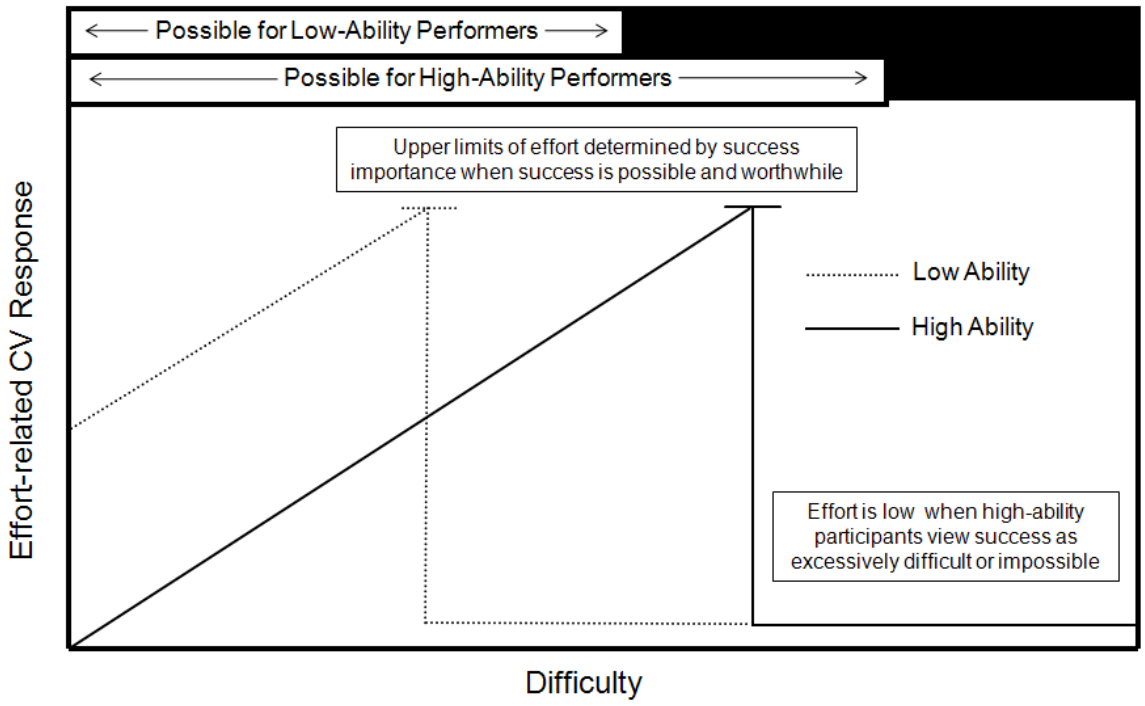

Figure 4: Wright's integrative model.

Specifically, Wright's integrative model makes at least four theoretical points:

1. Effort-related (i.e., sympathetically-mediated) CV responses for both low- and high-ability people should first rise with challenge difficulty and then fall sharply, with the falls occurring where success is viewed as excessively difficult or impossible.
2. Effort-related CV responses should be greater for low-ability performers than for high-ability performers so long as the low-ability group views success as possible and worthwhile. However, a reverse CV response pattern should be found where a challenge calls for more than low-ability performers – but not high-ability performers – can or will do. In this situation, CV responses should be weaker for low-ability performers than for high-ability performers.

3. Where a challenge calls for more than both low- and high-ability groups can or will do, both groups should exert low effort and experience low sympathetic CV arousal.
4. So long as the groups view success as possible, their point of disengagement along an (objective) difficulty continuum should depend on success importance, i.e., how much is at stake.

A related point worth noting here is that CV parameters vary in terms of their sensitivity to beta-adrenergic sympathetic nervous system influence on the heart. Commonly assessed CV parameters include systolic blood pressure (SBP) (pressure at the peak of the pulse), diastolic blood pressure (DBP) (pressure between pulses), mean arterial pressure (MAP) (average pressure during a pulse), heart rate (HR) (pulses per minute), and pre-ejection period (PEP) (a measure of heart contraction force). Effort effects should be most aptly reflected in PEP responses (a relatively clean measure of sympathetic nervous system activity), followed by SBP responses, and, to a lesser extent, in MAP and DBP responses. By contrast, HR responses are strongly influenced by both sympathetic and parasympathetic activity and thus may not be sensitive to effort effects (Levick, 2003; Richter, Friedrich, & Gendolla, 2008).

Wright's Integrative Model, Part II: Empirical Evidence

An exhaustive review of empirical literature examining Wright's integrative model is beyond the scope of the current study. Instead, the review that follows focuses on a few exemplary studies that illustrate proof of concept of Wright's integrative model. Reviewed studies can be organized into three categories: (1) those studies that manipu-

lated objective challenge difficulty, (2) those that directly manipulated ability, and (3) those that indirectly manipulated ability.

Studies that manipulated challenge difficulty. The most simplistic studies examining the influence of effort on the CV system have manipulated challenge difficulty. An example of this is a relatively early study by Smith, Baldwin, and Christenson (1990) in which CV responses were monitored as participants prepared and delivered a persuasive speech to a confederate. Instructions to participants described the persuasive challenge as being easy, difficult, or very difficult. Instructions also indicated that participants would receive a monetary incentive if their presentations were judged to be compelling by the confederate. Results showed that SBP, DBP, and HR responses were strongest for participants in the difficult condition versus those in the easy or very difficult condition. The interpretation of these data was that effort and associated CV responses were greater in the difficult condition versus the easy condition, presumably because participants in the difficult condition viewed challenge success as more difficult to attain (than the easy challenge) yet still possible and worthwhile. However, effort and associated CV responses were lower in the very difficult condition versus the difficult condition, presumably because participants in the very difficult condition viewed success as excessively difficult and thus withheld effort.

In a related but more recent study by Richter, Friedrich, & Gendolla (2008), participants performed versions of the Sternberg memory task that differed in difficulty. The Sternberg memory task requires participants to determine whether a target character is included in a preceding character string by responding (e.g., pressing a button) (Sternberg, 1966). Richter et al. manipulated difficulty across four levels by varying the dura-

tion that the character string could be viewed by participants (low difficulty version = 1000ms; medium difficulty = 550ms; high difficulty = 100ms; impossible = 15ms). Results showed that SBP responses and pre-ejection period responses increased across the low, medium, and high difficulty conditions but precipitously dropped in the impossible condition. The interpretation of these data was that participants' effort and associated CV responses progressively increased across the low, medium, and high difficulty conditions because these participants viewed success on these conditions as possible and worthwhile. By contrast, CV responses were minimal in the impossible condition because participants in this condition viewed success as beyond their capabilities and thus withheld effort.

Studies that directly manipulated ability. Adding a layer of complexity to the previous studies are those that manipulate both challenge difficulty and ability. To reiterate a previous point, such studies are of importance because the subjective appraisal of difficulty (the proximal determinant of effort) should be determined in part by the challenge's characteristic features (i.e., objective difficulty) and in part by the performer's performance capacity (i.e., ability).

In an early study that crossed factors of difficult and ability perception, Wright and Dill (1993) had participants first perform a letter-scanning task and then gave them phony feedback about their performance, telling one-half of participants that they performed poorly (12^{th} percentile; low-ability) and the other half that they performed well (87^{th} percentile; high ability). Following this, half of the participants were told that they would receive a modest incentive if they attained a relatively low performance standard on a second letter-scanning task (15^{th} percentile of other participants' performance; low

difficulty), whereas the other half of participants were told that they would receive the incentive if they attained a relatively high performance standing on the same scanning task (85th percentile of other participants' performance; high difficulty). Analysis of SBP and DBP responses to the second letter-scanning task showed that low-ability participants evinced stronger CV responses than high-ability people when the performance standard was low. Conversely, high-ability participants evinced stronger CV responses than low-ability participants when the performance standard was high. The interpretation of this crossover interaction was dual. First, effort-related CV responses were greater in low- versus high-ability participants when the performance standard was low because low-ability participants viewed the low-difficulty challenge as more difficult (than their high-ability/low-difficulty counterparts) but still possible and worthwhile. Second, effort-related CV responses greater in high- versus low-ability participants when the performance standard was high because low-ability participants viewed the high-difficulty challenge as excessively difficult or impossible (and thus withdrew effort), while their high-ability/ high-difficulty counterparts continued to exert effort. Multiple other studies manipulating ability have conceptually replicated and extended upon these findings, producing CV response patterns that generally comport with Wright's integrative analysis (Wright & Dismukes, 1995; Wright, Murray, Storey, & Williams, 1997; Wright & Lockard, 2006).

Studies that indirectly manipulated ability. A final line of studies to be reviewed are those that manipulated ability via a secondary factor. An example of such a secondary factor is fatigue. Fatigue is purported to affect ability on the premise that ability is inversely correspondent to fatigue. The broad implication of this is that fatigue effects

should match those of ability, with CV responses of fatigued performers corresponding to those of low-ability performers and CV responses of non-fatigued (i.e., rested or refreshed) performers corresponding to those of high-ability performers. Specifically, when fatigue leaves unaltered a belief that success is possible and worthwhile, it should augment effort and CV responsiveness. That is, it should lead performers to exert compensatory effort and experience heightened arousal as a result. By contrast, when fatigue causes success to appear impossible or excessively difficult, it should retard effort and CV responsiveness. That is, it should lead performers to withhold effort and experience minimal arousal as a result. Finally, when fatigue leaves unaltered a belief that success is impossible or excessively difficult, it should have no impact on effort and CV responsiveness. That is, it should leave unchanged performers' inclination to exert low effort and experience minimal arousal as a result. These points can be visualized in Figure 4 (above) by switching the labels "Low Ability" with "High Fatigue" and "High Ability" with "Low Fatigue".

An exemplary study by Wright, Martin, and Bland (2003) illustrates the first two points above, that is, that fatigue should (1) augment effort and associated CV responses when it leaves unaltered a belief that success is possible and worthwhile, but (2) retard those responses when it causes success to appear impossible or excessively difficulty. In this study, mental fatigue was manipulated on the assumption that mental systems can become resource depleted in the same fashion that muscular systems can (Baumeister, Vohs, & Tice, 2007). To this end, participants were randomly assigned to an easy counting task (mentally count forward from zero at a relatively slow pace; low fatigue condition) or difficult counting task (mentally count backward at a relatively fast pace; high

fatigue condition). After the counting task, participants performed a set of mental arithmetic problems with instructions that they could earn a prize if they attained a low (30^{th} percentile) or high (80^{th} percentile) performance standard. As expected, analysis of CV data collected during the arithmetic work period indicated a fatigue x difficulty interaction for SBP response. Whereas high fatigue participants tended to have stronger SBP responses than low fatigue participants when the standard was low, they had weaker SBP responses than low fatigue participants when the standard was high. Analysis of the DBP and MAP data revealed the same interactions with means in similar crossover patterns. The interpretation was that fatigue accentuated effort-related CV responses when the performance standard was low because high fatigue participants viewed this challenge as possible and worthwhile. By contrast, fatigue retarded effort-related CV responses when the performance standard was high because high fatigue participants viewed this challenge as excessively difficult or impossible. Findings from this study have been replicated and extended in multiple subsequent fatigue studies (Hogan, Shim, Duncan, Faunce, & Wright, 2010; Marcora, Bosio, & de Morree, 2008; Nolte, Wright, Turner, & Contrada, 2008; Wright & Penacerrada, 2002; Wright, Stewart, & Barnett, 2007). More generally, emerging evidence suggests that other secondary factors (e.g., mood), besides fatigue, can impact ability perception and effort-related CV responses in an analogous fashion (Gendolla & Brinkmann, 2005; Gendolla & Krusken, 2001; Gendolla & Krusken, 2002; Richter, Gendolla, & Krusken, 2006).

Summary. As a whole, the literature generally provides converging evidence supporting Wright's integrative model. Of special relevance to the present experiment, the reviewed studies provide proof of concept of three theoretical points (see Figure 4

above). First, those studies manipulating challenge difficulty have reliably demonstrated that effort-related CV responses first rise with challenge difficulty and then fall sharply, with the fall occurring where success is viewed as excessively difficult or impossible. Second, those studies manipulating ability, either directly or indirectly, have consistently demonstrated that effort-related CV responses are greater for low-ability performers than for high-ability performers so long as the low-ability group views success as possible and worthwhile. These studies have also demonstrated that CV responses are weaker for low-ability performers than for high-ability performers when a challenge calls for more than low-ability performers – but not high-ability performers – can or will do. Although not empirically tested, based on the ability effects observed, it seems reasonable to assume that both low- and high-ability groups will exert low effort and experience low sympathetic CV arousal where a challenge calls for more than both low- and high-ability groups can or will do. Third, although not reviewed in detail above, at least one study (Stewart et al., 2009) has empirically demonstrated that success importance determines the point at which performers withhold effort, so long as low- and high-ability performers view success as possible and worthwhile.

