On the intraindividual dynamics of blood pressure and cognitive functioning: An examination of short-term coupling

by

Amanda Kelly
B.Sc. (Hons.), University of Victoria, 2012

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Supervisory Committee

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Dr. Scott M. Hofer (Department of Psychology)
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Abstract

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While it is now understood that long-standing hypertension is predictive of later cognitive decline and risk for dementia, little research attention to date has focused on whether the short-term dynamics of blood pressure exert immediate influence on cognitive functioning. The present study contributes to this growing field with a conceptual replication and extension of work by Gamaldo, Weatherbee and Allaire (2008). A sample of 27 older adults (*M*=70.2 years) completed daily assessments of blood pressure, psychological stress and cognitive functioning for 14 consecutive days. Multilevel models conditional on demographic factors were applied to simultaneously estimate between- and within-person effects across three metrics of blood pressure (systolic, diastolic and pulse pressure) and five measures of cognitive functioning. To follow a suggestion proposed by Gamaldo *et al.*, the model was extended to include main effect and blood pressure interaction terms for stress at both levels. In secondary analyses, within-person mediation models were applied to explore blood pressure as a mediator between stress and cognition. Results from the first model demonstrated a direct, positive association between occasion diastolic pressure and episodic memory. A cross-level interaction term revealed that processing speed was impaired on high-diastolic pressure days for those with high diastolic pressure on average. We found no evidence that occasion blood pressure mediated the association between stress and cognition. Overall,

our results align with the hypothesis that age-related changes to vascular structures impair the carrying capacity of blood vessels and that occasions of increased blood pressure provide additional force to overcome these limitations, delivering larger quantities of blood and oxygen to cerebral tissue. We conclude that upward fluctuations in diastolic pressure may be cognitively beneficial for older adults; diastolic pressure is the most sensitive metric for detection of within-person associations with cognition; and episodic memory and processing speed exhibit sensitivity to occasion blood pressure levels.

Table of Contents

List of Tables

List of Figures

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Dedication

I would like to dedicate this work to my parents Peter and Lisa Kelly for their unwavering support of my education and to my husband Brendan Leddy for helping me see through moments of self-doubt. Their unconditional love and belief in my abilities has made this accomplishment possible.

Introduction

The purpose of this project is to investigate the short-term within-person dynamics of blood pressure and determine whether these fluctuations are coupled with same-day cognitive functioning in older adults. Given rapidly aging populations worldwide, the widespread prevalence of high blood pressure among older adults (Public Health Agency of Canada, 2010) and growing evidence that blood pressure levels may be related to long-term cognitive health and risk for dementia, there is increasing interest in furthering our understanding of this association. This is especially relevant given both the simplicity of monitoring and detecting high blood pressure and its amenability to prevention and treatment through medication and lifestyle changes, which several reviews have indicated reduce the risk for future dementia (Marpillat, Macquin-Mavier, Tropeano, Bachoud-Levi, & Maison, 2013; Peila, White, Masaki, Petrovitch, & Launer, 2006). The current study builds upon prior work through conceptual replication and expansion to address the following specific aims:

Specific Aim 1. To examine the short-term coupling of blood pressure and cognitive performance in older adults. An intensive measurement design was used to capture day-to-day within-person changes (i.e., intraindividual variability) over the study period in metrics of blood pressure and cognition as well as between-person differences. This aim provides a first replication of the design, measures and statistical approach of Gamaldo, Weatherbee and Allaire (2008) and contributes to the small body of literature on within-person blood pressure processes.

Specific Aim 2. To evaluate the influence of daily self-reported stress on the within-person association between blood pressure and cognition. Though short-term within-person variation has been observed in all three domains (e.g., Rothwell, 2010; Stawski, Mogle, & Sliwinski, 2011) and between-person associations between stress and blood pressure and stress and cognition are well-understood, a major issue not yet fully explored is the joint examination of all three processes from a within-person perspective.

What is Hypertension?

With every heartbeat, blood is pumped through the arteries to tissues and organs where it delivers oxygen and nutrients vital for cellular functioning. Blood pressure is a measure of the force of blood against arterial walls both when the heart contracts (systolic; peak pressure) and when it relaxes (diastolic; minimum pressure). Chronic high blood pressure, hypertension, is typically diagnosed when multiple clinic visits and/or home monitoring reveals that the systolic reading is at or above 140 mmHg or the diastolic reading is at or above 90 mmHg. The vast majority of cases are classified as primary hypertension and though the causal pathway is not always clear, risk factors such as older age, obesity, physical inactivity and overconsumption of sodium, alcohol or tobacco are common (Carretero & Oparil, 2000). The remainder develop as secondary complications of pre-existing conditions such as diabetes or kidney disease, or the use of some medications. Traditionally, physicians considered diastolic pressure to be the most clinically relevant indicator of health status, though this opinion began to change with early results from the Framingham Heart Study which revealed that systolic pressure, instead, was more often associated with increased risk for cardiovascular events (Kannel, 2000). The sixth report of the Joint National Committee on Detection, Evaluation and

Treatment of High Blood Pressure, published in 1997, was the first to formally recommend the prognostic relevance of systolic pressure (National Institutes of Health, 1997). It is now understood that isolated systolic hypertension is the most common presentation of the condition, particularly among older adults (Kaplan, 2000).

Hypertension is the key risk factor for more serious cardiovascular conditions such as stroke, myocardial infarction and coronary heart disease (Public Health Agency of Canada, 2010). Without regular monitoring it often goes undetected as observable symptoms only appear with the onset of complications, often years later. This has earned it the nickname 'the silent killer' (World Health Organization, 2013); globally, hypertension is responsible for an estimated 13% of all deaths, more than the independent impacts of each of tobacco use, high blood sugar, physical inactivity and obesity (World Health Organization, 2009). Canadian population-based surveys show that the overall prevalence of hypertension has remained stable but high over the past three decades, with approximately 20% of adults affected. In addition to lost productivity due to morbidity and early mortality, large direct healthcare costs are incurred for drug, hospital and physician care with recent estimates at approximately $12 billion for hypertension together with other cardiovascular diseases (Public Health Agency of Canada, 2014). Given this, it has long been a major public health concern. In 1999, the non-profit organization Hypertension Canada established the Canadian Hypertension Education Program to raise awareness of regular screening, provide treatment guidelines and make policy recommendations (Campbell, Tu, Brant, Duong-Hua, & McAlister, 2006). Data collected between 1986 and 2009 illustrate great strides in blood pressure care in this country; for example, the proportion of hypertensives unaware of their condition dropped

from 43.2% to 17.4% while the proportion with treated and controlled hypertension rose from 13.2% to 64.6% (McAlister *et al.*, 2011). The nearly one in five hypertensives who still do not receive treatment or do not receive treatment that controls their high blood pressure remain a challenge, related to myriad factors including under-treatment (i.e., physician satisfaction with slightly elevated blood pressure), inadequate understanding of or frustration with the treatment regimen, perceived lack of support and hopeless or careless attitudes toward the diagnosis (Gascón, Sánchez-Ortuño, Llor, Skidmore, & Saturno, 2004; Jokisalo, Kumpusalo, Enlund, Halonen, & Takala, 2002; Redon *et al*., 2011). Overall, however, the statistics are a vast improvement over the recent past.

Normative age-related changes in the vascular system mean that older adults are particularly at risk for the development of high blood pressure. This is borne out by health survey data which show a sharp increase in prevalence at age 50, eclipsing 50% at age 65 (Public Health Agency of Canada, 2010). In fact, hypertension recently surpassed arthritis/rheumatism to become the most common chronic disease among older adults (Canadian Institute for Health Information, 2011; Turcotte & Schellenberg, 2006). The Framingham Heart Study estimated the residual lifetime risk of developing the condition to be as high as 90% for normotensive individuals aged 55 to 65 years (Vasan *et al*., 2002). Healthcare professionals have long understood the importance of preventing and controlling hypertension to mitigate adverse effects on physical health. More recently, a growing body of evidence also implicates hypertension in cognitive health and risk for dementia. When considered together with Canada's rapidly aging population (Statistics Canada, 2011), the need to further our understanding of the links between blood pressure and cognitive functioning becomes imperative.

Blood Pressure and Cognition

Interest in blood pressure as a potential influence on cognition originated in the 1960s with observations from case-control studies that hypertensive individuals tended to perform more poorly on neuropsychological tests than their normotensive peers (Elias, Robbins, Schultz, & Pierce, 1990; Elias, Wolf, D'Agostino, Cobb, & White, 1993). From there, researchers began to hypothesize that processes similar to those mediating the association between stroke and vascular dementia may also be active in hypertension and deliberate cross-sectional study grew (Launer, Masaki, Petrovitch, Foley, & Havlik, 1995). With the exception of the Duke University Longitudinal Study of Hypertension in 1971, longitudinal studies and analysis were the exception until results from the Framingham Heart Study renewed this focus beginning in the late-1980s, a line of research that continues today (Elias, Goodell, & Dore, 2012).

