

A Systematic Review and Multilevel Modelling Analysis of Intraindividual and Interindividual Associations in Levels and Variability in Blood Pressure and Cognitive Functioning

by

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MSc, University of Victoria, 2015
BA, University of Victoria, 2013

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of
DOCTOR OF PHILOSOPHY
in the Department of Psychology

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We acknowledge and respect the lək'wəŋən peoples on whose traditional territory the university stands, and the Songhees, Esquimalt and WSÁNEĆ peoples whose historical relationships with the land continue to this day.

Supervisory Committee

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Abstract

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The aim of this dissertation was to address several gaps in the existing literature focused on the association between levels and variability in blood pressure (BP) and cognitive functioning. Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Chapter 1 synthesizes and critically analyzes the outcomes of research reporting the association between BP variability (BPV) and cognition. Fifty-five studies met eligibility criteria, including reports measuring short-term, mid-term, and long-term BPV. Despite substantial between-study heterogeneity in study characteristics, the majority of studies reported that higher systolic BPV is associated with adverse cognitive outcomes. Further, Chapter 1 identified several gaps in the existing literature. For instance, no research has investigated the association between BPV and short-term fluctuations in cognitive functioning, or the association between mid-term BPV and concurrent cognitive functioning.

Building on Chapter 1, Chapter 2 used an intensive measurement design to investigate the extent to which mid-term variability in BP, recorded using home-based BP monitoring, is associated with levels and variability in cognitive functioning in a sample of community-living older adults ($N=64$; $M_{\text{age}}=70.58$, $SD=3.5$; 77% female) assessed twice daily over a two-week period. Partial correlation coefficients estimated the association between BPV and variability in several ambulatory cognitive assessments, accounting for the learning effect during the study

protocol, while multi-level models (MLMs) estimated the association between BPV and concurrent cognitive functioning. In addition, MLMs examined the extent to which BP and cognitive functioning fluctuate within and between days at the intraindividual and interindividual levels. Findings suggest that more BPV may be associated with slower or more variable reaction time, while higher BP may be associated with worse performance on accuracy tasks.

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Acknowledgements

I feel extremely fortunate to have made it to the end of this graduate school journey and for all of the opportunities that have been afforded to me along the way. My deepest appreciation goes to my supervisor, Dr. Andrea Piccinin, for her exceptional mentorship and support throughout my graduate training. The steady encouragement to pursue my research interests, as well as her incomparably thorough and insightful feedback, have been instrumental in my development as a researcher and critical thinker. I am also thankful for my committee members, Dr. Graciela Muniz-Terrera for her wonderful guidance and generosity in supporting me as an emerging researcher, and Dr. Sam Liu for providing valuable feedback throughout the dissertation process. I also wish to express sincere gratitude to Dr. Scott Hofer for his enthusiasm, generosity, and support of DASH data, Jamie Knight and Kaylie Flett for their assistance with the systematic review, and my iLifespan lab mates for their contributions to data collection, especially Rebecca Vendittelli. I further thank Jamie Knight for her constant reinforcement and for reading an earlier, uglier version of this dissertation, Dr. Jonathan Rush and Nathan Lewis for their statistical advice, and all three of them for their invaluable friendship. I would also like to acknowledge the Alzheimer Society of B.C. for affording experiences that instigated my passion for pursuing research in the field, as well as funding from the Social Sciences and Humanities Research Council, Alzheimer Society of Canada Research Program, Integrative Analysis of Longitudinal Studies of Aging, and University of Victoria. Finally, words cannot express my gratitude for the steadfast love and support from my husband, Kris Ayres, and all of my friends and family, especially Garth Yoneda, Joanna Diemert, Satomi Yoneda, Ali Mitchell, Zoe Greig, Kayla Henry, Paul Hanson, Kyle Hitchcox, and Erin Chesal. With all my heart, I thank them for their emotional support and infinite confidence in me. A special thanks to my son, Fox, for being a constant source of inspiration and motivation.

Chapter 1

Systematic Review Examining the Association between Diurnal Blood Pressure Variability and Cognitive Functioning

Abstract

Objective: To systematically review the existing literature examining the relationship between blood pressure variability (BPV) and cognitive functioning in older adults.

Data Sources: PsycInfo and Web of Science, including papers reported in any year, as well as forward and backward searches of reference lists of reviews and included articles.

Eligibility Criteria: Published and unpublished empirical reports were included if diurnal BPV assessed at rest and cognitive functioning, change in cognition, or cognitive status were examined (using any type of assessments). Reports were excluded if the outcome was not in humans, the report was not written in English, or empirical data were not reported. Two researchers (TY and JK) independently screened titles and abstracts for reports meeting inclusion criteria.

Method: Two reviewers independently coded all reports meeting eligibility criteria using a standardized coding guide, including sample characteristics, type of BPV recording, timing between BP recordings, index of BPV, measurement of cognitive functioning, statistical approach, covariate adjustment, and main findings for systolic and diastolic BPV (sBPV and dBPV, respectively).

Results: Of the records identified ($N=1127$), 55 studies met eligibility criteria. Studies assessed short-term BPV via intra-visit consecutive in-clinic recordings ($k= 6$) and ambulatory BP monitoring (ABPM) ($k= 20$); mid-term BPV assessed in-clinic ($k= 3$) and via home-based BP monitoring (HBPM) ($k= 4$); long-term BPV via visit-to-visit recordings ($k= 24$). One additional study computed a composite index of BPV based on intra-visit, short-term, and mid-term BP recordings, and three studies assessed BPV according to two data sources. Despite substantial between-study heterogeneity in study characteristics, the majority of studies report a significant

inverse relationship between sBPV and cognition, indicating that higher sBPV is associated with adverse cognitive outcomes. Results were similar, though not as substantial, for dBPV. Of six studies using intra-visit BPV to assess participants with CVD, four showed an opposite pattern, specifically that higher BPV was associated with better cognitive functioning, suggesting that higher BPV may be adaptive when assessed via intra-visit BPV, or for individuals with CVD.

Conclusions: Overall, findings indicate that higher BPV is associated with cognitive impairment, cognitive decline, and dementia. However, multiplicity of analyses within most studies may contribute to Type 1 error.

Introduction

Shifts in societal demographics and age structure have led to increased interest in factors that threaten healthy longevity and quality of life in older adulthood, such as cognitive impairment and dementia. As such, researchers and the public are concerned with modifiable lifestyle factors that may be protective against adverse cognitive outcomes. Hypertension is widely accepted as a modifiable risk factor for cognitive impairment (*see meta-analysis*, Gifford et al., 2013) and Alzheimer's disease (*see meta-analysis*, Meng et al., 2014); however, the dynamic nature of blood pressure (BP) and measurement imprecision complicate this putative association. Resting BP is typically measured according to a standardized protocol in medical scenarios (Pickering, 2002), but natural fluctuations in BP and common phenotypes of BP present a challenge for delineating true BP. For example, BP can often be substantially higher (i.e., white coat hypertension) or lower (i.e., masked hypertension) in the presence of a medical practitioner, compared to an individual's typical average resting BP. Thus, BP ascertained by a single measurement or in a single context may not provide the most accurate representation of underlying vascular health. Indeed, evaluation of BP outside of clinical environments is highly recommended for accurate diagnosis of individuals with suspected hypertension (Stergiou et al., 2016).

Accordingly, taking multiple BP recordings in different situations (e.g., not only in clinical contexts) has become the gold-standard in clinical practice (Pickering, 2002). For example, BP measurements can be recorded in a medical office over several visits (i.e., mid-term or long-term visit-to-visit), at home over several days (i.e., home-based BP monitoring; HBPM), or every 15-60 minutes for a 24-hour period (i.e., ambulatory BP monitoring; ABPM). These repeated recordings are then used to compute an index of average BP at the within-person level

that more accurately reflects an individual's typical BP level compared to a single recording. In the last two decades, however, researchers have also used repeated recordings of BP to compute intraindividual indices of variability (e.g., coefficient of variation, standard deviation, range). Empirical evidence suggests that compared to a single measurement of BP, or the mean of multiple BP recordings, intraindividual blood pressure variability (BPV) may reflect alterations in regulatory mechanisms, and may be a more valuable metric for predicting adverse health outcomes (Gosmanova et al., 2016; Pickering, 2002). That is, although some variability in BP in response to physiological conditions reflects adaptive mechanisms, sustained fluctuations in BP may be indicative of defective regulation of the cardiovascular system (Stergiou et al., 2016). The existing literature indicates that substantial blood pressure variability (BPV) is associated with risk of cardiovascular disease (*see systematic reviews and meta-analyses*, Mena, Felix, Melgarejo, & Maestre, 2017; Stevens et al., 2016; Wang et al., 2017) and mortality (*see systematic reviews and meta-analyses*, Tai et al., 2015; Wang et al., 2017).

Variability in BP (measured at rest while adhering to standardized protocols) may also be involved in cognitive impairment and decline via neurological underpinnings. Alterations in cardiovascular regulatory mechanisms may lead to neurological injury and associated cognitive impairment; for instance, BPV is associated with an increased risk of cerebral microbleeds (Liu et al., 2012), as well as white matter lesions and atrophy (Goldstein et al., 2002; Havlik et al., 2002). The literature examining BPV and cognitive functioning or cognitive status (i.e. comparing cognitively healthy individuals to individuals with dementia), however, reveals some conflicting results between studies. For instance, several studies suggest that BPV is related to impaired cognitive functioning (e.g., Lee et al., 2014; Tsang et al., 2017) and cognitive decline (e.g., Lattanzi, Luzzi, et al., 2014; McDonald et al., 2017). Conversely, a small number of studies

examining individuals with prevalent cardiovascular disease (Gunstad et al., 2009; Keary et al., 2007; Okonkwo, Cohen, Gunstad, & Poppas, 2011) suggest that there may be a protective effect of high variability in BP for cognition for certain sub-samples of individuals. As such, the relationship may be impacted by additional factors (e.g., old age, cardiovascular disease, APOEε4 allele). Considering the disparities in the existing literature, a thorough systematic review synthesizing the association between these constructs is warranted.

When this project was initiated, in early 2018, only narrative and scoping reviews had evaluated the cumulative evidence for an association between BPV and cognitive function (Jung & Kim, 2013), Alzheimer's disease (e.g., Lattanzi et al., 2014; Nagai et al., 2017), and dementia (Nagai et al., 2015). Several research groups, including the current report, concurrently worked to address this gap in the literature. For example, the VARIABLE BRAIN consortium published a comprehensive protocol for a systematic review and meta-analysis outlining the intent to pool data from studies that include measurement of BPV, cognitive impairment, cognitive function, and incident dementia (Tully et al., 2018). The follow-up manuscript based on the pre-registration, however, is not yet published. Further, a conference proceeding meta-analyzed observational studies ($K = 13$) of older adults ($N_{\text{total}} = 12611$) with hypertension (Xin et al., 2018). Results revealed that individuals with higher systolic BPV (sBPV) were at a significantly greater odds of cognitive decline ($OR = 1.747$, $[1.25, 2.44]$, $p < 0.01$) and lower cognitive functioning compared to individuals with lower sBPV, and that the relationship was exaggerated in individuals without BP control (i.e., not taking anti-hypertensive medication) (Xin et al., 2018). However, the project focused specifically on observational studies of older adults with hypertension, and is missing detailed descriptions of the systematic search and results, as the authors were limited by space constraints characteristic of conference abstracts. These recent

initiatives, however, highlight the importance of synthesizing evidence in this area, and a systematic review identifying common approaches and findings in this area may assist in further understanding the relationship between BPV and cognition, as well as moderators that contribute to heterogeneity in the existing literature.

Study features in the field of BPV and cognition vary considerably, including between-study differences in the health of the targeted participants, number of assessments used to calculate variability, timing between BP measurements, index used to calculate variability, and assessments of cognition. This review aims to synthesize and critically analyze the outcomes of research reporting the association between blood pressure variability and cognitive functioning or cognitive status in order to identify which (if any) study characteristics may be contributing to inconsistencies in the field.

Method

Study justification, search strategy, and methodological approach for this research synthesis were documented and pre-registered through the Open Science Framework (OSF), which is publicly available for readers (<https://osf.io/vmnuq/>). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Moher et al., 2009) was used to create the protocol.

Search Strategy

A comprehensive literature search of studies examining BPV and cognition was executed on December 29, 2019 using Psyc Info and Web of Science databases. The full search strategy applied to each database was as follows: (((“blood pressure” NEAR/10 varia*) OR (BP varia*)) AND (cogniti* OR memory OR "executive function*" OR "mental processes" OR "mental ability" OR "neuropsychological testing" OR "mini mental state examination" OR dementia OR

"Alzheimer's disease" OR "mild cognitive impairment" OR MCI)). Here, ‘*“blood pressure”* NEAR/10 varia*

 identifies reports in which the term “blood pressure” appears within 10 words of “varia”, which intends to capture phrases such as “variation in blood pressure”, “blood pressure variability,” and even, “variability in heart rate and blood pressure.” As the intent is to submit this manuscript (or sections of this manuscript) for potential publication, an updated search utilizing the identical search strategy, but with date restriction of December 2019 and forward, will be conducted prior to submission for publication.

Eligibility Criteria

Empirical reports were included if BPV assessed via any data source (e.g., short-term, mid-term, or long-term) and any measure of cognitive functioning, cognitive status, or change in cognition were examined, and the association between the constructs was reported. Published and unpublished reports were eligible for inclusion. Reports were excluded if they a.) Did not measure BPV; b.) Did not measure cognitive functioning or cognitive status; c.) The participants were not at rest during BP measurements; d.) BPV was only assessed during nighttime, e.) The outcome was not in humans; f.) The report was not written in English; g.) Empirical data were not reported (e.g. a review article). Two researchers (the primary author and Jamie Knight) independently screened the titles and abstracts for reports that met inclusion criteria.

Study Selection, Literature Screening and Data Collection

Of the original 1262 citations (1127 unique), 357 records were selected for full-text screening and 285 reports did not meet eligibility criteria (disagreements = 19; inter-rater reliability = 99.98%). If the reviewers disagreed with regard to a report meeting study criteria, consensus was reached through discussion. The majority ($K=117$) were excluded because BPV was not assessed (e.g., examined cognition and BP, but not BPV) or not assessed at rest

(variability in BP assessed in response to stress tests or squat-stand maneuvers). Many reports ($K=78$) were excluded because the association between BPV and cognition was not reported (e.g., BPV and cognition were assessed, but the focus of the report was their association with another variable, rather than with each other). Several reports were excluded because cognition was not assessed ($K= 47$) or because the report was a review paper ($K= 31$; i.e., no novel empirical data were reported). Finally, a few were excluded because the report was not in English ($K= 4$) or because a full text copy of the report could not be obtained ($K= 5$). An additional inclusion criterion required that BPV was assessed, at least in part, during the daytime (i.e., not only assessed during nighttime), but this did not apply to any studies identified by the systematic review.

After further review, 17 reports of the 72 meeting eligibility were deemed to include redundant data; in these cases, either the most recently published report was included, while the older report(s) was excluded, or if the most recent report was a conference abstract, the full manuscript was included and the conference report was excluded. This process resulted in 55 reports meeting eligibility, published between 1991 and 2019. A standardized coding guide was used to extract data from the reports (two researchers coded each report). The original coding guide was relatively exploratory and iterative, due to the heterogeneity in the literature.

Analysis

A multi-level random effects approach was originally chosen to meta-analyze the results, because heterogeneity in effect sizes was expected beyond heterogeneity that could be explained by sampling error alone (Borenstein et al., 2010). Further, this approach was selected as the goal was to investigate the average true effect in the larger population of studies, and multi-level structure for meta-analysis provides the opportunity for several dependent effects to be assessed

within the same model (i.e., effects are nested within studies). However, upon systematically reviewing the literature, I decided that meta-analyzing the results would be inappropriate given the extreme heterogeneity in statistical approach between studies, detailed below. As such, the following sections review and summarize sample characteristics, timing between BP recordings, computation of BPV, assessments of cognition, statistical approach, and main findings.

Results

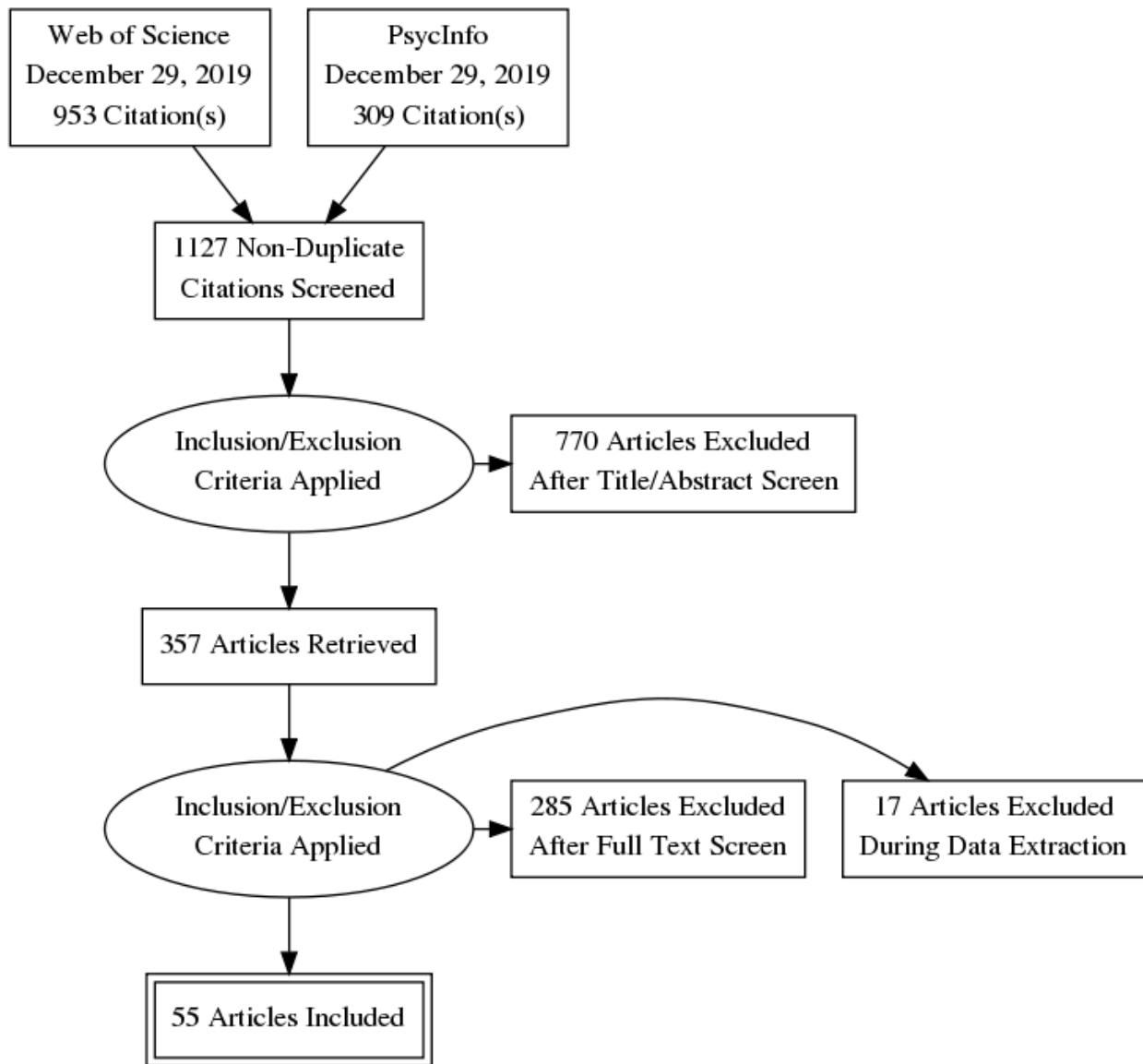
See Figure 1 for the PRISMA flow diagram visually depicting the selection process and meta-statistics. This qualitative synthesis includes the 55 studies that met the eligibility criteria. The vast majority ($k=49$) of the included studies were consistent with Stergiou and associates' (2016) expert consensus summarizing three main components of BPV classified based on temporal spacing of BP recordings, henceforth referred to as *BPV data sources*:

- Short-term BPV studies, in which BP is recorded every 15-60 minutes for a 24-hour period, using ABPM ($k=20$). While beat-to-beat BPV studies would be included here, no beat-to-beat BPV studies met eligibility as participants were not at rest during recordings (e.g., completing cognitive tasks or stress tests during recordings)
- Mid-term BPV studies, in which BP was recorded at home over several days (i.e., HBPM) ($k=4$) or in clinic ($k=3$)
- Long-term visit-to-visit (V2V) BPV studies, using repeated in-clinic BP recordings over time ($k=24$)

Although not identified by Stergiou et al.'s (2016) expert consensus as a BPV data source, several studies ($k=6$) computed BPV based on multiple BP recordings during a single occasion in clinic, referred to as *within-visit BPV* or *intra-visit BPV* (Zhou et al., 2019). These

intra-visit BPV studies are reported as a sub-section within the short-term BPV section. Further, three studies included two BPV data sources ((de Heus et al., 2019)(Daily & V2V); (Fujiwara et al., 2017) (ABPM & V2V); (Lande et al., 2016) (ABPM & V2V)). These studies are included within both relevant BPV data source subsections; as such, the subsection totals add up to more than 55. Finally, one study, reported within an independent section, combined three BPV data sources (intra-visit, ABPM, and HBPM) to compute a single composite z standardized BPV index (Zhou et al., 2019). The tables within the results are not entirely consistent across BPV data sources as there are differences and similarities in primary study characteristics within the subsections; instead, the tables reflect study attributes that vary extensively within subsections (e.g., country of origin is not included in the intra-visit table because all samples came from the USA).

Many studies focused on one main BPV index (e.g., standard deviation; SD), and executed sensitivity analyses using additional indices of BPV, though some studies reported associations between cognitive functioning and several indices of BPV. See Appendix 1 for common derivations of BPV, including coefficient of variation (CoV), average real variability (ARV), and variation independent of the mean (VIM).

Figure 1.1 PRISMA Flow diagram of meta-statistics

[<http://prisma.thetacollaborative.ca/>]

Short-Term BPV

Short-term BPV is typically assessed using continuous beat-to-beat BP measurement or ABPM (Stergiou et al., 2016). Twenty studies that examined BPV using ABPM met study eligibility. Studies assessing BPV via beat-to-beat measurement did not meet eligibility for this review, as their participants were not assessed at rest (e.g., during stress tests or cognitive tasks) (e.g., (Middleton, 1990; Sarlo et al., 2013)). As noted, six studies assessed BPV via consecutive recordings within the same in-clinic visit (i.e., intra-clinic BPV) are reviewed in a subsection following ABPM reports.

ABPM. Sample characteristics.

The participants included in these studies were recruited in Japan ($k=7$), the United States ($k=5$), Italy ($k=4$), and one study originated in each of England, Korea, Poland, and Spain. See Table 1.1a for specific country of origin information across studies. The sample size ranged extensively across studies, from 27 (Martí-Fàbregas et al., 2001) to 650 (Lande et al., 2016) ($M_{\text{sample size}} = 207.55$). Studies included middle-aged adults to very old adults (M_{age} range 59.9 years (Baranowski et al., 2018) to 93.2 years (Paganini-Hill et al., 2019)), with the exception of two studies examining children (Age range=10-18 years, (Kupferman et al., 2018); $M_{\text{age}}=15.4$ years, (Lande et al., 2016)). Percentage of female participants ranged from 38% (Lande et al., 2016) to 88% (Bellelli et al., 2001).

See Table 1.1a for participant recruitment focus across studies. Three studies focused on patients with hypertension, while one (Kanemaru et al., 2001) recruited participants from a hypertension clinic, though only 31% of the participants were taking antihypertensive treatments. A further study recruited patients receiving stable management for various chronic disease, including hypertension, hyperlipidemia, diabetes, osteoporosis (Sakakura et al., 2007). Several

studies recruited community-living older adults ($k=5$), and three recruited patients either randomly or consecutively from clinics. Five studies recruited patients from memory or neurology clinics. One study recruited older adult survivors of a tsunami (Cho et al., 2018), and one study recruited children with Chronic Kidney Disease (Lande et al., 2016).

Table 1.1a Sample Characteristics for Studies Using BPV Assessed via Ambulatory BP Monitoring (ABPM)

Study	Title	N	Country of origin	Focus of Recruitment
(Baranowski et al., 2018)	The association between cognitive decline and short-term blood pressure variability in middle-aged patients with primary hypertension - a pilot study	42	Poland	Patients with hypertension
(Bellelli et al., 2001)	Blood pressure (BP) variability and cognitive decline in hypertensive elderly	34	Italy	Consecutively from clinics
(Cho et al., 2018)	Relationship Between Blood Pressure Variability and Cognitive Function in Elderly Patients With Good Blood Pressure Control	232	Japan	Survivors of a tsunami
(Ciconetti et al., 2004)	Blood pressure variability and cognitive function in older hypertensives	40	Italy	Patients with hypertension
(Conway et al., 2015)	Relationship Between 24-Hour Ambulatory Blood Pressure and Cognitive Function in Community-Living Older Adults: The UCSD Ambulatory Blood Pressure Study	319	United States	Community-living older adults
(Fujiwara et al., 2018)	Exaggerated blood pressure variability in both office and ambulatory blood pressure monitoring are associated with cognitive dysfunction in extremely elderly patients	497	Japan	Community-living older adults
(Goldstein et al., 1998)	Relationship between 24-hour ambulatory blood pressure and cognitive function in healthy elderly people	148	United States	Community-living older adults
(Kanemaru et al., 2001)	The effects of short-term blood pressure variability and nighttime blood pressure levels on cognitive function	88	Japan	Participants from a hypertension clinic
(Kim et al., 2009)	Relationships between 24-Hour Blood Pressures, Subcortical Ischemic Lesions, and Cognitive Impairment	109	Korea	Patients from memory clinics
(Kupferman et al., 2018)	Ambulatory blood pressure monitoring and neurocognitive function in children with primary hypertension	150	United States	Patients with hypertension
(Lande et al., 2016)	Association of blood pressure variability and neurocognition in children with chronic kidney disease	650	United States	Children with Chronic Kidney Disease
(Martí-Fàbregas et al., 2001)	Blood Pressure Variability in Binswanger's Disease and Isolated Lacunar Infarction	27	Spain	Patients from memory clinics

(McDonald et al., 2017)	Blood pressure variability and cognitive decline in older people: a 5-year longitudinal study	302	England	Randomly from clinics
(Mossello et al., 2015)	Effects of Low Blood Pressure in Cognitively Impaired Elderly Patients Treated With Antihypertensive Drugs	172	Italy	Patients from memory clinics
(Paganini-Hill et al., 2019)	Blood Pressure Circadian Variation, Cognition and Brain Imaging in 90+Year-Olds	121	United States	Community-living older adults
(Sakakura et al., 2007)	Exaggerated ambulatory blood pressure variability is associated with cognitive dysfunction in the very elderly and quality of life in the younger elderly	202	Japan	Patients receiving stable management for various chronic disease, including hypertension, hyperlipidemia, diabetes, osteoporosis
(Tadic et al., 2019)	Relationships between residual blood pressure variability and cognitive function in the general population of the PAMELA study	471	Italy	Randomly from clinics
(Tohgi et al., 1991)	Twenty-four-hour variation of blood pressure in vascular dementia of the Binswanger type.	134	Japan	Patients from memory clinics
(Yamaguchi et al., 2014)	Impact of Ambulatory Blood Pressure Variability on Cerebral Small Vessel Disease Progression and Cognitive Decline in Community-Based Elderly Japanese	210	Japan	Community-living older adults
(Yamamoto et al., 2005)	The Relationship between 24-Hour Blood Pressure Readings, Subcortical Ischemic Lesions and Vascular Dementia	200	Japan	Patients from neurology clinics

Timing of BP recordings.

Considering that the majority of ABPM-BPV studies assessed BPV over 24 consecutive hours, with the exception of just two studies, there was substantial heterogeneity across the timing of BP recordings. As to the exceptions, Goldstein et al. (1998) included two 24-hour recording period separated by one week, while Lande et al. (2016) included 24-hour ABPM recordings at six months of age and then every two years. Half of the APBM studies ($k= 10$) assessed BP at consistent intervals: every 20, 30, or 60 minutes within a 24-hour period. The other half of the studies ($k= 10$) set different temporal period intervals for recordings taken during daytime (DT) and nighttime (NT). One of these studies recorded BP three times at random every hour during the day and one time at random every hour during the night (Goldstein

et al., 1998). See Table 1.1b for specific information regarding timing across studies using ABPM.