Wright's Integrative Model, Part III: Extension to Cognitive Impairment

Conceptual framework. Cognitive impairment is a previously uninvestigated factor that may secondarily influence effort-related CV responses by altering ability. Like fatigue, the idea that cognitive impairment might affect effort-related CV responses is premised on the assumption that ability is inversely related to the degree of cognitive impairment. Also analogous to fatigue, the broad implication of this is that cognitive impairment effects should match those of ability, with CV responses of impaired perform-

ers corresponding to those of low-ability performers and CV responses of non-impaired (i.e., cognitively intact) performers corresponding to those of high-ability performers. More specifically, when cognitive impairment leaves unaltered a belief that success is possible and worthwhile, it should augment effort and CV responsiveness. That is, it should lead performers to exert compensatory effort and experience heightened arousal as a result. By contrast, when cognitive impairment causes success to appear impossible or excessively difficult, it should retard effort and CV responsiveness. Lastly, when cognitive impairment leaves unaltered a belief that success is impossible or excessively difficult, it should have no impact on effort and CV responsiveness. These points can be visualized in Figure 4 (above) by switching the labels "Low Ability" with "Cognitively Impaired" and "High Ability" with "Cognitively Intact".

Theoretical assumptions. The preceding extension to cognitive impairment holds true only to the extent that a series of theoretical assumptions also hold true in individuals with cognitive impairment. These theoretical assumptions concern the ability to appraise objective challenge difficulty and success importance, the decisional capacity to either exert or withhold effort, the capacity to deploy effort, and the mediation of effort by beta-adrenergic activity. Such assumptions typically go unstated because it is reasonable to presume that they hold true in healthy individuals. However, their validity is less clear in individuals with cognitive impairment. One reason for this uncertainty is that cognitive impairment rarely (if ever) occurs in isolation. Rather, it most often is accompanied by physiological and psychological impairments associated with a specific etiology. Consider, for example, a person with a pituitary tumor that has both cognitive impairment and beta-adrenergic disruption (a physiological impairment), or alternatively, a person with

dementia that has both cognitive impairment and an impairment in appraising challenge difficulty (a psychological impairment). Clearly, these co-occurring physiological and psychological impairments could result in unexpected CV response patterns.

Below, some theoretical assumptions that seem most relevant to cognitive impairment are listed one-by-one. This list is not meant to be exhaustive. Although somewhat tedious, outlining relevant assumptions in this fashion sheds light on the complexity involved in predicting effort-related CV responses in persons with cognitive impairment. Doing so will also provide a framework to aid in the interpretation of results, particularly unexpected results. For the purposes of the present study, theoretical assumptions are organized into three groups: appraisal and decision assumptions, effort deployment assumptions, and mediation assumptions (please refer to Figure 5 on next page, as needed).

Appraisal and decision assumptions are concerned with the appraisal of challenge difficulty and success importance and the decisional capacity to exert or withhold effort. There are four assumptions. The first two assumptions each concern the appraisal of challenge difficulty. The first assumption is that cognitive impairment leaves unaltered the ability to appraise relative differences in challenge difficulty. That is, cognitive impairment leaves intact one's ability to appraise one challenge as being more (or less) difficult than a different challenge. The second assumption pertaining to challenge difficulty is that individuals will appraise a challenge as more difficult in light of their cognitive impairment. That is, people with cognitive impairment will appreciate that a challenge is more difficult than they would have found that same challenge before they

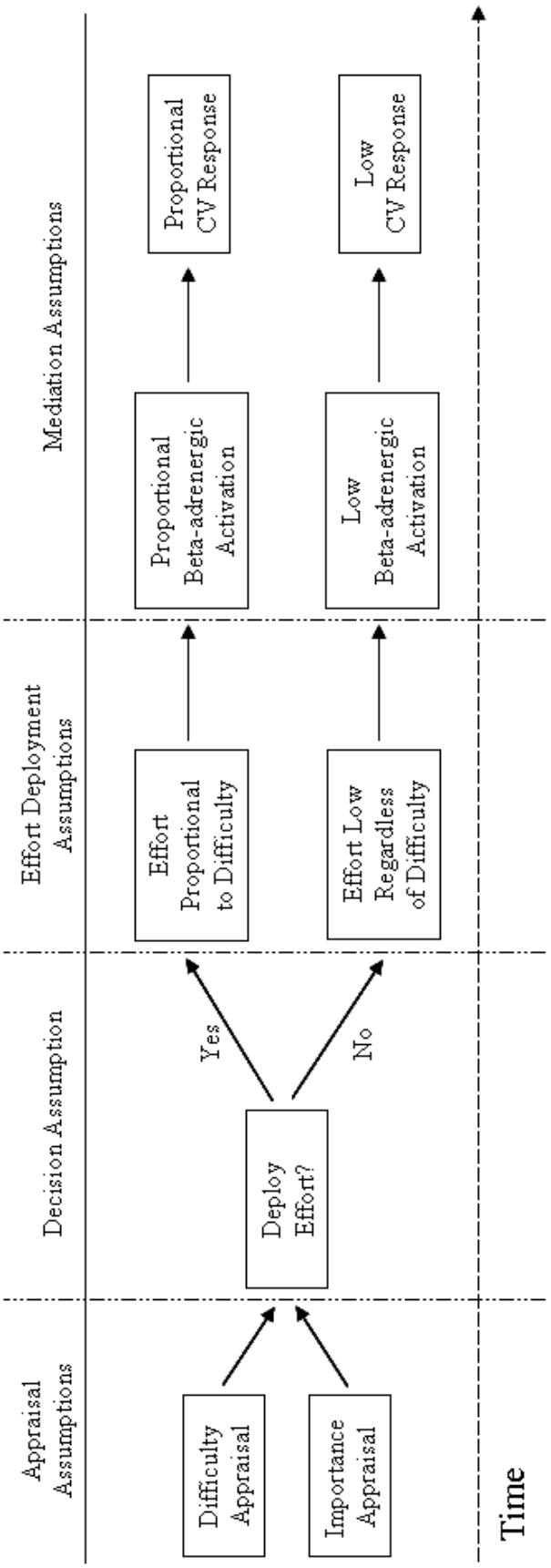

Figure 5: Flow chart of theoretical assumptions.

were cognitively impaired. The third assumption relates to success importance. It simply states that cognitive impairment has no impact on appraisals of success importance. The fourth assumption concerns the decisional capacity to exert or withhold effort. It states that cognitive impairment leaves unaltered the ability to determine whether challenge success is possible and worthwhile or excessively difficult or impossible.

The second set of assumptions pertains to the deployment of effort when persons with cognitive impairment are facing a challenge. There are three assumptions. The first assumption is that cognitive impairment leaves unaltered the deployment of effort (in proportion to challenge difficulty) so long as success is possible and worthwhile. That is, cognitive impairment leaves intact one's ability to deploy more (or less) effort in response to a challenge that is more (or less) difficult, should one perceive success as possible and worthwhile. The second assumption is that cognitive impairment leaves unaltered the ability to deploy compensatory effort in order to account for cognitive impairment. That is, cognitive impairment leaves intact one's ability to deploy extra effort to compensate for their cognitive impairment, so long as success is possible and worthwhile. The third assumption states that cognitive impairment leaves unaltered ability to withhold effort in situations that are deemed excessively difficult or impossible.

The third and final set of theoretical assumptions concern the mediation of effort by beta-adrenergic activity. There are two such assumptions. The first assumption is that cognitive impairment (and any associated physiological impairment) leaves unaltered the mediation of effort by beta-adrenergic activity. The second is that cognitive impairment (and any associated physiological impairment) leaves unaltered the relationship between beta-adrenergic activity and CV responses.

The Current Study

Applying the Cognitive Impairment Extension to AD and MCI

The current study aimed to examine effort-related CV responses in patients with AD or MCI, and in non-demented older adults (controls). Reasons for selecting AD and MCI as patient populations of interest were twofold. One reason was emerging evidence pointing to vascular contributions to AD, as reviewed at the outset. The other reason was that AD and MCI represent different stages of the same underlying dementing process, with amnestic MCI generally viewed as the prodromal stage of AD and with cognitive impairment being milder in MCI than in AD (Petersen et al., 2009). This permits examination of effort-related CV responses in individuals with different degrees of cognitive impairment.

Applying Wright's integrative model and the cognitive impairment extension to AD, MCI, and control groups is relatively straightforward. Five (familiar sounding) theoretical points emerge (see Figure 6 on next page):

1. For each group, effort-related CV responses should first rise with challenge difficulty and then fall sharply, with the falls occurring where success is viewed as excessively difficult or impossible.
2. Effort-related CV responses should be greater for the AD group than for the MCI and control groups, so long as the AD group views success as possible and worthwhile. However, the AD group should also view success as excessively difficult or impossible at a lower level of difficulty than MCI and control groups. Within this window, CV responses should be weaker for the AD group compared to the MCI and control groups.

3. Similarly, for the MCI group, effort-related CV responses should be greater than for the control group, so long as the MCI group views success as possible and worthwhile. However, the MCI group should also view success as excessively difficult or impossible at a lower level of difficulty than the control group. Within this window, CV responses should be weaker for the MCI group compared to the control group.
4. Where a challenge calls for more than control participants can or will do, all groups should exert low effort and show minimal CV responses.

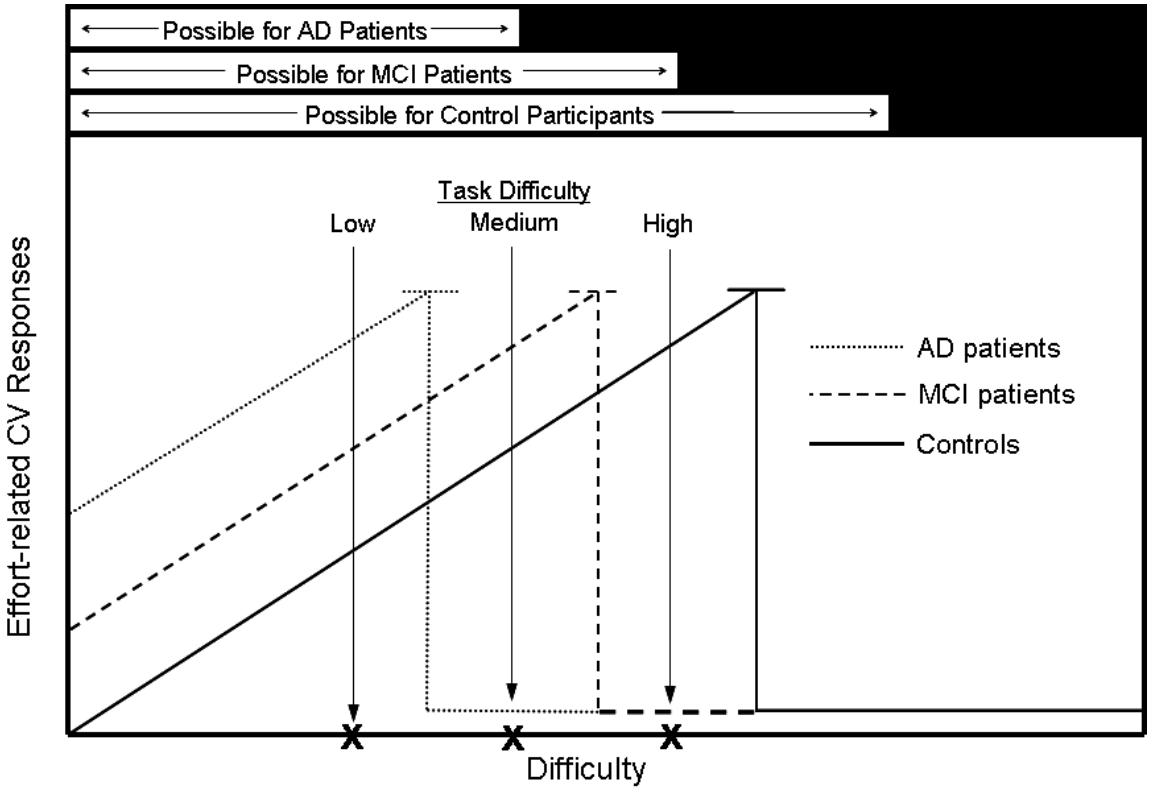

Figure 6: Extension of Wright's integrative model to AD and MCI.

5. So long as all groups view success as possible and worthwhile, success importance should determine the point along the difficulty continuum at which the groups determine that success is excessively difficulty or impossible and thus withhold effort and show minimal CV responses.

Study Summary and Study-Specific Assumptions

In the current study, AD, MCI, and control participants performed three versions of the Sternberg memory task that varied in difficulty (low, medium, and high difficulty) as their CV activity was monitored. Recall that the Sternberg memory task requires participants to determine whether a target character is included in a preceding character string by responding (e.g., pressing a button) (Sternberg, 1966). Similar to the Richer Friedrich, & Gendolla (2008) study reviewed above, difficulty was manipulated across the low, medium, and high difficulty levels by shortening the duration that the character string could be viewed by participants.