Long-standing hypertension (i.e., originating in midlife) in particular is a consistent predictor of later impairment and risk for dementia. A systematic review conducted by Qiu, Winblad and Fratiglioni (2005) reported that seven of eight longitudinal studies on cognition and all five longitudinal studies on dementia found that those with high blood pressure declined more quickly or were at higher odds for impairment 20 to 30 years after blood pressure assessment. This was confirmed by Kennelly, Lawlor and Kenny (2009). Another review calculated population attributable risk statistics for four cardiovascular risk factors at midlife and found the largest for hypertension, which contributed to as many as 30% of dementia cases (Kloppenborg, van den Berg, Kappelle, & Biessels, 2008). Though the overall picture shows a clear trend, interpreting this field of literature as a whole requires caution as reviews pool the findings of studies which use different

predictor and outcome variables. For example, findings may be reported based on continuous measures of systolic, diastolic or pulse pressure, or dichotomous indicators of high blood pressure based on self-report, use of medication, medical records or a range of diagnostic criteria. Outcome variables may include any number of neuropsychological tests, their composite score or formal diagnoses of mild cognitive impairment, Alzheimer's disease, vascular dementia or all-cause dementia. Whereas the association between hypertension and vascular dementia is straightforward via stroke, its relationship with Alzheimer's disease is less clear (Guan *et al.*, 2011). A recent systematic review and meta-analysis (Power *et al*., 2011) found no overall patterns based on midlife blood pressure level or diagnosis of hypertension; in another, only three of 12 studies found an increased risk (Kloppenborg *et al.*, 2008). Nonetheless, midlife hypertension is now considered an established risk factor for later cognitive impairment in general (Kennelly & Collins, 2012).

The present study is concerned with cognitive functioning as assessed by neuropsychological test performance. Despite the consensus described above, it is not yet fully understood which cognitive domains in particular are most vulnerable to the impacts of blood pressure, though global cognition (as measured by a dementia screening tool such as the MMSE), episodic memory and attention appear to be among the most frequently identified. Other domains, such as processing speed and language abilities, are more contentious (Gifford *et al*., 2013). The Atherosclerosis Risk in Communities study investigated changes in performance over 20 years of follow-up in a middle-aged sample (aged 45 to 65 at baseline) across tests of short-term memory, verbal learning, executive function and processing speed. The application of linear regression models adjusted for

demographic, health behaviour and cardiovascular factors found that individuals with hypertension at baseline exhibited steeper decline in global cognition, executive function and processing speed. This amounted to a 6.5% greater decline in global *z*-scores relative to those with normal blood pressure (Gottesman *et al*., 2014). In the Maastricht Aging Study, young, middle-aged and older adults were assessed at baseline and after six and 12 years on a range of neurocognitive and health measures. Age-stratified growth curve models with random effects demonstrated that middle-aged adults with hypertension declined more quickly than older, normotensive individuals on measures of episodic memory, executive function and processing speed. Subsequent chi-square tests compared slope estimates across blood pressure control categories for the full sample and revealed that even those with well-controlled high blood pressure exhibited steeper decline in executive function over the study period compared with normotensive peers (Köhler *et al.*, 2014).

Relative to midlife hypertension, the development of the condition in later life (age 65 or older) is much less often found to be associated with cognitive decline and, among the oldest-old (age 75 or older), is in fact more often related to preserved functioning (Kennelly & Collins, 2012; Power *et al.*, 2011). For example, Rastas and colleagues (2010) followed a sample of 339 Finnish octogenarians for nine years and monitored for the development of dementia as per DSM-III-R criteria. A variety of health-related factors were evaluated with Cox proportional hazards regression models to determine their association with cases of incident dementia over the study period. While prevalent diabetes and incident stroke were associated with the development of dementia, incident hypertension and higher educational attainment were protective factors. This supported

findings from an American sample from the Adult Changes in Thought Study where hazard ratios indicated a higher risk for dementia for a young-old sub-sample (aged 65 to 74 at baseline) with high systolic pressure, but not for older individuals with the same diagnosis. Furthermore, an interaction term in the full sample model indicated that with increasing age and systolic pressure, dementia risk declined (Li *et al*., 2007). Other work has shown that low blood pressure (hypotension) at advanced ages tends to predict elevated risk for dementia (Nilsson *et al*., 2007; Qiu, von Strauss, Winblad, & Fratiglioni, 2004; Verghese, Lipton, Hall, Kuslansky, & Katz, 2003). Further, a Cochrane review by McGuinness, Todd, Passmore and Bullock (2009) concluded that treatment of high blood pressure in later life (mean age of 75.4 at baseline) did not improve dementia diagnosis or MMSE score outcomes. Debate continues as to whether the relationship between blood pressure and cognition is conditional on age (Kennelly & Collins, 2012) or exposure time (Köhler *et al*., 2014).

The central mechanisms by which blood pressure affects cognitive functioning are similar for hyper- and hypotension as both may ultimately result in hypoperfusion of cortical tissue and chronic hypoxia. The principle of neurovascular coupling describes the close relationship between cerebral blood flow and regional neural activity, which is dependent upon metabolism of the oxygen and glucose carried by blood to produce adenosine triphosphate, the energy for cellular processes such as neurotransmission (Girouard & Iadecola, 2006). In undiagnosed, untreated and uncontrolled high blood pressure, hypoperfusion results from small vessel damage due to cumulative wear and tear of vascular and microvascular structures caused by long-term excess pressure. This damage in turn increases the likelihood for silent cardiovascular events such as vessel

tears, microbleeds and white matter lesions which may prevent some blood from reaching the brain (Charidimou & Weeing, 2011; Liu *et al.*, 2012). Chronic hypoxia is indicated in Alzheimer's disease (Khan & Davies, 2008) and even episodic hypoxia has been shown to disrupt regulation of cerebral circulation (Capone *et al.*, 2012). Other causal pathways from hypertension to impaired cognition include disrupted autoregulatory processes for cerebral blood flow, increased permeability of the blood-brain barrier to beta-amyloid protein and death of cerebral tissue following a stroke (Obisesan, 2009).

Cortical hypoperfusion may also occur due to normative age-related vascular changes such as increased atherosclerosis (narrowing of blood vessels due to accumulated cells, secretions and debris in the vessel wall) and arterial stiffness (loss of elasticity and reduced compliance). In healthy older adults aged 75 or older, these changes may impair blood and oxygen carrying capacity, leading to selection for the additional force provided by occasions of higher blood pressure levels to maintain cerebral perfusion. The combination of age- and hypertension-related changes to the vascular system may further exacerbate the impacts of both, effectively accelerating vascular aging (Wang & Bennett, 2012). Higher blood pressure in older age is also favoured by autoregulation of cerebral blood flow and neurotransmission which are sensitive to drops in blood pressure and may not fully recover (Kennelly *et al.*, 2009; Obisesan, 2009) and the additional concern that low blood pressure increases the risk of falling, an event which can have devastating consequences for an older adult's health, independence and quality of life (Sirkin & Rosner, 2009).

Daily Dynamics of Blood Pressure

Blood pressure levels follow the body's circadian rhythm, typically rising and reaching the day's peak early in the morning, remaining stable through the afternoon and falling in the early evening to reach a trough overnight (10% to 20% lower). This pattern occurs in conjunction with the rhythms of the sympathetic nervous system and other cardiovascular markers such as arterial stiffness, blood viscosity and vascular resistance (Hassler & Burnier, 2005). Altered diurnal rhythms, such as a flattened evening dip or steeper morning rise, are often observed in hypertensive individuals and may be indicative of increased risk for adverse cardiovascular events (de la Sierra *et al*., 2010; Mancia *et al*., 2003).

Transient within-person blood pressure variability within and across days is normative and can be characterized as ambulatory or visit-to-visit. Ambulatory variability occurs in response to a wide range of daily life events such as sleep, diet, exercise, setting and social interactions (Nagai & Kario, 2013). Visit-to-visit variability, that is, variability in blood pressure readings taken under controlled, standardized conditions, reflects more gradual fluctuations. It was long considered meaningless background noise but is now known to be a useful tool to inform health status assessment and treatment planning (Rothwell, 2010). For example, individuals with blood pressure within normal ranges but high visit-to-visit variability tend to show small and large vessel disease and are at increased risk for future cardiovascular events (Brickman *et al*., 2010). Mancia and colleagues (2001) reported that among hypertensive middle-aged adults, those with higher daily variability in systolic and/or pulse pressure showed greater arterial pathology and were at higher risk for target organ damage than more stable hypertensives.