The majority of studies ($k= 11$) included all BP recordings (from DT and NT periods) in the computation of the BPV indices. The remaining studies ($k= 9$) separated DT and NT periods for analysis (see Table 1.2). Four of these (Fujiwara et al., 2018; Kupferman et al., 2018; Lande et al., 2016; Sakakura et al., 2007) determined DT vs NT recordings based on participant diary, while the remainder assigned diurnal versus nocturnal temporal periods. With the exception of three of these reports (Bellelli et al., 2001; Conway et al., 2015; Goldstein et al., 1998), all studies noted specific times that were classified as DT and NT, though there was additional between-study heterogeneity in the temporal periods, with morning specified as 6:00 – 8:00 and evening specified as 21:00 – 23:00. As to the exceptions, Bellelli et al. (2001) and Conway et al. (2015) did not specify in text exact periods that were assigned to DT and NT or awake versus asleep. Conversely, Goldstein et al. (1998) asked participants to estimate their sleep schedule and subsequently programmed automatic readings, but also had participants note their actual sleeping times in a journal. One additional study (McDonald et al., 2017) also used different temporal periods for automatic BP recordings (DT=07:00-22:00; NT=22:00-07:00) versus measurements included in computation of BPV for analysis (DT=10:00-20:00; NT=00:00-06:00).

Computation of BPV.

The majority of studies using ABPM included computation of BPV as the SD of within-person repeated BP recordings ($k= 14$) and/or the weighted SD (wSD) of the mean systolic and diastolic BP for wake and sleep periods ($k= 4$) (see Table 1.1b). Several studies computed more than one index of BPV (e.g., CoV, ARV). One study only computed BPV as the within-person SD of sBP and dBP recordings together (Bellelli et al., 2001) and one study also computed

individual residual variability, after accounting for cyclic components of circadian BP profile (Tadic et al., 2019). Finally, computation of BPV was unclear in one study (Kim et al., 2009). Three studies did not report dBPV (Cho et al., 2018; Mossello et al., 2015; Sakakura et al., 2007).

Measurement of cognitive functioning.

Cognitive functioning assessments ranged extensively in both quality and quantity (see Table 1.1b for the measures administered across studies using ABPM). Almost half of the studies ($k=7$) investigated cognition using one measure. The remaining studies administered neuropsychological batteries or several cognitive tests assessing numerous domains of cognitive functioning ($k=9$). Four studies examined cognitive status. Overall, the majority of studies examined concurrent BPV and cognitive functioning ($k=17$), while three studies examined BPV and subsequent change in cognitive functioning (see Table 1.1b), all operationalized as within-person change in MMSE score compared to baseline.

Table 1.1b Cognitive Assessments for Studies Using BPV Assessed via Ambulatory BP Monitoring (ABPM)

Study	Timing of BPV recordings	BPV indices included DT and/or NT	BPV index/indices	Cog change	Cognitive assessment
(Baranowski et al., 2018)	20 mins DT / 30 mins NT	All R's	SD; CoV	0	CDT, MMSE clock drawing test, MoCa
(Bellelli et al., 2001)	15 mins DT / 20 mins NT	All R's	SD of sBP <i>and</i> dBP	0	MMSE
(Cho et al., 2018)	every 30 mins	All R's	wSD	0	MoCa
(Cicconetti et al., 2004)	15 mins DT / 20 mins NT	All R's	SD; CoV	0	MMSE
(Conway et al., 2015)	20 mins DT / 60 mins NT	All R's	ARV	0	MoCa
(Fujiwara et al., 2018)	every 30 mins	All R's	wSD	0	Figure recall
(Goldstein et al., 1998)	3x/hr at random DT / 1x/hr at random NT	All R's	SD	0	Digit span; Auditory Consonant Trigrams; California Verbal Learning Test; Trail Making Test; WAIS-R

					Digit Symbol; Benton Visual Retention Test
(Kanemaru et al., 2001)	15 mins DT / 30 mins NT	DT SBP	SD	0	MMSE; Hasegawa DRS; and Ravens cognitive test
(Kim et al., 2009)	every 60 mins	Separated	unclear	0	Seoul Neuropsychological Screening battery
(Kupferman et al., 2018)	every 20 mins	Separated	wSD	0	Six cognitive tests, including Rey AVLT, and the vocabulary subtest from the WAIS
(Lande et al., 2016)	every 20 mins	Separated	SD	0	Subtests from the Wechsler Abbreviated Scales of Intelligence (WASI); parent-rated tests of executive functioning
(Martí-Fàbregas et al., 2001)	20 mins DT / 30 mins NT	All R's; Separated	SD	0	Dementia diagnosis via clinical and neuropsychological data
(McDonald et al., 2017)	30 mins DT / 60 mins NT	Separated	CoV	1	MMSE; memory and executive functioning sub-scores from the CAMCOG
(Mossello et al., 2015)	15 mins DT / 20 mins NT	All R's	SD	1	MMSE
(Paganini-Hill et al., 2019)	every 60 mins	Separated	SD; CoV; ARV; Delta;	0	Dementia diagnosis via clinical and neuropsychological data
(Sakakura et al., 2007)	every 30 mins	Separated	SD	0	MMSE
(Tadic et al., 2019)	every 20 mins	All R's	SD; CoV	0	MMSE
(Tohgi et al., 1991)	every 30 mins	All R's	SD; CoV; Max Var	0	Dementia diagnosis via DRS
(Yamaguchi et al., 2014)	30 mins DT / 60 mins NT	All R's	SD; wSD; CoV; ARV	1	MMSE
(Yamamoto et al., 2005)	every 30 mins	DT SBP	SD	0	Dementia diagnosis via DRS

Note. DT= daytime; NT= nighttime; All R's= all BP recordings from the 24-hour period were included in computation of BPV indices; Separated= DT and NT recordings were separated for computing BPV indices; DT sBP= solely used systolic BP recordings for computation of BPV indices; SD= Standard deviation; wSD= weighted SD; CoV= Coefficient of variation; ARV= Average real variability; Max Var= difference between the maximum and minimum 24-hour BP recordings; Cognitive change: 0=concurrent BPV and cognition; 1=BPV and change in cognition; WASI=Wechsler Abbreviated Scales of Intelligence; Rey-AVLT= Rey Auditory Verbal Learning Tests; DRS= Dementia Rating Scale; MMSE= Mini Mental State Examination; CAMCOG= Cambridge Cognition Examination

Methodological approach.

Heterogeneity was evident in the methodological approaches used to assess the relationship between short-term BPV and cognitive functioning. Two studies analyzed BPV and

cognitive functioning as continuous variables, applying linear regression (Conway et al., 2015; McDonald et al., 2017), while another (Baranowski et al., 2018) ranked participants based on BPV and cognitive profiles, and then used Spearman's rank correlation to examine differences between rankings. The remainder of studies split participants based on BPV ($k=9$), hypertension ($k=1$), cognitive functioning ($k=6$) or cognitive status ($k=2$) for between-group comparison using t-tests, analysis of (co)variance, or odds ratios. Specifically, based on BPV, participants were split at the median (Cicconetti et al., 2004; Goldstein et al., 1998; Yamaguchi et al., 2014), or into tertiles (Lande et al., 2016; McDonald et al., 2017; Mossello et al., 2015; Sakakura et al., 2007; Yamaguchi et al., 2014) or quartiles (Cho et al., 2018). Kupferman et al. (2018) split participants based on hypertension versus no hypertension. Participants were split into two groups based on cognitive impairment (Fujiwara et al., 2018; Paganini-Hill et al., 2019; Tadic et al., 2019; Yamaguchi et al., 2014) or cognitive status (Martí-Fàbregas et al., 2001; Yamamoto et al., 2005). Participants were split into tertiles based on cognitive impairment (Bellelli et al., 2001; Kanemaru et al., 2001; Tadic et al., 2019) or cognitive status (Kim et al., 2009), and into quartiles based on cognitive status (Kupferman et al., 2018; Tohgi et al., 1991). Finally, one study (Tadic et al., 2019) split participants into two groups, and then into three groups, based on cognitive impairment in order to execute two sets of main analyses. Additionally, some studies implemented more than one analytic approach (e.g., (McDonald et al., 2017; Yamaguchi et al., 2014)).

Covariates.

The number and variety of covariates included in each analysis also ranged substantially. Five studies did not adjust for covariates (Baranowski et al., 2018; Cicconetti et al., 2004; Kanemaru et al., 2001; Tadic et al., 2019; Tohgi et al., 1991). Several studies controlled for just

age (Cho et al., 2018; Fujiwara et al., 2018) or age and one additional covariate (e.g., sex: (Bellelli et al., 2001; Yamamoto et al., 2005); education: (Kim et al., 2009); baseline BP: (Martí-Fàbregas et al., 2001)). Several studies adjusted analyses for age, sex and education, as well as up to 9 additional covariates (Conway et al., 2015; Goldstein et al., 1998; Kupferman et al., 2018; Lande et al., 2016; McDonald et al., 2017; Paganini-Hill et al., 2019). Additional covariates included further demographic variables (e.g., race), medical histories of cardiovascular and cerebrovascular diseases (e.g., heart attack, high BP, stroke, diabetes), health behaviours (physical activity, smoking and drinking status), and objective assessments of physical health or status (e.g., body mass index, estimated glomerular filtration rate, nephrotic proteinuria, albumin-to-creatinine ratio, calcium channel blocker, angiotensin-converting enzyme inhibitor). Mossello et al. (2015) did not adjust for sex or education, but did adjust for age, baseline MMSE score, vascular comorbidity score, SBP tertile, and anti-hypertensive drug treatment. The studies that examined children (Kupferman et al., 2018; Lande et al., 2016) included some covariates that were quite different compared to the other studies (e.g., maternal education, low birth weight, percentage of life with chronic kidney disorder). Three studies (Conway et al., 2015; McDonald et al., 2017; Yamaguchi et al., 2014) added covariates sequentially. Only a handful of studies (Goldstein et al., 1998; Lande et al., 2016; McDonald et al., 2017; Sakakura et al., 2007; Yamaguchi et al., 2014) adjusted for within-person mean BP based on the 24-hour BP recordings or office BP (Martí-Fàbregas et al., 2001), though Mossello et al. (2015) adjusted for sBP tertile.

Findings.

Despite extensive heterogeneity in study characteristics, the majority of studies using ABPM concluded that short-term BPV was significantly and inversely associated with cognition.

Results are somewhat challenging to synthesize, as many studies did not report (separate) results based on systolic BPV and diastolic BPV. While almost all studies reported results regarding sBPV ($k=19$), one study reported results including sBP and dBP recordings within the same index, and fewer than half of the studies reported results based on dBPV ($k=9$). Nevertheless, of 19 studies that reported findings based on sBPV, 14 (73.7%) reported a significant inverse relationship between sBPV and cognition, though three of these did not remain significant after adjusting for all covariates (Conway et al., 2015; Lande et al., 2016; Martí-Fàbregas et al., 2001). Further, the study that combined systolic and diastolic BPV found that higher BPV was significantly associated with lower cognitive performance on the MMSE and fluency category assessment (Bellelli et al., 2001). Likewise, of eight studies that reported findings based on dBPV, five (62.5%) reported a significant inverse relationship between dBPV and cognition. Importantly, no study reported a significant positive association between BPV and cognition.

These findings suggest that high variability in BP is consistently associated with lower cognitive functioning, cognitive decline, and impaired cognitive status (e.g., dementia); however, further consideration of the studies that did not find a significant association between BPV and cognition is warranted. That is, results that juxtapose the typical pattern of results may provide insight regarding underlying mechanisms or study characteristics that may contribute to the association between BPV and cognition. Five studies reported no significant relationship between sBPV and cognitive functioning (Cicconetti et al., 2004; Kupferman et al., 2018; Mossello et al., 2015) or cognitive status (Paganini-Hill et al., 2019; Yamamoto et al., 2005). Two of these studies (Cicconetti et al., 2004; Mossello et al., 2015) did not separate DT and NT BP recordings for computations of BPV indices, though many studies that did find a significant inverse association also did not separate DT and NT recordings. One of these studies (Cicconetti

et al., 2004) categorized participants into higher ($n= 28$) and lower ($n= 17$) BPV groups, and then used t-tests to examine if there were significant differences between groups on MMSE scores. Although Cicconetti et al. (2004) recruited participants who were suspected of having hypertension and cognitive impairment, the mean score on the MMSE for both groups was 29.3/30, with very little variability (1.35 and 0.80, respectively), which points to a potential ceiling effect and restriction of range. That is, because all participants tended to have quite high scores on the MMSE, delineating meaningful differences is challenging. Further, with only 40 participants, Cicconetti et al.'s (2004) study was the third smallest sample size, after Bellelli et al. (2001) and Martí-Fàbregas et al. (2001). Although Mossello et al. (2015) also only assessed cognitive functioning via the MMSE, all participants were formally diagnosed with MCI or dementia; as such, MMSE mean scores and SDs ($M=22.0$, $SD=4.5$ combined across tertiles of BPV) were not impacted by a ceiling effect. Given that Mossello et al. (2015) did not find an association between BPV and cognition, the association may be attenuated in individuals already suffering from cognitive impairment, as neurodegeneration and cognitive impairment characteristic of progression to dementia likely overshadows the association between BPV and cognition. Alternatively, Mossello et al.'s results may have been impacted by combining diurnal and nocturnal BP recordings.

In their examination of individuals who were 90+ years old, Paganini-Hill et al. (2019) also found that higher sBPV or dBPV was not associated with cognitive impairment, which may suggest that increased BPV is not related to cognitive functioning as substantially in very old adults. Yet, Paganini-Hill et al. (2019) did investigate several features of BP, and based on their findings (e.g., abnormal circadian BP patterns; nocturnal dipping status), concluded that dysregulation of BP, which is related to BPV, is likely associated with cognitive impairment.

Likewise, Yamamoto et al. (2005), which also did not report a significant association between BPV and cognition, focused on the relationships between various BP measurements (e.g., nocturnal BP dip), lacunar infarcts, and white matter lesions. As such, the only effect size reported between BPV and cognition was a Chi square test comparison of sBPV (split into two categories, < 15 mm Hg or > 15 mm Hg) and individuals with or without cognitive impairment and/or vascular dementia.

Furthermore, in their examination of children, Kupferman et al. (2018) did not find a significant association between sBPV or dBPV and cognitive functioning scores. These results are somewhat consistent with the second study examining children of a similar age (Lande et al., 2016), which found that the association between BPV and cognition did not remain significant after adjusting for (a similar set of) covariates. Although firm conclusions cannot be drawn based on two studies, these findings point to the possibility that the association between BPV and cognition may not be a life-long process. As dysregulation in cardiovascular regulatory mechanisms are hypothesized to lead to neurological injury and associated cognitive impairment, it is likely that the neurological wear-and-tear process develops over time.

Finally, Yamaguchi et al. (2014) reported that sBPV, but not dBPV, was significantly higher in individuals with cognitive decline. Although a relatively high percentage of the studies that reported the association between dBPV and cognition found a significant, inverse association, the association is potentially less consistent, as 11 studies did not report findings solely based on dBPV. While it is possible that studies did not analyze dBPV, it is also possible that this literature suffers from publication bias. That is, researchers may be more likely to report significant dBPV results.

Together, the literature examining the association between cognition and BPV assessed via ABPM primarily reports a consistent pattern indicating that higher BPV is associated with adverse cognitive outcomes (i.e., cognitive impairment, cognitive decline, and impaired cognitive status). However, the association may be less robust in very old adults, and when DT and NT BP recordings are not analyzed separately. Further, findings suggest that the association between BPV and cognition is not apparent in children. Finally, despite the consistency in regards to main findings across studies, several studies also reported some results that were non-significant. In general, the results are so different from one another that reporting effect sizes may not be particularly enlightening.

Within-visit BPV.

Sample Characteristics. Six reports, all American, examined cognition and BPV assessed via several BP recordings from the same clinic visit, referred to as within-visit or intra-visit BPV. The sample size ranged from 88 (Cohen et al., 2009) to 2573 (Gutierrez et al., 2015), with a mean sample size of 668.17 (see Table 1.2). Five of the studies were relatively homogenous in terms of mean age ($M_{age}=69.2$ -70.5 years), while Dore et al. (2018) stratified participants based on age, such that individuals over 60 and under 60 were analyzed separately. Percentage of female participants ranged approximately from 40% (Gunstad et al., 2009; Keary et al., 2007; Okonkwo et al., 2011) to 58% (Gutierrez et al., 2015; Dore et al., 2018). Two studies (Gutierrez et al., 2015; Dore et al., 2018) applied secondary data analysis to data drawn from pre-existing datasets. Dore et al. (2018) present data from The Maine-Syracuse Longitudinal Study (MSLS), which excluded participants who were institutionalized, diagnosed with a psychiatric disorder, or treated for diagnosed alcoholism. Gutierrez et al. (2015) present data from the nationally representative National Health and Nutrition Examination Survey

(NHANES). The remaining four studies recruited community-dwelling individuals with cardiovascular disease (CVD) (Gunstad et al., 2009; Keary et al., 2007; Okonkwo et al., 2011; Cohen et al., 2009).

Table 1.2 Sample Characteristics for Studies Using Short-Term BPV Assessed via Within-Visit BPV

Study	Title	N	M _{age} (SD)	Statistical Approach
(Cohen et al., 2009)	Vascular and cognitive functions associated with cardiovascular disease in the elderly	88	70.0 (7.7)	Pearson correlations; Hierarchical multiple regression
(Dore et al., 2018)	Age modifies the relation between intraindividual measurement-to-measurement variation in blood pressure and cognitive function: the Maine-Syracuse Study	> 60 =549; < 60 =431	> 60 =71.3 (7.6); < 60 =50.1 (6.6)	Hierarchical multiple regression
(Gunstad et al., 2009)	Blood Pressure And Cognitive Function In Older Adults With Cardiovascular Disease	99	69.2 (7.5)	Partial correlations
(Gutierrez et al., 2015)	Indirect Measures of Arterial Stiffness and Cognitive Performance in Individuals Without Traditional Vascular Risk Factors or Disease	2573	70.5 (1.4)	Linear regression; Logistic regression
(Keary et al., 2007)	Blood pressure variability and dementia rating scale performance in older adults with cardiovascular disease	97	69.8 (7.5)	Pearson correlations; Hierarchical multiple regression
(Okonkwo et al., 2011)	Cardiac Output, Blood Pressure Variability, and Cognitive Decline in Geriatric Cardiac Patients	172	69.2 (7.6)	

Note. M_{age} = Mean age; BPV = blood pressure variability; s = systolic

Timing of BP recordings.

Dore et al. (2018) computed BPV based on 15 BP recordings at 5-minute intervals, while Gutierrez et al. (2015) computed BPV based on three BP recordings at 30 second intervals. The remaining four studies computed BPV based on 12 BP recordings at 10-minute intervals (Gunstad et al., 2009; Keary et al., 2007; Okonkwo et al., 2011; Cohen et al., 2009).

Computation of BPV.

All studies assessed both sBPV and dBPV. Okonkwo et al. (2011) computed BPV as variability in trajectories assessed via within-visit latent growth models. The remaining studies

computed BPV as the SD of the occasion of BP recordings, though additional indices of BPV were also computed, including ARV (Gunstad et al., 2009), CoV (Cohen et al., 2009), and a BP variability function of sBPV and average diastolic pressure (Keary et al., 2007).

Measurement of cognitive functioning.

The majority of studies administered multiple tests to assess several domains of cognitive functioning, including language, working memory, organization, attention, episodic memory and visual-spatial functioning (Dore et al., 2018; Gunstad et al., 2009; Keary et al., 2007; Okonkwo et al., 2011; Cohen et al., 2009). One study (Gutierrez et al., 2015) assessed cognition solely using the digit symbol substitution test.

In terms of timing between BPV and cognitive functioning assessments, the majority of studies (Cohen et al., 2009; Dore et al., 2018; Gutierrez et al., 2015; Gunstad et al., 2009; Keary et al., 2007) assessed concurrent BPV and cognition. One study (Okonkwo et al., 2011) assessed the relationship between BPV at baseline and within-person decline over three years in a global composite of sample-specific z scores based on several indices of cognitive functioning.

Methodological approach.

There was limited overlap in methodological approaches between studies, though the majority of studies considered BPV and cognitive functioning as continuous variables within analyses (Cohen et al., 2009; Dore et al., 2018; Gunstad et al., 2009; Keary et al., 2007; Okonkwo et al., 2011). Conversely, Gutierrez et al. (2015) categorized individuals into low versus high BPV (operationalized as being in the highest BPV quartile), and into no cognitive impairment versus cognitive impairment (operationalized as being in the lowest cognitive performance quintile). Three studies implemented two different types of analyses (e.g., linear and logistic regression, Gutierrez et al., 2015; Pearson correlations and hierarchical regression,

Keary et al., 2007; Cohen et al., 2009), while the remainder of studies executed one main set of analyses; however, most fit several models to examine the association between different indices of BPV and cognitive functioning. For example, Dore et al. (2018) fit 28 linear regression models examining the relationships between sBPV and dBPV and five domains of cognitive functioning, plus a global composite and the MMSE, stratified by participants under and over 60 years. See Table 1.3 for information regarding statistical approach.

Covariates.

Of the basic demographic variables, four studies (Cohen et al., 2009; Dore et al., 2018; Gutierrez et al., 2015; Keary et al., 2007) adjusted for age, sex and education, while Gunstad et al. (2009) adjusted for age and education (but not sex), and Okonkwo et al. (2011) adjusted only for age (not sex nor education). All studies, except Gunstad et al. (2009), adjusted for additional covariates, including further demographic variables (e.g., ethnicity/race, living in poverty), medical history (e.g., diabetes, hypercholesterolemia, atrial fibrillation, heart surgery, CVD risk score), medications, health behaviours/status (sedentary lifestyle, BMI, obesity, depressive symptoms, smoking/alcohol habits), and objective assessments of physical health (e.g., brachial artery response, intima media thickness, cardiac output). One study adjusted for mean BP (Dore et al., 2018), two studies adjusted for hypertension (Gutierrez et al., 2015; Keary et al., 2007), and Cohen et al. (2009) adjusted for CVD risk score, operationalized as a count variable of risk factors for CVD, including hypertension.

Findings.

Two studies (Dore et al., 2018; Gutierrez et al., 2015) reported an inverse relationship between both sBPV and dBPV and cognitive functioning, consistent with the pattern of results reported by studies that recorded BP using ABPM. The pattern of main findings reported by the majority of reports assessing intra-visit BPV, however, was largely in the opposite direction.

Specifically, three studies reported a significant positive relationship between sBPV and cognition, indicating that high variability in systolic BP is associated with better cognitive functioning (Cohen et al., 2009; Gunstad et al., 2009; Okonkwo et al., 2011). Keary et al. (2007) combined sBP and dBP recordings to compute a BPV function (SD of sBP divided by the average dBP), and their results also revealed a significant positive relationship between BPV and cognitive functioning. Gunstad et al. (2009) and Cohen et al. (2009) reported no significant association between dBPV and cognitive functioning, while Okonkwo et al. (2011) reported that higher dBPV was associated with a faster rate of cognitive decline (consistent with the majority of main findings from studies using ABPM to assess BPV). Together, these results indicate that, as assessed via intra-visit BPV, higher sBPV may be protective against cognitive impairment and cognitive decline for individuals with CVD. Indeed, given that all four of these studies focused on participants with CVD, variability in BP in these studies may reflect participants who do not always have high BP (i.e., downward fluctuations in BP during the two-hours of BP recordings, relative to their own high levels of BP). As such, participants with CVD and high BPV may be relatively healthier than individuals with CVD and consistently high BP. However, these four studies overlap in several key characteristics, which may point to dependency between them (further explored in the discussion).

Mid-term BPV

Mid-term BPV can be assessed over consecutive days either in clinic or at home using HBPM. Seven studies examined midterm BPV and cognitive functioning, with reports computing BPV based on day-to-day home-based BP measurement (HBPM) ($k=4$) and short-term in-clinic measurements ($k=3$).

HBPM. Sample characteristics.

The four studies using HBPM did not overlap in terms of sample characteristics (see Table 1.3). De Heus et al. (2019) derived data from a randomized controlled trial located in several countries across Europe that investigated the effect of nilvadipine (anti-amyloid treatment), compared with a placebo, on patients with mild-to-moderate Alzheimer's disease. Day-to-day BPV was assessed in a sub-sample of participants from the Netherlands (de Heus et al., 2019). Liu et al. (2016) recruited very old community-dwelling adults from geriatric practices in China. Matsumoto et al. (2014) included a sub-study of participants from the Ohasama study, which is a community-based longitudinal study initiated in Japan in 1987. Oishi et al. (2017) selected older adults who originally participated in the Hisayama study (1961), a population-based prospective study of cerebro-cardiovascular diseases in Hisayama, Japan.

Timing of BP recordings.

The four studies using HBPM asked participants to measure their own BP three consecutive times each morning for 28 days (Oishi et al., 2017), twice each morning and twice each evening for seven consecutive days (de Heus et al., 2019; Liu et al., 2016), or once each morning for 28 days (Matsumoto et al., 2014). Two studies (Liu et al., 2016; Oishi et al., 2017) instructed participants to record their BP after at least five minutes of rest, while the other two (de Heus et al., 2019; Matsumoto et al., 2014) were unclear about time of rest prior to recordings.

Computation of BPV.

Two of the studies (de Heus et al., 2019; Oishi et al., 2017) took the mean of the 2-3 BP repeated recordings at each sitting prior to computing several within-person BPV indices. Additionally, two studies (de Heus et al., 2019; Liu et al., 2016) discarded the first day of recordings prior to computing BPV indices. Matsumoto et al. (2014) calculated BPV as the SD, while Liu et al. (2016) computed BPV as the SD and CoV. De Heus et al. (2019) computed BPV

as variation independent of the mean (VIM), but also completed secondary analyses using SD and CoV. Oshi et al. (2017) focused primarily on CoV, but also computed SD, max and min difference, ARV, and VIM.

Measurement of cognitive functioning.

All four studies using HBPM investigated the association between BPV and cognitive decline. Oshi et al. (2017) examined the risk of dementia diagnosis after median of 5.3 years. The remaining three studies measured decline in global cognitive functioning over 1 year and 1.5 years (de Heus et al., 2019), an average of 2.3 years (Liu et al., 2016) or median of 7.8 years (Matsumoto et al., 2014). In these three studies, cognitive decline was assessed using the 12-item Alzheimer’s disease Assessment Scale-cognitive subscale (ADAS-Cog; de Heus et al., 2019) or MMSE (Liu et al., 2016; Matsumoto et al., 2014).

Table 1.3 Sample Characteristics for Studies Using Mid-Term BPV Assessed via Home Based BP Monitoring (HBPM)

Study	Title	N	M _{age} (SD)	Years of follow-up	Statistical Approach
(de Heus et al., 2019)	Blood Pressure Variability and Progression of Clinical Alzheimer Disease	46	73.0 (6.2)	1.0 & 1.5	Multilevel linear regression
(Liu et al., 2016)	Excessive variability in systolic blood pressure that is self-measured at home exacerbates the progression of brain white matter lesions and cognitive impairment in the oldest old	232	84.4 (2.5)	Average of 2.3	Split participants into three groups based on tertiles of sBPV, then assessed change in cognitive functioning applying ANCOVA
(Matsumoto et al., 2014)	Day-to-Day Variability in Home Blood Pressure Is Associated With Cognitive Decline: The Ohasama Study	485	63.3 (4.7)	Average of 7.8	Split participants based on tertiles of BPV, then t tests and logistic regression
(Oishi et al., 2017)	Day-to-Day Blood Pressure Variability and Risk of Dementia in a General Japanese Elderly Population The Hisayama Study	1674	71.0 (7.0)	5.0	Split participants based on quartiles of BPV, then Cox proportional hazard models to examine the risk of dementia

Note. M_{age} = Mean age; BPV = blood pressure variability

Methodological approach and findings.

Given that only four studies assessed BPV via HBPM, and to avoid repetition, the statistical analyses, covariates, and findings for these four studies are included within this subsection (see Table 1.3). All four studies assessing mid-term BPV via HBPM reported a significant association between higher BPV and cognitive decline, consistent with the majority of reports. De Heus et al. (2019) used multilevel linear regression analyses to examine the association between BPV at baseline and change in cognitive functioning, adjusting for age, sex and intervention group. Results revealed a significant association between BPV and decline on the ADAS cognitive subscale after one year, but not after 1.5 years; importantly, this association reached statistical significance despite being based on only a small sample. Liu et al. (2016) split participants into three groups based on tertiles of sBPV, then assessed change in cognitive functioning applying ANCOVA, adjusting for age, sex, baseline body mass index, baseline official BP, baseline blood lipid and glucose, education, smoking and alcohol consumption. Unconditional and conditional models revealed that MMSE declined significantly more over an average of 2.3 years in the high sBPV group versus the middle and low sBPV groups.