The study's hypotheses followed from the Wright's integrative model, its extension to cognitive impairment as applied to AD and MCI, and three study-specific assumptions. The study-specific assumptions pertained to whether or not the study groups would deploy or withhold effort when performing the low, medium, and high difficulty versions of the Sternberg memory task. They were threefold. The first study-specific assumption was that the control group would view success as possible and worthwhile at all levels of challenge difficulty. The second assumption was that the MCI group would view success as possible and worthwhile on the low and medium difficulty levels; however, they would view success as excessively difficult at the high difficulty level. The final study-specific assumption was that the AD group would view success as possible and worth-

while on the low difficulty level; however, they would view success as excessively difficult or impossible on the medium and high difficulty levels.

Of note, it is very difficult to determine *a priori* the difficulty level at which participants will view success as possible and worthwhile versus excessively difficult or impossible, particularly for AD and MCI patients. For this reason, my study-specific assumptions were, to a degree, arbitrarily set. However, I reasoned that – should the study-specific assumptions prove invalid – the observed CV responses could still match the overall configural pattern depicted in Figure 6, so long as the theoretical assumptions held true. Alternatively stated, I reasoned that it was entirely possible that the study results would be in agreement with Wright's integrative model and its extension to cognitive impairment as applied to AD and MCI, even if the results and did not match the hypotheses below.

Study Hypotheses

With the study-specific assumptions in place, the following hypotheses were offered (also refer to Figure 6, above):

1. Controls' SBP and PEP responses will increase across the low to medium to high difficulty versions of the Sternberg memory task.
2. MCI patients' SBP and PEP responses will increase across the low to medium difficulty versions; however, their responses will precipitously drop on the high difficulty version. Moreover, MCI patients' SBP and PEP responses will be stronger than controls' responses on the low and medium difficulty ver-

sions, but their responses will be weaker than controls' responses on the high difficulty version.

3. AD patients' SBP and PEP responses will precipitously drop across the low to medium difficulty versions, and their responses will remain low on the high difficulty version. Moreover, AD patients' SBP and PEP responses will be stronger than MCI patients' responses on the low difficulty version; however, their responses will be weaker than MCI patients' responses on the medium and high difficulty versions.

METHODS

The study's methods were modified in several ways after the dissertation was proposed. Deviations from the initial proposal are described below, and explanations for alternative approaches are provided.

Participants

It was initially proposed that the study would consist of three participant groups: patients with probable mild AD, patients with amnestic MCI, and non-demented, older control participants. However, data collection on the AD group was discontinued with the permission of dissertation co-chairs due to a very low recruitment rate (Rex A. Wright, personal communication, April 9, 2009; H. Randall Griffith, personal communication, spring 2009). A total of three participants with dementia completed the full protocol over approximately one year of study recruitment. Compounding the recruitment issue, comprehension of task instructions, the performance standard, and subjective

measures appeared marginal to poor in those patients with dementia that started the study protocol. After removal of the AD group, two participant groups remained: patients with amnestic MCI and non-demented, older control participants. Thus, the study had a mixed 2 (study group; between-subjects factor) x 3 (challenge difficulty; within-subjects factor) factorial design.

MCI Patients

MCI patients were community-dwelling individuals recruited from the University of Alabama at Birmingham (UAB) Alzheimer's Disease Research Center (ADRC). MCI patients were diagnosed in the UAB ADRC diagnostic consensus conference on the basis of neurological, neuropsychological, and, in some cases, radiological findings. Diagnoses of amnestic MCI were made according to Mayo criteria: (1) subjective complaint of memory loss; (2) objective impairment on memory testing compared with age- and educationally-matched normative data; (3) otherwise generally normal cognitive performance; and (4) generally preserved activities of daily living (Petersen, Stevens et al., 2001; Petersen, Doody et al., 2001). By definition, patients diagnosed with MCI do not show evidence of a dementia. All MCI patients recruited into this study had received a Clinical Dementia Rating staging (Morris, 1993) of 0.5 based on the clinical consensus of a group of ADRC neurologists and neuropsychologists. An attempt was made to exclude non-amnestic forms of MCI by recruiting only those patients previously diagnosed with amnestic MCI. However, because ADRC diagnostic consensus conferences took place several weeks following study participation, exclusive recruitment of amnestic MCI patients was not certain.

Control Participants

Like MCI patients, non-demented, older control participants were community-dwelling individuals recruited from the UAB ADRC. Controls were characterized in the ADRC diagnostic consensus conference as neurologically and cognitively intact on the basis of neurological and neuropsychological findings. All controls received a CDR staging rating of 0.0.

Exclusion Criteria

Individuals were excluded from study participation if they had a history of heart disease or if they were taking certain BP medications. Heart disease included, but was not limited to, cardiomyopathy, cardiovascular disease (e.g., atherosclerosis), congenital heart disease, coronary heart disease, congestive heart failure, hypertensive heart disease, inflammatory heart disease, and valvular heart disease. In the dissertation proposal, the BP medication exclusion criteria included all medications listed under the following drug classes in the Tarascon Pocket Pharmacopoeia (Green, 2007): ACE inhibitors, angiotensin receptor blockers, antihypertensive combinations, alpha-blockers, antihypertensives – other, beta-blockers, calcium channel blockers – dihydropyridines, and other, diuretics – carbonic anhydrase inhibitors, loop, potassium sparing, and thiazide type. This exclusion criterion resulted in a low recruitment rate due to the large number of medications falling under these drug classes and their high prevalence in older adult populations. Moreover, it was unclear to what degree these medications would affect CV responses, with the exception of beta-blockers (J. Michael Wyss, personal communication, July 22, 2008; Dr. Wyss, a Professor in Cell Biology, Medicine, Neurobiology, and Psychology at

UAB, has previously studied blood pressure mechanisms and blood pressure medications in relation to cognition, aging, and dementia). For these reasons, the medication exclusion criterion was made less stringent with the permission of the dissertation committee (all committee members, personal communication, July 22 and 23, 2008). The modified criterion excluded those participants that were prescribed beta-blockers or anti-hypertensive combinations that included beta-blockers. However, because ADRC medication lists were not updated for the previous year until after study participation, exclusive recruitment of participants that were free of beta-blockers was not certain.

The Sternberg Memory Task

The versions of the Sternberg memory task used in this study were administered to participants on a computer. The current versions were created in Inquisit (Millisecond Software, Seattle, WA), a high-performance psychological experiment generator. They were based off programming code for a Sternberg memory task that was used in a past CV response study (Richter, Friedrich, & Gendolla, 2007).

Although many versions of the Sternberg memory task have been created, all ask performers to determine whether a target stimulus was or was not included in a preceding series of stimuli. In the current "go/no-go" version, participants were instructed to press the spacebar on the computer's keyboard if a target letter was included in the preceding letter series. If the target letter was not included in the preceding letter series, however, they were instructed to refrain from pressing the spacebar. Thus, for example, if the preceding letter series was "FPDL" and the target letter was "P", participants should press the spacebar. However, if the letter series was "FPDL" and the target letter was "Q", par-

ticipants should not press the spacebar (i.e., they should withhold their response). Participants were instructed that responding accurately was more important than responding quickly.

Each trial of the Sternberg memory tasks consisted of the following sequence: (1) a fixation cross (+) (displayed for approximately 1100ms); (2) a nonsense letter series consisting of four letters (e.g., FPDL) (these letters were presented simultaneously, not serially); (3) a masking stimulus of four X's (XXXX) with a single target letter centered above the masking stimulus; (4) the participant's response (i.e., press the spacebar or do not respond); and lastly (5) feedback about their response (i.e., "CORRECT" or "INCORRECT"). The within-subject factor of task difficulty was manipulated by varying the duration that nonsense letter series were displayed on the computer screen, with shorter durations corresponding to increases in difficulty. In the low difficulty version, participants had 2750ms to study the nonsense letter series. In the medium and high difficulty versions, they had 1000ms and 600ms, respectively, to study the nonsense letter series. The total duration of each trial was 10,000ms. Participants had ample time to respond following presentation of the target letter (at least 4000ms). On trials where participants responded (i.e., pressed the spacebar), feedback was displayed on the computer screen immediately following participants' responses until the start of the next trial. On trials where the participant did not respond, feedback was displayed for 1,500ms before the start of the next trial.

Regarding the counterbalancing of stimuli, upon starting a work period, the Inquisit program randomly drew (with replacement) from a pool of "potential" trials. The pool was balanced such that there were an equal number of trials with and without the target

letter included in the nonsense letter series. The pool was also balanced such that there was an equal likelihood that target letters were positioned in the 1st (leftmost), 2nd, 3rd, or 4th (rightmost) position within the letter series. Finally, stimuli were balanced so that individual letters occurred with equal frequency and so that individual letters occurred as target letters or distracter letters (i.e., non-target letters) in equal proportion.

Dependent Measures

CV Measures

It was originally proposed that CV parameters would include SBP, DBP, MAP, HR, and PEP. However, PEP was excluded from statistical analyses due to variability in signal quality that brought into question the validity of PEP measures. This decision was made with the approval of the dissertation chair (Rex A. Wright, personal communication, November 8, 2009). Reasons for variability in signal quality are unclear but may be due to sample characteristics. For example, signal quality may have been reduced due to looser skin or increased weight (relative to a healthy undergraduate population) in the current sample of older adults. Yet another issue was the experimenter's limited experience with post-acquisition analysis of raw impedance cardiography data from which PEP is measured. Impedance cardiography is a relatively novel technique to the laboratory and the experimenter's experience with PEP was limited prior to this study. Limited experience was a particular hindrance when the raw impedance cardiography data were of suboptimal quality.

The remaining CV parameters of SBP, DBP, MAP, and HR were measured using the Medwave Fusion Non-Invasive Blood Pressure Monitoring System (Model 50-9000)

(St. Paul, Minnesota) (Belani et al., 1999). The Fusion System employs a "sweep technique" to monitor BP by applying a varying force on the radial artery located on the wrist. The counter-pressure in the artery produces a signal that is digitized and used to calculate BP parameters. The Fusion System has been validated against direct radial arterial measurements, one of the gold standards for BP measurement (Belani et al., 1999).

SBP, DBP, MAP, and HR were measured continuously throughout the study, that is, from the start of the baseline period until the end of Work Period 3. Mean CV parameters were calculated for the baseline period and each of the three work periods. For the baseline period, mean CV parameters were the average of all samples of the parameter acquired between minute two and minute eight (the conclusion) of the baseline period. For work periods, mean CV parameters were the average of all samples of the parameter acquired during the work period, from start (minute zero) to finish (the end of minute 2). CV responses were defined as the mean of the CV parameter during the work period minus the mean of the parameter during baseline (Llabre, Spitzer, Saab, Ironson, & Schneiderman, 1991). Thus, for each participant, responses in SBP, DBP, MAP, and HR were calculated for Work Periods 1, 2, and 3.

Subjective Measures

As stated above, subjective measures were collected using the Subjective Measures Questionnaire (see Appendix A). The questionnaire asked participants first to rate on a Likert scale "How difficult do you think it will be to answer correctly on at least 75% of the trials in this work period? (1) Not difficult, (2) A little difficult, (3) Moderately difficult, (4) Very difficult, or (5) Excessively difficult or impossible", and second to rate "For you personally, how important will it be to respond correctly on at least 75%

of the trials in this work period? (1) Not important, (2) A little important, (3) Moderately important, (4) Very important". In each work period, the questionnaires were administered immediately after each practice block but before the work period block. They were administered at this point not only so participants would have familiarity with the tasks prior to making appraisals but also because difficulty appraisals in demented populations are thought to be most accurate when they are based on information still maintained in working memory (Cosentino & Stern, 2005; Duke et al., 2002). Other steps taken to maximize the likelihood that MCI patients could provide valid responses to the questionnaire included the following: (1) the questionnaire was presented visually and read aloud to participants in each work period to optimize comprehension of questions; (2) questionnaire items were designed to have a limited number of response options in order to simplify cognitive estimation, which may be impaired in MCI (Cosentino & Stern, 2005); and (3) the questionnaire was designed to resemble a past self-report questionnaire (MILES Self-Report Questionnaire; Okonkwo et al., 2009) that measured difficulty experienced in performing various tasks required for independent living in MCI patients (e.g., driving, medication/health care management).

Performance Measures

Performance measures were calculated for each participant for each of the three work periods and included accuracy (correct trials divided by total trials), hit rate (hits divided by the sum of hits plus misses), and false positive rate (false positives divided the sum of false positives plus correct rejections).

Participant Characteristics

The following participant characteristics were collected: age, gender, racial/ethnic group, education, blood pressure medication status, beta-blocker medication status, MCI subtype (amnestic/nonamnestic), Clinical Dementia Rating staging, Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), Dementia Rating Scale – Second Edition raw scores (DRS-2) (total score, memory score, attention score) (Jurica, Leitten, & Mattis, 2001). Participant characteristics were collected from participants' ADRC medical charts in the months following study participation. By this point in time, participants' ADRC charts had been updated to include findings from their most recent annual clinic visit. A list of screened blood pressure medications is presented in Appendix B. Participants were classified as taking blood pressure medications if one or more of the screened medications were listed as a current medication in their ADRC chart.

Procedure

The UAB Institutional Review Board (IRB) approved this study's protocol prior to data collection and monitored all phases of the protocol for issues related to human participant welfare (see Appendix C for IRB materials).