Given growing insight on the relevance of blood pressure variability for physical health, several recent studies have turned their attention to its relationship with cognitive functioning, though this has been almost exclusively limited to cross-sectional comparisons typically characterizing variability as the standard deviation of the mean (Bellelli, Bianchetti, & Trabucchi, 2006). Sabayan and colleagues (2013) followed a group of older adults at high risk for cardiovascular disease for three years to determine whether visit-to-visit variability was associated with brain pathology and neuropsychological test performance. Linear regression models adjusted for demographic and health factors demonstrated that individuals with the largest degree of systolic and diastolic variability during the study period performed more poorly on measures of global cognition, attention, processing speed and episodic memory. In addition, fMRIs showed they were more likely to have sustained cortical infarcts and reduced hippocampal volume. The authors noted that the differences in cognitive functioning between older adults in the bottom and top thirds of blood pressure variability (standard deviation values from .70 to 12.2 mmHg and 16.3 to 64.4 mmHg, respectively) were on the order of magnitude of differences between apolipoprotein E genotypes. In another study with older adults, Lattanzi, Luzzi, Provinciali and Silvestrini (2014) reported that fast decliners on the MMSE (i.e., decline of more than four points over a one-year period) were more likely to have greater systolic variability as indicated by the coefficient of variation, but were not different from slow decliners in terms of mean blood pressure level. Indeed, it has been suggested that the hazard ratio for future dementia may increase by as much as 10% for every one standard deviation increase in the coefficient of variation and that

those in the highest decile of variation may be at as much as a 77% increased risk for dementia relative to those in the lowest decile (Alpérovitch *et al.*, 2014).

The new and growing body of work on the association between blood pressure variability and cognitive performance has alerted researchers and healthcare professionals to the meaning inherent in the standard deviation, range, minimum and maximum values of blood pressure, often overlooked for the mean. However, the standard is to characterize change over time as a single summary value, typically the standard deviation of the mean. Individuals with small and large standard deviations are then compared on the basis of one-time or mean cognitive scores. Though several studies have made use of longitudinal data collected over months or years, most have used this cross-sectional analytic approach that can probe only stable between-person differences; that is, it asks whether the magnitude of blood pressure variability distinguishes cognitive performance across individuals. However, this is a different question than that which motivates much of the work, which asks whether intraindividual changes over time in blood pressure are related to intraindividual changes over time in cognition. To fully address this question and capture the person-level variability inherent in both measures, data and analytic approaches which characterize and evaluate dynamic within-person processes are required (Curran & Bauer, 2011; Mroczek, Spiro III, & Almeida, 2003).

A 2008 study by Gamaldo *et al.* was the first to distinguish the between- and within-person associations of blood pressure and cognitive functioning. The researchers used an intensive measurement design during which both key variables were assessed twice daily for 60 consecutive days from an older adult sample (mean age of 73.0 at baseline) to determine whether they were coupled (i.e., covaried) at the person-level. The rationale

behind this study originated with observations of cardiovascular reactivity to daily experiences, such as the findings that ambulatory increases in systolic and diastolic pressure were related to same-day negative affect (Ong & Allaire, 2005) and blood pressure reactivity to psychological stress was predictive of blood pressure levels five years later (Carroll, Ring, Hunt, Ford, & MacIntyre, 2003). The researchers used multilevel modeling (Raudenbush & Bryk, 2002) to simultaneously estimate between- and within-person main effects and to probe the possibility of a cross-level interaction between person-mean and occasion blood pressure after including linear and quadratic time trends and controlling for age, sex and education. No consistent patterns of significance were found for three cognitive tests of declarative memory, inductive reasoning and perceptual speed, nor were any direct associations between blood pressure and cognition at either level. However, a small but significant estimate for the cross-level interaction term emerged for inductive reasoning (Letter Series test) such that performance was impaired on days when one's systolic pressure was elevated (i.e., above their person-mean), but only for individuals with higher pressure on average (b=-.0004, p<.05). Specifically, this between-person moderation of a within-person association appeared with systolic readings of 130 mmHg or higher and grew in magnitude with increasing blood pressure. Gamaldo and colleagues speculated that psychological stress may have been involved, as days with high stress are likely to be days with elevated blood pressure (within-person level) and individuals who report experiencing a greater number or severity of stressful events may be more likely to have pre- or diagnosed hypertension (between-person level). However, as measures of stress were not collected,

this potential explanation remained a conjecture and has not yet been further investigated to the best of our knowledge.

The Current Study

The aim of the current study is to provide a conceptual replication and expansion of the work of Gamaldo *et al.* (2008) on the short-term dynamics of blood pressure and cognitive functioning at the within-person level. Though understanding of the established association between long-standing hypertension and risk for future cognitive impairment has grown substantially in past decades, little research attention to date has been paid to the question of whether short-term fluctuations in blood pressure have immediate cognitive consequences. If they exist, these consequences may be temporary or may accumulate over time and contribute to dementia risk. In addition, though previous research has shown that blood pressure is responsive to daily experiences such as perceived stress, its role in a short-term relationship between blood pressure and cognition has not been previously examined.

As a first step, this thesis explores daily fluctuations in blood pressure and cognitive performance over a 14-day period and characterizes the relationship between the two following the study design, measures and analytic approach of Gamaldo *et al.* (2008) (Specific Aim 1). Next, this study expands upon prior work by considering the role of daily psychological stress in interaction with daily blood pressure and, separately, as a predictor of daily cognition mediated by daily blood pressure (Specific Aim 2). In both aims, the comparison of findings across three metrics of blood pressure makes further novel contributions to the literature.

Specific Aim 1. To examine the short-term coupling of blood pressure and cognitive performance in older adults. A series of multilevel models applied to intensive measurement data will characterize the relative contributions of variance at the within- and between-person levels for variables assessed daily. This Specific Aim provides a conceptual replication of Gamaldo *et al.* (2008) in evaluation of the potential for intraindividual coupling between blood pressure and cognition and for moderation of the coupling by between-person (average) blood pressure. Further understanding of the role blood pressure may play in the development of cognitive impairment has implications for care guidelines (e.g., the threshold at which high blood pressure is treated), regular screening and the quality of life of those living with hypertension or unstable blood pressure. As this thesis is the first replication of the sole study on this topic it is somewhat exploratory, so we ground our hypotheses in the mechanisms proposed to underlie the cognitive impacts of blood pressure. These state that hypertension- and age-related changes to autoregulatory processes and the structural properties of blood vessels reduce the volume of oxygen-rich blood able to reach the brain with each heartbeat. In both cases, it follows that occasions of elevated blood pressure may overcome these limits to meet cerebral perfusion requirements, whereas a drop in blood pressure may exacerbate an already compromised system. Thus, we predict that across both specific aims, occasions of elevated blood pressure will be beneficial for same-day cognitive functioning. The hypothesis also predicts a positive cross-level interaction, unlike Gamaldo's negative finding.

Specific Aim 2. To evaluate the influence of daily self-reported stress on the within-person association between blood pressure and cognition. This Specific Aim expands

upon the suggestion put forward by Gamaldo *et al*. (2008) that individuals who experience periods of elevated blood pressure may also report higher levels of psychological stress, with the addition of main effect and interaction terms to the multilevel model at both levels. As both stress and blood pressure have been shown to be related to cognitive impairment, the within-person interaction term will estimate the additional cognitive impact of occasions with combined high blood pressure and high stress. A separate within-person mediation model will explore a second scenario; that is, a causal and temporal sequence whereby occasions of elevated stress lead to elevated blood pressure, resulting in cognitive change. Extending this line of inquiry will provide insight on the conditions under which older adults may be more vulnerable to the known impacts of daily stress on cognitive functioning. Following from the mechanisms that link blood pressure and cognition, detailed above, we predict that elevated blood pressure will have cognitive benefits while occasions of high stress will exert a negative influence on functioning. As investigation of their within-person interaction is largely exploratory, we make no formal hypothesis on how cognitive functioning will fare on occasions where both occur. Finally, we expect that occasion blood pressure will mediate the association between stress and cognition as sympathetic arousal is known to increase blood pressure. In addition, prior work has collectively demonstrated separate pieces of the puzzle; that is, higher stress coupled with poorer cognition (Sliwinski, Smyth, Hofer, & Stawski, 2006; Stawski, Mogle, & Sliwinski, 2013) and higher blood pressure (Carroll *et al.*, 2003; Uchino, Berg, Smith, Pearce, & Skinner, 2006; Waldstein, Giggey, Thayer, & Zonderman, 2005) and fluctuations in blood pressure coupled with fluctuations in cognition (Gamaldo *et al*., 2008).