Matsumoto et al. (2014) used t-tests, logistic regression adjusting for age, sex and follow-up duration, with participants split based on tertiles of BPV, and logistic regression in which BPV was entered as a continuous variable such that the OR indicates 1 SD unit increase in BPV, adjusting for covariates (e.g., history of CVD, low education, and MMSE < 27). Results revealed a significantly higher risk of cognitive decline, defined as <24 on the MMSE at follow-up, across tertiles of sBPV, after adjusting for covariates, such that higher sBPV was associated with a higher risk of decline after an average of 7.8 years. Oshi et al. (2017) used Cox proportional hazard models to examine the risk, over five years, of all-cause dementia, vascular dementia, and Alzheimer's disease across BPV levels split into quartiles based on CoV. The full conditional

model included age, sex, education, antihypertensive agents, ECG abnormalities, diabetes, cholesterol, BMI, history of CVD, smoking and alcohol habits, physical activity levels, and mean BP (based on all home recordings). Unconditional and conditional models revealed that the highest quartile had a significantly increased risk of dementia and all dementia subtypes, for both dBPV and sBPV based on CoV. Sensitivity analyses revealed consistent findings when BPV was computed based on all other computations of BPV, with the exception of BPV computed as ARV and VIM for risk of vascular dementia.

In-Clinic Mid-Term BPV. Sample characteristics.

Three studies examined mid-term BPV assessed in-hospital. All three studies (Appleton et al., 2019; Geng et al., 2017; J.-H. Lee et al., 2014) examined older adult patients who were hospitalized for stroke. Appleton et al. (2019) examined patients who were randomized to a control group or to receive a nitrate medication within 48 hours of stroke onset as part of the ENOS trial protocol in the United Kingdom. Geng et al. (2017) initiated a single-center observational study at the Hospital of Lianyungang, which recruited patients who were treated according to Chinese guidelines for the treatment of BP to within 140-159 mmHg. Lee et al. (2014) included a sub-study of patients admitted to hospital for cerebral infarction from the K-VCiHS study in the Republic of Korea. See Table 1.4 for sample characteristics.

Timing of BP recordings.

Two studies (Appleton et al., 2019; Geng et al., 2017) recorded BP by trained medical professionals for seven consecutive days during treatment, though Appleton et al. (2019) measured BP once daily and Geng et al. (2017) measured BP every four hours. Lee et al. (2014) computed BPV based on all available assessments (average number of recordings=16) taken on days 3-6 of hospitalization.

Computation of BPV.

Appleton et al. (2019) focused on BPV computed as the SD, while Geng et al. (2017) and Lee et al. (2014) computed both SD and CoV. All three reports included indices of diastolic and systolic BPV.

Measurement of cognitive functioning.

All three reports assessed the association between baseline BPV and cognition 90 days after incidence of stroke. Geng et al. (2017) also followed-up at 14 days, 6 months, and 12 months post stroke. At follow up, Appleton et al. (2019) used the telephone MMSE and a verbal fluency test, while Lee et al. (2014) used the Korean Vascular Cognitive Impairment Harmonization Standards protocol, which includes the Korean MMSE, Seoul VLT, and several tests assessing executive functioning (all z standardized for analyses). Geng et al. (2017) categorized cognitive impairment based on MoCA scores (<26).

Table 1.4 Sample Characteristics for Studies Using Mid-Term BPV Assessed via Repeated In-Clinic Visits

Study	Title	N	Mean Age (SD)	Statistical Approach
(Appleton et al., 2019)	Effect of Glyceryl Trinitrate on Hemodynamics in Acute Stroke Data From the ENOS Trial	4011	70.3 (12.2)	Split participants into quintiles according to BPV, then logistic regression
(Geng et al., 2017)	Midterm Blood Pressure Variability Is Associated with Poststroke Cognitive Impairment: A Prospective Cohort Study	708	63.1 (10.0)	Split participants into quintiles according to BPV, then linear regression
(Lee et al., 2014)	Highly Variable Blood Pressure as a Predictor of Poor Cognitive Outcome in Patients With Acute Lacunar Infarction	36	61.8 (N/A)	bivariate correlation analyses; linear regression

Note. M_{age} = Mean age; BPV = blood pressure variability;

Methodological approach and findings.

Again, given that only three studies assessed mid-term in-clinic BPV, the statistical analyses, covariates, and findings are included within this subsection (see Table 1.5). Geng et al.

(2017) split participants into quintiles according to BPV, then used logistic regression to examine the association between quintiles of BPV (defined according to CoV) and risk of cognitive decline at 90-day follow-up. Their analyses adjusted for age, gender, education, education, hypertension, SBP and DBP on hospital admission, cerebral infarct volume, location and volume measurement of infarction, and thrombolytic therapy. Geng et al. (2017) reported that, compared to the lowest quintile of sBPV, the other four quintiles were associated with a linearly increased odds of being cognitively impaired at follow-up. Using ordinal logistic regression, Appleton et al. (2019) reported that the highest quintile of BPV (defined by sBPV, dBPV, and MAP) was associated with significantly higher odds of lower cognitive scores compared to the lowest quintile of BPV, adjusting for demographics, medications, functional ability at baseline, and baseline SBP. Results based on quintiles of dBPV showed a significantly reduced risk of cognitive impairment for quintiles 4 and 5 compared to the lowest quintile. Finally, Lee et al. (2014) used Pearson correlation to assess the association between eight cognitive test z-scores and four continuous BPV indices (SD and CoV of sBP and dBP recordings). Results revealed significant inverse associations between the SD of sBP and three of eight cognitive tests, as well as CoV of sBP and four of eight cognitive tests. Analyses also revealed significant inverse associations between the SD and CoV of dBP across six of eight cognitive tests (Lee et al., 2014). The remaining associations were also consistently negative, but non-significant. These results indicate that higher sBPV, and especially higher dBPV, may be associated with lower cognitive scores. Lee et al. (2014) also executed linear regression analyses between the same eight cognitive test z-scores and four continuous BPV indices, adjusting for demographics, vascular risk factors, mean BP parameters and white matter hyperintensities. Results were similar to findings from the bivariate correlation analyses.

Overall, all seven studies assessing mid-term BPV reported a significant association between BPV and higher risk of cognitive decline or lower cognitive functioning scores, despite heterogeneity in timing between assessments, number of BP recordings, computation of BVP, cognitive tests administered, characteristics of the participants, or methodological approach.

Long-term visit-to-visit BPV

Finally, long-term variability is calculated based on repeated recordings at multiple in-clinic visits over time (i.e., visit-to-visit; V2V). This systematic review identified 24 reports examining long-term visit-to-visit BPV and cognition.

Sample characteristics.

The majority of studies (75%) conducted secondary analyses using existing datasets, four of which were clinical drug trials (de Heus et al., 2019; O’Caoimh et al., 2019; van Middelaar et al., 2018; Wijnsman et al., 2016). The remaining studies ($k=6$) were not based on existing datasets (de Oliveira et al., 2016; Kwon et al., 2016; Lattanzi et al., 2015; Lattanzi, Luzzi, et al., 2014; Lattanzi, Viticchi, et al., 2014; Tsang et al., 2017). Several studies included non-institutionalized ($k=2$), population representative ($k=3$), relatively healthy out-patient ($k=1$), and community-dwelling ($k=3$) older adults at baseline. One of these studies (Haring et al., 2019) focused specifically on postmenopausal women, and another (Tsang et al., 2017) focused on African American participants. The remaining studies recruited participants with existing medical conditions. See Table 1.5a for dataset acronyms and sample characteristics across studies.

The majority of reports examined older adults (M_{age} at baseline ranged 62.2 – 84.4 years), except for one study that assessed BPV over young to middle adulthood (baseline $M_{\text{age}}=50.4$ years; (Yano et al., 2014)) and one study included children (baseline $M_{\text{age}}=15.4$ years; (Lande et

al., 2016)). Sample sizes ranged from relatively small (e.g., $N = 47$, (Kwon et al., 2016); $N = 94$, 64.Tsang) to extremely large (e.g., $N = 24,593$, (Boehm et al., 2015); $N = 2,930,816$ (Lee et al., 2018)).

Study locations were dispersed across Asia ($k = 6$), South America ($k = 1$), Europe ($k = 9$), and North America ($k = 7$), while one study (ONTARGET and TRANSCEND) was based on participants from 40 countries (Boehm et al., 2015). Two studies included multiple sites across Europe (de Heus et al., 2019) and North America (Lande et al., 2016; Epstein et al., 2013). See Table 1.5a for country of origin across studies.

Table 1.5a Sample Characteristics for Studies Using Long-Term BPV Assessed via Visit-To-Visit Clinic Visits

Study	Title	N	Country of origin	Dataset / Focus of Recruitment
(Alperovitch et al., 2014)	Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study	6,506	France	3C DIJON MRI study; non-institutionalized older adults
(Boehm et al., 2015)	Systolic Blood Pressure Variation and Mean Heart Rate Is Associated With Cognitive Dysfunction in Patients With High Cardiovascular Risk	24,593	40 countries	ONTARGET/TRANSCEND; participants with a high risk of CVD
(Chuang et al., 2016)	Greater visit-to-visit blood pressure variability was associated with cognitive function impairment in an elderly population: Prospective study	320	Taiwan	CVDFACTS; participants with a high risk of CVD
(de Heus et al., 2019)	Blood Pressure Variability and Progression of Clinical Alzheimer Disease	460	Europe	NILVAD; participants with mild-to-moderate Alzheimer's disease
(de Oliveira et al., 2016)	Associations of Blood Pressure with Functional and Cognitive Changes in Patients with Alzheimer's Disease	191	Brazil	Consecutive outpatients with late-onset Alzheimer's disease
(Epstein et al., 2013)	Cognitive Dysfunction and Greater Visit-to-Visit Systolic Blood Pressure Variability	428	USA	ADNI; Participants with MCI and Alzheimer's disease, and health controls
(Fujiwara et al., 2018)	Exaggerated blood pressure variability in both office and ambulatory blood pressure monitoring are associated with cognitive dysfunction in extremely elderly patients	497	Japan	SEARCH study; healthy outpatient older adults
(Haring et al., 2019)	Blood pressure variability and brain morphology in elderly women without cardiovascular disease	558	USA	WHIMS-MRI; Community-dwelling postmenopausal older women

(Kwon et al., 2016)	Cognition and Visit-to-Visit Variability of Blood Pressure and Heart Rate in De Novo Patients with Parkinson's Disease	47	North America	Patients with Parkinson's disease with or without MCI, not yet been medicated
(Lande et al., 2016)	Association of blood pressure variability and neurocognition in children with chronic kidney disease	650	North America	CKiD; children with Chronic Kidney Disease
[31](Lattanzi, Luzzi, et al., 2014a)	Blood pressure variability predicts cognitive decline in Alzheimer's disease patients	240	Italy	Participants with mild-to-moderate Alzheimer's disease
[32](Lattanzi et al., 2015)	Blood Pressure Variability in Alzheimer's Disease and Frontotemporal Dementia: The Effect on the Rate of Cognitive Decline	81	Italy	Participants with Alzheimer's disease and participants with front-temporal dementia
[34](Lattanzi, Viticchi, et al., 2014b)	Visit-to-Visit Blood Pressure Variability in Alzheimer Disease	210	Italy	Participants with Alzheimer's disease and controls
(Lee et al., 2018)	Variability in metabolic parameters and risk of dementia: a nationwide population-based study	2,930,816	Korea	NHIS; Population representative; non-institutionalized older adults
(Ma et al., 2019)	Variation in blood pressure and long-term risk of dementia: A population-based cohort study	5,273	Netherlands	Rotterdam Study; Population representative; non-institutionalized older adults
(Nagai et al., 2012)	Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease	2011	Japan	Shobara City Soryon Town Cohort Study; participants with a high risk of CVD
(O'Caomh et al., 2019)	Effect of Visit-to-Visit Blood Pressure Variability on Cognitive and Functional Decline in Mild to Moderate Alzheimer's Disease	391	Canada	DARAD trial; participants with mild-to-moderate Alzheimer's disease
(Qin et al., 2016)	Visit-to-Visit Variability in Blood Pressure Is Related to Late-Life Cognitive Decline	976	China	CHNS; Population representative; non-institutionalized older adults
(Tsang et al., 2017)	Blood Pressure Variability and Cognitive Function Among Older African Americans: Introducing a New Blood Pressure Variability Measure	94	USA	Community-dwelling African American older adults
(Tully et al., 2017)	Systolic blood pressure variability is associated with depression and accelerated cognitive decline over 10 years: The 3c dijon mri study	2,870	France	3C DIJON MRI study; non-institutionalized older adults
(van Middelaar et al., 2018)	Visit-To-Visit Blood Pressure Variability and the Risk of Dementia in Older People	2,305	Netherlands	preDIVA; community-dwelling older adults
(Wijsman et al., 2016)	Blood Pressure Lowering Medication, Visit-to-Visit Blood Pressure Variability, and Cognitive Function in Old Age	5,606	Ireland, Scotland, Netherlands	PROSPER; participants with a high risk of CVD
[71](Yano et al., 2018)	Long-Term Blood Pressure Level and Variability From Midlife to Later Life and Subsequent	11,408	USA	ARIC; participants with atherosclerosis

[72](Yano et al., 2014)	Cognitive Change: The ARIC Neurocognitive Study Long-Term Blood Pressure Variability Throughout Young Adulthood and Cognitive Function in Midlife The Coronary Artery Risk Development in Young Adults (CARDIA) Study	2,326	USA	CARDIA; young adults with coronary artery risk
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Note. CVD= cardiovascular disease

Timing of BP recordings.

The number of BP recordings included in the computation of BPV was heterogeneous, though all studies included at least three BP recordings. The timing between measurement occasions varied extensively for long-term BPV, ranging from 30 days (Lattanzi, Viticchi, et al., 2014; Nagai et al., 2012) to four years (Ma et al., 2019). Studies recorded BP at intervals of approximately three months ($k=4$), four months ($k=1$), six months ($k=2$), one year ($k=1$), two years ($k=2$), and three years ($k=3$). Several studies measured patients at varying clinic visits, while some studies followed a consistent schedule between participants, but at irregular timing intervals. The follow-up period of BP recordings varied extensively, with studies recording BP for up to six months to 26 years. The length of follow-up was unclear in one retrospective study that used the three most recent clinic visits (Tsang et al., 2017); however, the study did note that the interval between consecutive visits ranged from 0 to 392 days (mean=49.9, SD=37.9), suggesting follow-up may have been up to 3 years. See Table 1.5b for approximate timing between BP recordings and years of follow-up.

Computation of BPV.

The majority of studies computed more than one index of BPV (see Table 1.5b). For instance, Tsang et al. (2017) computed BPV as SD, CoV, delta, and random slope (absolute difference between recordings, then used linear mixed effects model to model absolute changes as a function of number of days between clinic visits). One study (Haring et al., 2019) computed

the SD, as well as the SD around each participant's regression line (SD_{reg}). Some studies focused on one index of BPV, but also computed additional indices of BPV for sensitivity analyses. For instance, de Heus et al.'s (2019) main analyses used VIM, but also used SD and CoV in sensitivity analyses. Additionally, one study calculated BPV as the absolute difference in SBP divided by the mean SBP over two sequential visits ($|difference|/mean$) (Ma et al., 2019). Finally, the computation of BPV was unclear in one study (de Oliveira et al., 2016).

Measurement of cognitive functioning.

See Table 1.5b for cognitive tests administered across studies. Studies assessed cognitive functioning (as a continuous construct), cognitive dysfunction (as a categorical construct), cognitive decline (as a continuous construct), and/or diagnosis of dementia (as a categorical construct). Half of the studies used the MMSE to operationalize cognitive functioning ($k= 5$), cognitive dysfunction ($k= 3$) or cognitive decline ($k= 4$), though many also administered additional cognitive tests. Several studies administered a battery of neuropsychological tests to assess cognitive functioning ($k= 5$) or cognitive decline ($k= 1$). One study administered a simple delayed recall task of three items, and categorized participants as working memory impaired if they could only remember up to 1 of the objects after five minutes (Fujiwara et al., 2018). Finally, some studies identified individuals with a probable diagnosis of dementia at follow-up assessed according to neuropsychological batteries and/or clinical assessment ($k= 5$).

Table 1.5b Timing of BPV and Cognitive Assessments for Studies Using Long-Term BPV Assessed via Visit-To-Visit Clinic Visits

Study	Approx. time between BP measurements	Follow-up period	BPV index/indices	Cog change	Cognitive assessment
(Alperovitch et al., 2014)	2, 4, 7 and 10 years after baseline	8 years	SD, CoV	1	probable diagnosis of dementia via three step procedure (incl. battery of neuropsychological tests)
(Boehm et al., 2015)	6 months	13 years	CoV	0, 1	MMSE
(Chuang et al., 2016)	3 years	13 years	SD	0	MMSE
(de Heus et al., 2019)	6, 13, 26, 39, 52, 65 and 78 weeks after baseline	6.5 years	VIM (SD, CoV)	1	ADAS-cog
(de Oliveira et al., 2016)	4 months	1 year	Unclear	0	MMSE, CDR, CDR-SOB
(Epstein et al., 2013)	6, 12, 18, 24, and 36 months after baseline	3 years	SD, CoV, delta	0	MMSE, ADAS-cog, CDR, TMT-B, animal and vegetable fluency, DSST, REY-AVLT
(Fujiwara et al., 2018)	varying clinic visits	1 year	SD, CoV, delta	0	Figure recall
(Haring et al., 2019)	1 year	9 years	SD, SD _{reg}	1	3MSE
(Kwon et al., 2016)	varying clinic visits	2 years	SD, CoV	0	MMSE, SNSB
(Lande et al., 2016)	6 months and then annually after baseline	4 years	CoV	0, 1	WASI, Matrix reasoning, CPT-II, Brief GEC, WISC-IV, D-KEFS, 3 verbal fluency tests
[31](Lattanzi, Luzzi, et al., 2014a)	3 months	1 year	CoV	1	MMSE
[32](Lattanzi et al., 2015)	3 months	1 year	SD, CoV, delta	1	MMSE
[34](Lattanzi, Viticchi, et al., 2014b)	1 month	6 months	SD, CoV, delta	1	probable dx of dementia via neuropsychological battery
(Lee et al., 2018)	2 years	7 years	SD, CoV, VIM	1	probable diagnosis of dementia via neuropsychological battery
(Ma et al., 2019)	4 years	Up to 26 years	difference/mean	1	probable diagnosis of dementia via MMSE and GMSS (incl. CAMCOG)
(Nagai et al., 2012)	1 month	1 year	SD, CoV, delta	0	MMSE, probable diagnosis of dementia via GMSS (incl. CAMCOG)
(O’Caoimh et al., 2019)	3 months	1 year	SD, CoV, delta, random slope	1	MMSE, Quick MCI screen, CDR-SOB, SADAS-Cog

(Qin et al., 2016)	2 years	11 years	SD, CoV, VIM	1	Modified TICS (immediate and delayed recall, serial 7's, date orientation)
(Tsang et al., 2017)	varying clinic visits	unclear	SD, CoV, delta, random slope	0	MMSE, CAMCI
(Tully et al., 2017)	2, 4, 7 and 10 years after baseline	10 years	CoV	0	MMSE, TMT, IST, BVRT, FTT
(van Middelaar et al., 2018)	2 years	8 years	CoV	1	probable dementia via MMSE
(Wijisman et al., 2016)	3 months	3 years	SD	0	MMSE, Stroop, DSST, Picture word learning test
[71](Yano et al., 2018)	3 years	25 years	SD, ARV	0	Delayed word list recall, DSST, Word fluency
[72](Yano et al., 2014)	3 years	25 years	SD, CoV, delta, ARV	0	DSST, WAIS, REY-AVLT, Stroop

Note. Cognitive change: 0=concurrent BPV and cognition; 1=BPV and change in cognition; SD= Standard deviation; wSD= weighted SD; CoV= Coefficient of variation; ARV= Average real variability; MMSE= Mini Mental State Examination; REY-AVLT= Rey Auditory Verbal Learning Tests; WASI=Wechsler Abbreviated Scales of Intelligence; WISC-IV= Wechsler Intelligence Scale; WAIS= Wechsler Adult Intelligence Scale; DSST= Digit symbol substitution test; CDR= Clock Drawing Test; SADAS-cog= Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale; CDR-SOB= Clinical Dementia Rating Scale Sum of Boxes; CPT-II= Conner's continuous performance test; Brief GEC= Brief Global Executive Composite; GMSS= Geriatric Mental State Schedule; SNSB= Seoul neuropsychological battery; TICS= Telephone Interview for Cognitive Status; IST= Isaac Set Test; TMT= Trail Making Test; BVRT= Benton Visual Retention Test; FTT= Finger Tapping Test; DRS= Dementia Rating Scale; CAMCOG= Cambridge Cognition Examination.

Methodological approach.

Heterogeneity was evident in the methodological approaches used to assess the relationship between long-term BPV and cognition (see Table 1.5c). Many studies analysed the data using more than one approach ($k= 5$). Several studies used simple ($k= 4$), multiple ($k= 6$), multivariate ($k= 2$), and multilevel ($k= 1$) regression to examine the association between BPV and cognition. One of these studies (de Oliveira et al., 2016) stratified participants and subsequent analyses by APOE+/- alleles. Studies also used ANOVA ($k= 1$) or ANCOVA ($k= 2$). One study used linear mixed-effects models to evaluate the association between BPV tertile and cognitive status over time (Qin et al., 2016), and one study used linear mixed models to evaluate

the association between BPV and cognitive change (Yano et al., 2018). Several studies used logistic regression to examine the risk of cognitive dysfunction or cognitive decline during study follow-up, with BPV considered as a continuous ($k= 7$) or categorical (quartiles, $k= 1$; quintiles, $k= 1$) variable. Four studies used Cox proportional models to estimate the risk of dementia based on quartiles ($k= 2$), quintiles ($k= 1$) or deciles ($k= 1$) of BPV, or BPV considered as a continuous variable ($k= 1$).

Table 1.5c Methodological Approach for Studies Using Long-Term BPV Assessed via Visit-To-Visit Clinic Visits

Study	Analysis	Treatment of BPV
(Alperovitch et al., 2014)	Cox proportional hazard models	Continuous, deciles
(Boehm et al., 2015)	ANOVA, logistic regression	Continuous, quintiles
(Chuang et al., 2016)	Simple regression, logistic regression	Continuous, quartiles
(de Heus et al., 2019)	Multilevel regression	Continuous
(de Oliveira et al., 2016)	Simple regression	Continuous
(Epstein et al., 2013)	ANCOVA	Continuous
(Fujiwara et al., 2018)	Logistic regression	Continuous
(Haring et al., 2019)	Multivariate regression	Continuous
(Kwon et al., 2016)	ANCOVA, logistic regression	Continuous
(Lande et al., 2016)	Multiple regression	Continuous
[31](Lattanzi, Luzzi, et al., 2014a)	Simple regression, multiple regression, logistic regression	Continuous
[32](Lattanzi et al., 2015)	Logistic regression	Continuous
[34](Lattanzi, Viticchi, et al., 2014b)	Logistic regression	Continuous
(Lee et al., 2018)	Cox proportional hazard models	Quartiles
(Ma et al., 2019)	Cox proportional hazard models	Quintiles
(Nagai et al., 2012)	Multiple regression	Continuous
(O’Caoimh et al., 2019)	Simple regression, multiple regression, logistic regression	Continuous
(Qin et al., 2016)	Linear mixed-effects	Tertiles, continuous

(Tsang et al., 2017)	Multiple regression	Continuous
(Tully et al., 2017)	Multiple regression	Continuous
(van Middelaar et al., 2018)	Cox proportional hazard models	Quartiles
(Wijsman et al., 2016)	Multivariate regression	Continuous
[71](Yano et al., 2018)	Linear mixed-effects	Continuous
[72](Yano et al., 2014)	Multiple linear regression	Continuous

Note. BPV= blood pressure variability.

Covariates.

The number of covariates adjusted for in statistical analyses ranged from zero (de Oliveira et al., 2016) to 18 (Qin et al., 2016). Of the basic demographics, almost all studies adjusted for age. Exceptions to this include one study that solely executed simple regression analyses examining the relationship between BPV and cognition (de Oliveira et al., 2016) and one study that used age as the time scale for analyses (Alperovitch et al., 2014). The majority of studies also adjusted for basic demographics, such as sex/gender and education, though Haring et al. (2019) did not adjust for sex, as all participants were post-menopausal women. Very few studies adjusted for ethnicity (Boehm et al., 2015; Lande et al., 2016; Yano et al., 2014, 2018) (Boehm et al., 2015; Lande et al., 2016; Yano et al., 2014; Yano et al., 2018). One study that included multiple countries adjusted for country of origin (Wijsman et al., 2016). Six studies additionally adjusted for APOE e4 alleles (Epstein et al., 2013; Haring et al., 2019; Lattanzi, Viticchi, et al., 2014; Ma et al., 2019; Tully et al., 2017; Yano et al., 2018), and seven studies adjusted for cognition at baseline (Boehm et al., 2015; de Heus et al., 2019; Epstein et al., 2013; Kwon et al., 2016; Lattanzi et al., 2015; Lattanzi, Luzzi, et al., 2014; Lattanzi, Viticchi, et al., 2014). Eleven studies adjusted for BMI (Boehm et al., 2015; Epstein et al., 2013; Lande et al., 2016; Lattanzi, Viticchi, et al., 2014; Lee et al., 2018; Ma et al., 2019; Tsang et al., 2017; Tully

et al., 2017; van Middelaar et al., 2018; Yano et al., 2014, 2018), and three for depressive symptoms (Epstein et al., 2013; Kwon et al., 2016; Tully et al., 2017).

Several studies adjusted for BP level, in order to exemplify the association between BPV and cognition beyond BP level. For instance, several studies adjusted for corresponding mean BP (de Heus et al., 2019; Haring et al., 2019; Lande et al., 2016; Ma et al., 2019; O’Caoimh et al., 2019; Qin et al., 2016; Tully et al., 2017; Wijnsan et al., 2016; Yano et al., 2018; Alperovitch et al., 2014) or baseline BP (Lee et al., 2018; Yano et al., 2014). Two further studies adjusted for diastolic BP (Boehm et al., 2015; Chuang et al., 2016). Several studies also adjusted for history of hypertension (Lattanzi et al., 2014; Lattanzi et al., 2015; Lattanzi et al., 2014; Tully et al., 2017; Wijnsan et al., 2016) or use of anti-hypertensive medications (de Heus et al., 2019; Lattanzi et al., 2014; Lattanzi et al., 2015; Lattanzi et al., 2014; Ma et al., 2019; O’Caoimh et al., 2019; Qin et al., 2016; Wijnsan et al., 2016; Yano et al., 2018; Yano et al., 2014; Alperovitch et al., 2014).

Additional covariates included lifestyle factors (e.g., physical activity, smoking/alcohol/coffee intake), body characteristics (e.g., burden of white matter disease, hyperlipidemia, cholesterol and lipoprotein levels), and medications (e.g., memantine, cholinesterase inhibitors, cholesterol-lowering drugs, aspirin, beta blockers, diuretics, nitrates, statins, and hypoglycemics), as well as comorbidities and medical history (e.g., diabetes, stroke, vascular diseases). The study that examined children with CKD (Lande et al., 2016) included a substantially different set of covariates, including estimated glomerular filtration rate, percentage of life with CKD, nephrotic proteinuria, and low birth weight.

Findings.

Almost all studies examining long-term visit-to-visit BPV and cognition report results based on sBPV (100%) and dBPV (91.7%). The majority of studies reported that sBPV was negatively associated with cognition; specifically, increased sBPV was associated with cognitive impairment (Boehm et al., 2015; Chuang et al., 2016; Epstein et al., 2013; Fujiwara et al., 2018; Lande et al., 2016; Nagai et al., 2012; Wijsman et al., 2016; Yano et al., 2014), cognitive decline (Boehm et al., 2015; de Heus et al., 2019; Lattanzi, Viticchi, et al., 2014; Qin et al., 2016; Tully et al., 2017; van Middelaar et al., 2018), and risk of dementia (Alperovitch et al., 2014; Lee et al., 2018; Ma et al., 2019). One study also found significantly higher sBPV in individuals with AD compared to controls (Lattanzi, Luzzi, et al., 2014). In one case, the association did not remain significant after adjusting for age and sex (Chuang et al., 2016). Likewise, in other studies, the association was not significant for select cognitive tasks (e.g., Stroop task, Yano et al., 2014), and was not associated with increased risk of dementia despite sBPV being negatively associated with cognitive decline (van Middelaar et al., 2018). A few studies reported no significant association between sBPV and cognition (Kwon et al., 2016; Tsang et al., 2017) or decline in global cognition (Yano et al., 2018); however, in all three of these cases, dBPV was negatively associated with cognition.