Participant Recruitment

Recruited participants were individuals presenting at the UAB ADRC for their annual clinic visit who did not meet exclusion criteria based on review of their ADRC medical charts. The experimenter (C.S.) conducted all reviews of potential participants' ADRC medical charts prior to study recruitment.

A description of this study was initially presented to recruited participants by ADRC neuropsychology technicians. The technicians explained the study in general terms, including the approximate duration of the study (40 minutes) and compensation ($20). If recruited participants expressed interest, they then met with the experimenter in the ADRC research room, where the study was described in greater detail. If recruited participants chose to partake in the study at this time, the experimenter proceeded with informed consent.

Informed consent

To determine whether AD or MCI participants had the capacity for research consent, the participants' ADRC consent form for their annual clinical evaluation was referenced (the annual clinical evaluation was conducted on the same day but prior to study participation). If a participant consented on the ADRC clinical evaluation consent form, then the participant also provided consent for this study. Alternatively, if a participant's legal representative consented on the ADRC clinical evaluation consent form, then the participant's legal representative also provided consent for this study. All control participants provided their own consent.

Two informed consent agreements were presented to participants and their representatives (if applicable). Important points explained to participants both verbally and in writing (in the consent form) were (1) that that the purpose of the study was to examine cardiovascular activity while they rested and as they performed challenges that required sustained attention and (2) that they would receive $20 for their participation, regardless of their performance on the challenges or whether they completed the study. Following this explanation, the experimenter left the research room so participants could read pri-

vately and sign the two copies of the consent form. Upon returning, the experimenter signed both consent forms and gave one consent form to the participant and retained the other form. Legal representatives (if applicable) were then directed to the ADRC waiting room, where they remained until the conclusion of the study. This point in the procedure marked the beginning of the experiment itself.

Baseline Period

The experiment started by connecting participants to the CV recording hardware. This involved attaching the Fusion blood pressure cuff to participants' non-dominant wrists and applying the Bionex spot electrodes to participants' torsos according to established methodological guidelines (Berntson, Lozano, Chen, & Cacioppo, 2004; Lozano et al., 2007; Sherwood et al., 1990). In cases where the participant was female, the (male) experimenter left the research room while a female undergraduate research technician applied the Bionex spot electrodes to participants. Once participants were hooked up to the CV recording hardware, the study procedure was outlined by the experimenter. Specifically, the procedure was described as involving a 10-minute resting baseline period followed by three 3-minute work periods during which participants would perform a sustained attention challenge. Although participants were told that the baseline duration was 10 minutes, it was actually 8 minutes. Participants were misled in this way to prevent increases in CV activity associated with anticipation of performing the challenges. Prior to starting the baseline period, participants were instructed to make themselves comfortable in their chair and sit quietly and remain relatively still. Next, the CV recording software was started to ensure accurate recording, and adjustments to CV hardware were made, if necessary. Once accurate recording was confirmed, participants completed the

8-minute resting baseline period. Of note, the experimenter remained in the research room at all times but was situated on the opposite end or the room (well removed from the participant) and did not interact with participants during baseline or work periods.

Work Periods

Following the baseline period, participants completed three work periods. In each work period, participants performed one 3-minute version of the Sternberg memory task (Sternberg, 1966). Participants first performed a low difficulty version of the Sternberg memory task in Work Period 1; next, they performed a medium difficulty version in Work Period 2; and last, they performed a high difficulty version in Work Period 3.

To start each work period, task instructions were explained or reiterated to participants to ensure comprehension. Participants were then informed that they would first complete "practice" trials (the practice block) before performing the "actual" or "real" challenge (the work period block). Trials in the practice block were identical to trials in the work period block and were described as such to participants. Prior to starting the practice block, participants were told to "try to answer correctly on at least 75% of the trials." Participants then performed the practice block, which lasted approximately one minute and consisted of eight trials. Immediately following the practice block, the Subjective Measures Questionnaire (see Appendix A) was presented visually and read aloud to participants. The Subjective Measures Questionnaire asked participants to rate the difficulty of the task they had just practiced ("How difficult do you think will it be to answer correctly on at least 75% of the trials in this [upcoming] work period?") and how important they viewed task success ("For you personally, how important will it be to respond correctly on at least 75% of the trials in this [upcoming] work period?"). Prior to starting

the work period, challenge instructions were reiterated to ensure comprehension, and participants were reminded to "try to answer correctly on at least 75% of the trials." In addition, participants were informed that the experimenter would check to determine whether the 75% performance standard was met following the experiment. Participants then performed the work period block, which lasted approximately three minutes and consisted of 20 trials. Following completion of the work period block, participants rested for a 2-minute "recovery" period before starting the next work period.

This general procedure was followed for Work Periods 1, 2, and 3. The only deviation from this was the experimenter's description of the difficulty manipulation. Specifically, during challenge instructions in Work Periods 2 and 3, it was explained to participants that they would have "less time to study the letter string" than in the preceding work period Participants were not, however, explicitly told that they should find the tasks more difficult as they proceeded through the work periods 1, 2, and 3.

Debriefing

Following Work Period 3, the blood pressure cuff and the Bionex spot electrodes were removed from participants. In cases where the participant was female, the (male) experimenter left the research room while the female undergraduate research technician removed the Bionex spot electrodes. Participants' legal representatives were then retrieved from the ADRC waiting room (if applicable) and debriefed about the study. Participants were not informed of their overall performance on the challenges. Participants and their representatives were then presented with $20 as compensation and directed to the ADRC waiting room. This concluded the study session.

Statistical Analyses

The statistical approaches used to examine this study's data were modified significantly from those originally presented in the dissertation proposal. Changes were made to accommodate amendments to study groups and the procedure, based on the characteristics of dependent measures (e.g., normality characteristics), and based on statistical guidelines that were unfamiliar to the experimenter at the time of dissertation proposal. Deviations from the statistical approaches that were originally proposed are described below, and explanations for alternative approaches are provided.

A two-tailed alpha of .05 was adopted for all analyses.

Analysis of Participant Characteristics

The purpose of examining participant characteristics was twofold. First, it served to describe the characteristics of the MCI patients and controls. Second, it served to identify naturally-occurring differences between study groups in variables that were not of interest but could potentially confound CV responses. It was necessary to examine group differences in participant characteristics because it was not certain that characteristics would be balanced across groups, nor was it certain that participants did not meet certain exclusion criteria (e.g., that participants were not prescribed beta-blocker), as ADRC medical charts were not updated until after study participation.

Participant characteristics were examined via independent t-tests (for ratio variables) and chi-square tests (for categorical variables). In the event that control and MCI groups showed unexpected or potentially confounding differences on a characteristic, auxiliary analyses were performed to examine their impact on CV response findings. Of particular concern was the potential influence of blood pressure medication status, beta-

blocker medication status, and MCI subtype on CV response measures. The type of the auxiliary analyses performed depended on the specific variables showing differences and are described in the Results section, as needed.

CV Responses Under Investigation

In the dissertation proposal, it was originally proposed that the only CV responses to be formally investigated were SBP and PEP responses. These responses were of special interest because they are most closely related to beta-adrenergic sympathetic influence on the heart, the purported mediator of effort. However, as stated above, PEP was dropped due to measurement issues. This left SBP response as the lone CV measure of interest.

Following the dissertation proposal, it was decided that DBP and MAP responses would be examined statistically, in addition to SBP response. Reasons for this were twofold. First, DBP and MAP responses are associated with beta-adrenergic sympathetic influence, albeit to a lesser extent than SBP and PEP (Levick 2003; Richter, Friedrich, & Gendolla, 2008). Second, several similar CV response studies have reported significant effort effects in DBP and MAP responses (Smith, Baldwin, & Christensen, 1990; Wright & Dill, 1993; Wright, Martin, & Bland, 2003). Thus, statistical analysis of these measures seemed prudent.

In addition, it was decided that HR response would be examined as an "exploratory" variable as opposed to a primary variable. HR is strongly influenced by both sympathetic and parasympathetic activity (Levick 2003; Richter, Friedrich, & Gendolla, 2008) and thus may not be sensitive to effort effect. Accordingly, any significant HR response effects were to be regarded as tentative.

Summarizing, the final list of CV responses under statistical investigation were SBP, DBP, and MAP responses (the primary measures), and HR response (an exploratory measure). To reiterate, because effort is purported to be mediated by beta-adrenergic sympathetic influence on the heart, effort effects should be most aptly reflected in SBP response, followed by DBP and MAP responses, and they may or may not be reflected in HR response.

Preliminary Analysis of CV Measures

In the dissertation proposal, it was originally proposed that CV responses were to be examined via the Fisher test using 2 (study group) X 3 (challenge difficulty, repeated) mixed omnibus analyses of covariate (ANCOVAs). The proposed covariate was the CV measure at baseline. However, following proposal, it became apparent that use of ANCOVA in this manner is problematic when dealing with naturally occurring (non-randomized) groups, as is the case in this study (Miller & Chapman, 2001). The reason is that ANCOVA assumes that group differences on the covariate are independent of group membership, which is the case when participants are randomly assigned to groups but is not the case when the groups are naturally occurring. Violations of this assumption have been shown to adjust means inappropriately and produce biased conclusions (Jamieson, 2004).

As an alternative, Jamieson (2004) offered the following: "A rough guideline might be to avoid using covariates with naturally occurring groups, unless the relationship between the covariate and the dependent variable is much larger than the relationship between the covariate and the independent variable" (p. 282). Examination of these relationships in the current sample showed that associations between baseline CV activity

(covariates) and CV responses (dependent variables) were comparable in strength compared to the association between baseline CV activity at baseline (covariates) and study group (independent variable) (e.g., average of all *r's* for baseline SBP with SBP responses = -.29; *r* for baseline SBP with Study Group = .20). Moreover, associations between baseline CV activity (covariates) and CV responses (dependent variables) generally fell short of significance and did not show consistent associations across levels of the between- or within-subjects factors (study group and challenge difficulty, respectively). Given these findings, it was decided that CV responses would be examined via analyses of variance (ANOVAs) rather than ANCOVAs.

Analysis of Baseline CV Activity

Resting baseline CV activity was compared between controls and MCI patients via independent t-tests.

Analysis of CV Responses

Per the Fisher test, CV responses were first examined via 2 (study group) X 3 (challenge difficulty, repeated) mixed omnibus ANOVAs. In the dissertation proposal, significant interaction effects were to be followed by simple effects analyses examining the effect of study group at each level of task difficulty. However, removal of the AD group resulted in decreased statistical power for analyses that examined the between-group effects (study group). It did not alter the power of simple effects analyses that examined within-group effects (challenge difficulty). For this reason, it was decided that significant interactions in the omnibus ANOVA would be followed by simple effects analyses that examined the effect of challenge difficulty at each level of study group. Significant simple effects analyses, in turn, would be followed by all possible pairwise

comparisons within the group under investigation (i.e., low versus medium difficulty; low versus high difficulty; medium versus high difficulty).

Alternatively, if the initial omnibus ANOVAs showed significant main effects of challenge difficulty (and non-significant interaction effects), then all possible pairwise comparisons would be performed with the data collapsed across study group. If, on the other hand, the omnibus ANOVAs showed significant main effects of study group (and non-significant interaction effects), then post-hoc analyses would not be required (because study group has only two levels).

Lastly, if main effects or interaction effects for the omnibus ANOVAs trended but fell short of significance or if post-hoc analyses were indicated upon qualitative (visual) inspection of CV response data, then post-hoc analyses were performed. Such analyses were warranted due to the linear effects predicted in the control group and also were warranted because cell sample sizes were likely to be reduced relative to other CV response studies and because the expected effect sizes were unclear (due to the novelty of this study), which brought into question the power associated with statistical analyses.

Analysis of Subjective Measures

In the dissertation proposal, it was originally proposed that ratings of task difficulty and success importance (each rated on a 5-point Likert scales) were to be analyzed via the Fisher test in a fashion analogous to CV responses. In addition, it was proposed that a two-pronged nonparametric approach would be conducted in conjunction with ANOVAs if subjective measures were not normally distributed. The first prong of the nonparametric approach would examine the effect of challenge difficulty (the within-subjects factor) at each level of study group via Friedman tests. Any significant Fried-

man tests would be followed by Wilcoxon tests that examined adjacent levels of difficulty within the group under investigation (i.e., low versus medium difficulty and medium versus high difficulty). The second prong of the nonparametric approach would examine the effect of study group (the between-subjects factor) at each level of challenge difficulty via Mann-Whitney U tests.

Following data collection, however, the need to deviate from this dual inferential and nonparametric approach became apparent. Preliminary qualitative (visual) inspection of histograms and statistical tests of normality (Shapiro-Wilk W test) revealed unexpected range restriction and larger-than-expected normality violations in subjective measures. For this reason, it was decided that the Fisher test (i.e., inferential analyses) would not be conducted on subjective measures and that the nonparametric approach would serve as the sole method to investigate subjective measures.

Analysis of Performance Measures

Although not addressed in the dissertation proposal, it was decided that performance measures of accuracy, hit rate, and false positive rate should be investigated statistically. These measures were examined via the Fisher test using ANOVAs in a fashion analogous to CV responses.