Methods and Procedures

Participants

Data collection took place between July 2013 and February 2015 with participants aged 60 and older. Recruitment occurred in Victoria, BC through notices placed on public bulletins, advertisements in Senior Living magazine and through a series of knowledge translation workshops in partnership with five local seniors groups. The sample for analysis is comprised of 27 individuals of whom 81.5% (N=22) are female and 77.8% (N=21) are university-educated, with an average age of 70.2 years (*SD*=7.4). Baseline life satisfaction as rated on a 10-point scale was high on average (*M*=8.0, *SD*=1.2). Three individuals had diagnosed hypertension, all of whom also reported treatment with a diuretic drug alone or in combination with another antihypertensive and whose blood pressure readings indicated control of the condition. Overall, mean baseline blood pressure was within the normal range at 117.4 over 72.2 mmHg and pulse pressure of 45.2 mmHg. The prevalence of other cardiovascular conditions was low, with most of the sample (70.4%) reporting no diagnoses.

Procedure

Ethical approval to conduct this study was received by the University of Victoria Human Research Ethics Board in May 2013 (protocol number 13-157) and all participants provided written informed consent prior to involvement. Data collection followed an intensive measurement design of 14 consecutive testing session days after an initial baseline session at which the demographic survey and training for proper use of the

blood pressure monitor (Omron 5 Series BP742, certified by Hypertension Canada) and cognitive tests were completed. This training occurred with the researcher and all participants practiced until comfortable with both. The remainder of the study was completed at home with self-assessed blood pressure and the delivery of a survey by email with measures of stress and cognitive functioning (all completed via LimeSurvey version 2.05+; Schmitz, 2012). Upon completion of the 14-day period, participants met with the researcher for a debriefing session and were provided with a brief report containing group-level findings from preliminary analysis for their information. A mean of 13.4 sessions was completed (*SD*=1.3) for a total of 362 observations out of a possible 378 (95.8%).

Measures

On testing session days, participants self-assessed blood pressure within one hour of waking and one hour of retiring (6:00 p.m. or later) by taking three consecutive readings from the left arm while seated quietly with feet on the floor. Due to a change in study protocol, the first nine participants did not assess morning blood pressure; given this, only evening readings were used in the present analysis to maximize sample size. Therefore, the mean of the three evening readings was taken as the measure of occasion-specific blood pressure. Both systolic and diastolic levels were recorded and pulse pressure was computed as their difference.

The baseline survey provided information on basic demographic characteristics, personal and family history of diagnosed cardiovascular disease and use of blood pressure medication. The daily survey included the Daily Inventory of Stressful Events (DISE; Almeida, Wethington, & Kessler, 2002) to assess the frequency and severity of

psychological stressors experienced “over the course of today.” Severity was rated on a four-point scale and assigned a value of 0 if the corresponding stressor was not reported on a given occasion. This measure was selected as daily hassles such as interpersonal disagreements have been shown to relate more strongly to psychological and health outcomes than major life events such as bereavement (Aldwin, 2012).

Cognitive tests administered as part of the daily survey were the same measures, with the same assessment parameters, used by Gamaldo *et al.* (2008). Verbal declarative memory was assessed with the Rey Auditory Verbal Learning Test (Rey, 1941), which allows one minute for immediate recall of a 15-item word list after a one-minute study period. The delayed recall portion was administered after completion of the following two tasks. The Letter Series test (Thurstone, 1962) assessed inductive reasoning by asking participants to give the letter that comes next in a pattern. A total of 30 different patterns were listed and four minutes were allowed for completion of as many items as possible. Processing speed was assessed with the Number Comparison test (Ekstrom, French, Harman, & Derman, 1976) where participants compare a series of paired number strings (from three to 13 digits in length) and select the pairs that are identical. Ninety seconds were allowed for completion of as many of the 100 items as possible. The final measure administered, not included in the Gamaldo study, was the Symbol Digit Modalities Test (Smith, 1982) to assess attention and processing speed. This test requires participants to match the correct symbol to the digits zero through nine according to a legend. This was also speeded, allowing ninety seconds for completion of as many of the 102 items as possible.

Other measures collected during the course of the study period but not used in the present analysis include personality traits (Denollet, 2005; Digman, 1990), the Positive and Negative Affect Schedule (Watson, Clark, & Tellegen, 1988), a checklist of time spent engaging in different types of physical activity and items on the amount of alcohol, caffeine and tobacco consumed.

To provide some defence against re-test gains, seven versions of each test were used. Where not previously published, alternate forms were created in accordance with the original rules of the task; for example, the Letter Series test item 'B E C F D' becomes 'C F D G E' through a simple alphabet shift. A random numbers table determined the order of test versions presented to all participants with the condition that identical versions were never presented consecutively.

Statistical Plan

To investigate Specific Aim 1, multilevel modeling (Raudenbush & Bryk, 2002) was applied to distinguish the relative contributions of between- and within-person sources to the variance in repeated measures variables. The unconditional random intercept-only model yields the intraclass correlation coefficient (ICC), a statistic computed by dividing between-person variance by total variance for the variables of interest (Singer & Willett, 2003). Next, the same model with added covariates and a random linear time trend estimated the unique contributions of demographic factors (age, sex and education) and blood pressure to the initial level and change in cognitive outcome variables. The final version of the model added a term to test for a cross-level interaction between person-mean and occasion blood pressure and a random quadratic time trend, in replication of

the model presented by Gamaldo *et al.* (2008). The basic equation for this model is shown as Eq. 1 (covariate terms omitted for clarity).

(Eq. 1)

$$\text{Level 1: } y_{ti} = \beta_{0j} + \beta_{1j}\left(Time_{tj}\right) + \beta_{2j}\left(Time_{tj}\right)^2 + \beta_{3j}\left(Blood\ Pressure_{tj} - \overline{Blood\ Pressure_{.j}}\right) + \varepsilon_{tj}$$

$$\text{Level 2: } \beta_{0j} = \gamma_{00} + \gamma_{01}\left(\overline{Blood\ Pressure_{.j}} - \overline{Blood\ Pressure}\right) + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + u_{2j}$$

$$\beta_{3j} = \gamma_{30} + \gamma_{31}\left(\overline{Blood\ Pressure_{.j}}\right) + u_{3j}$$

Here, level 1 defines cognitive performance for person *j* at time *t* by specifying an intercept β_{0j}, effects of linear and quadratic time (β_{1j} and β_{2j}), the within-person component of blood pressure (β_{3j}, the difference between occasion-specific and person-mean values) and the within-person residual (ε_{tj}). Level 2 specifies fixed effects for the common intercept (γ_{00}) and between-person component of blood pressure (γ_{01}, the difference between person-mean and sample-mean values), fixed effect slopes for linear and quadratic time (γ_{10} and γ_{20}) and person-mean blood pressure (γ_{30}). The cross-level interaction is indicated by γ_{31}. Person-specific deviations (random effects) from the fixed intercept (u_{0j}) and fixed linear and quadratic effects of time (u_{1j} and u_{2j}) and blood pressure (u_{3j}) are also included and assumed to have multivariate normal distributions.

Specific Aim 2 was accomplished by extending the linear multilevel model with demographic covariates to include main effect and blood pressure interaction terms for stress severity (summed across all stressors) at both levels. Separately, unconditional

within-person mediation models as described in Figure 1 were applied following Bolger and Laurenceau (2013). Important differences from the seminal description of mediation analysis by Baron and Kenny (1986) include allowance of between-person heterogeneity in all three paths (indicated by the subscript *j*) such that a unique mediation model may exist for each individual in the sample and inclusion of a term representing covariance between paths *a* and *b* ($\sigma_{a_j b_j}$), used to calculate the average total effect of *X* on *Y*. As all model terms were centred at the person-mean, estimates represent purely within-person effects while intercepts and intercept random effects equal zero.

All models described in both Specific Aims were applied to the fifteen combinations of the three blood pressure predictors and five cognitive outcomes. As three participants reported use of antihypertensive medication and exhibited normal blood pressure, indicating controlled hypertension, we re-ran the final models from both aims with the systolic pressure of those individuals adjusted upward by 15 mmHg as a check on the influence of medication use (Tobin, Sheehan, Scurrah, & Burton, 2005).