Results were similar for dBPV, with articles reporting that increased dBPV was associated with cognitive impairment (Chuang et al., 2016; Fujiwara et al., 2018; Kwon et al., 2016; Nagai et al., 2012; Tsang et al., 2017; Yano et al., 2014), cognitive decline (de Heus et al., 2019; Lattanzi, Viticchi, et al., 2014; Qin et al., 2016; Tully et al., 2017; Yano et al., 2014), and increased risk of dementia (Alperovitch et al., 2014; Lee et al., 2018; Ma et al., 2019). One study also found significantly higher dBPV in individuals with AD compared to controls (Lattanzi, Luzzi, et al., 2014). In one of these studies (Tully et al., 2017), results revealed less consistent

findings for dBPV compared to sBPV across various cognitive outcomes. Three studies reported no significant association between dBPV and cognition (Epstein et al., 2013; Lande et al., 2016; Wijsman et al., 2016); further, some studies did not present results for dBPV (Boehm et al., 2015; van Middelaar et al., 2018).

One study (de Oliveira et al., 2016) reported findings in the opposite direction compared to the majority of other studies for a very specific subgroup. Specifically, of individuals who were APOE carriers with moderate to severe AD, those who had a greater rise in sBP and dBP (computed as MMD) during one year study follow-up, tended to have significantly better cognitive functioning (lower scores on the CRD-SOB). However, the association was non-significant for individuals with moderate to severe AD but who were *not* APOE carriers, nor for the association between dBPV/sBPV and MMSE in any participants (de Oliveira et al., 2016). These results are suggestive that the association between BPV and cognition may be impacted by APOE alleles.

Additionally, two studies reported no significant association between sBPV *or* dBPV and cognition; specifically, in post-menopausal women (Haring et al., 2019), and patients with mild to moderate AD (O’Caoimh et al., 2019). Finally, Lattanzi et al. (2015) reported results based on individuals with FTD, as well as the same AD sub-sample from another included report (Lattanzi, Viticchi, et al., 2014). Although higher BPV was associated with cognitive decline in the AD group, it was not in individuals with FTD (Lattanzi et al., 2015).

Composite BPV index

The final study (Zhou et al., 2019) computed a composite z standardized BPV index based on within-visit BPV, short-term BPV, and mid-term BPV. The study used data from The Maastricht Study, which is a population-based cohort based in the Netherlands focused on type 2

diabetes mellitus in middle to older adulthood (participants meeting study eligibility=1804). Short-term BPV was assessed as ARV of ABPM with 15-minute DT and 30 minute NT recordings, while mid-term BPV was assessed as the SD of two recordings every morning and evening over a seven-day HBPM protocol. The authors also computed “very short-term BPV”, calculated as the intra-visit BPV as the SD of three consecutive office BP measurements. Individual BPV measures were then standardized into Z scores, summed, and averaged into a composite index representing sBPV and dBPV. Cognition was assessed using a neuropsychological battery of tests that were standardized and separated into three cognitive domains: memory function, information processing speed and executive function. Analyses adjusted for five sets of covariates, including typical demographics (e.g., age, sex, education), life-style factors (e.g., smoking/alcohol status, BMI), medical history (e.g., CVD risk factors including glomerular filtration rate), medications, and depressive symptoms. Regression analyses revealed that the highest tertile of sBPV had significantly lower memory scores, but not information processing speed or executive functioning, compared to the lowest tertile. Individuals in the highest tertile of dBPV had significantly lower cognitive scores across all three cognitive domains.

Discussion

This systematic review identified 55 individual studies examining the relationship between BPV and cognition that met eligibility criteria. Studies assessed the relationship between cognition and intra-visit BPV via consecutive in-clinic recordings ($k= 6$), short-term BPV via ABPM ($k= 20$), mid-term BPV assessed in-clinic ($k= 3$) and via HBPM ($k= 4$), long-term BPV via multiple visit-to-visit recordings ($k= 24$), and a composite index of BPV based on intra-visit, short-term and mid-term BP recordings ($k= 1$). Three of these studies assessed two BPV data

sources within the same publication (de Heus et al., 2019; Fujiwara et al., 2018; Lande et al., 2016). Study attributes varied substantially, including extensive between-study heterogeneity in sample characteristics (e.g., size, percent female, age range, health of sample, and country of origin). Studies also varied in the index/indices of BPV that were computed (e.g., SD, CoV, ARV, VIM, wSD, MMD), as well as the number of BP recordings included in the computation of BPV indices (range= 2 (de Oliveira et al., 2016) to 88 (Cicconetti et al., 2004)). Studies differed in number of BPV indices computed and used in analyses (range = 1-5), and assessment of cognitive functioning (e.g., MMSE, comprehensive cognitive batteries treated as continuous or standardized scores, diagnosis of dementia). Further heterogeneity was evident in statistical approach (e.g., t-tests, chi-square tests, Pearson correlation, ANOVA, ANCOVA, logistic regression, and Cox regression, as well as simple, multiple, hierarchical, multivariate, and multilevel regression), and number and variety of covariates included in models.

Despite substantial heterogeneity across studies, the majority of studies reported an inverse relationship between BPV and cognition, indicating that higher BPV is associated with cognitive impairment, cognitive decline and adverse cognitive status categories (e.g., Alzheimer's disease, MCI). Of 55 studies that presented results regarding the association between sBPV and cognition, the majority reported a significant inverse association between BPV and cognition (75%), while the remainder reported no significant association (17.9%), or a significant positive association (7.1%). Likewise, of 42 studies that presented results regarding the association between dBPV and cognition, the majority reported a significant inverse association between BPV and cognition (69%), while the remainder reported no significant association (28.6%), and one study reported a significant positive association (2.4%). Finally, two studies combined

recordings of sBP and dBP in their computation of BPV. One of these studies also reported a significant inverse association, while the other reported a significant positive association.

These meta-statistics paint an overall picture, but considering the BPV data source provides a more nuanced delineation of this literature. For instance, when considering the studies that combined indices of sBP and dBP as well as the studies reporting on sBPV, 78.9% of short-term based on ABPM, 100% of mid-term based on visit-to-visit and HBPM, and 75% of long-term based on visit-to-visit reported an inverse association between BPV and cognition. These results suggest that higher BPV is associated with adverse cognitive outcomes, including cognitive impairment, cognitive decline, and dementia. In contrast, only 33.3% of studies using intra-visit BP recordings reported a significant inverse association between sBPV and cognition, while 66.7% reported findings in the opposite direction, namely a significant *positive* association between sBPV and cognition. As such, the studies using several recordings of BP at a single clinic visit (i.e., intra-visit short-term BPV), which revealed a significant positive association between BPV and cognition, account for the majority of divisive findings.

Indeed, only five studies across all BPV data sources reported that higher BPV is associated with *better* cognition. Of these, one used long-term visit-to-visit BPV to examine patients with moderate to severe AD ($N=191$), stratified by APOE4 allele (de Oliveira et al., 2016). The association between BPV and cognitive functioning was non-significant for participants who were not APOE carriers; however, for participants who were APOE carriers, those who had a greater rise in sBP and dBP tended to have significantly better cognitive functioning after one year of study follow-up. These results suggests that variability in BP may differentially influence cognitive functioning based on individual differences in APOE alleles. The authors suggested that increased BPV may interfere with amyloidogenesis and taupathy in individuals with

Alzheimer's disease and APOE4+ allele, which then positively impacts cognitive performance over time (de Oliveira et al., 2016). In some ways, however, comparing this study to the others is challenging, as the index of BPV was simply baseline BP minus final BP recording. Specifically, relying on only two BP recordings likely results in some measurement imprecision; indeed, although other studies included in this review computed BPV as MMD, this was the only study to solely rely on two recordings of BP for the computation of a BPV index.

As previously mentioned, the four additional studies that found a positive relationship between BPV and cognition used intra-visit, within-clinic BPV. All four studies examined community-dwelling older adults (M_{age} 69.8-70.0; M_{educ} 14.3-14.5 across studies) living in the USA. Importantly, all participants included within these four studies had an established history of CVD. All four studies also abided by an identical protocol (e.g., participants fasted and refrained from smoking and medications prior to recording, which occurred in a quiet, darkened room), and also use the same automatic BP monitor (Pressmate 880, Colin Medical Instruments Corp, San Antonio, TX). These studies reported that they included participants “enrolled in a prospective study of neurocognitive consequences of CVD” (Gunstad et al., 2009; Keary et al., 2007) or “in a prospective study examining cognitive function among older adults with CVD” (Okonkwo et al., 2011) based in the United States (unspecified). Cohen et al. (2009) also recruited participants from the US, but specified the exact location (Rhode Island Hospital Heart Failure Clinic). Across all studies, participants were ineligible for participation if they “had one or more of the following: neurological diseases, end-stage heart disease, or major psychiatric illness.” Additionally, these studies were largely by the same author group. As such, there is some evidence suggesting dependency between these four studies (i.e., overlap of participants).

A few possible alternative explanations, however, may account for the differences in results. For instance, it is possible that BPV assessed according to intra-visit protocols measures a different construct compared to other BPV data sources based on the very short-term nature of the recording, or based on the precision of the recordings. For instance, these studies ensured that participants fasted, held vasoactive medication, and did not smoke for 6 hours prior to the assessment. Further, assessment occurred in a quiet, darkened room, and the participants were seated for the entire recording. Recording BP every 10 minutes for 2 hours in a clinical setting according to a rigorous protocol provides an exceptional opportunity to ensure that BP recordings occur in a controlled environment and that BPV is assessed truly at rest.

Alternatively, as all four of these studies focused on patients with CVD, it is possible that there is a differential impact of BPV on cognition for individuals with CVD. As mentioned, high BPV in participants with CVD may reflect individuals who do not always have high BP (i.e., downward fluctuations in BP during the two-hours of BP recordings, relative to their own high levels of BP). That is, in individuals with CVD, more variability may reflect not consistently high BP, whereas in individuals without CVD, more variability may reflect upward fluctuations reflective of unhealthy mechanisms. As such, participants with CVD *and* high BPV may be relatively healthier than individuals with CVD and *consistently* high BP. While these studies reported mean BP, it is impossible to know if the individuals with high BPV had relatively lower mean BP. Further, the possibility that individuals with CVD and more BPV may have lower BP (and are relatively healthier) is challenging to evaluate based on this review, as no other studies explicitly recruited participants with CVD. Several studies recruited participants with a *high risk* of CVD (Boehm et al., 2015; Chuang et al., 2016; Nagai et al., 2012; Wijsman et al., 2016) or various circulatory conditions, including hypertension (Baranowski et al., 2018; Cicconetti et al.,

2004; Kanemaru et al., 2001; Kupferman et al., 2018; Yamaguchi et al., 2014), stroke (Appleton et al., 2019; Geng et al., 2017; Lee et al., 2018), and various chronic disease (Sakakura et al., 2007). Yet, findings from these reports revealed a pattern in opposition to the papers examining participants with CVD (and consistent with the majority of studies); specifically, 11 out of 13 studies (84.6%) reported that higher sBPV is associated with worse cognitive outcomes. Future research investigating individuals with CVD assessed using other BPV data sources would improve the literature.

Precision of BP recording across BPV data sources

This review highlights that measurement of BPV is complicated, due to a multitude of differences in operational definitions that vary based on temporal spacing, tools used, and calculation of variability. First, BPV can be classified into three main categories depending on the temporal spacing of measurements (short-term, mid-term and long-term BPV (Stergiou et al., 2016)), as well as one sub-category of short-term BPV (i.e., intra-visit BPV). Second, BPV can be assessed using a variety of techniques (e.g., ABPM, HBPM, and visit-to-visit in-clinic recordings using auscultatory or oscillometric techniques). Third, various expressions of BPV exist based on the calculation used to compute BPV indices (e.g., SD, CoV, MMD, ARV, VIM). Fourth, extensive researcher decisions are involved in using BPV in statistical models (discussed further in the next sub-section). Together, heterogeneity in operational definitions and researcher decisions represents marked differences in precision of BPV as an indicator of true variability in resting blood pressure, as well as widespread possibilities for future investigations. In particular, variation in temporal spacing may reflect distinct underlying mechanisms. For instance, variability in BP over one day (i.e., BPV assessed using ABPM) may effect neural integrity in vastly different ways than variability in BP recordings assessed over several years or even

decades (e.g., Yano et al., 2014). Importantly, studies that assess variability in BP based on recordings taken several years apart (e.g., every four years (Ma et al., 2019)) may reflect *change* in BP rather than *variability* in BP.

Further, although some studies applied more than one approach to assess BPV (de Heus et al., 2019; Fujiwara et al., 2018; Lande et al., 2016), no study assessed all three BPV data sources (e.g., short-term, mid-term, and long-term BPV) to examine the association between BPV and cognition. Future longitudinal research could use the same sample, assess short-term, mid-term and long-term BPV data sources, and compute BPV according to various indices (e.g., SD, CoV), as well as concurrent measurement of cognitive functioning and follow-up assessments to assess cognitive decline. Such an approach may provide nuanced understanding of characteristics of BPV that may be the most valuable as an indicator of cognitive impairment and decline.

Importantly, BPV data sources are characterized by strengths and limitations. For instance, strengths of ABPM include BP recordings over a concentrated period, facilitating BP assessment in daily context and thereby eliminating anxiety that a clinic setting may evoke. However, the precision of ABPM recordings, as a measure of resting BP, depends on the degree to which participants are truly sedentary during each recording and have been sedentary for at least five minutes prior to the recording. Within the ABPM literature, the majority of studies did not include information regarding participant instructions during their ambulatory monitoring (Baranowski et al., 2018; Bellelli et al., 2001; Cho et al., 2018; Conway et al., 2015; Kanemaru et al., 2001; Lande et al., 2016; Tohgi et al., 1991; Yamamoto et al., 2005). Some studies requested that participants record when they went to sleep and woke up (Goldstein et al., 1998; Sakakura et al., 2007) and/or to record the time of daily activities (Goldstein et al., 1998; Martí-Fàbregas et al., 2001). Some studies instructed participants to perform daily activities as normal

(Kim et al., 2009; Martí-Fàbregas et al., 2001; Paganini-Hill et al., 2019; Yamaguchi et al., 2014), but to avoid strenuous physical activity (Cicconetti et al., 2004), or to keep their arm still during the recording (McDonald et al., 2017; Mossello et al., 2015; Tadic et al., 2019). These factors make it challenging to delineate the extent to which ABPM truly captures at rest BPV.

Consistent with the imprecision of ABPM recordings discussed here, a study examined the reliability of ABPM by comparing hypertensive patients to themselves via two 24-hour ABPM sessions within 14 weeks (Keren et al., 2015). Analyses revealed that the within-person correlations between the sessions for mean BP and 24-hour BPV were only moderate ($r= 0.56$ and $r= 0.40$, respectively), indicating that these indices based on ABPM are only moderately reproducible (Keren et al., 2015). Indeed, BP is a dynamic physiological parameter, influenced by behaviour, emotion, and environmental factors; BP naturally rises with minimal physical movement (e.g., walking across a room or up a flight of stairs) and may remain elevated for several minutes. Since participants using ABPM were not strictly sedentary during daytime recordings, the precision of ABPM recordings in the measurement of resting BP may be questionable. This issue may be particularly problematic if some participants engaged in physical activity during ABPM as part of their daily routine. That is, individuals who engage in activity during monitoring would certainly present as more variable in BP over the course of a day, but such variability would likely be indicative of a vastly different underlying mechanism compared to individuals with similarly high levels of BPV who were primarily sedentary during recordings.

Indeed, consideration of physical activity is important when assessing variability in BP; however, very few studies addressed the impact that physical activity may have on BPV. One study (Goldstein et al., 1998) instructed participants to note BP recordings that may not be at rest; specifically, participants completed a diary, in which they noted the time, and their location,

activity and posture, at each BP recording. Additionally, participants wore an activity monitor during ABPM, which recorded activity levels at one-minute intervals and assisted in differentiating sleep-wake cycles. Activity data were then used as a between-person covariate within analyses, but because activity accounted for a very small amount of the BP effects, it was not included in final analyses. Although it was unclear how the diary data were used, recording physical activity via subjective and objective measures, in addition to ABPM, was remarkably progressive for the time (Goldstein et al., 1998). Marti-Fabregas et al. (2000) also instructed participants to note activity engagement on the day of ABPM. Likewise, this study was also published two decades ago, and how or whether these data were used in analyses or anomaly detection was also unclear. Given advances in digital, wearable technology, as well as innovations in statistical analyses (e.g., multilevel modelling), future research applying a similar technique to track physical activity during ABPM, but using trackers to determine which BP recordings occurred truly at rest, would provide a systematic, refined and powerful approach for determining the impact of activity on short-term variability in *resting* BP.

Furthermore, although alterations in diurnal and nocturnal profiles have prognostic value (Stergiou et al., 2016), several ABPM studies did not separate DT and NT BP recordings when calculating BPV (Baranowski et al., 2018; Cho et al., 2018; Cicconetti et al., 2004; Fujiwara et al., 2018; Kupferman et al., 2018; Mossello et al., 2015; Tadic et al., 2019; Tohgi et al., 1991; Yamaguchi et al., 2014). While three of these studies adjusted for circadian rhythm in their computation of BPV (Kupferman et al., 2018; Tadic et al., 2019; Yamaguchi et al., 2014), research shows that BP naturally decreases by approximately 10% during sleeping hours compared to waking hours in healthy individuals (Kario et al., 1999). Individuals who do not show typical nighttime decreases in BP or a reduction in the typical decrease, identified as “non-

dippers,” are at higher risk of cardiovascular events and cardiovascular death despite average daytime level of BP (i.e., non-dippers who are hypertensive or normotensive are both at increased risk) (Izzedine et al., 2006; Liu et al., 2003). Non-dipping is also more common in individuals who are obese (Kotsis et al., 2005), individuals who are African American (Mokwatsi et al., 2019) and individuals with subcortical vascular dementia and subcortical vascular mild cognitive impairment (Kim et al., 2009). Furthermore, reverse dipping, which is higher nighttime BP compared to daytime BP, is associated with elevated mean (Paganini-Hill et al., 2019) and periventricular (Chesebro et al., 2020) white matter hyperintensity volume, as well as lower memory scores (Chesebro et al., 2020). Likewise, in a sample of very old adults (90+ years; $N=121$), participants with non-impaired cognitive functioning had greater nocturnal dips (Paganini-Hill et al., 2019). Overall, ABPM studies suggest healthier individuals are characterized by a natural BP dip during sleep. In other words, day-to-night variability in BP is typical of healthy individuals, particularly because parameters defining NT are unlikely to align perfectly to being awake versus asleep (i.e., imprecision in estimated sleeping times is likely, even in studies that asked participants to record when they went to sleep).

As such, separating indices of daytime and nighttime BPV for statistical analyses is critical. Alternatively, researchers can also apply a computational approach to adjust for nighttime dipping; specifically, weighted SD selectively removes the impact of nocturnal BP fall by weighting the SD (wSD) of DT and NT periods. Likewise, individual residual variability in BP uses spectral analysis to identify the cyclic components of each participants’ individual circadian BP profile, and then computes the residual variability after accounting for natural cyclic components. Interestingly, only two studies used wSD (Kupferman et al., 2018; Yamaguchi et al., 2014) and only one used individual residual variability (Tadic et al., 2019). Importantly, by

analysing various indices of BPV, Tadic et al.'s (2019) methodological approach exemplifies the importance of separating DT and NT recordings. Specifically, they did not find an association between cognition and BPV computed as the SD or CoV based on combined DT and NT recordings (for either sBPV or dBPV). However, results based on their individual residual variability index, which accounts for natural nocturnal dips in BP, revealed that sBPV and dBPV were significantly higher in individuals with lower cognitive scores. These results are consistent with studies that computed indices of BPV based on both DT and NT BP recordings, as well as BPV indices based on *just* DT and *just* NT recordings. For example, results presented by Marti-Fabregas et al. (2000) reveal a significant inverse association between cognitive impairment and BPV based on DT recordings, but not when DT and NT recordings were combined in the computation of BPV.

The strengths and weaknesses of the ABPM approach tend to be a mirror image of the strengths and weakness of visit-to-visit approaches for assessing BPV. For instance, trained medical professionals or researchers can ensure visit-to-visit mid-term and long-term BPV recordings adhere to standardized and recommended procedures (e.g., seated, following at least five minutes rest). Recording BP in a clinic or research context, however, is a considerable limitation of both approaches. Measurement of BP based on office BP measurements are vulnerable to several phenotypes of BP, including white coat hypertension (WCHT), masked hypertension, and the white coat effect (Stergiou et al., 2016). WCHT, a phenomenon that is isolated to medical offices, is diagnosed when BP readings are significantly higher when obtained by medical personnel or researchers who are perceived as having high authoritative standing. WCHT is formally identified when individuals present as normotensive via ABPM or home measurement, and present as hypertensive (e.g., SBP >140) in medical scenarios.

Relatedly, the white coat effect is elevated BP in response to medical practitioners and settings, though not necessarily to hypertensive levels. The white coat effect occurs in most individuals, with a mean increase of 27 mm Hg SBP, but is more prominent in older individuals, females, and patients who have been diagnosed with hypertension (Franklin et al., 2013).

To address the prevalence of hypertension misdiagnoses due to WCHT, the 2013 guideline release from the European Society of Cardiology and European Society of Hypertension recommended increasing the use of HBPM and ABPM (Mancia et al., 2013). Conversely, masked hypertension is a phenomenon that occurs when individuals appear to be below hypertensive range (i.e., SBP <140) in office settings, but in hypertensive ranges outside of clinical settings. Masked hypertension carries similar adverse health risks as hypertension (Boggia et al., 2014; Cuspidi et al., 2019), though the risks are likely exacerbated due to the challenge of diagnosis; that is, individuals with masked hypertension are often not diagnosed and consequently not treated. All three of these BP phenotypes tend to complicate diagnosis of hypertension, and may also lead to imprecision in assessing visit-to-visit BPV.

Finally, the precision of BP recordings based on HBPM is dependent on the ability and accuracy of participants to self-measure their BP. Across all four of the studies included within this systematic review, however, participants were trained to record their BP adhering to criteria for accurate BP measurement (e.g., seated, after at least five minutes rest, prior to breakfast and taking medication). For instance, a family member or primary care nurse aided participants during recordings (de Heus et al., 2019), or physicians and/or public health nurses trained participants on how to perform HBPM (Matsumoto et al., 2014; Oishi et al., 2017). Likewise, Liu et al. (2016) had all participants, as well as at least one relative, attend classes for systematic training of self-measured HBPM. Further, all four studies used validated devices, which are

recommended by independent researchers (e.g., (Lamarre-Cliché et al., 2011)) and the 2018 Canadian Hypertension Task Force (Nerenberg et al., 2018). These studies also used devices that were memory-equipped, which minimizes bias and/or recording errors potentially introduced by participants' recording their own BP each day.

A recent review also found that HBPM is valuable beyond office BP measurement for confirming hypertension diagnosis and evaluating efficacy of BP medication, and should be used as best practice approach for managing hypertension (Liyanage-Don et al., 2019). Likewise, HBPM is recommended by several national consensus panels for routine use in clinical management of hypertension and detection of additional BP phenotypes (e.g., (Nerenberg et al., 2018; Sharman et al., 2015)). Although results were fairly consistent across studies using different approaches to repeatedly record BPV, findings based on HBPM were particularly robust. All four studies included in this review assessing mid-term BPV via HBPM found that higher BPV was significantly associated with cognitive decline on the ADAS cognitive subscale (de Heus et al., 2019) and MMSE (Liu et al., 2016; Matsumoto et al., 2014), as well as all-cause dementia, vascular dementia, and Alzheimer's disease (Oishi et al., 2017). Importantly, Oishi et al. (2017) adjusted for almost all covariates that have been considered to be critical across this literature, including age, sex, education, mean BP (based on all home recordings), antihypertensive agents, ECG abnormalities, diabetes, cholesterol, BMI, history of CVD, smoking and alcohol habits, and physical activity levels. However, including APOE allele status in future research would benefit the literature. Further, Oishi et al.'s (2017) results were consistent across all dementia subtypes, for both dBPV and sBPV based on CoV.

All four studies using HBPM to assess mid-term BPV and cognition, however, assessed the relationship between BPV and cognitive decline or likelihood of dementia over time (1 year and

1.5 years, (de Heus et al., 2019); an average of 2.3 years, (Liu et al., 2016); a median of 7.8 years, (Matsumoto et al., 2014); 5 years, (Oishi et al., 2017)). Future research examining the relationship between concurrent BPV based on HBPM and cognitive functioning may benefit the literature. Specifically, such an investigation would contribute to existing understanding of the extent to which the association between cognition and BPV based on HBPM corresponds to the association between cognition and BPV assessed according to alternative BPV data sources and timing of recordings. Further, research in this area provides information regarding BPV and cognition at the between-person level (e.g., an individual with higher BPV is more likely to have cognitive impairment or cognitive decline *compared to other individuals*). Although interindividual associations provide important information regarding risk, intraindividual relationships have the opportunity to capture dynamic individual differences in biological and psychological processes (Bauer, 2011). Day-to-day measurement of BP using short-term visit-to-visit or HBPM approaches, as well as daily occasion-specific assessments of cognitive functioning, may provide an ideal opportunity to permit thorough investigation of the association between fluctuations in both BP and cognition at the intraindividual level.

Adjustment for Key Covariates

The number and type of covariates included within analyses varied between studies, though there was substantial overlap. Although 7 out of 54 studies (13%) did not adjust for any covariates (Baranowski et al., 2018; Cicconetti et al., 2004; de Oliveira et al., 2016; Gunstad et al., 2009; Kanemaru et al., 2001; Tadic et al., 2019; Tohgi et al., 1991), the majority of studies controlled for socio-demographic variables. For instance, the majority of studies adjusted for age ($k=40$), sex/gender ($k=36$), and education ($k=32$). Interestingly, only a handful of studies adjusted for ethnicity (Boehm et al., 2015; Lande et al., 2016; Yano et al., 2014, 2018) or country

(Wijsman et al., 2016), though only Boehm et al. (2015) and Wijsman et al. (2016) included participants from more than one country. Indeed, the commonality of not adjusting for ethnicity reflects the relatively homogenous samples of the studies within this field. Studies additionally adjusted for APOE e4 alleles ($k= 6$), cognition at baseline ($k= 9$), BMI ($k= 13$), and depressive symptoms ($k= 4$).

Several studies also adjusted for vascular risk factors (e.g., Lee et al., 2018) or, more specifically, history of hypertension or CVD ($k= 12$). A handful of the studies that adjusted for hypertension or CVD also adjusted for anti-hypertensive medications ($k= 4$), while many others adjusted for anti-hypertensive medications but not hypertension/CVD explicitly ($k= 10$). One study included within this review (Wijsman et al., 2016) investigated the extent to which the association between BPV and cognitive impairment is mediated by BP lowering medication. Findings revealed differences in associations between cognitive functioning and dBPV/sBPV depending on the type of medication that participants were taking (e.g., participants taking beta-blockers declined more substantially on the Stroop and Letter-Digit coding tests compared to participants taking other types of medications). However, the association between BPV and cognitive impairment was not mediated by type of BP lowering medication (Wijsman et al., 2016). Specifically, 1 mm Hg of variation in sBP was associated with significantly poorer performance consistently across four cognitive assessments when not adjusting for medications, as well as when accounting for class of BP lowering medication (diuretics, beta-blockers, calcium antagonists, and RAS inhibitors). A further study (Tohgi et al., 1991) stratified analyses based on participants who were antihypertensive-untreated and antihypertensive-treated. Findings revealed more significant and substantial differences between groups of participants (controls, Binswanger dementia, lacunar stroke and lacunar dementia) among those who were

taking antihypertensive medications (Tohgi et al., 1991). Specifically, sBPV was higher in participants with untreated Binswanger dementia (but not lacunar stroke or lacunar dementia) compared to untreated controls, while sBPV was higher in participants with treated Binswanger dementia, lacunar stroke, and lacunar dementia compared to treated controls (Tohgi et al., 1991).