RESULTS

Participant Characteristics

Participant characteristics are reported in Table 1 (below, on next page). Participants were 20 controls and a group of 15 MCI patients composed of 13 amnestic MCI patients and 2 nonamnestic MCI patients. As expected, Clinical Dementia Rating staging

differed between controls and MCI patients ($X^2(1, N=35) = 35.0$, $p < .001$). MMSE score and DRS-2 total score were lower in MCI patients compared to controls (MMSE score: $t(16) = 2.8$, $p = .01$; DRS-2 total score: $t(21) = 2.4$, $p = .03$). Examination of DRS-2 memory and attention subtest scores showed that the Memory score, but not the Attention score, was lower for MCI patients than controls (Memory score: $t(16) = 2.5$, $p = .02$; Attention score: $t(31) = 0.2$, $p = .82$). Controls and MCI patients did not significantly differ in terms of age, gender, racial/ethnic group, or education (all p's > .20). A larger proportion of MCI patients were on blood pressure medications compared to controls ($X^2(1, N=35) = 4.4$, $p = .04$). Two MCI patients were prescribed beta-blockers at the time of study participation, and no controls were prescribed beta-blockers ($X^2(1, N=35) = 2.8$, $p = .09$).

Table 1

Characteristics of Control and MCI Groups

(Group)	Control	MCI	*p* value
n	20	15	--
MCI type, amnestic/non-amnestic	--	13/2	--
CDR staging, 0/0.5/1	20/0	0/15	<.001
MMSE, *M* (*SE*)	29.4 (0.2)	28.0 (0.4)	.01
DRS total score, *M* (*SE*)	140.1 (0.7)	136.7 (1.3)	.03
DRS memory score, *M* (*SE*)	24.1 (0.3)	22 (0.8)	.02
DRS attention score, *M* (*SE*)	35.9 (0.3)	35.8 (0.5)	.82
Age, *M* (*SE*)	68.9 (1.9)	71.3 (2.4)	.44
Gender, female/male	11/9	5/10	.20
Ethnic group, Cauc./African Amer.	15/5	12/3	.73
Education, years, *M* (*SE*)	15.0 (0.5)	15.9 (0.5)	.28
Blood pressure medication, yes/no	5/15	9/6	.04
Beta-blocker medication, yes/no	0/20	2/13	.09

Note: MCI = mild cognitive impairment; Cauc. = Caucasian; African Amer. = African American; CDR = Clinical Dementia Rating staging; MMSE = Mini-mental Status Examination; DRS = Dementia Rating Scale – Second Edition; *n* = number of participants per group; *M* = mean; *SE* = standard error.

Baseline CV Activity

Resting baseline CV values are presented in Table 2 (below, on next page). Controls and MCI patients did not show significant differences in baseline CV activity (SBP: $t(33) = 1.17$, $p = .25$; DBP: $t(31) = -.74$, $p = .47$; MAP: $t(31) = -.95$, $p = .35$; HR: $t(33) = .95$, $p = .35$).

Table 2

Baseline Measures of Cardiovascular Activity

(Group)		Control	MCI
SBP	*M*	151.4	158.7
	SE	4.6	3.7
DBP	*M*	83.5	86.5
	SE	3.5	2.3
MAP	*M*	106.3	110.6
	SE	3.8	2.5
HR	*M*	70.9	67.0
	SE	2.7	3.2

Note: MCI = mild cognitive impairment; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial blood pressure; HR = heart rate; *M* = mean; *SE* = standard error. For all measures, $n = 20$ for the control group, and $n = 15$ for the MCI group.

CV Responses to the Sternberg Memory Tasks

CV responses to the low, medium, and high difficulty versions of the Sternberg memory task are displayed in Table 3 (below, on next page). 2 (group) x 3 (difficulty, repeated) mixed omnibus ANOVAs showed that BP responses increased or tended to increase as difficulty increased (SBP: $F(1.8, 59.5) = 4.4$, $p = .02$; MAP: $F(1.7, 55.5) = 3.6$, $p = .04$; DBP: $F(1.6, 53.9) = 2.4$, $p = .11$). However, BP responses did not differ signifi-

cantly between controls and MCI patients (SBP: $F(1, 33) = 2.2$, $p = .14$; MAP: $F(1, 33) = 1.0$, $p = .31$; DBP: $F(1, 33) = .57$, $p = .46$), and the effect of difficulty on BP responses did not vary significantly between groups (SBP: $F(1.8, 59.5) = .25$, $p = .14$; MAP: $F(1.7, 55.5) = .63$, $p = .51$; DBP: $F(1.6, 53.9) = .41$, $p = .63$). Follow-up simple comparisons showed that BP responses were stronger or tended to be stronger in the high difficulty version compared to the low and medium difficulty versions (SBP: high versus low difficulty: $p = .02$, high versus medium difficulty: $p = .02$) (MAP: high versus low difficulty: $p = .05$, high versus medium difficulty: $p = .03$) (DBP: high versus low difficulty: $p = .11$, high versus medium difficulty: $p = .06$). However, BP responses to the low and medium difficulty versions did not differ significantly (SBP: $p = .38$) (MAP: $p = .50$) (DBP: $p = .70$). Effects of difficulty, group, or their interaction on HR responses did not approach statistical significance (Difficulty: $F(1.6, 53.1) = .57$, $p = .53$; Group: $F(1, 33) = .39$, $p = .54$; Difficulty X Group: $F(1.6, 53.1) = 1.8$, $p = .18$).

Table 3

Cardiovascular Responses to Low, Medium, and High Difficulty Versions of the Sternberg Memory Task

(Task Version)		Low		Medium		High	
(Group)		Control	MCI	Control	MCI	Control	MCI
SBP	*M*	11.3	7.7	14.4	7.0	17.2	9.5
	SE	2.4	2.8	2.9	3.4	3.3	3.8
DBP	*M*	7.1	6.2	8.9	5.4	11.0	8.3
	SE	1.7	1.9	2.3	2.6	2.9	3.3
MAP	*M*	8.4	6.7	10.9	5.9	13.3	9.3
	SE	1.9	2.2	2.4	2.8	3.1	3.6
HR	*M*	3.9	3.3	2.5	3.4	1.8	4.1
	SE	1.3	1.5	0.9	1.1	0.9	1.1

Note: CV response values are change from baseline in mmHG. MCI = mild cognitive impairment; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial blood pressure; HR = heart rate; *M* = mean; *SE* = standard error. For all measures: $n = 20$ for control group and $n = 15$ for MCI group.

Simple effects ANOVAs were performed to examine the effect of difficulty on BP responses within study groups. These analyses were warranted because of the linear effect hypothesized in the control group, because the interaction effect for SBP responses showed a very weak trend towards significance ($p = .14$), and, lastly, because visual inspection of BP responses suggested that the effect of difficulty was more robust in controls than MCI patients (see Figure 7, on next page, for SBP responses). Indeed, these analyses showed that BP responses increased as difficulty increased in controls (SBP: $F(1.7, 31.4) = 6.5$, $p = .01$) (MAP: $F(1.7, 31.6) = 4.5$, $p = .02$.) (DBP: $F(1.6, 30.2) = 2.9$, $p = .08$) but not in MCI patients (SBP: $F(2, 28) = .70$, $p = .51$) (MAP: $F(1.6, 22.2) = .92$, $p = .39$) (DBP: $F(1.6, 21.7) = 0.7$, $p = .48$). Follow-up simple comparisons showed that

controls' BP responses were stronger or tended to be stronger in the high difficulty version versus the low and medium difficulty versions (SBP: high versus low difficulty: p = .01, high versus medium difficulty: p = .02) (MAP: high versus low difficulty: p = .02, high versus medium difficulty: p = .06) (DBP: high versus low difficulty: p = .07, high versus medium difficulty: p = .09). Although falling short of statistical significance, SBP showed a weak trend for stronger responses to the low versus medium difficulty versions in the control group (p = .10). The same contrast fell short of statistical significance for MAP and DBP responses (p = .14; p = .28, respectively).

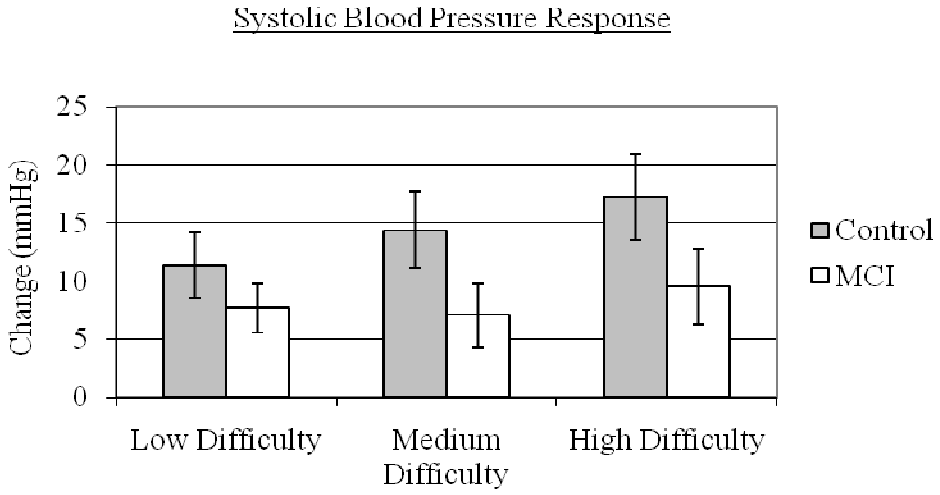

Figure 7. Systolic blood pressure responses to low, medium, and high difficulty versions of the Sternberg memory task.

Auxiliary Analyses on CV Responses

Auxiliary analyses were performed to examine the effect of extraneous but potentially confounding variables on BP responses. Specifically, based on the participant characteristics reported above, it seemed prudent to examine the potential influence of BP medication status (prescribed/not prescribed BP medications), beta-blocker medication status (prescribed/not prescribed beta-blocker medications), and MCI subtype (amnes-

tic/non-amnestic). As explained above, ANCOVAs that statistically correct for these variables were avoided due to problems associated with ANCOVA when groups are naturally occurring (non-randomized) (Jamieson, 2004).

To examine the potential influence of BP Medication Status on BP responses, 2 (study group) x 3 (difficulty, repeated) x 2 (BP medication status) ANOVAs were conducted and terms with BP medication status as a factor were examined. These analyses indicated that the effect of BP medication status varied or tended to vary across control and MCI groups (SBP: $F(1, 31) = 3.6$, $p = .07$; DBP: $F(1, 31) = 4.5$, $p = .04$; MAP: $F(1, 31) = 4.3$, $p = .05$). Follow-up simple effects analyses indicated that BP responses were stronger or tended to be stronger in MCI patients that were not prescribed BP medications compared to those who were prescribed BP medications (SBP: $F(1, 13) = 4.0$, $p = .07$) (DBP: $F(1, 13) = 4.4$, $p = .06$) (MAP: $F(1, 13) = 4.5$, $p = .05$). Controls, however, showed the converse pattern, with stronger BP responses observed in those controls on BP medications, although this contrast did not approach statistical significance (all $p's > .22$). All other terms with BP medication status as a factor did not approach statistical significance (all $p's > .47$).

Although three-way interactions (study group x difficulty x BP medication status) did not approach statistical significance in the previous analysis, it seemed prudent to investigate whether BP medication status differentially impacted the effect of difficulty on BP responses within study groups. To this end, 3 (difficulty, repeated) x 2 (BP medication status) ANOVAs were conducted at each level of study group and the interaction term was examined for statistical significance. Because the cell sample sizes associated with these analyses were limited, corresponding BP responses were graphed and qualita-

tively (visually) inspected as well. ANOVAs indicated that the effect of difficulty on BP responses did not significantly vary between controls that were not prescribed BP medications and those who were prescribed BP medications (difficulty x study group: all *p's* > .29). Similarly, the effect of difficulty on BP responses did not significantly vary between MCI patients that were not prescribed BP medications and those who were prescribed BP medications (difficulty x study group: all *p's* > .72). Visual inspection of BP responses appeared consistent with this finding (data not shown).

To examine the potential influence of beta-blocker medication status and MCI subtype on difficulty effects within MCI patients, one-way repeated measures ANOVAs were performed, first with the two MCI patients who were prescribed beta-blockers removed from analyses and second with the two MCI patients who were diagnosed as non-amnestic removed. Consistent with the initial analyses that included these MCI patients, ANOVAs indicated that the effect of difficulty on BP responses did not approach statistical significance following removal of MCI patients who were prescribed beta-blockers (all *p's* > .49) and following removal of the MCI patients who were diagnosed as non-amnestic (all *p's* > .33). Also of note, 2 (group) x 3 (difficulty, repeated) mixed omnibus ANOVAs with following removal of these MCI patients were consistent with the initial analyses that included all MCI patients.