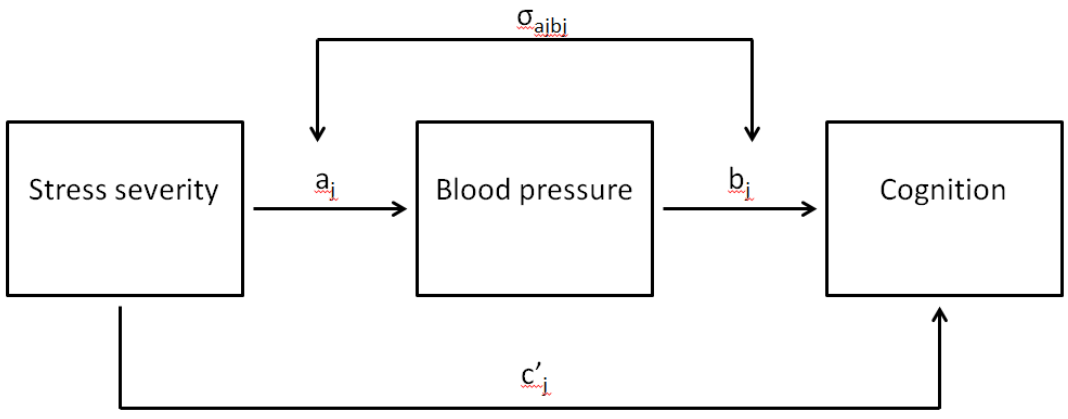

Figure 1. The within-person mediation model run separately for each combination of blood pressure predictor and cognitive outcome variables.

To quantify the improvement in model fit achieved between the model with adjustment for demographic factors only and the final models for both specific aims, measures of global effect size were computed. We are interested to know whether the model in replication of Gamaldo *et al.* (2008), with terms for quadratic time trends and a cross-level interaction, explained a larger proportion of outcome variance than a simpler model with linear time trends and demographic covariates only; likewise, improvements between this model and that with main effect and interaction terms for stress are of interest. Similar to the traditional R^2 statistic used in multiple regression, the pseudo-R^2 statistic compares changes in residual variance between two models as shown as Eq. 2 (Singer & Willett, 2003).

(Eq. 2)

$$\text{Pseudo } R^2 = \frac{\sigma^2{}_\varepsilon(demographic\ model) - \sigma^2{}_\varepsilon(subsequent\ model)}{\sigma^2{}_\varepsilon(demographic\ model)}$$

Because the sample for analysis is small, literature on power analyses for repeated measures designs was consulted to ensure sufficient statistical power to detect significant effects where they may exist. Rush, Rast and Hofer (2014) conducted Monte Carlo simulations with intensive measurement data and demonstrated that a minimum sample size of approximately 20 individuals is required for within-person power of .80 in a 14-day study. As the present sample includes 27 individuals, we can be confident in our estimates of within-person effects. However, with only one-fifth of the approximately 130 individuals required to achieve the same power at the between-person level, we must exercise caution when interpreting between-person associations and the cross-level interaction term. Due to sample homogeneity, estimates for the unique associations of age, sex and education with outcome variables are not interpreted.

Continuous within-person variables were centred at the person-mean while between-person variables were centred at the grand-mean. Education was dichotomized as low (completion of elementary school, high school/GED or a 2-year college program) or high (completion of a bachelor's, master's or professional degree). Thus, model intercepts represent the initial level of performance for a seventy-year-old man with low education and average systolic pressure of 118 mmHg (or diastolic pressure of 72 mmHg or pulse pressure of 46 mmHg, depending on model) who experiences an average stressor severity of 1.3 on a four-point scale. Data management was handled with SPSS (Version 22) and analyses were conducted with MPlus Version 7 (Muthén & Muthén, 1998-2012).

Results

Sixteen occasions, or 4.2% of the total possible observations, were missing data on all variables. Of the remaining cases, seven were missing data for one or more cognitive outcome variables and were therefore not eligible for inclusion in their respective models, though multilevel modeling does not require that the cluster as a whole be dropped. No cases were incomplete with regard to blood pressure or stress variables. Although it cannot be tested, it is reasonable to assume that these data were missing at random given the short duration of the study period, rather than due to processes more common in long-term longitudinal studies such as mortality (Schafer & Graham, 2002).

Univariate data checks revealed non-normal distributions for the stress and all cognitive measures as assessed by the Kolmogorov-Smirnov and Shapiro-Wilks tests (all $p<.01$), though multilevel models were estimated using robust maximum likelihood (MLR) to account for non-normality. Blood pressure measures were normally distributed. Two cases were identified as multivariate outliers but not removed from the dataset as other checks did not recognize them as extreme outliers.

Due to the limited nature of the sample, crosstabs were run to better understand distributions of demographic variables. Findings showed that while females were evenly distributed between the low and high education groups, the majority of males were classified under high education. Though age spans a large range from 60 to 88 years, only four individuals were over the age of 76. This, in addition to 81.5% of the sample being female, supports the decision not to interpret estimates for age, sex or education but to include them in models to partial out their unique effects on the outcomes.

Short-term Coupling of Blood Pressure and Cognition

Means, standard deviations and ICC values for repeated measures variables are presented in Table 1. Measures of blood pressure exhibited slightly more variation at the between-person level with an average of 38% of the variance due to daily fluctuations. The range was from .50 for diastolic pressure, indicating that half of the variation was attributable to stable between-person differences, to .76 for pulse pressure. Figure 2 provides an illustrative example of the extent of within- and between-person variability in systolic pressure.

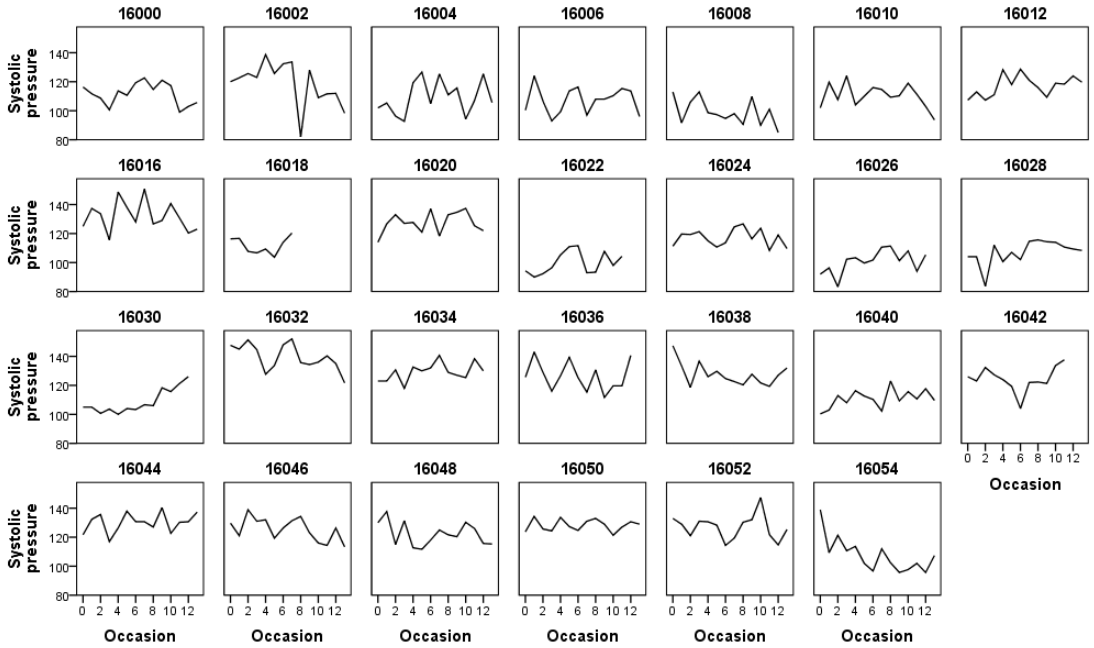

Figure 2. Panel plot of the 14-day time course of systolic pressure across participants.

The ICC values for measures of cognitive functioning ranged from .38 (Letter Series test) to .60 (delayed recall) with an average of 44% of the variance due to daily fluctuation. The measure of stress severity exhibited the most within-person variation with the smallest ICC value at .33.

Results from the multilevel models adjusted for demographic factors and with a linear time trend revealed a positive estimate for diastolic pressure on the delayed recall task

(*b*=.03, *p*<.05) at the within-person level. Positive estimates were also observed for systolic (*b*=.11, *p*<.05) and pulse pressure (*b*=.10, *p*=.053) on the Number Comparison test at the between-person level. These findings were maintained after expansion of the model to include a cross-level interaction and quadratic time trend with the addition of a significant cross-level interaction for diastolic pressure on the Number Comparison test (*b*=-.01, *p*<.05). This set of results provides limited evidence for between-person moderation of within-person coupling of diastolic pressure and cognition. Though this model resulted in increased residual variance at the between-person level, pseudo-R^2 statistics indicated improved within-person fit by 2.8% on average relative to the demographic-only model, with the largest improvements for the diastolic pressure predictor (3.0%) and the Symbol Digit Modalities Test outcome (4.6%). Table 2 displays estimates for all terms across the series of final models.