Importantly, several studies adjusted for corresponding mean BP ($k= 18$) or baseline BP ($k= 6$). Two studies also adjusted for diastolic BP (Boehm et al., 2015; Chuang et al., 2016) in analyses examining sBPV. Adjusting for mean BP, or baseline BP at minimum, is important in the investigation of the association between BPV and cognition, as an intent in this line of research is typically to determine the extent to which BPV provides prognostic value for cognitive impairment and decline, above and beyond BP levels. Adjusting for intraindividual *mean* BP (computed based on all available BP recordings), as opposed to baseline BP, is ideal for minimizing potential bias due to measurement imprecision or phenotypes of BP (e.g., white coat hypertension) that are more prevalent in-clinic. Several studies, however, did adjust for mean BP based on all BP recordings, and findings from the majority (77.8%) revealed a significant, inverse relationship between sBPV and cognition, providing compelling evidence that variability in BP adversely affects factors involved in cognitive functioning *beyond* BP levels.

Multiplicity and Heterogeneity in Statistical Methodology

It is important to note that although the majority of studies noted an inverse association between at least one index of BPV and cognition in main findings, associations between all computed indices of BPV (e.g., SD, CoV, ARV), and/or all cognitive functioning assessments, were not always consistently associated with cognition *within* studies. Inconsistency in results within studies is not uncommon in the physiological and psychological literature, particularly

when multiple models are fit, but such inconsistency is still worrisome. Discrepancies within studies may suggest that BPV may differentially affect certain domains of cognitive functioning, or that the literature in this area is assailed by type I error. Indeed, the majority of studies executed several main analyses. For example, Zhou et al. (2019) applied an approach to reduce the likelihood of type I error by creating a composite BPV measure based on intra-visit, short-term, and mid-term BPV using BPV computations for each type of BPV consistent with previous literature and recommendations. As such, a strength of their analyses was the inclusion of only one index of BPV, which was relatively uncommon in the literature. Yet, their main regression analyses included unconditional and conditions models (with five increasing sets of covariates) for three cognitive domains for sBPV and dBPV, resulting in 36 separate models, as well as over 200 additional models presented in supplementary materials. In this case, higher dBPV was significantly associated with lower memory functioning, executive functioning, and information processing, but not across all models once all covariates were added to the models. Likewise, higher sBPV was significantly associated with lower memory functioning, but not executive functioning nor information processing. This example is discussed to illustrate that even though the “main findings” or the “majority of findings” may suggest that higher BPV is associated with lower cognitive functioning, there are inconsistent findings when considering all tested associations.

Perhaps more convincing (or at least more consistent) evidence is reported in an examination of individuals with mild to moderate AD (O’Caoimh et al., 2019). O’Caoimh et al. (2019) used logistic regression models (unadjusted, as well as two sets of adjusted models) for sBPV and dBPV for 5 indices of BPV, as well as for sBPV and dBPV split based on quartiles for change on a cognitive dementia rating scale (CDR-SOB), resulting in 36 models. Main

analyses also included linear regression (unadjusted and two sets of adjusted models) for sBPV and dBPV for 5 indices of BPV on the CDR-SOB, Q-MCI screen, and MMSE, resulting in an additional 120 models. Further, sensitivity analyses included models in which covariates were operationally defined using various approaches, and models in which CoV values were divided into quintiles rather than quartiles. Interestingly, O’Caoimh et al.’s (2019) extensive analyses revealed no significant associations between BPV and cognition, despite the statistical improbability of no significant results across 156 primary models.

Despite the limitation of multiple comparisons throughout this literature, relatively few studies applied a correction for multiplicity. Seven studies used the Bonferroni procedure (Cho et al., 2018; Haring et al., 2019; Kwon et al., 2016; Liu et al., 2016; McDonald et al., 2017; Sakakura et al., 2007; van Middelaar et al., 2018), and seven reports noted an increased risk of multiplicity as a study limitation (Cho et al., 2018; de Heus et al., 2019; Epstein et al., 2013; Kim et al., 2009; Lande et al., 2016; Nagai et al., 2017; Sakakura et al., 2007). Executing multiple models, particularly when those models are based on alternative operational definitions of the same construct (e.g., multiple possibilities for computing indices of BPV), is problematic because separate analyses assume independence between models. Analyses within a study, however, are based on the same individuals and data; that is, the data, and resulting effect sizes, are dependent.

Agreement throughout the literature to apply a consistent, “gold-standard” computation for each BPV data source may help to regulate this limitation. For instance, Yano (2017) suggests that residual SD or VIM are the best approaches for calculation of visit-to-visit BPV; while these approaches statistically adjust for change in BP over time, each is characterized by an important limitation. Namely, residual SD assumes linear change in BP, and VIM is estimated

based on the sample distribution of BPV, which limits cross-study comparison (Yano, 2017). Likewise, weighted SD, which removes the impact of nocturnal BP fall by weighting the SD (wSD) of DT and NT periods, may be an ideal approach for ABPM as all BP recordings can be included in the computation of the index. While the expert consensus by Stergiou et al. (2016) notes all possible BPV indices for each BPV data source, as well as studies that suggest which BPV indices may better reflect BPV for each BPV data source, the report does not suggest a gold-standard for each BPV data source.

An effective approach for addressing multiplicity is direct or conceptual replication. Conceptual replication involves executing independent but conceptually identical analyses (to the extent possible) across multiple studies or datasets (i.e., coordinated analysis; (Hofer & Piccinin, 2009)). Both direct and conceptual replication permit a powerful foundation to evaluate generalizability, and protect against type I and type II errors. Fundamentally, systematic reviews accompanied by meta-analysis also provide the opportunity to evaluate the generalizability of a particular phenomenon. Indeed, the current project initially aimed to execute a meta-analysis (*see* OSF: osf.io/vmnuq/). To address expected heterogeneity in the literature, we had planned to execute subset and between-study moderator analyses based on sample characteristics (e.g., age, % female, location, health of the sample, etc.), BPV data source, timing between BP recordings, computation of BPV index, type of cognitive functioning measure, and covariates included in models. Further, since all studies report several effect sizes between BPV and cognition, multi-level meta-analysis would have addressed within-study dependency of effects. This approach would have, ideally, provided effect sizes for the association between BPV and cognition for each of the mentioned study characteristics, as well as quantitative measures of publication bias and heterogeneity (e.g., I^2 , the proportion of true variability of the effect relative to the total

variation in observed effects). However, studies in this literature employed a wide range of methodological approaches; for instance, simple, multiple, multivariate, and multilevel regression, ANOVA, ANCOVA, linear mixed-effects models, logistic regression, and Cox proportional models. Furthermore, BPV was entered into models in different ways: as a continuous and/or categorical variable with different divisions across studies (e.g., dichotomous groups, tertiles, quartiles, quintiles, and deciles) *and also* occasionally inconsistent within studies (e.g., some studies repeated analyses after categorizing the same participants based on various cut offs, such as tertiles and then quartiles). As such, the extensive heterogeneity in statistical methodology restricted the ability to quantitatively synthesize this literature using meta-analysis. Interestingly, many studies noted general inconsistencies between studies as a limitation of existing research (e.g., previous studies do not always account for anti-hypertensive medications). None, however, noted that heterogeneity in analytic strategies across studies was a limitation in this field.

Recent work by Hoffmann et al. (2021) notes that disregard for the extensive variability in analytic strategies and researcher decisions within a literature can limit precision of results, lead to inability to replicate findings using independent data, and create confusion for the general public and decision makers by fostering distrust in scientific results. As such, literature examining BPV and cognition may benefit from a concerted and strategic effort to coordinate analyses; for example, even if authors have overarching aims to investigate BPV and cognition using a particular methodology, they could also report findings according to a straightforward analytic strategy in supplementary analyses or within an OSF repository associated with publications. A further approach for improving cumulative scientific knowledge is a community-augmented meta-analysis (CAMA; (Tsuji et al., 2014)), which is a combination of meta-analysis

and an open repository. A CAMA is a dynamic repository that initially includes the systematic steps required for a meta-analysis (e.g., identification of a topic, coding of reports, extraction of standardized effect sizes), but then the database of meta-data (e.g., available variables, operational definitions of variables, standardized effect sizes) is made public online for accumulation of additional meta-data from the scientific community. CAMA contributes to cumulative science via integration of existing research, augmentation of meta-analysis by community members, and documentation of file-drawer studies. Such an approach may be especially valuable for the investigation of BPV and cognition, given the prevalent multiplicity of analyses within this literature.

Differences in outcomes between datasets deemed redundant

Seventeen studies were excluded due to use of overlapping data. Two used data from the Maastricht Study (Geijselaers et al., 2017; Zhou et al., 2019); Geijselaers et al. (2017) was excluded because Zhou et al. (2019) utilized a more precise method of defining BPV and further, Geiselaers et al. (2017) focused on hyperglycemia, insulin resistance and diabetes, though did report associations between BPV and cognition. Two studies used data from The Maine-Syracuse Longitudinal Study (Crichton et al., 2014; Dore et al., 2018) and the PROSPER dataset (Sabayan et al., 2013; Wijnsman et al., 2016); in both cases, the more recently published report was included (Dore et al., 2018; Wijnsman et al., 2016). Several conference proceedings presented by the same corresponding author also overlapped with reports meeting eligibility ($k=13$); in all cases, the manuscript was included while the conference publication was excluded. Additionally, our review identified one unpublished dissertation overlapping with a more recently published report by the same first author (Qin et al., 2016). Finally, although both Tully et al. (2017) and Alperovitch et al. (2014) used data from the Three-City Dijon MRI study, both studies were

included as Tully et al. (2017) examined the association between BPV and cognitive decline, while Alperovitch et al. (2014) examined the association between BPV and risk of dementia.

The majority of reports using redundant data present internally consistent findings, particularly when the repeated reports were by the same first author or author group (e.g., conference proceedings). Related to the multiplicity of statistical analyses exemplified in this literature, however, results were occasionally inconsistent between studies using the same dataset. These inconsistencies may provide the opportunity to consider how and whether research decisions contribute to type 1 or type 2 error. Alternatively, differences in results based on the same dataset may hint at underlying mechanisms implicated in the association between BPV and cognition. For example, Zhou et al. (2019) created a composite BPV index based on intra-visit, ABPM and mid-term BPV. Findings indicated that individuals in the highest tertile of sBPV had significantly lower memory scores (but not processing speed or executive functioning), and individuals in the highest tertile of dBPV had significantly lower cognitive scores across all three cognitive domains. Conversely, Geijselaers et al. (2017) only report a significant inverse association between dBPV (computed as wSD based on ABPM) with two out of three cognitive functioning domains (not memory), and none of the sBPV-cognition associations. It is not surprising that results are slightly different, especially considering Zhou et al. (2019) maximized available BP data and created a composite index of BPV. Likewise, Geijselaers et al. (2017) entered BPV into models as a continuous variable, while Zhou et al. (2019) categorized participants into tertiles based on BPV. In this case, differences in results likely suggest that Zhou et al.'s (2019) composite BPV index may be more precise, that the association between BPV and cognition is not linear, or that splitting participants based on tertiles contributes to capitalizing on chance.

Limitations

As noted, the majority of studies computed several indices of sBPV and dBPV, using each index in subsequent statistical analyses. Likewise, studies often administered several cognitive functioning assessments, and subsequently fit models for each assessment. Some studies also executed more than one type of analysis. As such, most studies reported numerous results characterizing the association between BPV and cognition. Main findings, however, typically focused on the index/indices of BPV that were significantly associated with cognition (i.e., what was reported “overall”). Due to space constraints, this review is regrettably limited by focusing on the “main findings” reported by studies. That is, summarization is challenging. We identified and discussed the prevailing focus on significant findings as a limitation of this literature; yet, something similar has been done here. Again, a quantitative meta-analysis, coordinated analysis, or CAMA would provide the opportunity to synthesize this literature with less bias. Relatedly, a further limitation of this review was the inability to follow-through on our pre-registered plan to meta-analyze this literature. As discussed, heterogeneity in statistical approach made quantitative synthesis inappropriate.

Conclusion

This review identified 55 reports investigating the association between BPV and cognition across the lifespan. The majority of studies reported that higher BPV was significantly associated with adverse cognitive outcomes (e.g., cognitive impairment, cognitive decline, dementia, Alzheimer’s disease). While meta-analysis of literature in this area would be highly beneficial to quantitatively improve our understanding of factors that may contribute to, mediate, and attenuate the association between BPV and cognition, the extreme heterogeneity in methodological approach made quantitative synthesis impossible. Albeit qualitative, this

systematic review highlights numerous avenues for future research. Several opportunities for future research address the precision of BPV measurement. For instance, given innovations in affordable activity monitors, as well as multilevel modelling, future ABPM research could use physical activity trackers to determine BP recordings that occur truly at rest. Furthermore, future longitudinal research undertakings may use the same sample and apply intra-visit, short-term, mid-term and long-term approaches to assess BPV (computed according to various indices) to elucidate which (if any) BPV data sources and indices are most sensitive to cognitive impairment and decline. Indeed, these investigations would benefit from also administering concurrent assessments of cognitive functioning, as well as follow-up assessments to assess cognitive decline. The outcome of such research may provide critical and nuanced understanding of the characteristics of BPV (e.g., BPV data source, timing between recordings, number of recordings, index/indices of BPV) most valuable for risk stratification of cognitive impairment and decline. Further, this systematic review provides additional evidence for the importance of separating indices of daytime and nighttime BPV for statistical analyses. Alternatively, wSD or individual residual variability in BP allows maximization of data (use of all BP recordings), while still accounting for natural cyclic components of individual circadian BP profiles.

Differences in results based on variations in assessment of cognitive functioning, conversely, were less clear. Certainly, a more refined assessment of cognitive functioning is warranted in cases where assessments of cognitive functioning may be impacted by ceiling effects. For example, several studies assessed cognitive functioning using the MMSE, which has been criticized for lack of sensitivity and specificity (e.g., (Rajji et al., 2009)). As mentioned, this was likely an issue for Cicconetti et al. (2004) where the mean of both groups was 29.3 out of 30. Overall, reliance on the MMSE may be appropriate for samples comprised of individuals with

MCI and dementia, but perhaps less suitable for samples of relatively healthy older adults. Likewise, one study administered a simple delayed recall task of three items, and categorized participants as working memory impairment if they could only remember up to 1 of the objects after five minutes (Fujiwara et al., 2018), which is unlikely to fully capture cognitive functioning. Interestingly, though, Fujiwara et al. (2018) reported that very old adults ($M_{age} = 83$) with working memory impairment (defined as recalling 0 or 1 figures, out of 3) at follow-up were significantly more likely to have higher ABPM-BPV (wSD) at baseline and visit-to-visit BPV over one year, while mean ABPM-BP and office BP were not associated with working memory impairment. These results suggest that, in some cases, BPV may be predictive of relatively general cognitive decline.

Results based on this review also allude to populations and contexts in which the inverse association between BPV and cognition may be attenuated, or exist in opposition to the pattern of the majority of reports. For example, findings of studies using ABPM to examine BPV in children revealed no significant association between BPV and cognitive functioning (Kupferman et al., 2018; Lande et al., 2016), indicating that the neurological wear-and-tear of BPV may develop over time (i.e., the association may not exist early in the lifespan). Somewhat consistent with this pattern, results based on long-term visit-to-visit BPV (assessed over a median of 4 years), as opposed to short-term ABPM-BPV, and the same sample of children (Lande et al., 2016) revealed that higher BPV *is* associated with cognitive impairment. As such, short-term variability in BP assessed via ABPM may be less indicative of cognitive impairment in children compared to longitudinal variability in BP. However, long-term visit-to-visit BPV may reflect intraindividual change in BP (specifically increases), rather than true variability in BP.

Furthermore, research stratifying participants by APOE status suggests that higher BPV may be protective for individuals with moderate to severe Alzheimer's disease who are also APOE carriers (de Oliveira et al., 2016). Specifically, participants with moderate to severe AD who were APOE carriers and had higher BPV during one-year of study follow-up tended to have significantly better cognitive functioning scores. Although six studies adjusted for APOE status (Epstein et al., 2013; Haring et al., 2019; Lattanzi, Viticchi, et al., 2014; Ma et al., 2019; Tully et al., 2018; Yano et al., 2018), additional research focusing on potential differences in the association between BPV and cognition based on APOE status, rather than simply adjusting for APOE, may be valuable. While variability in BP may not have "easy" pharmacological solutions, individuals may be able to engage in lifestyle changes (e.g., in psychological, emotional, and physical realms) to reduce variability in BP. However, further understanding of the importance of APOE status in the association between BPV and cognition (as well as additional positive and/or adverse health outcomes) is important prior to universal recommendations.

This review also provided the opportunity to identify critical covariates that should be adjusted for in analyses. For instance, basic demographics (age, sex, education, race), APOE status, depressive symptoms, medical histories of cardiovascular and cerebral vascular diseases (e.g., hypertension, heart attack, high BP, stroke, diabetes), and health behaviours (physical activity, smoking and drinking status) should be adjusted for given individual associations between these factors and BPV and cognition. Further, while one study specifically focused on African American older adults (Tsang et al., 2017), only five studies adjusted for ethnicity (Boehm et al., 2015; Lande et al., 2016; Yano et al., 2018; Yano et al., 2014) or country (Wijsman et al., 2016), which reflects the relative homogeneity of included samples. Future

research including more diverse samples would improve the generalizability of existing literature. Importantly, in a literature aiming to exemplify the predictive value of BPV beyond mean BP or BP level, adjusting for corresponding mean BP seems critical. However, less than half of studies adjusted for corresponding mean BP or baseline BP. Across the studies that did adjust for BP level, results were not substantially impacted. Future research in this area has the opportunity to be more compelling if mean BP is included within models as a covariate.

An additional opportunity to address prevailing questions in the existing literature is in the area of intra-visit BPV. Studies identified by this systematic review indicate that higher BPV, assessed according to several successive BP recordings, may be protective for cognitive functioning for individuals with CVD, which is opposite to the typical pattern of results. This postulation is supported by research examining indices of the autonomic nervous system, such as heart rate and heart rate variability (Gunstad et al., 2009). Specifically, greater vagal control is associated with better cognitive functioning, but disruption of the autonomic nervous system, and subsequent lower vagal control, is characteristic of participants with CVD (Gunstad et al., 2009). For example, greater heart rate reactivity is associated with improved cognitive functioning (Cohen & Waters, 1985). Thus, Gunstad et al. (2009) suggest that higher BPV in individuals with CVD reflects better vagal control, which explains the positive association between BPV and cognitive functioning. However, more research is needed, and this postulation has only been explicitly examined using BPV assessed via intra-visit BP recordings (research has examined individuals at high-risk of CVD, but not diagnosed CVD). While intra-visit BPV provides a highly controlled, experimental setting to assess variability in BP, the mechanisms underlying very short-term BPV may not extend to the mechanisms underlying other BPV data sources (e.g., short-term, mid-term, and long-term BPV). Therefore, investigations of individuals with

CVD using short-term, mid-term and long-term approaches to capture BPV would provide an opportunity to potentially expand upon studies reporting findings in opposition to the typical pattern of results (Gunstad et al., 2009; Keary et al., 2007; Okonkwo et al., 2011; Cohen et al., 2009).

In some regards, this review addresses Stergiou et al.'s (2016) call for studies clarifying which BPV data source may be used as the best parameter for risk stratification. Indeed, in addition to the finding that the majority of studies assessing intra-visit BPV revealed that more BPV was associated with worse cognition, all seven studies assessing mid-term BPV and cognition addressed the relationship between BPV and cognitive decline or likelihood of dementia over time. Future research examining the relationship between HBPM or mid-term visit-to-visit BPV and concurrent cognitive functioning would contribute to existing understanding of the extent to which mid-term BPV findings correspond to the association between cognition and BPV assessed according to alternative BPV data sources. Likewise, future research using HBPM or visit-to-visit approaches to record BP, simultaneously with repeated measurements of cognitive functioning, would allow rigorous investigation of the association between fluctuations in BP and cognition at the intraindividual level.

Finally, this systematic review identified several important areas to strengthen methodology in this literature. Although a relatively high percentage of the studies that reported the association between dBPV and cognition found a significant, inverse association, 13 studies did not report dBPV findings. To contribute to transparent research and reduce publication bias, future research should ensure that dBPV results are reported if models are fit, despite the significance of findings, even in supplemental material or on an online repository. Additionally, application of a correction for multiple analyses would reduce the probability of reporting type I

error. Likewise, specifying research plans in advance (i.e., pre-registration) would contribute to quality and transparency of findings within this literature.

Relatedly, limiting the extensive heterogeneity in statistical methodology would assist in comparability between studies. For instance, agreement throughout the literature to apply consistent operational definitions for the “gold-standard” BPV index (e.g., *SD or CoV*) may help to regulate the number of models estimated within each study. Likewise, even if authors are intent on investigating BPV and cognition using a particular statistical approach, they could also report findings according to a straightforward (agreed upon) analytic strategy in supplementary analyses, within an online repository associated with their publication, or within a dynamic online repository for accumulation of additional meta-data from the scientific community (i.e., a community-augmented meta-analysis; CAMA). Alternatively, a concerted and strategic effort to coordinate analyses would be beneficial for future research.

Overall, this review contributes to the literature by systematically identifying studies that have examined BPV and cognition, and summarizing similarities and differences in study characteristics. Despite extensive heterogeneity, results suggest a significant, inverse association between BPV and cognition, such that higher BPV is typically associated with worse cognitive outcomes. The pattern of results, however, may be diminished or reversed depending on age of individuals, APOE status, and health of the sample (e.g., CVD). This systematic and methodical process provided the opportunity to identify strengths and limitations in existing literature, as well as to emphasize areas for future research.

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Appendix 1.1 Common derivations of BPV

1. Standard Deviation (SD)

$$\text{Within-person SD } (S_w) = \sqrt{\left(\frac{\sum s_i^2}{n}\right)}$$

Where s_i^2 are the within-person variances of measurements for each participant, and n is the number of within-person measurement occasions

2. Coefficient of variation (CoV)

$$\text{CoV} = \left(\frac{SD_{BP}}{M_{BP}}\right) * 100$$

Where SD_{BP} is the within-person SD of BP recordings and M_{BP} is the within-person mean of BP recordings.

3. SD_{reg}

SD_{reg} = within-person SD around their own regression line

4. Weighted Standard Deviation (wSD)

$$\text{wSD} = \frac{(DT_{SD} * DT_N) + (NT_{SD} * NT_N)}{DT_N + NT_N}$$

Where DT_{SD} and NT_{SD} are the within-person SD of the recordings from the daytime and nighttime, respectively, and $DT_N + NT_N$ are the number of recordings during each time period

5. Delta

Maximum BP value – Minimum BP value

6. Random Slope of BP

Absolute difference between recordings, then linear mixed effects modelling to model absolute changes as a function of number of days between clinic visits

7. Average real variability (ARV)

$$\text{ARV} = \frac{1}{N-1} \sum_{K=1}^{N-1} |BP_{K+1} - BP_K|$$

Where N is the number of within-person valid BP measurements and K is the order of measurements from the ABPM data corresponding to each participant.

8. Variation independent of the mean (VIM)

$$\text{VIM} = \frac{(\underline{\text{SD}})^x \text{BP}_{\text{Mean}}}{\text{WP}_{\text{Mean}}}$$

Where VIM is computed by fitting a curve through a plot of within-person sBP SD (y axis) against within-person mean sBP (x axis) with the parameter x estimated from the curve, then multiplied by the between-person (sample) mean (Yano, 2017).

9. Residual SD

Root-mean-square error of the residuals (differences between observed BP and predicted BP) from the regression

10. BPV function

$$\text{BPV}_{f(x)} = \frac{\underline{\text{sBP}}_{\text{SD}}}{\text{dBP}_{\text{mean}}}$$

Chapter 2

Short-Term Interindividual and Intraindividual Dynamics of Blood Pressure, Blood Pressure Variability, and Cognitive Functioning

Abstract

Objective: Though an extensive body of research has investigated the association between cognition and blood pressure (BP), as well as cognition and BP variability (BPV), very limited research has examined the association at the within-person, daily level. Additionally, no study has investigated the association between BPV and variability in cognitive functioning, or midterm BPV and concurrent cognitive functioning.

Method: Healthy adults ($N=64$; $M_{\text{age}}=70.58$, $SD=3.5$; 77% female) residing in Victoria, B.C. recorded their BP and completed cognitive tasks twice per day for 14 days. Partial correlation coefficients estimated the association between BPV and variability in several brief assessments of cognition across varying cognitive domains (executive functioning, short-term memory, cognitive interference, reaction time, localization error in memory, relational binding, and visual short-term memory in binding), while multi-level models (MLMs) estimated the association between BPV and concurrent cognitive functioning. Further MLMs estimated the intraindividual and interindividual relationships across systolic BP (sBP), diastolic BP (dBP), and cognitive functioning, adjusting for time-varying effort, stressors and physical activity, as well as time-invariant variables (sex, anti-hypertensive medication, age, and education).

Results: Adjusting for several covariates, partial correlation coefficients and MLM analyses revealed that more sBPV and dBPV were related to slower or more variable reaction time on the Symbol Search and Stroop tasks, whereas higher BP tended to be related to lower accuracy on the Colour Dot and Colour-Shape tasks at both the intraindividual and interindividual levels.

Conclusions: Findings suggest that more BPV may be associated with slower or more variable reaction time, while higher BP may be associated with lower accuracy. However, analyses were

relatively exploratory in nature and not well powered for between-person comparisons. Further, Type 1 error may be a factor given the multiplicity of analyses.

Introduction

Blood pressure (BP) is a dynamic physiological parameter influenced by behaviour, emotion, and environmental factors. Over the past decade, medical professionals and the research community have questioned the traditional use of single recordings of BP to diagnose hypertension, particularly when recordings are confined to clinical contexts and recorded by medical practitioners (e.g., Mancia et al., 2013; Nerenberg et al., 2018). Likewise, many researchers are turning to mobile technologies to address concerns regarding ecological validity and reliability of cognitive testing in artificial, clinical environments using standardized methods (Allard et al., 2014; Sliwinski et al., 2018). The existing literature suggests an inverse relationship between high BP and adverse cognitive outcomes in adulthood (Breteler et al., 1994; Cherbuin et al., 2009; Elias et al., 2003; Kilander et al., 1998; Meng et al., 2014; Reitz et al., 2007). However, the association is complicated by common phenotypes of BP and natural variability in these constructs, which both contribute to measurement imprecision. Furthermore, to my knowledge, only two studies have examined the extent to which interindividual associations between BP and cognition persist at the intraindividual level (Gamaldo et al., 2008; Kelly et al., 2015). Finally, no research has investigated the association between BPV and short-term fluctuations in cognitive functioning. The current project used an intensive measurement design to investigate how these dynamic variables fluctuate within and between days to address these gaps in the literature by investigating short-term, daily BPV, BP and cognitive functioning in a sample of community-living older adults ($N=64$) assessed twice daily over a two-week period.

Hypertension and Cognition

Hypertension, or consistently high BP, is associated with many adverse outcomes, particularly in older adulthood. Simply put, hypertension is a risk factor for vascular disease, atherosclerosis (plaque build up inside arteries) and stroke, all of which increase risk of dementia (Breteler et al., 1994). The overall cerebrovascular dysfunction that is associated with aging is thought to account for the association between high BP and adverse neural outcomes. Specifically, hypertension accelerates reduction in quantity of cerebral capillaries, in addition to thickened and fibrotic membranes, which may contribute to lower resting cerebral blood flow and dysfunction in cerebral circulation regulation (Gasecki et al., 2013). Importantly, hypertension is a consistent and substantial predictor of cerebral microbleeds; for instance, a systematic review ($K = 20$) and meta-analysis of magnetic resonance imaging (MRI) studies found that older adults with hypertension were at a significantly increased risk of cerebral microbleeds (Cordonnier et al., 2007). Likewise, using MRI, Gao and associates (2014) examined the association between cerebral microbleeds, white matter hyperintensities, and lacunar infarcts, revealing that individuals with hypertension were at an increased risk of cerebral microbleeds and white matter hyperintensities. Hypertension can also damage or weaken blood vessels in the brain, which tends to increase risk of stroke, small vessel disease, grey matter volume loss (Peters, 2006) and vascular dementia (Breteler, Claus, Grobbee, & Hofman, 1994). For example, prospective longitudinal research found that longer duration of hypertension was associated with periventricular and subcortical white matter lesions (de Leeuw et al., 2002), which are indicative of small vessel vascular brain disease. Likewise, a systematic review revealed that 26 out of 28 studies found a significant association between hypertension or high BP and reduced brain volume (Beauchet et al., 2013).