Ratings of Difficulty and Success Importance on the Sternberg Memory Tasks

Ratings of subjective difficulty and importance to meet the performance standard on the low, medium, and high difficulty versions of the Sternberg memory task are listed in Table 4 (below, on next page). As expected, difficulty ratings increased as task difficulty increased for both controls (X^2(2, n=19) = 17.9, $p < .001$) and MCI patients (X^2(2,

n=15) = 11.5, $p < .01$). Follow-up Wilcoxon tests indicated that, within each study group, the low difficulty version was rated as easier than the medium difficulty version (controls: $z = -1.94$, $p = .05$) (MCI: $z = -2.33$, $p = .02$), and the medium difficulty version was rated as easier than the high difficulty version (controls: $z = -3.05$, $p < .01$) (MCI: $z = -2.0$, $p = .05$). Comparisons across study group indicated that difficulty ratings of the low, medium, and high difficulty task versions did not significantly differ between controls and MCI patients (low difficulty: $U = 138$, $p = .80$) (medium difficulty: $U = 137$, $p = .82$) (high difficulty: $U = 137$, $p = .84$). Descriptively, modes for difficulty ratings on the low, medium, and high difficulty task versions corresponded to ratings of *"Not Difficult"*, *"Not Difficult"*, and *"A Little Difficult"*, respectively, for both controls and MCI patients.

Table 4

Self-ratings of Task Difficulty and Importance on the Low, Medium, and High Difficulty Versions of the Sternberg Memory Task

(Task Version)		Low		Medium		High	
(Group)		Control	MCI	Control	MCI	Control	MCI
Difficulty	*M*	1.2	1.1	1.6	1.7	2.2	2.2
	SE	0.1	0.1	0.2	0.2	0.2	0.3
	n	19	15	19	15	19	15
Importance	*M*	3.9	3.6	3.9	3.3	3.7	3.3
	SE	0.2	0.3	0.2	0.3	0.2	0.3
	n	19	15	19	15	19	15

Note: MCI = mild cognitive impairment; *M* = mean; *SE* = standard error; *n* = number of participants. For difficulty: (1) Not difficult, (2) A little difficult, (3) Moderately difficult, (4) Very difficult, or (5) Excessively difficult or impossible. For importance: (1) Not important, (2) A little important, (3) Moderately important, (4) Very important.

Analyses examining importance to meet the performance standard indicated that difficulty did not have a statistically significant impact on success important ratings for controls (X^2(2, N=19) = 3.8, p = .37) or MCI patients (X^2(2, N=15) = 2.3, p = .31). Comparisons across study group showed that ratings of importance did not differ significantly between controls and MCI patients on the low, medium, and high difficulty task versions (low difficulty: U = 115, p = .26) (medium difficulty: U = 109, p = .18) (high difficulty: U = 113, p = .25). Descriptively, modes for importance on all task versions corresponded to ratings of *"Very Important"* for both controls and MCI patients.

Performance on the Sternberg Memory Tasks

Performance measures of accuracy, hit rate, and false positive rate are presented in Table 5 (below, on next page). On each of these measures, controls performed better or tended to perform better than MCI patients (accuracy: F(1, 33) = 6.7, p < .001) (hit rate: F(1, 33) = 3.6, p = .07) (false positive rate: F(1, 33) = 7.6, p = .01), and performance decreased as difficulty increase (accuracy: F(2, 66) = 17.0, p < .001) (hit rate: F(1.8, 57.7) = 5.4, p = .01) (false positive rate: F(1.8, 58.9) = 12.2, p < .001) (see Figure 8 for false positive results, below, on next page). The effect of difficulty on performance measures did not vary significantly across levels of study group (all p's > .32). Post-hoc comparisons showed that accuracy and false alarm rate, but not hit rate, decreased or tended to decrease from the low to medium difficulty task (accuracy: t(34) = 2.6, p = .01) (false positive rate: t(34) = -2.9, p = .01) (hit rate: t(34) = 0.5, p = .80) and that all three measures decreased or tended to decrease from the medium to high difficulty task (accuracy: t(34) = 3.0, p <.01) (hit rate: t(34) = 2.6, p = .01) (false alarm rate: t(34) = -2.0, p =

.05). Both the MCI and control study groups met the 75% performance standard on all tasks.

Table 5

Performance on Low, Medium, and High Difficulty Versions of the Sternberg Memory Task

(Task Version)		Low		Medium		High	
(Group)		Control	MCI	Control	MCI	Control	MCI
Accuracy	*M*	0.99	0.92	0.97	0.88	0.92	0.83
	SE	0.01	0.04	0.01	0.04	0.01	0.04
	n	20	15	20	15	20	15
Hit Rate	*M*	0.99	0.92	0.98	0.93	0.95	0.88
	SE	0.01	0.05	0.01	0.04	0.02	0.04
	n	20	15	20	15	20	15
FP Rate	*M*	0.02	0.08	0.05	0.17	0.11	0.23
	SE	0.01	0.03	0.01	0.05	0.02	0.06
	n	20	15	20	15	20	15

Note: MCI = mild cognitive impairment; FP = false positive; *M* = mean; *SE* = standard error; *n* = number of participants.

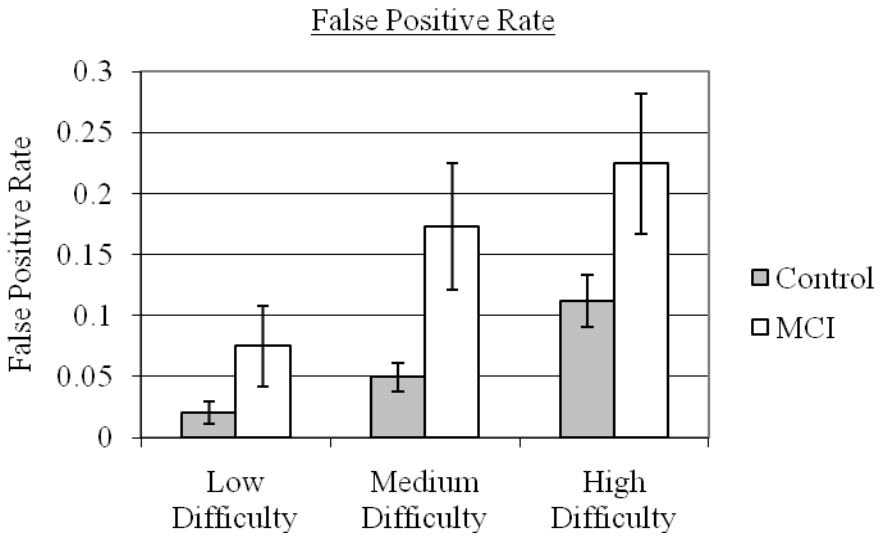

Figure 8. False positive rate on low, medium, and high difficulty versions of the Sternberg memory task.

DISCUSSION

To reiterate, the study hypotheses were that BP responses (i.e., SBP, DBP, and MAP responses) of the MCI group would increase across the low to medium difficulty versions of the Sternberg memory task but would precipitously drop during performance of the high difficulty version. Moreover, BP responses of the MCI group were expected to be accentuated relative to the control group on the low and medium difficulty versions but attenuated relative to the control group on the high difficulty version. For the control group, BP responses were expected to increase across the low to medium to high difficulty versions.

The study's results did not support the MCI hypothesis but were in agreement with the control hypothesis. Contrary to expectations, BP responses of the MCI group generally remained stable as challenge difficulty increased. Also contrary to expectations, BP responses of the MCI group were mildly attenuated relative to the control group

across all difficulty levels, although this attenuation was not statistically significant. As hypothesized, BP responses of the control group increased as challenge difficulty increased. Significant effects of difficulty and study group on HR responses were not observed. This result was not surprising because HR responses are under the influence of sympathetic and parasympathetic control and thus may not be sensitive to effort effects (Levick, 2003; Richter, Friedrich, & Gendolla, 2008).

Secondary analyses examining subjective measures and performance (e.g., accuracy) showed that ratings of challenge difficulty increased across the low, medium, and high difficulty challenges and were very similar between MCI and control groups. Ratings of challenge importance did not differ significantly across difficulty levels and were mildly attenuated in the MCI group relative to the control group, although this attenuation was not statistically significant. Challenge performance decreased across the low, medium, and high difficulty challenges in terms of accuracy, hit rate, and false positive rate, and challenge performance was or tended to be superior in the control group versus the MCI group.

Interpretation of Results

In the introduction section, study-specific and theoretical assumptions were presented to shed light on the complexity involved in predicting effort-related CV responses in individuals with cognitive impairment and to aid in result interpretation. The study-specific assumptions pertained to whether or not study groups would view the low, medium, and high difficulty versions of the Sternberg memory task as possible and worthwhile (and thus deploy effort) or excessively difficult or impossible (and thus withdraw

effort). By contrast, the theoretical assumptions pertained to whether certain abilities and processes were intact in individuals with and without cognitive impairment.

Possible study outcomes were threefold. The first possible outcome was that CV responses comported with the study hypotheses (as depicted in Figure 6). This result would indicate that both the study-specific and theoretical assumptions held true, as the study hypotheses followed directly from these assumptions. The second possible outcome was that CV responses did not follow the pattern described in the study hypotheses but still matched the overall configural pattern of Wright's integrative model and its extension to AD and MCI (i.e., the configural pattern depicted in Figure 6). This result would suggest that the study-specific assumptions were violated but that the theoretical assumptions held true. This outcome seemed plausible because it is very difficult to determine *a priori* the difficulty level at which participants will view success as possible and worthwhile versus excessively difficult or impossible. The final possible outcome was that CV responses did not match the configural pattern of Wright's integrative model and its extension to AD and MCI. This outcome would suggest that the study-specific assumptions and at least one of the theoretical assumptions were violated.

Interpretation of CV Responses in the Control Group

In comportment with the control hypothesis, BP responses of the control group increased across the low to medium to high difficulty versions of the Sternberg memory task. This suggests that controls viewed success as possible and worthwhile for all challenges and, accordingly, exerted more effort as challenge difficulty was ramped up. Controls' performance and ratings of challenge difficulty also support this interpretation. Their accuracy remained well above the performance standard (75% accuracy), suggest-

ing that they remained engaged in all challenges (95% confidence intervals for accuracy in the control group was .98-.99, .95-.98, and .89-.95 on the low, medium, and high difficulty versions, respectively). In addition, increases in (objective) challenge difficulty were accompanied by increases in subjective difficulty ratings and decreases in performance, thus supporting the interpretation that controls found the challenges to be increasingly difficult as they progressed through the study.

Interpretation of CV Responses in the MCI Group

In contrast to the control group, interpreting the CV results of the MCI group is complicated. The reason is that multiple study-specific and theoretical assumptions appear to have been violated in the MCI group. Below, the validity of the study-specific and theoretical assumptions is evaluated, to the extent that this is possible.

The study-specific assumption in the MCI group. The study specific-assumption for the MCI group maintained that they would view the low and medium difficulty versions of the Sternberg memory task as possible and worthwhile (and thus exert effort), but view the high difficulty version as excessively difficult or impossible (and thus withhold effort). The relatively flat and mildly attenuated BP response pattern exhibited by the MCI group across difficulty levels does not appear to comport with this assumption.

One reasonable alternative explanation for the observed BP response pattern is that the MCI group viewed all challenges, including the low difficulty version, as excessively difficult or impossible. If this were the case, the MCI group would be expected to withhold effort and evince relatively stable and attenuated BP responses on all challenges. Although this explanation might account for the BP response pattern of the MCI

group, it contradicts other evidence suggesting the MCI group viewed all challenges as worthwhile and possible and that, as a result, they exerted a nontrivial amount of effort.

The most compelling evidence suggesting that the MCI group viewed success as possible and worthwhile is that their performance was statistically above chance (50% accuracy) and statistically at or above the performance standard (75% accuracy) (95% confidence intervals for accuracy in the MCI group was .84-.99, .79-.96, and .75-.91 on the low, medium, and high difficulty versions, respectively). It is difficult to imagine a scenario in which the MCI group could perform at this high a level if they completely disengaged from the challenges. It also seems unlikely that they would perform at this high a level if they covertly adopted a performance standard that was grossly lower than the 75% accuracy mark indicated in the challenge instructions and thus were obliged to exert only low amounts of effort to achieve success.

Although less compelling than the performance results, the physiological and subjective results provide some evidence that the MCI group viewed success as possible and worthwhile, and that they deployed a nontrivial amount of effort. One relevant finding is that BP responses of the MCI group were statistically different from zero (i.e., no BP response), suggesting that the MCI group deployed at least some effort during challenge performance (e.g., 95% confidence intervals for SBP response in the MCI group was 3.1-12.2, 1.2-12.8, and 2.5-16.5). A related finding is that BP responses did not significantly differ between the MCI group and the control group. In fact, the BP responses of the MCI group were similar to those of the control group on the low difficulty challenge. This is potentially noteworthy because the control group clearly deployed effort and showed corresponding BP elevations during the low difficulty challenge. By extension, it

might follow that the comparable BP elevations exhibited by the MCI group during the low difficulty challenge should also reflect effort deployment. Moreover, that the MCI group did not show relative decreases in BP responses on the medium and high difficulty challenges might also suggest that they deployed some effort on these challenges as well.