Table 1. Means, standard deviations (SD) and intraclass correlation coefficients (ICC).

Variable	Mean	*SD*	ICC
Systolic pressure (mmHg)	117.7	10.5	.60
Diastolic pressure (mmHg)	71.5	5.3	.50
Pulse pressure (mmHg)	46.1	10.0	.76
Stress severity	1.3	.82	.33
Immediate recall task	9.2	2.1	.60
Letter Series test	4.9	1.7	.38
Number Comparison test	16.2	3.3	.57
Delayed recall task	7.1	2.5	.63
Symbol Digit Modalities Test	23.7	5.7	.61

Table 2. Estimates and standard errors (SE) from multilevel models examining the effects of blood pressure on cognitive functioning after adjustment for age, sex and education, linear and quadratic time trends and a cross-level interaction between person-mean and occasion blood pressure.

	Fixed effects		Systolic blood pressure Estimate (*SE*)	Diastolic blood pressure Estimate (*SE*)	Pulse pressure Estimate (*SE*)
Immediate recall task	Within-person variables	Intercept	6.46 (.78)***	6.92 (.70)***	6.53 (.86)***
		Occasion	.03 (.07)	.03 (.08)	.02 (.07)
		Quadratic occasion	-.00 (.01)	-.00 (.01)	-.00 (.01)
		Blood pressure	-.01 (.01)	-.02 (.01)	-.00 (.02)
	Between-person variables	Age	-.12 (.05)**	-.11 (.04)**	-.11 (.05)*
		Sex	2.81 (.57)***	2.47 (.56)***	2.75 (.65)***
		Education	.70 (.76)	.36 (.71)	.67 (.81)
		Blood pressure	.04 (.04)	.06 (.06)	.02 (.04)
	Cross-level interaction	Person-mean X occasion blood pressure	.00 (.00)	.01 (.01)	.00 (.00)

Table 2 (Cont.)

	Fixed Effects		Systolic blood pressure Estimate (*SE*)	Diastolic blood pressure Estimate (*SE*)	Pulse pressure Estimate (*SE*)
Letter Series test	Within-person variables	Intercept	2.41 (.89)**	2.89 (.86)***	2.37 (1.04)*
		Occasion	-.01 (.10)	-.00 (.10)	-.00 (.10)
		Quadratic occasion	.02 (.01)**	.02 (.01)**	.02 (.01)*
		Blood pressure	.01 (.02)	.00 (.03)	.02 (.02)
	Between-person variables	Age	-.02 (.04)	.00 (.04)	-.01 (.03)
		Sex	1.45 (.66)*	1.10 (.56)*	1.46 (.70)*
		Education	.58 (.60)	.21 (.70)	.67 (.75)
		Blood pressure	.04 (.03)	.06 (.05)	.02 (.04)
	Cross-level interaction	Person-mean X occasion blood pressure	.00 (.00)	.00 (.00)	.00 (.00)
Number Comparison test	Within-person variables	Intercept	11.68 (1.36)***	12.69 (1.66)***	11.43 (1.35)***
		Occasion	.59 (.13)***	.59 (.11)***	.57 (.11)***
		Quadratic occasion	-.02 (.01)*	-.02 (.01)**	-.02 (.01)*
		Blood pressure	.00 (.02)	-.02 (.03)	.03 (.03)
	Between-person variables	Age	-.25 (.08)**	-.20 (.08)**	-.24 (.08)**
		Sex	1.58 (1.17)	.85 (1.49)	1.75 (1.14)
		Education	1.41 (1.19)	.64 (1.09)	1.68 (1.23)
		Blood pressure	.11 (.05)*	.10 (.08)	.10 (.05)†
	Cross-level interaction	Person-mean X occasion blood pressure	.00 (.00)	-.01 (.00)*	.00 (.00)

Table 2 (Cont.)

		Fixed Effects	Systolic blood pressure Estimate (*SE*)	Diastolic blood pressure Estimate (*SE*)	Pulse pressure Estimate (*SE*)
Delayed recall task	Within-person variables	Intercept	3.55 (.89)***	3.77 (.82)***	3.72 (.90)***
		Occasion	-.02 (.12)	-.01 (.08)	-.01 (.09)
		Quadratic occasion	.01 (.01)	.01 (.01)	.01 (.01)
		Blood pressure	.02 (.01)	.03 (.02)*	.01 (.05)
	Between-person variables	Age	-.12 (.06)†	-.12 (.05)**	-.10 (.05)*
		Sex	3.12 (.70)***	2.97 (.65)***	2.97 (.73)***
		Education	1.50 (.88)†	1.30 (.84)	1.37 (.93)
		Blood pressure	.01 (.05)	.05 (.06)	-.02 (.04)
	Cross-level interaction	Person-mean X occasion blood pressure	.00 (.00)	.00 (.00)	.00 (.00)
Symbol Digit Modalities Test	Within-person variables	Intercept	17.19 (1.97)***	17.29 (2.10)***	16.64 (1.87)***
		Occasion	1.15 (.20)***	1.19 (.27)***	1.15 (.20)***
		Quadratic occasion	-.05 (.01)***	-.06 (.02)***	-.05 (.01)***
		Blood pressure	.01 (.03)	-.01 (.03)	.03 (.05)
	Between-person variables	Age	-.51 (.12)***	-.47 (.11)***	-.53 (.12)***
		Sex	1.92 (1.72)	1.81 (2.02)	2.36 (1.45)
		Education	1.43 (1.61)	1.28 (1.69)	1.86 (1.75)
		Blood pressure	.05 (.08)	-.04 (.12)	.09 (.09)
	Cross-level interaction	Person-mean X occasion blood pressure	-.00 (.00)	-.01 (.01)	-.00 (.00)

Note. WP = within-person. BP = between-person. †$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

Influence of Stress on Coupling of Blood Pressure and Cognition

The linear multilevel model with demographic covariates was extended to include main effect and blood pressure interaction terms for stress severity at both levels. Within-person results revealed positive estimates for stress severity on the Letter Series test and negative estimates on the immediate recall task; in both cases, the findings held across each of the three measures of blood pressure (all $p<.05$). The within-person interaction terms for systolic and diastolic pressure approached significance on the immediate recall task (both $b=.01$, $p=.08$). None of the blood pressure measures exhibited unique associations with cognition. The pseudo-R^2 statistics indicated improved within-person fit by 3.1% on average from the demographic-only model, with the largest improvements for the pulse pressure predictor (3.3%) and the delayed recall task outcome (5.4%).

At the between-person level, several estimates were marginally significant (i.e., $p<.10$). Models with systolic pressure on the delayed recall task showed positive estimates for stress severity ($b=.81$, $p=.08$) and the interaction term ($b=.09$, $p=.06$; p also $<.10$ for pulse pressure). The interaction term was negatively associated with the Number Comparison in the model with pulse pressure ($b=-.10$, $p=.07$) and a positive estimate for pulse pressure itself ($b=.09$, $p=.07$). The change in model fit from the demographic-only model was larger on average than that for the within-person level (pseudo-R^2=8.4%). The estimates for all terms across all models are shown in Table 3.

Within-person mediation models were run for each of the fifteen combinations of blood pressure variables (as mediators) and cognitive outcomes, regardless of whether the multilevel models described above found direct effects of stress on cognition, as advised by current statistical thinking (Hayes, 2009; Rucker, Preacher, Tormala, & Petty, 2011). All of the models yielded non-significant estimates for each of the three paths with the exception of the immediate recall task, which revealed a direct effect of stress severity (b=-0.20, p<.05). The between-person heterogeneity in this effect was moderate with a standard deviation of .19 and 95% confidence intervals ranging from -0.37 to -.03. However, there was no evidence of mediation by blood pressure regardless of metric.

Finally, to check whether effects were underestimated due to the use of antihypertensive medication by some participants, the final models for both specific aims were re-run with an adjustment to correct for the medication's effects (systolic pressure increased by 15 mmHg). With the exception of the emergence of a positive between-person association between systolic pressure and Number Comparison test performance in the multilevel model of Specific Aim 2, no changes to the pattern of results were observed (results not shown).

Table 3. Estimates and standard errors (SE) from linear multilevel models examining the effects of blood pressure on cognitive functioning after adjustment for demographic factors, stress severity and the interaction between blood pressure and stress severity.