The mechanistic relationships linking hypertension with adverse neural changes is consistent with epidemiological evidence examining BP and cognitive functioning. Existing literature in this area consistently indicates an inverse association between BP and cognition in middle to older adulthood. Specifically, hypertension is associated cognitive impairment (Elias et al., 2003) and increased risk of incident mild cognitive impairment (Cherbuin et al., 2009; Reitz et al., 2007), cognitive decline (Kilander et al., 1998), Alzheimer's disease (see meta-analysis Meng et al., 2014) and vascular dementia (Breteler, Claus, Grobbee, & Hofman, 1994). In addition, longitudinal research suggests that management of hypertension positively affects cognitive functioning. For instance, in a sample of men ($N = 999$) aged 50 years old on average at baseline, high baseline diastolic BP (dBP) was associated with cognitive decline 20 years later, and the association was strongest in men with un-medicated hypertension during follow-up (Kilander et al., 1998). The association between BP and cognition, however, is possibly age-dependent. For instance, both cross-sectional (Axelsson et al., 2008) and longitudinal (Beckett et al., 1999) research suggests that, at approximately 75-80 years of age, moderately high BP (e.g., 130-139 mm Hg SBP) stops being a risk factor, and actually becomes a protective factor for cognitive decline and dementia (Kennelly et al., 2009; Waldstein et al., 2005). That is, high BP may be a biologically adaptive function in older age.

BP phenotypes, measurement imprecision, and alternative BP recording options

The association between BP and cognition may be obscured or less reliable due to the occurrence of several common BP phenotypes characteristic of measuring BP in clinical or research scenarios. Though resting BP is typically measured adhering to a standardized protocol in medical circumstances (Pickering, 2002), the presence of a health practitioner can substantially impact BP. For instance, masked hypertension is a phenomenon that occurs when

individuals appear to be below hypertensive range (i.e., SBP <140) in office settings, but in hypertensive ranges outside of clinical settings. Correlates of masked hypertension include being male, older age, and higher education, body mass index, smoking and alcohol intake (Trudel et al., 2019), as well as higher fasting blood glucose values, high job stress, and obstructive sleep apnea syndrome (Cuspidi et al., 2019). Identifying masked hypertension is particularly challenging due to indeterminate criteria for screening (Anstey et al., 2019). As such, the prevalence of masked hypertension is difficult to estimate, but has been reported as 10.3% in a Canadian study (Trudel et al., 2019) and 13% based on international studies (Costa & Lima, 2017).

More commonly, the White Coat Effect is a general phenomenon in which individuals present with heightened BP in clinical settings. Research suggests that, on average, individuals tend to report a mean increase of 27 mm Hg in systolic BP (sBP), but that the White Coat Effect is more prominent in older adults, women, and individuals diagnosed with hypertension (Franklin et al., 2013). As demonstrated by the White Coat Effect, BP is typically higher in most clinical settings; white coat hypertension (WCHT), however, is diagnosed when individuals have BP readings indicative of hypertension *only* in medical settings, and is thought to be a conditioned reflex caused by anticipation that high BP may indicate current or future illness (Bloomfield & Park, 2017). The prevalence of WCHT varies depending on the country, sample, and research technique (Bloomfield & Park, 2017). For example, WCHT has been reported at 15% in the general Danish population (Hansen et al., 2006), 15-30% in the general British population (O'Brien et al., 2000), and 9% in an American hypertensive clinic (Ogedegbe et al., 2008). WCHT is more prevalent in individuals with high anxiety levels (Shehab & Abdulle,

2011) and those who are obese (Kotsis et al., 2005), and can result in inaccurate diagnosis if physicians do not elicit alternative approaches to BP recordings.

These BP phenotypes have important implications within clinical settings, as patients may be misdiagnosed or erroneously undiagnosed, and subsequently treated incorrectly. As such, many national recommendations endorse multiple physician visits, in conjunction with ambulatory BP monitoring (ABPM) or home-based BP monitoring (HBPM), for diagnosis of hypertension, control of antihypertensive medications, and maintenance of normotensive BP levels (Mancia et al., 2013; Muntner et al., 2019; Nerenberg et al., 2018; Sharman et al., 2015). For instance, a meta-analysis of randomized controlled trials ($K = 18$) found that individuals with hypertension using HBPM are more likely to achieve BP target levels compared to standard BP monitoring in the healthcare system (Cappuccio et al., 2004). A more recent review also suggests that HBPM is valuable beyond office BP measurement for confirming hypertension diagnosis and evaluating efficacy of BP medication, and should be used as best practice approach for managing hypertension (Liyanage-Don et al., 2019).

Both ABPM and HBPM are strong approaches for avoiding the anxiety that a clinic setting may induce. In particular, ABPM is excellent for delineating very short-term variability in BP in daily context, as well as capturing certain phenotypes of BP that occur within a day (e.g., morning BP surge, morning hypertension, and nocturnal hypertension). However, the precision of ABPM recordings for evaluation of *resting BP* may be problematic because individuals are not necessarily at rest during recordings. Specifically, our systematic review identified 20 studies using ABPM to assess the association between short-term BP variability (BPV) and cognition. Many of the identified ABPM studies did not include information about the instruction given to participants during the day of recording (Baranowski et al., 2018; Bellelli

et al., 2001; Cho et al., 2018; Conway et al., 2015; Kanemaru et al., 2001; Lande et al., 2016; Tohgi et al., 1991; Yamamoto et al., 2005). Though some studies instructed participants to engage normally in their daily activities (Kim et al., 2009; Marti-Fabregas et al., 2001; Paganini-Hill et al., 2019; Yamaguchi et al., 2014), others instructed participants to avoid strenuous physical activity (Cicconetti et al., 2004) or to just keep their arm still during the recording (McDonald et al., 2017; Mossello et al., 2015; Tadic et al., 2019). These types of instructions likely result in some variability in BP that simply reflects engagement in daily activities, as BP levels naturally rise during and after even a small amount of physical activity (e.g., walking up the stairs), and naturally drop during relaxation and sleep. Importantly, individuals who do engage in physical activity as part of their daily routine are likely healthier than individuals who do not. According to 24-hour ABPM, these individuals may then appear to have higher BP on average, and more variability in BP over the course of a day, compared to mostly sedentary individuals. Importantly, delineating the individuals who have high BP or high BPV due to physical activity versus circulation regulation dysfunction is challenging or impossible when using ABPM, depending on the research design. Across the studies that we identified within our systematic review, only two asked participants to note ambulatory BP recordings that may have been at rest (Goldstein et al., 1998; Marti-Fabregas et al., 2001), and neither used an approach to adjust those particular BP recordings accordingly.

Conversely, HBPM is a markedly strong approach for providing information about resting BP (Bonafini & Fava, 2015), in the context of proper training. For example, individuals are not to ingest food or caffeine within two hours of recording. They are instructed to be seated with the back supported and at rest for at least five minutes with their feet flat on the floor (Pickering, 2002). Additionally, individuals are instructed to have the BP cuff fastened on their

bare, non-dominant, upper arm at heart level, with their forearm completely supported and the palm of the hand turned up (Pickering, 2002). Such careful training using HBPM ensures a high degree of measurement precision for accurate recording of resting BP. Using this approach, some variability in day-to-day resting BP is natural; excessive variability in the absence of physical activity, however, may be associated with adverse cognitive outcomes, which will be discussed next.

Blood pressure variability

Beyond the importance of identifying the common phenotypes of BP that occur within medical scenarios and the ability to more precisely capture BP at rest, HBPM is also able to capture day-to-day fluctuations in BP. While some variability in at-rest BP is normal, an expert panel in India reviewed the literature on BPV and concluded that BPV reaches pathological significance when fluctuations in BP exceed acceptable limits, which was identified as 10 SDs above the mean (Kumar et al., 2017). Given measurement factors, in addition to common phenotypes of BP that are not detectable via a single office measurement, recent research has focused on outcomes associated with a computed index of variability based on repeated recordings of BP (i.e., BPV). Standard computation of BPV is based on at least three within-person BP recordings using a variety of approaches, such as ABPM, HBPM or visit-to-visit office measurements. Studies using mean BP and indices of BPV indicate that BPV is actually a stronger correlate of many adverse health outcomes, such as coronary heart disease, stroke and renal disease (Gosmanova et al., 2016), as well as cardiovascular events (Mehlum et al., 2018) and cognitive impairment (Cho et al., 2018; Lattanzi et al., 2018) compared to mean BP. These findings are consistent with animal studies, which suggest that higher BPV is a more accurate predictor of cardiac damage, renal lesions and aortic hypertrophy in rats, compared to mean BP

(Miao et al., 2006). Based on the existing literature, many national guidelines recommend that medical professions and their patients should monitor BP using HBPM and ABPM, and subsequently aim to control both mean BP and BPV to effectively maximize health outcomes and cognitive functioning.

Further, the association between cognitive impairment or decline and high variability in blood pressure, beyond mean BP, may have neurological underpinnings. For instance, increased variability in neural blood flow may negatively impact brain circuitry and increase risk of cerebral microbleeds caused by blood leakage from small blood vessels (Liu et al., 2012). Further, individuals with high systolic BPV have increased risk of white matter lesions and more atrophy compared to individuals with low systolic BPV (Havlik et al., 2002). Likewise, MRI volume measurements suggest that, adjusting for age and sex, individuals with a combination of high BP and high BPV have the strongest relationship to brain atrophy compared to either high BP or high BPV alone (Goldstein et al., 2002). BPV is also associated with cerebral microbleed development in deep and intratentorial brain regions, independent of mean BP (Liu et al., 2012).

Though the existing literature suggests that indices of BPV based on multiple BP recordings may capture an important predictor of adverse cognitive outcomes, several research questions are currently unexplored. Our systematic review identified four studies investigating the association between cognitive decline and day-to-day (i.e., midterm) BPV using HBPM. All four studies found that higher BPV was associated with risk of dementia (Oishi et al., 2017) or cognitive decline (de Heus et al., 2019; Liu et al., 2016; Matsumoto et al., 2014). Furthermore, our review identified three studies investigating the association between midterm BPV assessed via short-term repeated in-clinic BP recordings. All three revealed that more BPV was associated with higher risk of cognitive impairment at follow-up (Appleton et al., 2019; Geng et al., 2017;

Lee et al., 2014), though all three studies focused on the associations between baseline BPV (during hospital stay) and cognitive functioning after incident of stroke (i.e., in a very specific population). While this literature portrays a consistent picture of the association between midterm BPV and change in cognition, no study has investigated either the concurrent association between midterm BPV and cognition, or the association between any type of BPV and daily variability in cognition.

Overall, research or diagnoses based on BP recorded by health professionals in clinical contexts may contribute to bias and imprecision due to common phenotypes of BP. Likewise, natural fluctuations in BP present a challenge for delineating true resting BP based on a single measurement. Further, using multiple recordings of resting BP to compute an index of variability in BP may provide additional important information for adverse cognitive outcomes. Moreover, HBPM may be best suited for assessing resting BP and BPV, compared to other types of out-of-office BP monitoring, such as ABPM. Finally, examination of the within-person coupled association between BP and cognition has received limited attention thus far, and may reveal additional understanding of the link between BP and adverse cognitive outcomes, discussed next.

Interindividual and intraindividual processes between BP and cognition

To this point, the discussed associations between cognitive functioning, BP and BPV are at the between-person, interindividual level, which is consistent with the vast majority of research in this area. The between-person approach examines the extent to which individuals who have higher BP or BPV in general also experience lower levels of cognitive functioning in general, relative to other individuals. While interindividual associations are informative and valuable, investigation of within-person intraindividual relationships can take situational and

contextual influences into account, providing the opportunity to capture dynamic individual differences in biological and psychological processes (Bauer, 2011).

In particular, while high BP is a pronounced risk factor for many adverse physical and cognitive outcomes, the extent to which high BP negatively affects day-to-day cognitive functioning has been relatively unclear. Importantly, high BP is the leading risk factor for global disease burden and death (Padwal et al., 2015; Vos et al., 2013; *WHO | A Global Brief on Hypertension*, n.d.). Although hypertension only began to be considered as a treatable condition in the 1960's (Saklayen & Deshpande, 2016), pharmacological advances and further understanding regarding the importance of committing to a healthy lifestyle have substantially reduced mortality and death due to hypertension (Jordan et al., 2018; Saklayen & Deshpande, 2016). Despite pharmacological and non-pharmacological treatment options, a high proportion of Canadians that have been identified as having hypertension continue to have uncontrolled hypertension (Padwal et al., 2015). Research based on intraindividual associations may have the opportunity to provide additional motivation for lifestyle modifications, similar to the biofeedback permitted by activity trackers (e.g., Fitbit), which can be a powerful method for instigating behaviour change (Cheatham et al., 2018). That is, knowledge that fluctuations in performance on cognitive tasks may be associated with fluctuations in BP may provide motivation for healthy lifestyle modifications.

Though indices of BPV do consider within-person variability in BP to some extent, computation of a single index based on multiple recordings may miss the opportunity to thoroughly investigate dynamic, intraindividual associations, such as the within-person association between BP and cognition. In the computation of BPV, BP is measured at the within-person level several times during a 24-hour period (e.g., ABPM), across several days (e.g.,

HBPM), or on several independent occasions (e.g., visit-to-visit BPV). Researchers then use these repeated measurements to compute indices of within-person central tendency (e.g., mean BP) or variability (e.g., coefficient of variation, standard deviation). Subsequently, the focus of investigation becomes the association between the BP index and the outcome of interest, such as cognitive functioning, at the between-person level. Our systematic review identified 55 independent studies that have examined the association between BPV and adverse cognitive outcomes (e.g., cognitive impairment, cognitive decline, and dementia). No study has yet investigated the association between BPV and short-term variability in cognitive functioning, which contributes to the novelty of the current research.

Additionally, very few studies have examined the short-term dynamics of BP and cognitive functioning at the within-person level using intensive measurement designs, which are well suited for investigation of dynamic variables that fluctuate within and between days. Though one study examined HBPM and everyday cognition over 8-30 days, analyses did not explore the dynamic within- and between-person associations between BP and cognition (Yeung & Thornton, 2017). Conversely, using a daily diary design, Gamaldo and colleagues (2008) instructed participants ($N = 36$; $M_{Age} = 73$) to measure their own BP and to complete handwritten cognitive tasks twice per day for 60 consecutive days. Results revealed that neither hypertension nor hypotension were associated with worse cognitive functioning, though they were unable to adjust for use of antihypertensive medications and their analyses were not well powered for testing between-person associations. However, they did find a within-person interaction between BP and cognition at the daily level: individuals with high systolic BP (e.g., prehypertensive and hypertensive range; mean systolic BP ≥ 129) performed poorly on inductive

reasoning tasks compared to their average cognitive performance on days when their systolic BP was above their personal average (Gamaldo et al., 2008).

Gamaldo et al. (2008) hypothesized that stress may contribute to increased BP, which may then lead to compromised cognitive functioning. However, they did not explain the reasoning behind this hypothesis, nor did they assess daily stressors, which makes further elucidation of their findings difficult. Nevertheless, research and theories from neurology and cardiovascular fields may help. Specifically, the cardiovascular system is regulated by a cortical network, including the insular cortex, anterior cingulate gyrus, and amygdala, which is critical in the regulation of the central autonomic nervous system and is also activated in response to psychological stress (Kitamura et al., 2020). Importantly, researchers hypothesize that this network is involved in the neural regulation of the neuroendocrine, pulmonary, and visceromotor systems, and that dysfunction within the central nervous system may lead to hypertension (Benarroch, 1993). The network, which is located in the middle cerebral arteries, is particularly vulnerable to cerebrovascular disease, and research suggests that high BP and BPV are associated with damage to the network, particularly within the insular cortex (Kitamura et al., 2020; Nagai et al., 2017). However, drawing conclusions about the association between stress and BP/BPV based on these underlying mechanisms is challenging, as research primarily investigates the cortical networks regulating stress *or* BP/BPV, rather than stress and BP/BPV in tandem.

Empirical research examining the association between BP change and neural activation in response to cognitive tasks and stress testing has found that individuals with greater BP reactivity also had higher occasion-specific stress-induced activation in particular neural areas (mostly overlapping with the aforementioned cortical network responsible for regulation of the central

nervous system) (Gianaros et al., 2009). The researchers concluded that increased stress-induced brain activation in the cortical network responsible for regulating the cardiovascular system may partly account for exaggerated BP reactivity, which may contribute to vascular disease (Gianaros et al., 2009). Follow up research by the same working group extended these findings by identifying a multivariate brain phenotype that partly accounts for individual differences in cardiovascular reactivity in response to stress (Gianaros et al., 2017). Simply put, stress may damage the neural network responsible for regulating the cardiovascular system, which may lead to high BP and BPV. Importantly, similar associations emerge at both the within-person and between-person level. Specifically, at the within-person level, the researchers observed a task-induced BP covariation with activation of the previously mentioned cortical network (as well as some additional neural regions). At the between-person level, individuals with exaggerated BP reactivity, compared to individuals with relatively more consistent BP through stress testing, showed more activation in those regions of the brain associated with psychological stress.

This research focused on the mechanisms involved in linking stress to increased risk of cardiovascular disease and cerebrovascular disease, exemplified, in part, by high BP. While cognitive tests were administered in these studies as a method of stress testing, cognitive performance data were not reported. Importantly, however, their investigation also revealed that psychological stress leads to neural activation in regions of the brain distinct from regions of the brain that are typically activated during cognitive testing. These underlying mechanisms may help to explain Gamaldo et al.'s (2008) finding of covariation between upward fluctuations in sBP and downward fluctuations in cognition at the intraindividual level, and that the coupled associations between BP and cognition were stronger in individuals with higher BP on average. That is, at the within-person level, occasion-specific stress may divert cerebral blood and oxygen

to areas of the brain involved in psychological stress, which also results in increased BP and BP reactivity. Concomitantly, occasion-specific stress may divert blood and oxygen away from areas of the brain responsible for cognitive functioning, given the spatial dissociation between brain regions activated during cognitive tests and responsible for regulating BP. At the between-person level, cumulative stress may damage the neural networks responsible for regulating BP, potentially leading to heightened BP and increased BPV over time, in addition to increased risk of cardiovascular risk and essential hypertension.

In a second study utilizing a daily diary design to examine the intraindividual relationships between BP and cognition, Kelly et al.'s (2015; unpublished master's thesis) conceptually replicated and extended Gamaldo's research. Participants ($N = 27$; $M_{Age} = 70$) were instructed to measure their BP, and complete cognitive tasks and stress inventories on the computer once per day during a 14 day protocol. Results suggested that on days when individuals' reported upward fluctuations in diastolic BP compared to their personal average, they performed better on a delayed recall task. Results also showed interactive effects between BP, cognition, and stress severity at the within-person level. Specifically, immediate recall was impaired on days with elevated stress severity (Kelly et al., 2015). However, elevated BP attenuated the impairment, suggesting that although stress and BP may differentially impact cognition, BP may be more influential. These results are in opposition to the pattern of results compared to research at the between-person level in individuals up to age 75 and are also inconsistent findings with Gamaldo et al.'s research at the within-person level; however, the comparison is challenging, as Gamaldo et al. (2008) did not report results based on diastolic BP.

As Kelly et al.'s (2015) study was based on a small sample of very old adults ($M_{age} = 70.2$, $SD=7.4$), she hypothesized that this effect may be attributed to the protective nature of

moderately high BP in very old age. As discussed, long-term excess pressure within vascular structures tends to cause cumulative weakening and damage to vascular and microvascular structures by accelerating reduction in quantity of cerebral capillaries (Gasecki et al., 2013) and increasing risk of cerebral microbleeds (Cordonnier et al., 2007; Gao et al., 2014). However, age-related changes to the vascular system (e.g., atherosclerosis and arterial stiffening) may impair blood flow capacity through neural tissues, resulting in cortical hypoperfusion and ultimately impairing the capacity to carry blood and oxygen to areas of the brain. As such, in very old adults, upward fluctuations in BP may help to maintain cerebral perfusion, and actually improve neural blood and oxygen flow, thereby improving occasion-specific cognitive functioning. That is, upward fluctuations in BP may be a biologically adaptive function in very old age.

As mentioned, the intraindividual relationship between BP and cognitive functioning may be related to daily stressors, though further research is needed to clarify the association. For example, previous research shows a positive between-person association between higher BP variability and stress (Carroll et al., 2003). Likewise, compared to younger adults (< 42 years), older adults (> 62 years) have greater increases in ambulatory diastolic BP when dealing with daily stressors (Uchino et al., 2006). At the within-person level, research suggests that reactions to daily stressors may compromise response time performance in older adults (Stawski, Cerino, Witzel, & MacDonald, 2019). Likewise, research reveals an inverse intraindividual relationship between daily stress and cognitive performance on working memory tasks in both younger and older adults (Sliwinski et al., 2006) and between daily stress and cognitive interference in older adults (Stawski, Mogle, & Sliwinski, 2011), which is linked to poorer cognitive function.

Thus, investigation of the role of daily stressors may be important when examining the intraindividual relationship between BP and cognitive functioning. Specifically, daily stressors

and higher BP may individually or cumulatively contribute to lower occasion specific cognitive functioning. It is also possible that daily stressors lead to increased BP, which then negatively influences cognitive functioning (i.e., stress mediates the association between daily BP and cognition), or that stress negatively affects both BP and cognition. Although Gamaldo et al. (2008) did not assess daily stressors, they did recommend investigation of these relationships for future research. Subsequently, Kelly and colleagues (2015) included measurement of daily stressors, finding that although immediate recall was impaired on days with elevated stress severity, elevated BP was associated with less impairment despite stress severity, such that higher occasion-specific BP provided a protective effect. In combination with the research suggesting an age-dependent phenomenon in which high occasion BP may be biologically adaptive in very old age, these results are consistent with the underlying mechanisms linking stress, BP, and cognition. Namely, occasion-specific stress may increase activation of regions of the brain involved in psychological stress, thereby diverting cerebral blood and oxygen away from areas of brain responsible for cognitive functioning (i.e., explains why Kelly et al. found that immediate recall was impaired on days with elevated stress severity). Further, age-related changes to the vascular system may cause cortical hypoperfusion in very old adults, such that upward fluctuations in BP may help to maintain cerebral perfusion, thereby improving occasion-specific cognitive functioning (i.e., explains why Kelly et al. found that elevated BP was associated with less impairment despite stress severity).

In addition, physical activity may also be important in the association between BP and cognitive functioning (Allen & Morelli, 2011), at the within- and between-person levels. The existing literature consistently documents an interindividual positive relationship between physical activity and cognition (Baumgart et al., 2015; Bherer et al., 2013; Cheng, 2016). For

example, a meta-analysis synthesizing prospective studies found that both low-to moderate and vigorous physical activity were associated with a decreased risk of cognitive decline at follow-up occasions (Sofi et al., 2011). Beyond a mere association, intervention studies suggest that physical activity may improve cognitive performance. For example, a meta-analysis including 25 independent studies examining the effect of controlled PA interventions on executive functions in older adults (Karr, Areshenkoff, Rast, & Garcia-Barrera, 2014) found that intervention groups significantly outperformed control groups ($d = .12$, $p < .01$) on executive functioning tasks.

Physical activity is also associated with BP. For instance, research suggests that being physically active is associated with lower resting sBP and dBP in older adults ($N = 137$, $\text{Mage} = 69$, $\text{SD} = 8.9$) (Swartz et al., 2008). Research also suggests that being sedentary, particularly in combination with being overweight or obese, is associated with high BP (Werneck et al., 2018). Likewise, a randomized crossover design study found that sBP and dBP were significantly lower after each accumulated physical activity session (10 minute sessions every hour for four hours) in adults with prehypertension (120-139 mmHg systolic BP, 80-89 mmHg diastolic BP, or both) (Park et al., 2006). Though this study did not use multilevel modeling, which is ideal for analysis of within-person associations, the results are suggestive of a within-person relationship; namely, physical activity was associated with a greater reduction in sBP after the accumulated physical activity condition compared to the control condition and the single physical activity session condition. Given that this study used a crossover design (i.e., the participants are compared to themselves), results suggest that at the within-person level, more physical activity is associated with lower BP.

The Current Study

Overall, existing literature has typically focused on interindividual associations between BP and cognitive functioning, showing a consistent negative relationship between high BP and cognition in middle to older adulthood. The two existing studies that have examined dynamic fluctuations in BP and cognitive functioning at the within-person level reveal less consistent associations. However, both studies included relatively small samples that were demographically homogenous (e.g., highly educated, majority European American/Canadian participants) and lacking in BP phenotypes. For example, Kelly and colleagues' sample only included three participants reporting use of anti-hypertensive medications. In addition, although systolic and diastolic BP typically vary in similar directions (e.g., if systolic BP is higher, diastolic BP is also likely higher, though not to the same extent), Gamaldo et al. (2008) did not report diastolic BP, making it impossible to compare to the main results reported by Kelly and associates.

Further, Gamaldo et al. (2008) asked participants to record their own measurements, which may have resulted in a process impacted by the influences of social desirability. Indeed, applying a daily diary design, Matsumoto and colleagues (2014) examined concordance between self-recorded BP and objectively recorded BP by not disclosing the memory function of BP monitoring devices to participants. Results suggested that self-recorded BP was significantly lower and less variable than measurements stored in the device (Matsumoto et al., 2014). Thus, objective BP recordings that cannot be modified by participants are important when investigating day-to-day BP. Finally, neither existing study used a battery of daily cognitive assessments developed for unsupervised administration. As such, no study in this area has yet applied a daily diary design utilizing the convenience and objectivity of mobile devices for assessment of cognitive functioning and automated BP monitors that electronically track recordings. The

specified design utilizes digital health technology and is critical for detecting the complex nature of and interplay between both intraindividual and interindividual physiological and cognitive processes. The following research questions were investigated: *Do individuals with higher variability in BP, assessed twice daily over two weeks, have lower and more variable cognitive functioning? Are daily deviations in BP reliably associated with daily deviations in cognitive functioning? Are particular ambulatory cognitive assessments more sensitive to the within-person association between day-to-day BP and cognition? Is the relationship stronger for some individuals (e.g., individuals with higher mean BP; adults younger within the 65-75 year range) than for others?*

Based on the inverse associations between BPV and cognitive functioning at the between-person (see Chapter 1) and within-person (Gamaldo et al., 2008) levels, as well as neurology research pointing to mechanisms underlying these associations, several predictions were made prior to handling the data. The first two predictions were at the between-person level. Research suggests that cumulative stress may damage the neural networks responsible for regulating BP, potentially leading to heightened variability in BP over time, and further, that more BPV increases risk of cerebral microbleeds, white matter lesions, and neural atrophy. As such, we predicted that individuals with higher BPV would have lower and more variable cognitive functioning during the study protocol (Prediction 1). Second, based on research showing that hypertension accelerates reduction in quantity of cerebral capillaries, and also contributes to fibrotic membranes, lower resting cerebral blood flow, and dysfunction in cerebral circulation regulation, we predicted that individuals with higher BP would have lower cognitive functioning during the study protocol (Prediction 2). At the within-person level, we predicted an inverse association between BP and cognitive functioning, based on research suggesting that

occasion-specific stress may divert cerebral blood and oxygen to areas of the brain involved in psychological stress (which also results in increased BP), while simultaneously deflecting blood and oxygen away from areas of the brain responsible for cognitive functioning. Specifically, we expected that on occasions when individuals have higher BP than their personal average, their cognitive performance would also be lower than their personal cognitive average (Prediction 3). Further, given the role of stress within the BP-cognition coupling association, we predicted that the intraindividual association between BP and cognitive functioning would be attenuated once time-varying daily stressors were added to the models (Prediction 4).

Pre-hypertension may be biologically adaptive starting at approximately 75-80 years of age at the interindividual (Kennelly et al., 2009; Waldstein et al., 2005) and intraindividual (Kelly et al., 2015) levels, as age-related vascular system changes may contribute to maintaining cerebral perfusion, thereby improving occasion-specific cognitive functioning. However, the participants included in the current analyses were mostly less than 75 years old (Range = 64-78; 11% over 75). As such, we do not expect a positive coupled association between BP and cognition). Finally, simulations for intensive measurement designs indicate that a minimum of 20 participants are required for intraindividual power of .80 in a 14-day study, though 130 individuals are required for similar power at the interindividual level (Rush, Rast & Hofer, 2014). Due to limited time and resources, we planned to recruit approximately 80 - 100 participants.