Regarding the subjective data, the modal ratings of difficulty on the low, medium, and high difficulty challenges for the MCI group were *"Not Difficult"*, *"Not Difficult"*, and *"A Little Difficult"*, respectively, whereas the modal ratings for importance to meet the performance standard was *"Very Important"* for all challenges. These ratings roughly matched the ratings of the control group and would appear to promote the perception that the challenges were possible (i.e., within their capabilities) and worthwhile (i.e., worth the effort investment) in both groups, at least when these ratings are taken at face value. The relatively low difficulty ratings (i.e., *"Not Difficult"* and *"A Little Difficult"*) also provide some evidence that the MCI group did not covertly adopt a performance standard that was grossly higher than the 75% accuracy mark (e.g., 100% accuracy) and then withdraw effort upon realizing that their covert standard was excessively difficult or impossible.

Theoretical assumptions in the MCI group. If indeed MCI participants viewed all challenges as worthwhile and possible, their expected response pattern would be stepwise increases in BP responses across difficulty levels and accentuated BP responses relative to controls. Why then did the MCI group show relatively stable BP responses across difficulty levels and mildly attenuated BP responses relative to controls? Working off the premise that MCI participants viewed all challenges as worthwhile and possible, it follows that one or more of the theoretical assumptions were violated.

Identifying the theoretical process or processes that may have broken down in the MCI group is difficult. The current results sometimes provide partial evidence in favor of one explanation over another. Other times the results do not provide supporting or weakening evidence for an explanation. Below, the legitimacy of the theoretical assumptions as applied to the MCI group is systematically inspected, one-by-one, to the extent that this is possible. Readers may find Figure 5 helpful in visualizing the theoretical assumptions and their interrelations with one another. Following review of the merits of individual theoretical assumptions, important factors that may help partially explain the BP responses of the MCI group are brought together.

Appraisal and decision assumptions in the MCI group. These assumptions related to the appraisal of challenge difficulty and success importance and the decisional capacity to exert or withhold effort. Two of these assumptions related to the appraisal of challenge difficulty. The first held that cognitive impairment leaves unaltered the ability to appraise relative differences in challenge difficulty, that is, the capacity to judge and report that one challenge is more (or less) difficult than a different challenge. This assumption appears to have held true in the MCI group, as increases in (objective) challenge difficulty were accompanied by increases in difficulty ratings. This finding suggests that difficulty appraisals in the current MCI group were determined in part by objective difficulty (i.e., the characteristic features of the challenges).

The second assumption related to the appraisal of challenge difficulty held that individuals with cognitive impairment appraise challenges as more difficult in light of their cognitive impairment. That is, individuals with cognitive impairment can and will appreciate a given challenge as being more difficult now (i.e., with cognitive impairment)

versus prior to the onset of cognitive impairment. The implication of this assumption is that the MCI group should have found all challenges to be more difficult than the control group.

Comparison of difficulty ratings across study groups does not appear to support this assumption. Instead, they indicate that the MCI group perceived the challenges to be as difficult, but not more difficult, than the control group. Of note, difficulty ratings between the groups roughly matched despite the fact that both groups had familiarity with the challenges and despite the fact that the MCI group received more negative feedback than controls about their performance. Although these factors might be expected to lead to increases in perceived difficulty in the MCI group, this does not appear to be the case. The implication of this finding is that difficulty appraisals in the MCI group were not based in part on ability (i.e., performance capacity).

Moving forward, the next assumption concerned the appraisal of challenge importance. It simply stated that cognitive impairment has no impact on appraisals of success importance. This assumption appears to have held up reasonably well in the MCI group, as their importance ratings did not significantly differ across difficulty levels and were comparable to the importance ratings of the control group. Evidence indicating that the MCI group covertly minimized challenge importance is also lacking. Theoretically, this would lower the difficulty level at which success is deemed excessively difficult and promote effort withdrawal. This possibility contradicts multiple lines of evidence suggesting that the MCI group viewed all challenges as worthwhile and possible and exerted nontrivial amounts of effort, as reviewed above.

The final assumption within the appraisal and decision set concerned the decisional capacity to exert or withhold effort. It maintained that cognitive impairment leaves unaltered the ability to determine whether challenge success is possible and worthwhile or excessively difficult or impossible. The current data do not adequately address this type of decisional capacity (e.g., by including an impossible condition, as in Richter, Friedrich, & Gendolla, 2008). However, the data do suggest that the MCI group viewed all challenges as worthwhile and that they appropriately decided to exhibit nontrivial amounts of effort. The data also suggest that the MCI group viewed all challenges as possible and, indeed, MCI participants were generally able to meet the performance standard. Thus, although the supporting evidence is weak, there is no obvious evidence indicating that decisional capacity to exert or withhold effort was grossly impaired in the MCI group.

Evaluation of effort deployment assumptions in the MCI group. The second set of assumptions pertained to the deployment of effort during challenges. Specific assumptions were that cognitive impairment leaves unaltered (1) the deployment of effort in proportion to challenge difficulty, so long as success is possible and worthwhile, (2) the deployment compensatory effort in order to account for cognitive impairment, and (3) the withholding of effort in situations where success is deemed excessively difficult or impossible. The third assumption does not appear to apply to the current study, as most evidence indicates that MCI participants viewed all challenges as worthwhile and possible.

Regarding the first assumption, BP responses of the MCI group generally remained stable as challenge difficulty increased. This may suggest that the MCI group did

not deploy effort in proportion to challenge difficulty under conditions where success was deemed possible and worthwhile. Rather, they may have tended to deploy a constant amount of effort regardless of challenge difficulty, despite reporting increases in subjective difficulty across challenges.

Regarding the second assumption, the BP data generally do not support the view that the MCI group deployed compensatory effort, as BP responses of the MCI group were mildly attenuated relative to the control group across all difficulty levels. Of note, difficulty ratings were very similar between MCI and control groups, suggesting that MCI participants may not have felt that compensatory effort was necessary.

Evaluation of mediation assumptions in the MCI group. The third and final set of theoretical assumptions related to the mediation of effort by beta-adrenergic activity. One of these assumptions maintained that cognitive impairment (and associated physiological impairment) leaves unaltered the mediation of effort by beta-adrenergic activity. The other assumption held that cognitive impairment (and associated physiological impairment) leaves unaltered the relationship between beta-adrenergic activity and CV responses.

These assumptions were of concern for a number of issues. One of the most serious concerns was the substantial proportion of MCI participants taking BP medications at the time of study participation. These medications could plausibly alter beta-adrenergic activity that, in turn, could exert unknown downstream effects on effort-related CV responses. Indeed, auxiliary analyses showed that BP responses were stronger or tended to be stronger in MCI participants that were not prescribed BP medications compared to those who were prescribed BP medications. Surprisingly, controls showed the converse

pattern, with stronger BP responses observed in those controls on BP medications, although this contrast did not approach statistical significance. Although it is unclear why BP medications would attenuate BP responses in MCI patients but have no effect or perhaps accentuated BP responses in controls, the potential influence of BP medications on the current results is concerning.

At least three additional findings are noteworthy with regard to BP medications. One is that removal of the two MCI patients who were prescribed beta-blockers from statistical analyses had no effect on the study's overall findings. Second, neither on-medication MCI participants nor off-medication participants showed compelling evidence of difficulty effects on BP responses. Third, results of analyses including only off-medication participants were consistent with the results obtained when all participants were included (i.e., BP responses of the off-medication MCI subgroup generally remained stable as challenge difficulty increased, whereas BP responses of the off-medication control subgroup significantly increased as challenge difficulty increased) (data not shown). Although analyses based on study subgroups should be considered tentative due to limited power, they nonetheless suggest that BP medications may have had a general dampening effect on BP responses in the MCI group. However, they also tentatively suggest that null difficulty effects on BP responses observed in the MCI group likely cannot be fully attributed to BP medication status, as the off-medication MCI group did not show compelling evidence of difficulty effects.

Summary

Regarding controls, the BP response data, the performance data, and the subjective data converge to indicate that the control group viewed success on all challenges as

possible and worthwhile and thus exerted more effort and showed stronger BP responses as challenge difficulty was ramped up.

Interpretation of the MCI data is clouded. In light of the results reviewed above, the following tentative interpretation is put forward: the MCI group viewed success as possible and worthwhile on all challenges and appropriately deployed a nontrivial amount of effort on all challenges. However, contrary to expectations, the MCI group evinced relatively stable BP responses across difficulty levels, perhaps because they did not deploy effort in proportion to challenge difficulty, despite rating challenges as increasingly difficult and experiencing decrements in performance as (objective) challenge difficulty was increased. Reasons why the MCI group may have shown mildly attenuated BP responses relative to the control group may be twofold. First, the MCI group appears to have perceived the challenges to be as difficult, but not more difficult, than the control group. Thus, MCI participants may not have felt that deployment of compensatory effort was necessary. Second, BP medications may have general dampening BP responses in the MCI group. The additive effect of these two factors could plausibly account for the mildly attenuated BP responses exhibited by the MCI group, although the evidence supporting this explanation is circumstantial.

Implications

Violations of this study's theoretical assumptions in the MCI group would be of considerable importance should they garner addition evidence in follow-up studies. Below, some potential implications of each violation are considered individually.

The finding that the MCI group did not appear to view challenges as more difficult than controls was surprising. One alternative explanation that possibly accounts for the between-group overlap in difficulty ratings is that the MCI group based their difficult appraisals according to their *perceived* ability and that their perceived ability more closely corresponded to their premorbid level of cognitive functioning rather than their current level of cognitive functioning. If this were the case, then difficult appraisals in the MCI group would be expected to match those of controls (assuming that premorbid ability was equivalent in the MCI and control groups).

This explanation in many ways resembles the concept of anosognosia, that is, lack of (or limited) awareness of cognitive deficits. Although anosognosia is well documented in AD, the degree of awareness of deficits in MCI is unclear, with some studies showing intact awareness (Correa et al., 1996; Feher et al., 1994; Small et al., 1995) and others showing impaired awareness (Albert et al., 1999; Collie et al., 2002). Although there is no "gold standard" assessment for impaired awareness, most studies have deployed one of three methods: (1) structured or unstructured evaluation by a clinician; (2) discrepancy scores on parallel version of ratings scales given to the patient and a close relative; or (3) discrepancy scores between the patient self-rating versus their objective performance on some measure (e.g., a memory test) (Vogel et al., 2004). The current study falls under the latter category and provides some, albeit preliminary, evidence suggesting that patients with MCI show limited ability to adjust difficulty ratings in light of their cognitive impairment and, as a result, do not exhibit compensatory effort that may (or may not) aid performance. That they did not adjust difficulty ratings despite more frequent negative feedback may speak to a degree of rigidness this type of ability percep-

tion in MCI. This finding has important clinical implications because subjective cognitive complaint (typically memory complaint) is one of the diagnostic criteria for MCI. The current findings suggest that this criterion should be deemphasized due to the potential of limited awareness of deficits in MCI. Continued study of anosognosia via the confluence of physiological, performance, and subjective ratings appears warranted, as limited awareness of deficits has been shown to be an early diagnostic marker for conversion from MCI to AD (Devanand et al., 2000; Tabert et al., 2002).

Additionally, continued study of the theoretical assumptions related to the mediation of effort by beta-adrenergic activity is warranted. Contrary to long-term longitudinal research, which associates mid-life hypertension with dementia, longitudinal research at late-life indicates that low BP (at late-life) is associated with risk of dementia and AD (Razay et al., 2009). Although these studies do not address BP responsivity directly, they do suggest broad abnormalities in BP regulation that could plausibly influence BP responsivity.

Limitations

The current study has several limitations. First, the current study's sample size is small and likely resulted in underpowered statistical analyses. Moreover, although well-characterized and carefully diagnosed, some of the characteristics of the MCI sample, particularly with regard to BP medication status, complicated the interpretation of unexpected results and introduced confounds that could not be fully accounted for. Third, it is unclear to what extent the current results generalize to cognitive challenges that are more closely related to the type of cognitive impairment that is characteristic of amnestic MCI

(i.e., memory impairment). The Sternberg memory task used in this study involves attention and working memory but does not load on long-term memory processes. Future studies need to address the specificity of the current findings to a broader range of cognitive domains and challenges that are more demanding. On a related point, future studies might also want to determine whether MCI patients will rate challenges as more difficult and exhibit compensatory effort under a broader range of experimental conditions (e.g., when task instructions explicitly state that challenges will tap into cognitive domains that are impaired in MCI).

Summary and Conclusions

The current study examined the effect of challenge difficulty on cardiovascular responses on patients with MCI. Contrary to expectations, challenge difficulty did not significantly influence BP responses in patients with mild cognitive impairment. Controls, however, showed the expected increase in blood pressure responses as challenge difficulty increased. Subjective ratings of challenge difficulty increased across the low, medium, and high difficulty challenges and were comparable between patients with mild cognitive impairment and controls. Accuracy decreased as challenge difficulty increased, and patients with mild cognitive impairment were less accurate than controls, although both study groups met the 75% performance standard.