	Fixed Effects		Systolic blood pressure Estimate (*SE*)	Diastolic blood pressure Estimate (*SE*)	Pulse pressure Estimate (*SE*)
Immediate recall task	Within-person variables	Intercept	7.50 (.74)***	7.17 (.71)***	7.12 (.87)***
		Occasion	.00 (.04)	.01 (.04)	.01 (.04)
		Blood pressure	-.00 (.02)	-.00 (.02)	.00 (.02)
		Stress severity	-.19 (.09)*	-.19 (.09)*	-.19 (.08)*
		Blood pressure X stress severity	.01 (.01)†	.01 (.01)†	.01 (.01)
	Between-person variables	Age	-.16 (.05)***	-.10 (.05)*	-.13 (.05)*
		Sex	1.79 (.72)*	2.28 (.64)***	2.18 (.86)*
		Education	.46 (.67)	.24 (.69)	.56 (.75)
		Blood pressure	.05 (.04)	.06 (.06)	.02 (.03)
		Stress severity	.56 (.36)	.45 (.39)	.39 (.40)
		Blood pressure X stress severity	.05 (.04)	.09 (.08)	.02 (.03)

Table 3 (Cont.)

	Fixed Effects		Systolic blood pressure Estimate (*SE*)	Diastolic blood pressure Estimate (*SE*)	Pulse pressure Estimate (*SE*)
Letter Series test	Within-person variables	Intercept	1.74 (.83)*	2.12 (.86)*	1.33 (1.06)
		Occasion	.24 (.04)***	.23 (.04)***	.23 (.04)***
		Blood pressure	.01 (.02)	-.01 (.02)	.02 (.02)
		Stress severity	.16 (.08)*	.17 (.08)*	.17 (.08)*
		Blood pressure X stress severity	-.00 (.01)	.00 (.02)	-.01 (.02)
	Between-person variables	Age	-.01 (.05)	.02 (.05)	.02 (.04)
		Sex	1.69 (.79)*	1.45 (.73)*	2.10 (.86)*
		Education	.59 (.57)	.20 (.69)	.74 (.74)
		Blood pressure	.04 (.03)	.06 (.05)	.02 (.04)
		Stress severity	-.17 (.31)	-.12 (.37)	-.25 (.30)
		Blood pressure X stress severity	.00 (.03)	.06 (.06)	-.03 (.03)

Table 3 (Cont.)

	Fixed Effects		Systolic blood pressure Estimate (*SE*)	Diastolic blood pressure Estimate (*SE*)	Pulse pressure Estimate (*SE*)
Number Comparison test	Within-person variables	Intercept	11.40 (1.36)***	12.66 (1.60)***	1.09 (1.48)***
		Occasion	.32 (.04)***	.32 (.04)***	.32 (.04)***
		Blood pressure	.01 (.02)	.01 (.02)	.03 (.03)
		Stress severity	-.02 (.09)	-.02 (.09)	-.03 (.09)
		Blood pressure X stress severity	.00 (.01)	.00 (.01)	.01 (.01)
	Between-person variables	Age	-.22 (.09)*	-.16 (.07)*	-.17 (.08)*
		Sex	2.45 (1.45)†	1.47 (1.60)	3.69 (1.47)*
		Education	1.57 (1.17)	.62 (1.10)	2.02 (1.28)
		Blood pressure	.10 (.06)	.09 (.09)	.09 (.05)†
		Stress severity	-.56 (.62)	-.35 (.66)	-.70 (.58)
		Blood pressure X stress severity	-.03 (.05)	.10 (.10)	-.10 (.05)†

Table 3 (Cont.)

	Fixed Effects		Systolic blood pressure Estimate (*SE*)	Diastolic blood pressure Estimate (*SE*)	Pulse pressure Estimate (*SE*)
Delayed recall task	Within-person variables	Intercept	4.96 (1.34)***	3.97 (.77)***	4.96 (.87)***
		Occasion	.06 (.53)	.06 (.05)	.06 (.04)
		Blood pressure	.02 (.33)	.02 (.02)	.01 (.03)
		Stress severity	.01 (.27)	.01 (.10)	.01 (.10)
		Blood pressure X stress severity	-.00 (.04)	.00 (.01)	.01 (.02)
	Between-person variables	Age	-.17 (.13)	-.11 (.06)†	-.16 (.05)**
		Sex	1.51 (.68)*	2.63 (.62)***	1.53 (.75)*
		Education	1.13 (1.38)	1.15 (.84)	1.09 (.91)
		Blood pressure	.03 (.16)	.05 (.06)	-.01 (.03)
		Stress severity	.81 (.46)†	.56 (.47)	.63 (.41)
		Blood pressure X stress severity	.09 (.05)†	.09 (.09)	.06 (.03)†

Table 3 (Cont.)

	Fixed Effects		Systolic blood pressure Estimate (*SE*)	Diastolic blood pressure Estimate (*SE*)	Pulse pressure Estimate (*SE*)
Symbol Digit Modalities Test	Within-person variables	Intercept	18.20 (2.39)***	19.17 (2.43)***	16.94 (2.08)***
		Occasion	.47 (.10)***	.48 (.10)***	.46 (.09)***
		Blood pressure	.01 (.03)	-.01 (.04)	.003 (.04)
		Stress severity	.22 (.19)	.18 (.20)	.20 (.18)
		Blood pressure X stress severity	.00 (.03)	.05 (.03)	-.04 (.05)
	Between-person variables	Age	-.50 (.13)***	-.48 (.13)***	-.49 (.12)***
		Sex	2.09 (2.20)	1.12 (2.21)	3.32 (1.81)†
		Education	1.67 (1.67)	1.27 (1.66)	2.30 (1.83)
		Blood pressure	.04 (.08)	-.06 (.12)	.10 (.09)
		Stress severity	.35 (.87)	.52 (.98)	.30 (.79)
		Blood pressure X stress severity	-.05 (.08)	.02 (.18)	-.08 (.07)

Note. WP = within-person. BP = between-person. †$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

Discussion

Broadly, the aims of the current study were to explore the short-term dynamics of blood pressure and cognitive functioning, their relationship at the within-person level and the involvement of daily psychological stress in this context. In so doing, it provides a replication and expansion of past work. Current understanding of whether short-term fluctuations in blood pressure have immediate cognitive consequences is limited to Gamaldo, Weatherbee and Allaire (2008), who found no evidence of a direct relationship but reported a small cross-level interaction between person-mean and occasion systolic pressure on the Letter Series test of inductive reasoning. However, what implications this finding may have for clinical practice and overall understanding of the cognitive impacts of hypertension remains difficult to elucidate without further exploration of the topic by subsequent research. The present project sheds some light on the interpretation of Gamaldo's findings and offers new avenues for future inquiry.

Daily Dynamics of Blood Pressure and Cognition

In the first phase of this study, we applied multilevel models to intensive measurement data and found a direct correlation between diastolic pressure and episodic memory as assessed by the delayed recall task, such that on days with elevated blood pressure memory performance was slightly improved. This is in line with our hypothesis and the longitudinal literature, which describes a point at which hypertension switches to become a cognitively protective factor, often cited as approximately ages 75 to 80 (Kennelly & Collins, 2012; Qiu *et al.*, 2005). As our sample was 70 years old on average, the age-related structural changes to the vascular system that may favour elevated blood pressure

to maintain cerebral perfusion, such as atherosclerosis and arterial stiffness (Kennelly *et al.*, 2009; Obisesan, 2009), may have been emerging or in effect for some individuals. From this, it follows that occasions of high blood pressure may overcome the damage to vascular structures caused by age to deliver a larger volume of blood and oxygen to cortical tissue. Obisesan and colleagues (2008) made a similar speculation when they found, in a cross-sectional study with individuals aged 60 to 69 years, that higher pulse pressure related to better MMSE scores. However, in that case, the authors suspected that this adaptive mechanism was selected for by pre-hypertensive processes. Though this follows the same logic as our hypothesis, it is less likely to be the case in the present study as the majority of blood pressure readings were well within normal ranges.

Interestingly, neither systolic nor pulse pressure were associated with cognition in any Specific Aim 1 models at the within-person level. An explanation for this remains unclear as comparison of the predictive values of each metric is largely absent from the literature. Of the studies which do not use a dichotomous indicator of hypertension, the majority appear to consider only systolic pressure, which may be an artifact of the focus by healthcare professionals on systolic pressure as the strongest indicator of health status and risk for future cardiovascular events. Studies which have compared findings across metrics, including Obisesan *et al.* (2008), have also reported mixed results. Waldstein *et al.* (2005) found that systolic and diastolic pressure were differentially associated with cognitive domains and hypothesized that the specific genetic, hormonal and hemodynamic factors underlying an individual's development of hypertension may result in unique interactions between blood pressure and cognition. Another explanation can be found in a cross-sectional study by Tsivgoulis *et al.* (2009) with over 19,000 middle-aged

individuals, in which logistic regression models conditional on demographic, environmental, cardiovascular, depressive and antihypertensive medication use factors revealed an association between cognitive impairment (assessed by a screening tool) and diastolic pressure only. Specifically, odds ratios estimated that the odds of cognitive impairment increased by 7% on average for every 10 mmHg increase in diastolic pressure but were not related to increases in systolic and pulse pressure. In discussion of their results, the authors refer to findings that diastolic pressure disproportionately influences blood vessel structure to exacerbate damage caused by age-related processes and independently predicts white matter hyperintensities and cortical atrophy. Though several of these citations were conducted as animal experiments or correlational autopsy studies and published over 15 years ago, more recent work provides additional support (e.g., den Heijer *et al.,* 2005). In addition, the fact that our pattern of findings, across dozens of models, so clearly demarcated between diastolic pressure and other metrics suggests a biological difference in their impacts on the vascular system and cognition in general, which requires further investigation.