Method

Under the study title “DASH” (Daily experiences of Affect, Stress, and Health), this project used an intensive measurement design in which participants completed brief surveys and measured their own BP twice daily for 14 consecutive days. The surveys were administered on

Android phones, which were provided for use during the two-week protocol, taking approximately 7-10 minutes to complete at each occasion. Participants were also provided with and trained to self-measure their own BP using validated electronic FORA P20 BP monitoring systems (ForaCare Inc.). When set in the “average” mode, the monitor records the mean of three consecutive measurements taken 20 seconds apart. BP measurements were automatically time-stamped and stored within the device. Adhering to the 2018 Canadian Hypertension Guidelines (Nerenberg et al., 2018), participants were trained to measure their BP twice per day, upon waking (or at least within 1 hour of waking) and within 1 hour of going to bed. For the morning occasions, participants were instructed to record their BP before taking medication, ingesting caffeine or tobacco, or engaging in exercise. For the evening occasions, participants were instructed to record their BP at least one hour after engaging in any of these activities. Directly following self-measurement of BP at each occasion, participants were instructed to complete the phone survey, which included cognitive tests, psychological assessments, and questions regarding environmental context. Participants were trained in proper protocols for BP recordings, and then they practiced recording their own BP under the supervision of a researcher. At the end of the intake session, participants were given a training guide for the study devices to take home with them, which included descriptions and pictures delineating proper recording procedures.

Participants were provided with a \$75 honorarium (\$25 at intake and \$50 at debrief) to acknowledge the time spent participating in the 14-day study. The project was approved by the University Of Victoria Human Research Ethics Board in the spring of 2019 under ethics protocol number 18-1069.

Sample

The study aimed to recruit healthy, community residing adults aged 65-75 years old. Participants were recruited through printed posters displayed in community centres, activity centres, medical clinics, pharmacies and local businesses. An electronic version of the poster was also distributed via the Institute of Aging and Lifelong Health email list and sent to club leaders (e.g., bowling clubs, chess clubs, etc.) for distribution to members. The poster provided basic information about the study, and invited interested individuals to contact the iLifespan lab via phone call or email. Once individuals initiated contact, a lab member called the individual and completed the screening process using a script and brief questionnaire. Individuals met eligibility if they could read and write English, had not participated in similar studies at UVic (e.g., Cognitive Health Initiative), and were relatively healthy for their age. This meant excluding individuals who had health concerns that might be exacerbated by participating in the study (e.g., psychiatric illnesses, cognitive impairment) or make effective participation challenging (e.g., uncorrected vision and hearing problems, diagnosed cognitive impairment, stroke, neurological disease, serious head injury, recent concussion or surgery that required general anesthesia).

Baseline Measures

Participants attended intake (~2 hours) and debrief (~1 hour) sessions at the Institute of Aging and Lifelong Health on the University of Victoria campus. During the intake session, participants reviewed and signed the consent form, and were provided with paper copies of the device manuals, as well as a personalized calendar to assist with tracking their daily measurements. The majority of the intake sessions were focused on training participants to use the devices. Participants were taught how to use the Android devices and how to start the correct

survey (e.g., morning or evening). Participants also received training in measuring their own BP adhering to the standardized set of recommendations (Pickering, 2002).

At both intake and debrief sessions, participants had physiological measurements taken (e.g., BP, height, weight, arm circumference, olfactory testing). Additionally, participants completed an online survey through LimeSurvey to collect demographic information and complete baseline measurements (e.g., Self-efficacy, PANAS, Satisfaction with Life, Psychological Well-Being, Big Five Inventory, etc.). The debrief session also consisted of collecting feedback on study design (e.g., questions, challenges with certain aspects of participating in the study, participant burden, etc.). At debrief, participants were asked to take their BP one last time, and the investigator leading the debrief session took notes on how closely the participant adhered to the recommendations for self-measurement of BP, thus providing an estimate for measurement accuracy during the 14-day protocol.

Covariates. Demographic information collected at baseline was used to adjust for time-invariant variables: baseline age, sex, and education. Age was measured in years and centered at the grand mean. Sex was assessed by a categorical item with the following response options: female, male, intersex, and other. Gender was assessed using an open-ended response option. Since all participants selected female or male, and their gender identity aligned in a traditional sense with their sex information (i.e., female/woman; male/man), we used male/female for sex/gender information with female as the reference, since the majority of the sample was female. Participants were also asked to indicate their highest level of education obtained from the following categorical response options in which higher values indicate more education: 1=did not complete high school; 2=high school; 3=trade school; 4=some university/college; 5=undergraduate degree; 6=graduate, law or medical school. Education was treated as a

continuous scale and mean-centered. Though treating an ordinal variable as continuous is not ideal, years of education can be misleading if individuals took longer to complete a degree than what is typical.

Anti-hypertensive BP medications. Although anti-hypertensive medication use may be time-varying (e.g., if a participant forgets to take a daily medication), we did not want to burden participants by asking them to type out every medication used at every survey. Therefore, anti-hypertensive medication use reported at baseline was dichotomized (0 = not taking BP medications; 1 = taking anti-hypertensive medications) and included in models as a time-invariant, between-person covariate.

Daily Measures

Participants self-measured their BP and completed surveys twice every day: in the morning within the first hour of waking, and within one hour before going to bed. In addition to cognitive tests, all surveys included several questions pertaining to the participants' current psychological state and contextual situation. The first day of surveys and BP recordings were not included within analyses.

Cognition. Each morning and evening survey included five mobile cognitive tests measuring several aspects of cognition, which were presented as “brain games” to participants. Each session included 2 -12 trials of each cognitive task. The average of the within test trials for each occasion was computed for use as the outcome variable in analyses. The survey results are stored on the Android phone. At debrief, the de-identified data files were downloaded onto a drive shared by the iLifespan lab. All occasions with incomplete trials were excluded, as this indicated that participants did not complete the task. This resulted in excluding 8 out of 42391 trials for Symbol Search, 93 out of 7077 trials for Colour Dot, 94 out of 7098 trials for Dot

Memory, 124 out of 11194 trials for Colour-Shape, and 246 out of 7098 trials for the Stroop task. Trial exclusions increase linearly because the cognitive tasks were consistently presented in this order. We also visually examined the distribution of reaction time for each cognitive variable, and made decisions as a lab regarding exclusion of trials that were not completed within an appropriate amount of time. Eligibility times, in seconds, and resulting excluded trials are reported in each of the following subsections that detail each cognitive task.

Symbol Search Test. Participants were presented with a row of three symbol pairs at the top of the screen and two symbol pairs at the bottom of the screen. Participants were instructed to select the symbol pair on the bottom of the screen that is identical to the symbol pair on the top of the screen as quickly as possible. The task is correlated with in-lab reaction time tasks, and has been previously validated for use on a mobile device (Sliwinski et al., 2018). Participants completed 12 trials in each survey. Some sessions were excluded based on reaction time (inclusion eligibility= 0.5-5.5 seconds), which resulted in excluding 1286 trials (3% of the symbol search trials). Though this task includes an element of accuracy, scores on accuracy were extremely left skewed in our sample (skewness = -5.57, SE=0.04), indicating that almost everyone was able to select the correct symbol pairs. Indeed, this is primarily a reaction time task. As such, the test is scored according to reaction time in seconds, such that lower values represent higher occasion specific cognitive ability. The within-person session mean of reaction time across trials was not skewed, and was used within analyses.

Dot Memory Test. A 5X5 grid including three red dots was briefly presented, before the participants were presented with a distracter task (locating F's in a screen full of E's). Then, the grid reappears, and the participant must identify where the original three dots were located. The task is correlated with in-lab working memory tests, and has been previously validated for use on

mobile devices (Sliwinski et al., 2018). If the participant correctly recalled the location of the dots, a score of zero is given. If the dots are incorrectly placed, the scoring system first identifies the closest coupling of the original three dots to the participant-selected three dots. The Euclidian distance discordance between the original dot location and the selected dots was calculated, to provide a continuous score (in grid units) in which lower values indicate higher cognitive performance. Two trials were presented at every session, and the mean accuracy of the two trials was computed to represent the participants score at each occasion. Response options from 0.5 to 25 seconds were included, which resulted in exclusion of 148 trials (2.11% of the dot memory trials).

Colour Dot Test. Three different coloured dots were briefly presented on the screen before disappearing. Then, a non-coloured dot was shown in the same location as one of the original three dots, and the participant was instructed to select the colour of the dot. Next, participants were asked where another one of the coloured dots was originally presented (e.g., “where was the blue dot?”) and participants had to touch the screen precisely where they recall the dot was located. Participants completed two trials in each survey. The test is a variation on a delayed reproduction task developed by Liang and colleagues (2016). Based on reaction time eligibility (0.5-7.5 seconds), 246 trials were excluded (3.6% of the colour dot trials).

The test is scored according to several metrics to provide various indicators of cognitive functioning: dichotomously (correct/incorrect colour selected), providing an indication of short term memory; continuously for the location of the placed dot to the original dot, providing an indication of localization error in memory; and frequency that an object is misplaced or moved, providing an index of relational binding, which has been shown to be compromised in individuals with familial AD (Liang et al., 2016). All computed performance variables were

skewed, though some more than others. Scores on the location question (e.g., “where was the blue dot located?”) were less skewed (Skewness statistic=2.09) and more variable across trials. As such, the session mean for the location of the dot was used within analyses. The Euclidian distance discordance between the original dot location and the selected dot was calculated to provide a continuous score (in grid units) in which lower values indicate higher cognitive performance.

Colour-Shape Test. Three objects of various shapes and colours were briefly presented on a single screen. Participants were instructed to remember the shape and colour of the objects. Then, a new screen was presented with three objects of various shapes and various colours. The location of the objects on the second screen is always different (e.g., new placement, rotation), but participants had to identify if the colour-shape combinations of the three objects are the same or different from the original objects. The test assesses visual short-term memory in binding (i.e., temporary retention of complex objects), and has been shown to be more demanding than memory for shape-only or colour-only conditions (Parra et al., 2010). Further, the test has been shown to provide more sensitivity and specificity for identifying patients with Alzheimer’s disease (AD) and asymptomatic carriers of the presenilin-1 mutation, which causes familial AD (Parra et al., 2010).

Some sessions were excluded based on reaction time (trials must be within 0.5-6 seconds), which resulted in excluding 286 trials (3.5% of the colour-shape trials). Participants completed six trials in each survey, with each trial scored dichotomously (correct/incorrect). Accuracy results based on the session mean across trials was not skewed and was used for analyses.

Stroop (Cognitive Interference). Participants were presented with discordant word-colour pairs, which represents a demonstration of cognitive interference (a.k.a. interference resistance ability) due to a mismatch in stimuli (e.g., the word *purple*, in red font). Participants were instructed to select whether the word-colour pairs are consistent or inconsistent as quickly as possible. The test is typically considered a test of executive functioning, and performance on the test has correlated highly with stronger resting-state-related left-lateralized activity in various regions of the prefrontal cortex (Ambrosini & Vallesi, 2017), indicating that neurophysiological characteristics may contribute to individual differences in executive functioning. The task is used extensively in the literature, and a version has been previously administered on a mobile device (Bouvard et al., 2018).

Participants completed 12 trials of the test at each session. Some trials were excluded based on reaction time (eligibility =0.5-3.5 seconds), which resulted in excluding 536 trials (2.4% of the Stroop task trials). Though this task can be scored according to accuracy, the vast majority of participants correctly identified the discordant word-colour pairs. Indeed, accuracy on the Stroop task in our sample was highly skewed; only 1.2% of the sessions included one or more trials that were incorrectly identified ($N=42$) across 1742 occasions. For the current research, the test was scored according to reaction time in milliseconds, such that lower values represent higher occasion specific cognitive ability.

Blood Pressure. Each occasion (morning and evening daily measurements) included three automatic BP recordings completed 20 seconds apart. The device automatically computes the mean based the three systolic BP (sBP) and diastolic BP (dBP) measurements, and stores the date- and time-stamped mean. At debrief, the recordings were uploaded via Bluetooth to the iFORA online health portal, and then downloaded as an excel data file. The BP data were

screened for within-person outliers by subtracting the within-person systolic and diastolic mean and median from each BP recording. Five occasions of BP (four systolic and one diastolic) were identified that were potentially outliers at the within-person level. These outliers were identified for sensitivity analyses.

Preliminary analyses focus on the partial correlation between BPV and fluctuations in cognitive functioning. For these models, the SD of morning and evening daily measures for sBP and dBP were computed at the within-person level, while intraindividual residual SD was computed for each cognitive assessment. Next, the multi-level models focused on the within-person coupled association between each cognitive assessment and BP recording (sBP and dBP). Separate within-person means were computed for each participant's systolic and diastolic BP recordings, and that value was subtracted from each corresponding BP occasion. This approach permits interpretation of the estimates, such that a significant inverse association between cognitive performance and BP would suggest that on days when individuals have higher BP fluctuations compared to their personal average, they have downward fluctuations in cognitive functioning relative to their personal average.

Effort. At the end of each survey, participants were asked, "*How much effort were you putting into the Brain games?*" They could then select on a slider from 0-100 the extent to which they were "*Not at all trying*" to "*Trying my best*," where higher values indicated more effort. The variable was entered into all models as a time-varying covariate to account for the occasions that should potentially be discarded due to limited exertion and/or distractions within the environment that may have contributed to lower cognitive performance unrelated to true cognitive functioning.

Physical activity. Given the associations between BP and physical activity (Park et al., 2006; Swartz et al., 2008), as well as cognitive functioning and physical activity (Allen & Morelli, 2011; Baumgart et al., 2015; Bherer et al., 2013; Cheng, 2016; Karr, Areshenkoff, Rast, & Garcia-Barrera; Sofi et al., 2011), the current project adjusts for time-varying physical activity. In the evening survey, participants were asked to self-report the number of minutes that they engaged in moderate to vigorous physical activity that day. The item was an ordinal variable with the following response options: 0, 20, 30, 45, 60, 90, 120, or 150 minutes, or more than 3 hours, of moderate to vigorous physical activity. Ordinal responses were treated as a continuous scale, since creating a dichotomous variable may fail to capture important aspects of the data, and treating it as ordered categories would strain estimation of the model. The within person mean across all occasions was computed for each individual, and that value was subtracted from each daily value. This approach permits appropriate interpretation of the estimates, such that a significant positive association between within-person physical activity and cognitive functioning would suggest that on days when individuals had higher physical activity compared to their personal average, they also had better cognitive functioning compared to their own personal average.

Stressors. Given the associations between cognitive functioning and stressors (Sliwinski et al., 2006; Stawski, Cerino, Witzel, & MacDonald, 2019; Stawski, Mogle, & Sliwinski, 2011), as well as between BP and stressors (Carroll et al., 2003; Kelly et al., 2015; Uchino et al., 2006), the current project adjusted for time-varying daily stressors in the coupled association between BP and cognitive functioning. In the evening survey, participants were provided with a definition of stressful experiences: “*A stressful experience is any experience that presented a challenge or affected you negatively.*” Participants were asked to select the most relevant stressful experience

that occurred since the last survey from ten options, such as “*heard bad or upsetting news,*” “*negative social interaction,*” or “*another stressful experience.*” A dichotomous variable was computed, in which 0 indicated no stressors occurred and 1 indicated that a stressor did occur, and was entered into the models as a time-varying covariate.

Analytic Approach

Due to repeated measurements at the within-person level (i.e., daily measurements are nested within people), multi-level modelling (MLM) analyses were used to answer the proposed research questions. This approach allows systematic separation of intraindividual variability (Level 1) and interindividual variability (Level 2), permitting identification of the level at which the association operates (Bauer, 2011). Within-person coupling procedures (Hoffman & Stawski, 2009) provide the opportunity to examine the extent to which daily fluctuations in cognitive functioning are accounted for by daily fluctuations in BP (as well as self-rated effort, stressors, and physical activity). This approach permits investigation of whether these variables covary together, such that deviations in cognitive functioning are reliably associated with deviations in BP, at the intraindividual level.

Although inconsistent within- versus between-person associations are not unusual (Curran & Bauer, 2011; Rush & Hofer, 2017), intraindividual and interindividual variability sources may be conflated in the case of BP and cognition (Hoffman & Stawski, 2009). This possibility is demonstrated by Gamaldo et al.’s research showing that only individuals with high systolic BP (e.g., prehypertensive and hypertensive range; mean systolic BP ≥ 129) performed poorly on inductive reasoning tasks compared to their average cognitive performance on days when their systolic BP was also above their personal average.

Blood pressure variability and variability in cognitive functioning. Partial correlation coefficients represent the extent to which BPV (SD of sBP and SD of dBP) is associated with variability in cognitive functioning, adjusting for sex and anti-hypertensive medications, as well as mean BP, age, education, effort, physical activity and stressors. Since cognitive functioning scores are expected to improve during the study protocol (i.e., demonstrate a learning effect), the within-person deviations (i.e., error/residuals) around the linear time trend over the two-week protocol were saved from the MPlus models for each cognitive task. Computation for the within-person variability for each cognitive outcome (i.e., intraindividual residual SD) is depicted by the following equation:

$$\text{Residual SD}_i = \sqrt{\frac{\sum |Y_i - (B_i + (\text{slope}_i * \text{time}))|^2}{N_{occasions}}}$$

where Y represents each individuals' observed cognitive value, B represents each participants' unstandardized intercept, slope represents each individuals' estimated cognitive value, time represents the occasion of measurement, and N represents the number of occasions each participant completed during study protocol. This computational approach is preferred for the cognitive functioning assessments (as opposed to using the within-person SD), as there are expected learning effects during the study. The partial correlations explored whether individuals with more variability in BP have more variability in cognitive functioning over the study protocol, adjusting for covariates and the learning effect.

MLMs were built up in terms of complexity. A series of fully unconditional univariate models were fit to partition the variance across the variables into within-person and between-person variability (i.e., the ratio of level-2 residual variance relative to the total variance; intraclass correlation coefficient, ICC). Linear terms were added to the models to investigate

possible learning effects (i.e., systematic changes) over time in the cognitive tasks during the two-week protocol. The trajectories of all outcome and predictor variables were plotted to provide a visual depiction of change and variability. Next, BPV (grand mean centered) was added to the models as a time-invariant variable, along with occasion-specific self-reported effort (i.e., time-varying), and time-invariant covariates: sex, anti-hypertensive medications, grand mean centered effort, mean age, and mean education. These models explored the extent to which BPV is associated with concurrent cognitive functioning.

Blood pressure and cognitive functioning. To examine the extent to which each index of BP (systolic and diastolic) accounts for daily fluctuations in each mobile cognitive assessment (Stroop, Dot Memory, Symbol Search, Colour-Shape, and Colour Dot), time-varying BP and effort were added as predictor variables to the MLMs. These analyses also adjusted for time-invariant, Level 2 covariates: corresponding BP index, grand mean centered; effort, grand mean centered; age in years, mean centered; education as a continuous variable, in which higher values indicate more education; sex, with female as the reference; anti-hypertensive medications, with the reference as no medications. Within-person coupling analyses (Hoffman & Stawski, 2009) provide an indication of the extent to which the variables covary together, and permit investigation of potential systematic deviations in the variables. Specifically, the models examine whether deviations in one variable (e.g., cognitive functioning) are reliably associated with deviations in the other (e.g., BP), adjusting for time-varying effort.

Next, physical activity, included as a time-varying predictor variable, was added to the MLMs examining the coupled association between evening BP and cognitive functioning, adjusting for time-varying effort. These models include only the evening survey and BP recording, since daily physical activity was only recorded in the evening survey. These models

excluded Level 2, between-person covariates due to model complexity and the relatively small sample for between-person comparisons. These models examine the extent to which between-day intraindividual variability in self-reported moderate to vigorous physical activity accounts for the coupling relationship between evening BP and evening cognitive functioning.

Finally, stressors, included as a time-varying predictor variable, was added to the MLMs examining the coupled association between BP and cognitive functioning, adjusting for time-varying effort and physical activity. Again, these models focused on evening measurements, excluded Level 2 covariates, and examined the extent to which between-day intraindividual variability in stressors accounts for the coupling relationship between evening BP and evening cognitive functioning. The full maximum likelihood parameter estimates with robust standard errors (MLR) estimator was used for all models unless otherwise specified; in the case the models would not converge with MLR, the maximum likelihood parameter estimates with standard errors approximated by first-order derivatives (MLF) estimator was used.

Statistical Formula

The primary conditional time-varying covariation models with person-mean centered Level 1 and Level 2 predictors can be displayed as follows:

$$\text{Level 1: } \text{Cognition}_{ij} = \beta_{0i} + \beta_{1i}(\text{Time}_{ij}) + \beta_{2i}((\text{BP} - \text{PM_BP})_i) + \beta_{3i}((\text{effort} - \text{PM_effort})_i) + e_{ij}$$

$$\text{Level 2: } \beta_{0i} = \gamma_{00} + \gamma_{01}(\text{PM_BP}_i) + \gamma_{02}(\text{PM_effort}_i) + \gamma_{03}(\text{Age}_i) + \gamma_{04}(\text{Educ}_i) \\ + \gamma_{05}(\text{Sex}_i) + \gamma_{06}(\text{BPMeds}_i) + u_{0i}$$

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

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

$$\beta_{3i} = \gamma_{30} + u_{3i}$$

where $Cognition_{ij}$ is the cognitive score (for each of the five mobile cognitive assessments) for person i on day j , represented by the predicted cognitive score as a function of that person's intercept (β_{0i}), rate of change with respect to linear trends ($\beta_{1i}(Time_{ij})$). The predicted cognitive score is based on the within-person fluctuations from each individual's average occasion of blood pressure ($\beta_{2i}(BP - PM_BP_i)$), adjusting for within-person effort at each occasion ($\beta_{3i}(effort - PM_effort_i)$), such that the time-varying predictors (BP and effort) represent variation around each individual's own mean level (a within-person association). Additionally, e_{ij} represents the within-person residual variance in daily cognitive functioning. The residuals are assumed to have a multivariate normal distribution with a mean of zero and a variance τ .

At Level 2, γ_{00} represents the average intercept, γ_{10} represents the average within-person effect of linear time on cognitive functioning, and γ_{20} and γ_{30} represent the average within-person effect of BP and effort on cognitive functioning (the within-person coupled associations). The between-person association between average cognitive functioning and grand mean centered BP and effort, mean age and education, sex (with female as the reference) and anti-hypertensive medication use (with no medication as the reference) are represented by γ_{01} to γ_{06} . That is, γ_{01} to γ_{06} are between-person predictors that would indicate whether individual differences (e.g., in BP, effort, education, age, sex, antihypertensive medications) moderate the within-person coupling of cognitive functioning, BP, and effort. If there is residual variability left to be accounted for in cognition, a cross-level interaction term will be added ($\beta_{2i} = \gamma_{20} + \gamma_{21}(PM_BP_i) + u_{2i}$) to represent the within-person association (cognition-BP) as a function of individual differences in average (between-person) level of BP; that is, whether individuals with higher BP on average demonstrate a stronger coupled association between cognitive functioning and BP. Finally, u_{0i} to u_{3i} represent individual deviations from average intercepts and slopes (i.e., random effects).

Though the statistical formulae are not depicted here, the models were built up in terms of complexity, such that physical activity minutes, and then stressors, were added to the models as time-varying covariates. Within these analyses, the predicted cognitive score is also based on the within-person relationship for an average occasion of blood pressure ($\beta_{2i}(\text{BP} - \text{PM_BP}_i)$), as a function of time ($\beta_{1i}(\text{Time}_{ij})$), effort ($\beta_{3i}(\text{effort} - \text{PM_effort}_i)$), physical activity minutes ($\beta_{4i}(\text{Physical Activity} - \text{PM_Physical Activity}_i)$) and the proportion of stressors ($\beta_{5i}(\text{Stressors} - \text{PM_Stressors}_i)$). This results in estimates for the role of time-varying predictors (time, BP, effort, physical activity, and stressors), which represent variation around an individual's own mean level (within-person associations).

It is important to note that the final models included variables that were only assessed at the evening survey (physical activity and stressors), which meant that the morning occasions were omitted from the built-up models and there was no time-of-day effect present within the models. Indeed, this is why a three-level model was not selected for these analyses. However, a series of sensitivity analyses assessed the extent to which time-of-day may have impacted the associations between time-varying cognition, BP, and effort (models that included data from the morning and evening surveys). For example, data from the morning surveys were omitted within these models. Additionally, a time-varying time-of-day predictor variable was added to the models. There were only negligible differences across all sensitivity analyses (i.e., no change in p values).

Results

Twenty-six participants who were contacted for the telephone-screening interview were not eligible to participate. Most exclusions ($N=21$) were due to serious medical concerns (e.g., having undergone recent surgery or chemotherapy treatment, recent stroke, substantial hearing loss, etc.) and five participants were already participating in a study using the same battery of

cognitive measures. In all, 65 community-residing older adults ($M_{\text{age}}=70.5$ years) from Victoria, B.C. and the surrounding communities participated. However, the COVID-19 pandemic halted research that required in-person sessions, and we were forced to cancel intake sessions with the remaining participants. One participant dropped out after only three occasions, bringing our final sample for analysis to 64.

The sample consisted primarily of female (76.6%) and White (84.4%) participants, which is relatively representative of the older adult population in the area. Most participants were highly educated, with 28.1% having completed an undergraduate program, and an additional 39.1% completing a graduate program, law school, or medical school. A quarter of the participants ($n = 17$; 25.8%) were medicated for hypertension. Though the study protocol was intended to be 14 days, scheduling meant that some participants had the devices for more than two weeks. Some participants continued to complete the assessments until their debrief session, which resulted in up to 16 days of assessments. The total number of occasions across participants for all surveys was 2112 ($M_{\text{occasions}}=27.34$, $SD=3.14$; $\text{range}=7-33$) and the total number of occasions across participants for just the evening survey was 861 ($M_{\text{occasions}}= 13.45$; $SD=1.75$; $\text{range}=7-16$). Available data varied slightly across cognitive tests, stressors, and number of physical activity minutes, as some participants exited the survey prior to completion. Further, items regarding stressors and physical activity were only administered at the evening survey. BP data from two participants were lost due to administration errors. These data were missing completely at random, so the participants' cognitive, stressor, physical activity, and demographic variables could be included despite missing BP data (full maximum likelihood estimator was used). Data for 1630 BP recordings were obtained. Characteristics of the participants are reported in Table 1.

Table 2.1 Baseline Characteristics of Participants (N=64)

Variable	M (SD)	N (%)	Range
Age	70.58 (3.5)		64 – 78
Education	4.83 (1.28)		1 – 6
Did not complete high school		1 (1.6)	
High school		4 (6.3)	
Trade school		4 (6.3)	
Some college/university		12 (18.8)	
Undergraduate degree		18 (28.1)	
Graduate, law or medical school		25 (39.1)	
Sex			
Female		49 (76.6)	
Male		15 (23.4)	
Ethnicity			
Caucasian		54 (84.4)	
Asian		4 (6.3)	
NA		6 (9.4)	
BP Indices (N=62)			
Systolic WP	124.53 (12.51)		100.54 – 159.85
Diastolic WP	77.45 (8.38)		59.61 – 105.62
Systolic WP SD	9.61 (2.44)		5.71 – 16.47
Diastolic WP SD	6.33 (1.92)		2.85 – 13.95
Cognitive functioning			
Symbol Search RT	2.78 (0.65)		1.44 – 4.60
Dot Memory accuracy	11.36 (7.38)		0.00 – 28.58
Colour Dot accuracy	84.48 (63.28)		12.43 – 272.99
Colour-Shape accuracy	0.58 (0.35)		0 – 1
Stroop RT	1.75 (0.34)		0.98 – 2.63
Effort WP	86.76 (16.28)		25 – 100
Physical Activity WP	54.72 (31.69)		11.43 – 180.00
Stressors WP	0.29 (0.25)		0 – 1

Note. WP=the within-person mean across the study protocol (i.e., the sample level mean of within-person means is reported); SD=Standard deviation; RT=reaction time in seconds; Physical Activity = self-reported moderate to vigorous physical activity minutes per day

Intraclass Correlation Coefficients for Main Variables

The ICCs indicated that the percentage of within-person variance across cognitive tasks ranged from 37% for Stroop reaction time to 84% for accuracy on the Colour Dot task. In addition to the Colour Dot task, both the Dot Memory (67%) and Colour-Shape (70%) accuracy tasks were characterized by more within-person variance, indicating that individuals vary more occasion-to-occasion, compared to others on cognitive assessments of accuracy. In contrast, both the reaction time tasks (Symbol Search (40%) and Stroop) were characterized by more variability at the between-person level, indicating that some individuals are faster relative to other individuals on average. Both sBP and dBP were characterized by approximately 60% variability at the between-person level and 40% variability at the within-person level across measurement occasions.