One tentative interpretation of the results is that patients with mild cognitive impairment can accurately appraise relative differences in challenge difficulty but have problems adjusting their difficulty appraisals to account for their neuropsychological weaknesses, even when their performance mildly decreases (but is still successful). The

cardiovascular response data suggest that patients with mild cognitive impairment may not deploy compensatory effort because they may not appreciate challenges as more difficult than their cognitively intact counterparts. Other alternative explanations, including the influence of BP medications or abnormalities in BP regulation in MCI, cannot be ruled out and require further investigation. Future studies might also address the specificity of the current findings to a broader range of cognitive challenges and experimental conditions.

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APPENDIX A

SUBJECTIVE MEASURES QUESTIONAIRRE

Subjective Measures Questionnaire (Work Period 1)

Subject Number: _____

Date: _____

The following questions will be asking about how you feel about the task you just practiced. One question will ask about how difficult the task was, and a second question will ask about how important it is for you to succeed at the task. Please answer each question below as honestly and accurately as you can. Also, please feel free to ask me to clarify any questions that may not be clear to you.

Work Period 1:

1A. How difficult do you think will it be to answer correctly on at least 75% of the trials in this work period?

- Not difficult.....1
- A little difficult.....2
- Moderately difficult.....3
- Very difficult.....4
- Excessively difficult or impossible.....5

2A. For you personally, how important will it be to respond correctly on at least 75% of the trials in this work period?

- Not important.....1
- A little important.....2
- Moderately important.....3
- Very important.....4

Note: Identical Subjective Measures Questionnaires were administered in Work Periods 2 and 3.

APPENDIX B

SCREENED BLOOD PRESSURE MEDICATIONS

Drug Class	Ending	Brand Names/Generic Name
Ace Inhibitors	-pril	Accupril, Aceon, Altace, Capoten, Coversyl, Lisodur, Lopril, Mavik, Novatec, Prinivil, Ramace, Ramiwin, Renitec, Tritace, Univasc, Vasotec, Vaseretic, Zestoretic, Zestril
Angiotensin Receptor Blockers	-sartan	Atacand, Avapro, Benicar, Cozaar, Diovan, Hyzaar, Micardis, Teveten
Beta-blockers	-olol	Apo-Timol, Betaloc, Betapace, Blocadren, Brevibloc, Cartrol, Coreg, Corgard, Inderal, Kerlone, Levatol, Lopressor, Monitan, Normodyne, Novo-Atenol, Novometoprol, Novo-Pindol, Novo, Timol, Sectral, Sotacor, Tenormin, Toprol-XL, Trandate, Trasicor, Visken, Zebeta
Alpha-blockers	-osin	Cardura, Flomax, Hytrin, Minipress, Uroxatral
Calcium Channel Blockers	-ipine -azem -amil	Adalat, Calan, Cardene, Cardizem, CD (diltiazem), Cardizem SR, Cartia, Covera-HS, Dilacor XR, Diltia XT, DynaCirc, Isoptin, Lotrel, Nimotop, Norvasc, Plendil, Procardia, Procardia XL, Sular, Tiamate, Tiazac, Vascor, Verelan
Thiazide Diuretics	-azide -azone -idone -HCTZ	Aquatensen, Diucardin, Diulo, Diuril, Enduron, Esidrix, Hydro-chlor, Hydro-D, HydroDIURIL, Hydromox, Hygroton, Metahydrin, Microzide, Mykrox, Naqua, Naturetin, Oretic, Renese, Saluron, Thalitone, Trichlorex, Zaroxolyn
Potassium-sparing Diuretics		Aldactone (spironolactone), Dyrenium (triamterene), Midamor (amiloride)

Drug Class	Ending/suffix	Brand Names (Generic Name)
Loop-acting Diuretics	-ide	Bumex (bumetanide), Demadex (torsemide), Edecrin (ethacrynic acid), Lasix (furosemide), Myrosemide (furosemide), Lasix (furosemide)
Carb. Anhyd. Inhibit. Diuret.	-amide	Acetazolamide, Methazolamide, Dorzolamide, Topiramate
Antihypertensive Comb.	-HCTZ	Aldactazide, Aldoril , Apresazide, Capozide, Combipres, Corzide, Diovan HCT, Dyazide, Hyzaar, Inderide, Lexxel, Lopressor HCT, Lotensin HCT, Lotrel, Maxzide, Minizide, Moduretic, Prinzide, Tarka, Tenoretic, Timolide, Uniretic, Vaseretic, Zestoretic, Ziac
Vasodialators		Hydralazine, Minoxidil, Sodium Nitroprusside
Antihypertensives – other		Clonidine, Moxonidine
Antiarrhythmics		Betapace (sotalol), Cardizem (diltiazem), Cordarone (amiodarone), Covera (verapamil), Inderal (propranolol), Pacerone (amiodarone), Isoptin (verapamil), Ethmozine (moricizine), Lopressor (metoprolol), Mexitil (mexiletine), Norpace (disopyramide), Procanbid (procainamide), Pronestyl (procainamide), Quinaglute Dura-tabs (quinidine gluconate), Quinidex Extentabs (quinidine sulfate), Rythmol (propafenone), Tambocor (flecainide), Tenormin (atenolol), Tiazac (diltiazem), Tikosyn (dofetilide), Tonocard (tocainide), Toprol XL (metoprolol)

Drug Class	Ending/suffix	Brand Names (Generic Name)
Digitalis Medicines		Lanoxicaps (digoxin), Lanoxin (digoxin), Lanoxin Elixir Pediatric (digoxin), Lanoxin Injection (digoxin), Lanoxin Injection Pediatric (digoxin)
Nitrates		IMDUR (isosorbide mononitrate) ISMO (isosorbide mononitrate), Isordil (isosorbide dinitrate), Monoket (isosorbide mononitrate), Nitro-Dur (nitroglycerin), Nitrogard (nitroglycerin), Nitrolingual (nitroglycerin), Nitrostat (nitroglycerin), Sorbitrate (isosorbide dinitrate), Transderm-Nitro (nitroglycerin)

Note: Carb. Anhyd. Inhibit. Diuret = Carbonic Anhydrase Inhibitors Diuretics; Antihypertensive Comb. = Antihypertensive Combinations.

APPENDIX C

INSTITUTIONAL REVIEW BOARD FOR HUMAN USE FORMS

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on November 24, 2003 and expires on October 26, 2010. The Assurance number is FWA00005960.

Principal Investigator:	STEWART, CHRISTOPHER C.
Co-Investigator(s):	GRIFFITH, HENRY RANDALL WRIGHT, REX ALTON
Protocol Number:	**X080321007**
Protocol Title:	*Cardiovascular Responses in Patients with Alzheimer's Disease and Mild Cognitive Impairment*

The IRB reviewed and approved the above named project on 4/8/08. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 4-8-08

Date IRB Approval Issued: 4/8/08

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

470 Administration Building
701 20th Street South
205.934.3789
Fax 205.934.1301
irb@uab.edu

The University of
Alabama at Birmingham
Mailing Address:
AB 470
1530 3RD AVE S
BIRMINGHAM AL 35294-0104

Project Revision/Amendment Form

(PLEASE TYPE: In MS Word, highlight the shaded, underlined box and replace with your text; double-click checkboxes to check/uncheck.)

- Federal regulations require IRB approval before implementing proposed changes.
- Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator's Brochure, questionnaires, surveys, advertisements, etc.).
- Complete this form and attach the changed research documents.

4/28/09 GW

Today's Date: *4/28/2009*

RECEIVED
APR 28 2009
OFFICE OF INSTITUTIONAL REVIEW BOARD

1. Contact Information

Principal Investigator's Name: *Christopher Conley Stewart*
BlazerID: *ccstewrt* E-mail: *ccstewrt@uab.edu*

Contact Person's Name: *Christopher Conley Stewart*
BlazerID:*ccstewrt* E-mail: *ccstewrt@uab.edu*
Telephone: *(205) 934-3345* Fax: *(205) 975-6110*
Campus Address: *SRC 530 • 1717 6th Ave. South, 619 19th St. South*

2. Protocol Identification

Protocol Title: *Cardiovascular Reactivity in Patients with Alzheimer's Disease and Mild Cognitive Impairment*
IRB Protocol Number: *X080321007*

Current Status of Project (check only one):

- ☒ Currently in Progress (Number of participants entered: *42*)
- ☐ Study has not yet begun (No participants entered)
- ☐ Closed to participant enrollment (remains active)—
  Number of participants on therapy/intervention:_____
  Number of participants in long-term follow-up only:_____
- ☐ Closed to participant enrollment (data analysis only)—
  Total number of participants enrolled:_____

This submission changes the status of this study in the following manner (check all that apply):

- ☒ Protocol Revision
- ☐ Protocol Amendment
- ☐ Study Closed to participant entry
- ☐ Study Closure
- ☒ Revised Consent Form
- ☐ Addendum (new) consent form
- ☐ Enrollment temporarily suspended by sponsor
- ☐ Change in protocol personnel
- ☒ Other, (specify) *We are proposing to add a fourth group of participants to our three preexisting groups of patients with (a) mild cognitive impairment, (b) mild Alzheimer's disease, and (c) healthy, older controls. This fourth group will consist of healthy, younger adults; they will be drawn from the Psychology 101 subject pool. Adding this fourth group with alter the IRB-approved study protocol in two principle respects. First, the fourth group of healthy, younger adults will have their own consent form. This consent from will differ primarily from the current consent form only in that it will indicate that participants will receive Psychology 101 class credit for their participation rather than $20.00. Second, experimental sessions for the fourth group of healthy, younger adults will be conducted in Professor Rex Wright's psychophysiological laboratory, which is located in the 323 research suite on the third floor of Campbell Hall. Of note, on our preexisting IRB-approved protocol, Dr. Wright is listed as a staff member involved with the design, conduct, and reporting of the research. We have also added an undergraduate research assistant, Sara Walker, as a staff member on the new IRB protocol. She will collect data from the fourth group of PY101 participants only. Also of note, She has conducted similar psychophysiological experiments with PY101 participatns in Dr. Wright's lab and has a current record of training. As a final note, it is worth mentioning that this fourth group of healthy, younger adults has minimal associated risks, as they are healthy (i.e., have a low base-rate of disease) and will be screened for cardiovascular conditions/treatments (e.g., history of heart disease and cardiovascular medications) and neurological conditions (attention deficit disorder, language impairment, etc.) via self-report.*

3. Reason for change

Briefly describe, and explain the reason for, the change. If normal, healthy controls are included, describe in detail how this change will affect those participants.

Include a copy of the protocol and any other documents affected by this change (e.g., consent form, questionnaire) with all the changes highlighted.

Our primary reason for this change is to compare results from the healthy, older group against those from the healthy, younger group. This comparison is of importance because it allows us to examine changes in cardiovascular reactivity to mental challenges that are associated with normal, healthy aging, as opposed to those associated with dementia (i.e., mild cognitive impairment and Alzheimer's disease).

4. Does this change revise or add a genetic or storage of samples component? ☐Yes ☒No

If yes, please see the Guidebook to assist you in revising or preparing your submission, or call the IRB office at 934-3789.

5. Does the change affect subject participation (e.g., procedures, risks, costs, location of services, etc.)? ☒Yes ☐No

If yes, Fiscal Approval Process (FAP)-designated units complete a FAP submission and send to fap@uab.edu. For more on the UAB FAP, see www.uab.edu/ohr.

Note: This is not a clinical trail; thus, we have not completed a FAP submission. The procedures and risks are identical to that indicated in our IRB-approved study protocol. However, payment/compensation for participation and location will differ for the forth group of healthy, younger participants only. As detailed in #2 above, these participants will receive Psychology 101 class credit for their participation rather than $20.00. In addition, experimental sessions for the fourth group of healthy, younger adults will be conducted in Professor Rex Wright's psychophysiological laboratory, which is located in the 323 research suite on the third floor of Campbell Hall. All other aspects of the study procedure are identical to that outlined in our preexisting IRB-approved study protocol.

6. Does the change affect the consent document(s)? ☒Yes ☐No

If yes, briefly discuss the changes. *As indicated in #2 above, the fourth group of healthy, younger adults will have their own consent form. This consent from will differ primarily from the current consent form only in that it will indicate that participants will receive Psychology 101 class credit for their participation rather than $20.00.*

Include the revised consent document with the changes highlighted.

Will any participants need to be reconsented as a result of the changes? ☐Yes ☒No

If yes, when will participants be reconsented?_____

Signature of Principal Investigator [signature] Date *4/28/2009*

OOA 4-3-09

APPROVED

[signature] 4-29-09

MARILYN DOSS, M.A.
Vice Chair – IRB

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

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Identification and Certification of Research
Projects Involving Human Subjects

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Principal Investigator: STEWART, CHRISTOPHER C.

Co-Investigator(s):

Protocol Number: **X080321007**

Protocol Title: *Cardiovascular Reactivity in Alzheimer's Disease and Mild Cognitive Impairment*

The IRB reviewed and approved the above named project on 4-27-10. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 4-27-10

Date IRB Approval Issued: 4-27-10

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review
Board for Human Use (IRB)

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