A second significant estimate from the final model under Specific Aim 1 demonstrated that for individuals whose diastolic pressure tended to be high on average, days with pressure above one's person-mean resulted in impaired processing speed (indicated by the cross-level interaction term). This is contrary to our hypothesis, which expects that the sign of this association would instead be positive. It provides mixed support for Gamaldo *et al.* (2008), who found the same interaction for systolic pressure and the Letter Series test of inductive reasoning, though we urge caution in interpretation of these interaction terms. In both cases, the magnitude of the estimate is small ($b < .01$) and the

power to detect effects at the between-person level is limited due to the sample sizes. In addition, this model resulted in increased between-person residual variance relative to the demographic-only model. Though the threshold for statistical significance was met, examination of the confidence intervals of significant effects is the preferred method to inform clinical decisions as they provide an indication of whether the association is likely to be found in the wider population (Davies & Crombie, 2009; Fethney, 2010). In both the present and the Gamaldo study, the upper and lower limits of the 95% confidence intervals are negative values, providing some assurance that the interaction estimates were not artifacts of sample composition. However, the relevance of this interaction for clinical significance remains unclear as of yet.

Though a wide consensus has yet to be reached on the cognitive domains most vulnerable to the impacts of blood pressure, the recent meta-analysis performed by Gifford *et al.* (2013) found episodic memory to be consistently affected across both cross-sectional and longitudinal prospective studies. The fact that our immediate recall measure of episodic memory did not exhibit the same sensitivity to blood pressure changes as the delayed recall task in Specific Aim 1 is indicative of the influence that choice of neuropsychological test may have on model estimates. For example, some have suggested that immediate recall is in part a measure of short-term memory (Hassing *et al*., 2004; Johnson, Storandt, & Balota, 2003).

In addition to episodic memory, we found that processing speed, as assessed by the Number Comparison test, was sensitive to fluctuations in diastolic pressure. Whether processing speed is generally affected by blood pressure is a contentious issue (Gifford *et al.*, 2013). One study with individuals aged 48 to 67 years at baseline found greater

decline for uncontrolled hypertensives on a measure of processing speed over 6 years relative to those with stable or normal blood pressure and no differences between the groups on other tests of cognitive functioning (Alves de Moraes, Szklo, Knopman, & Sato, 2002). However, Bucur and Madden (2010) suggested that measures of executive function and speed are often confounded and that change in the latter may be more likely driven by the effects of blood pressure on the former. While this important discussion continues, it should be noted that the present study only found processing speed to be impaired in the context of a cross-level interaction which is subject to concerns of power and clinical significance.

Stress in the Context of Blood Pressure and Cognition

The second phase of this study involved exploratory follow-up on a suggestion made by Gamaldo *et al.* (2008) that psychological stress may be involved in the dynamic coupling of blood pressure and cognition. This applies to both the within-person level, as days with high stress are likely to be days with elevated blood pressure, and the between-person, as individuals who report a greater severity of stressful events may be more likely to have high blood pressure. We included main effect and interaction terms with blood pressure at both levels in multilevel models to better understand the interplay among these two key factors. In accordance with daily diary studies on stress and cognition which have shown temporary impairments in working memory and self-reported memory failures on stress days (Neupert, Almeida, Mroczek, & Sprio III, 2006; Sliwinski, Smyth, Hofer, & Stawski, 2006), we found impaired immediate recall performance on days with elevated stressor severity. This improved on days with both elevated stressor severity and elevated blood pressure (regardless of metric) as indicated by the within-person

interaction term. Together, these findings fit with our prediction that psychological stress and blood pressure exert opposing forces on cognitive functioning and indicates that blood pressure may have a greater impact. However, the fact that no main effect terms for blood pressure were significantly associated with cognition speaks to the need for future work to explore the robustness of the present findings and clarify the interplay between daily stress and blood pressure. The pattern observed for the immediate recall task did not hold for the Letter Series test, on which scores tended to be better during days with high stress severity, or other cognitive measures. This may again indicate the influence of choice of neuropsychological measure, or perhaps fundamental differences in episodic memory and inductive reasoning processes which favour different blood pressure levels.

Our final major question was whether a causal and temporal sequence from stress to cognition through blood pressure exists at the within-person level, probed with a series of within-person mediation models. Given that the experience of stress leads to sympathetic arousal and increased blood pressure, and given prior research which has examined each of the three pathways involved in our mediation model, this approach appeared to be a natural extension of the present analyses. Model results found no evidence that daily blood pressure mediates, or has an indirect effect on, the stress-cognition pathway. This suggests that a different, unmeasured process may underlie our observation of impaired immediate recall on days with higher stress. Others have reported that cognitive interference and neuroticism are involved in the association of stress and memory failures (Neupert, Mroczek, & Spiro III, 2008; Stawski, Mogle, & Sliwinski, 2011; 2013).

A number of considerations must be taken into account when interpreting the present results. In addition to our low power to detect associations at the between-person level,

our sample was quite homogeneous. Of 27 participants five were male, four were over the age of 76 and only three reported chronically high blood pressure now treated and under control. These limitations are particularly relevant when considered together with the mechanisms proposed to underlie the cognitive impacts of long-standing hypertension. Given the damage caused by hypertension and age-related changes to the vascular system, both of which reduce the carrying capacity of blood vessels, one might expect the most vulnerable to fluctuations in blood pressure to be those with hypertension or those aged 75 or older; in particular, days with lower blood pressure than usual would seem to have the greatest impactful on an already compromised system. However, the sample did not permit investigation of these sub-groups in any detail and may have led to underestimated effects. In addition, longitudinal research has established that hypertensives whose condition is treated and controlled tend to have better health and cognitive outcomes than their untreated or uncontrolled peers. For example, Peila and colleagues (2006) reported slower decline in global cognition for older male hypertensives who had used medication for between five to 12 years, relative to untreated peers. Every year of medication use reduced the risk for dementia and Alzheimer's disease by 5% while long-term use (more than 12 years) was associated with no greater risk than that for normotensive individuals. As the present sample included only treated hypertensives, some of the subtleties of the blood pressure and cognition relationship may have eluded us. To provide some defence, we ran final models with adjusted pressure for treated individuals and did not find any substantial changes to our pattern of results. This was likely because the participants who reported diagnosed hypertension and use of medication exhibited well-controlled blood pressure which remained within

normal ranges even after adjustment following Tobin *et al.* (2005). Though several different approaches may be used to take medication use into account, adding a constant as was done in the present study is recommended by Tobin *et al.* as an option that preserves statistical power and is robust to the specific value added.

The present study has considerable strengths, including the application of an intensive measurement design and multilevel modeling of intraindividual variability, which presents several advantages over the design and analytic approaches used in the bulk of related literature. Crucially, our method allows estimates at the within-person level to be distinguished from the between-person level so that research questions can focus on intraindividual variability; that is, whether changes in blood pressure are related to changes in cognitive performance. More commonly, even studies with longitudinal data are limited to cross-sectional assessment of stable between-person differences which, as the present findings demonstrate, may reveal different patterns than the within-person level. Another strength of this study is its conceptual replication and expansion of past work on a relatively new topic, exploring suggestions put forward by Gamaldo *et al.* (2008) on the nature of psychological stress in the context of blood pressure and cognition.

In sum, we conclude that 1) older adults demonstrate improvements in episodic memory on days with upward fluctuations in diastolic pressure; 2) diastolic pressure is the most sensitive metric for detection of within-person associations with cognition; and 3) episodic memory and processing speed exhibit sensitivity to occasion blood pressure levels. To expand upon this growing body of work, we recommend that future research continue these lines of investigation with larger samples to improve power at the

between-person level, permitting a more thorough investigation of the cross-level interaction term, and more heterogeneous samples for further exploration of the hypertensive and oldest-old subgroups. Together, these next steps will permit further evaluation of the hypotheses presented here and provide a first demonstration of the robustness of the present findings.

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