Trajectories of Main Variables

The impact of time was examined for each outcome and predictor variable. While participants were expected to improve on the cognitive tasks over the two-week study protocol, sBP or dBP were not expected to show a systematic trajectory. Indeed, there was a significant linear trend for all cognitive tasks, suggesting that participants improved gradually on all five cognitive tasks over the two-week protocol (see Figures 2.1a-2.1b). The linear time trend was significant across all MLMs ($p < 0.001$), regardless of the time-varying and time-invariant covariates included in the models.

As expected, systolic and diastolic BP did not change systematically (see Figures 2.2a and 2.2b). While effort (see Figure 2.3) and stressors (see Figure 2.4) also did not change systematically, physical activity minutes decreased slightly over the study protocol (see Figure 2.5), suggesting that initiation of the study protocol may have instigated increased engagement in

physical activity initially. However, the motivation to engage in more physical activity may have gradually decreased over time, on average, such that participants returned to their typical levels of physical activity. These results are consistent with research suggesting that participating in observational studies that include wearing trackable biofeedback devices increases engagement in physical activity (Franssen et al., 2020; Stockwell et al., 2019).

Figure 2.1a Trajectories of Reaction Time on the Symbol Search Task

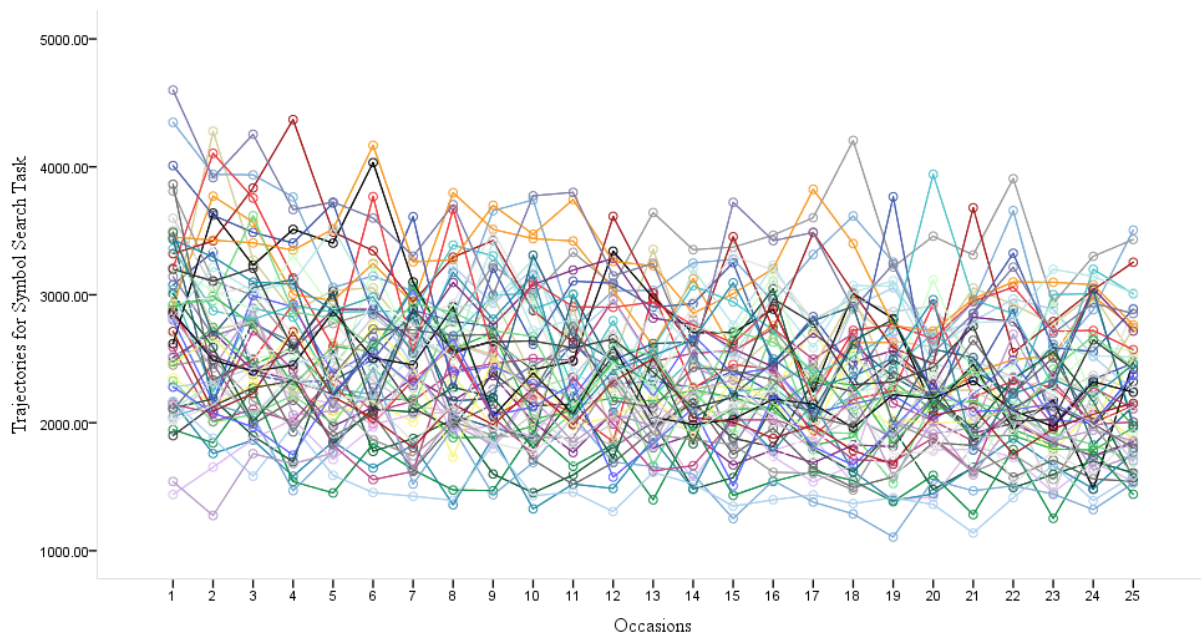


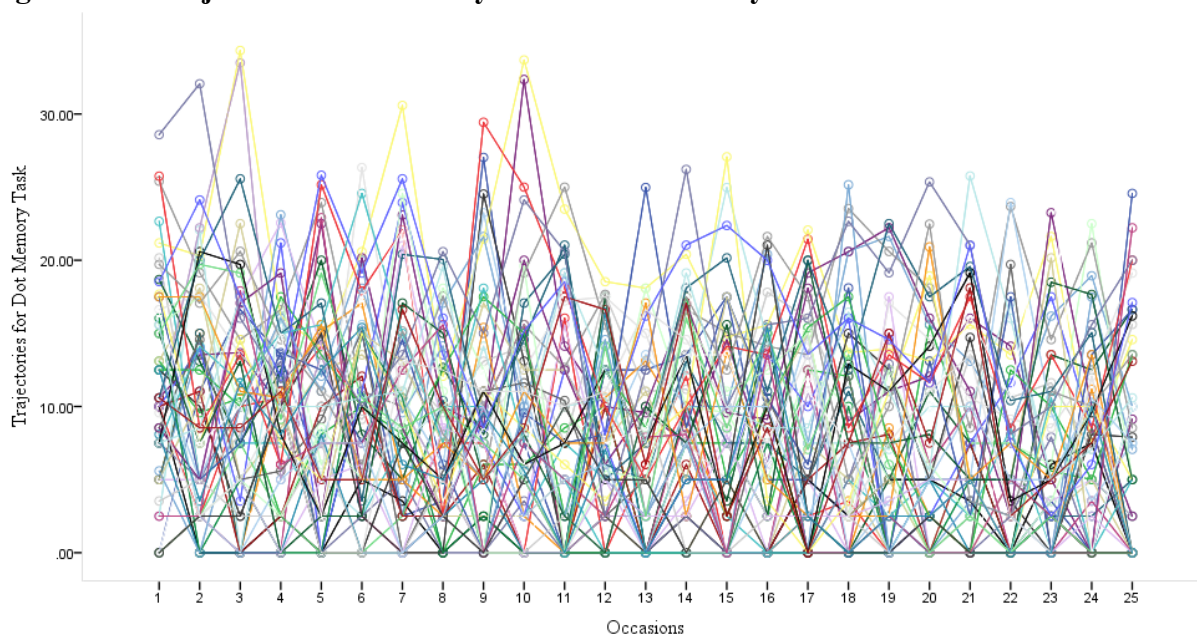
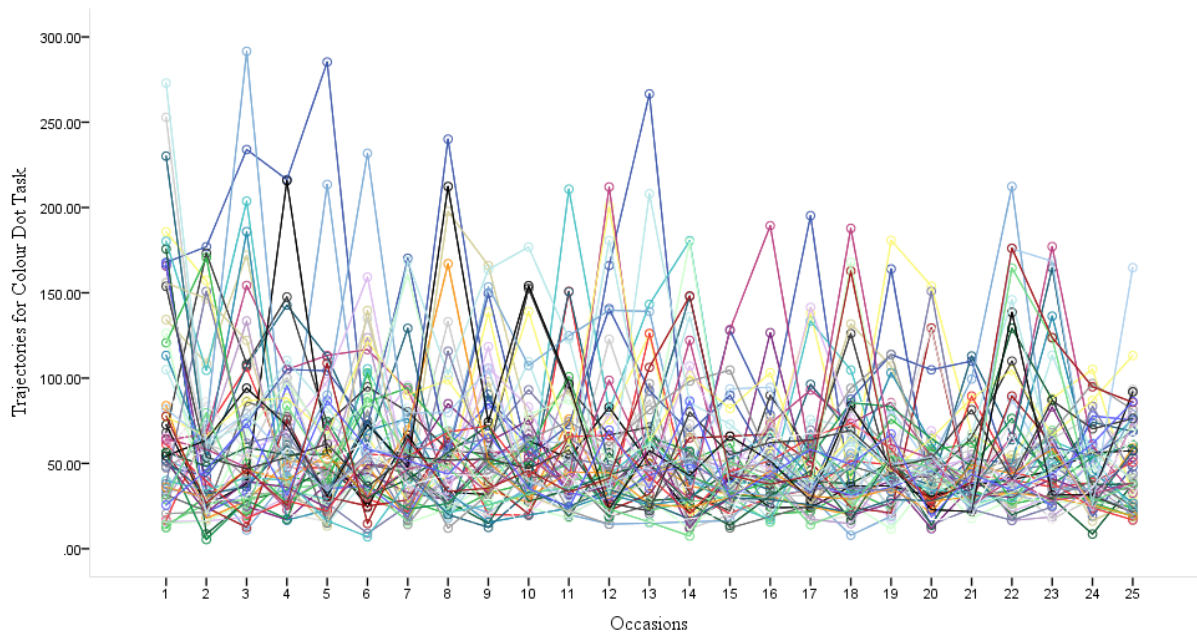
Figure 2.1b Trajectories of Accuracy on the Dot Memory Task**Figure 2.1c Trajectories of Accuracy on the Colour Dot Location Task**

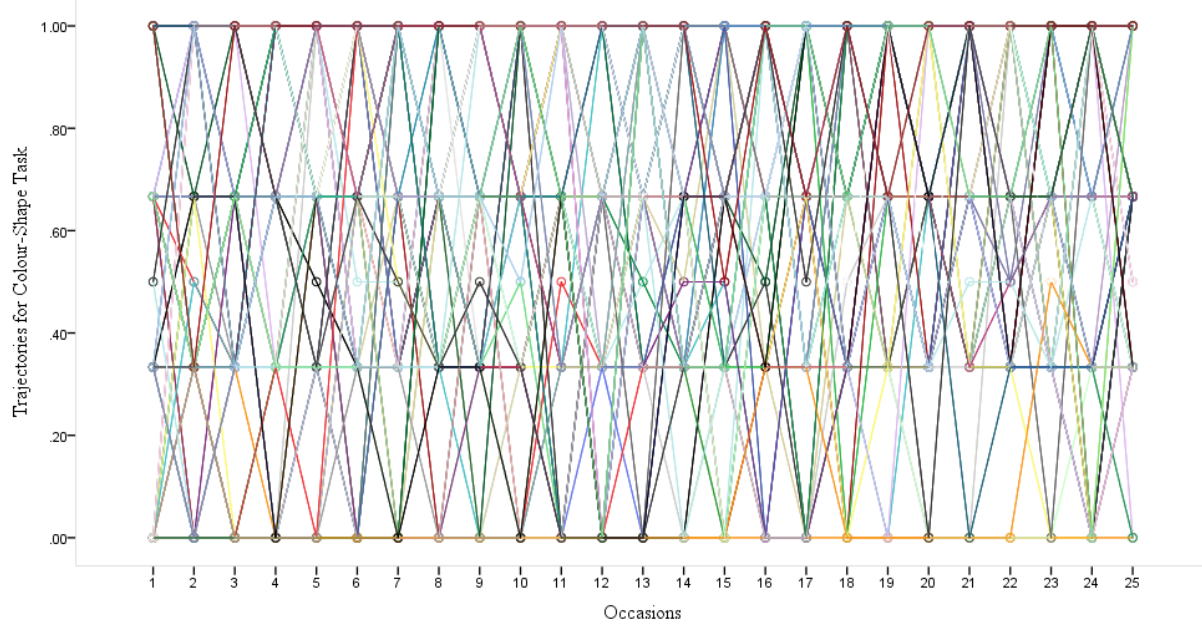
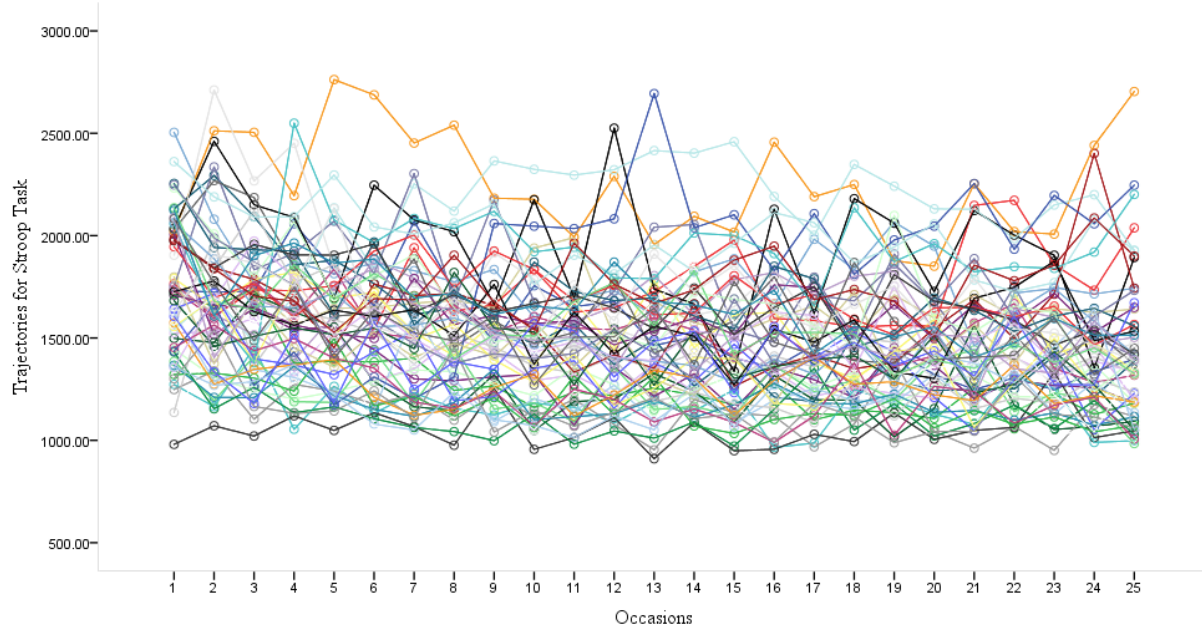
Figure 2.1d Trajectories of Accuracy on the Colour-Shape Task**Figure 2.1e Trajectories of Reaction Time on the Stroop Task**

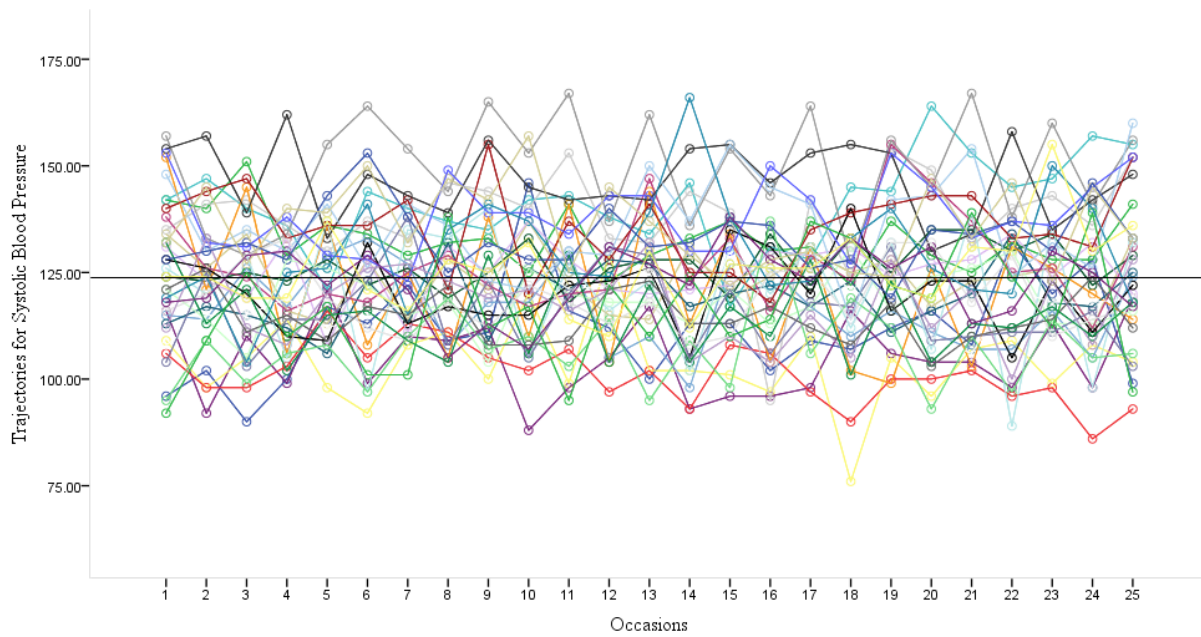
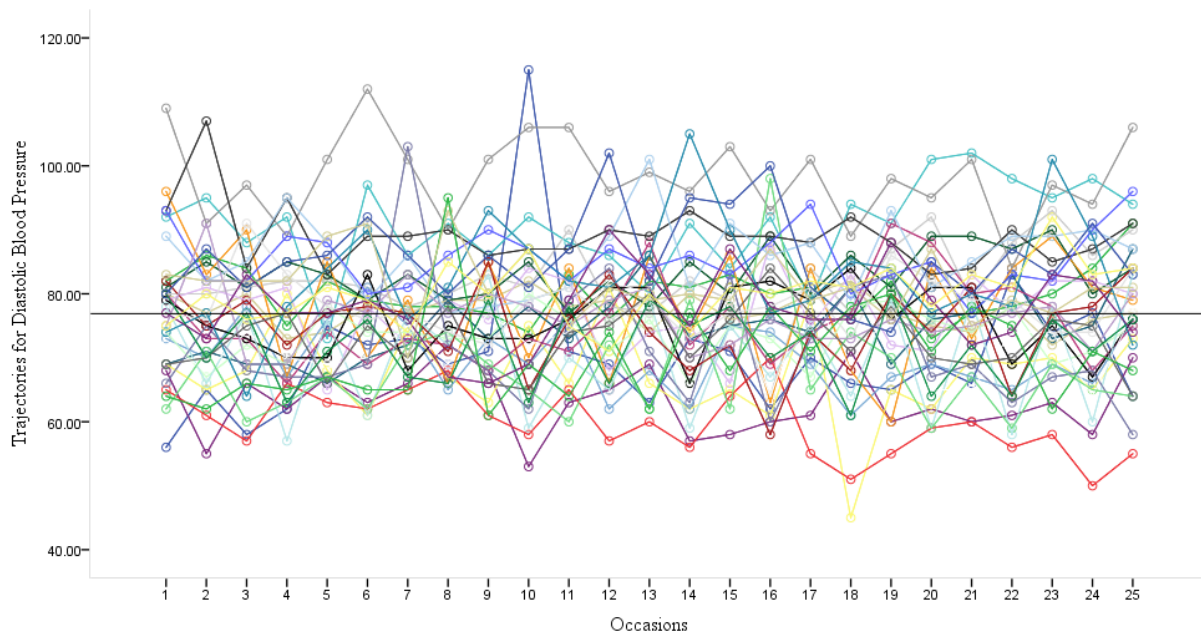
Figure 2.2a Trajectories of Systolic Blood Pressure**Figure 2.2b Trajectories of Diastolic Blood Pressure**

Figure 2.3 Trajectories of Self-Reported Effort

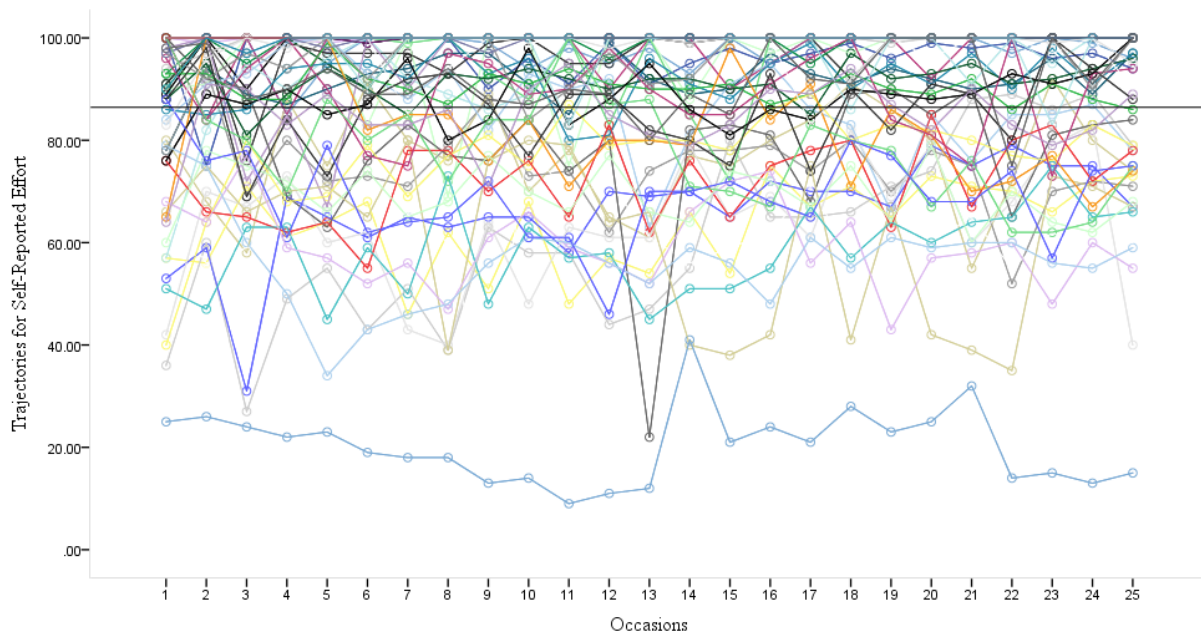


Figure 2.4 Trajectories of Stressor Days

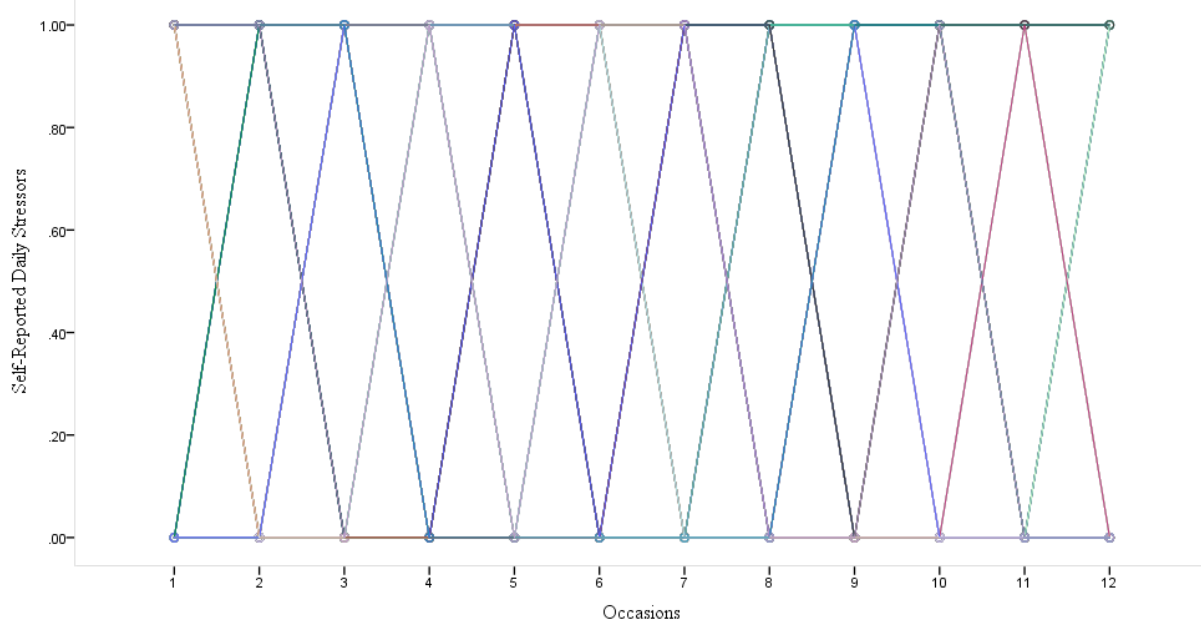
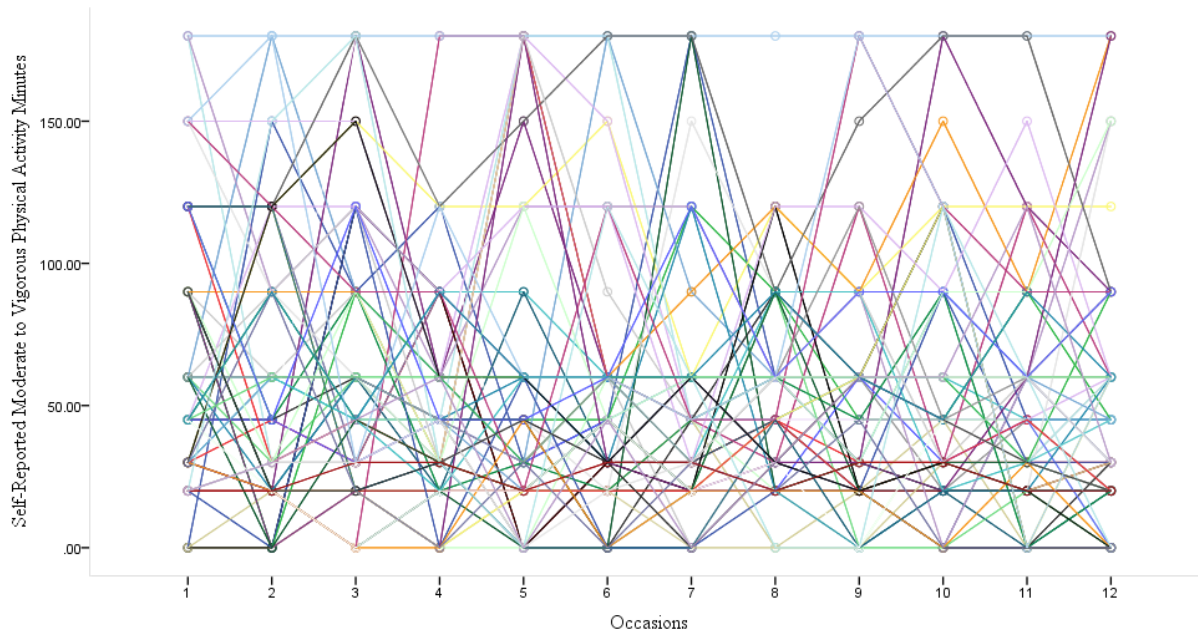


Figure 2.5 Trajectories of Self-Reported Physical Activity Minutes



Partial Correlations for BPV and Cognitive Functioning

Within-person variability in each cognitive outcome was computed, adjusting for individual learning effects during the study protocol (i.e., the within-person SD in cognitive performance around each individual's learning trend). These intraindividual variabilities (IIV, accounting for the learning trend) and the within-person SDs (i.e., ignoring the learning trend) for four out of five cognitive outcomes were highly correlated (Symbol Search SD and IIV $r=0.87, p<0.001$; Dot Memory SD and IIV, $r=0.87, p<0.001$; Colour Dot SD and IIV, $r=0.98, p<0.001$; Stroop SD and IIV, $r=0.91, p<0.001$). In the case of no learning trend during the study protocol, the correlation between the IIVs and SDs would be 1.0. As such, these high correlations reflect minimal learning effects during the study protocol, such that within-person variability in these cognitive tasks is not impacted substantially when accounting for improvement over time, despite a statistically significant linear trend within the multilevel

models. In contrast, the correlation between the IIV and the within-person SD was very small and non-significant ($r=0.03$, $p=0.816$) for the Colour-Shape accuracy task. This low correlation reflects a substantial learning effect during the study protocol; on average, individuals initially performed very poorly on the task, but increased quickly during the study protocol, and eventually many participants accurately identified the shapes in 6/6 trials within a session.

Adjusting for mean age and corresponding mean BP, BPV was not significantly associated with variability in cognitive functioning, with one exception (see Table 2). Specifically, dBPV and Stroop reaction time were associated, suggesting that individuals with more variability in dBP were more variable in resistance to interference during the study protocol. Adjustment for sex, mean education, anti-hypertensive medications, mean physical activity, and mean stressors did not meaningfully impact the correlation results.

Table 2.2 Partial Correlation Coefficients between Intraindividual Variability in the Cognitive Tasks and BPV

Cognitive Task	sBPV	dBPV
	<i>r</i>	
Symbol Search RT	0.31	0.02
Dot Memory accuracy	0.17	0.24
Colour Dot accuracy	0.04	-0.01
Colour-Shape accuracy	0.00	0.10
Stroop RT	0.23	0.28*

Note. Partial correlation coefficients adjust for sex, anti-hypertensive medications, age, education, corresponding BP, effort, moderate to vigorous physical activity minutes, and stressors. BPV=blood pressure variability; s=systolic; d=diastolic; RT=reaction time; * $p<0.05$

Between-Person Associations for BPV and Cognitive Functioning

At the between-person level, MLMs suggested that sBPV was associated with Symbol Search and Stroop reaction times (see Table 2.3a), and dBPV was associated with Symbol

Search reaction time (see Table 2.3b). In all three cases, individuals with more BPV responded significantly more slowly on the cognitive tasks. However, only the association between sBPV and Symbol Search reaction time remained significant above and beyond mean BP. Variability in BP was not associated with accuracy on the Dot Memory, Colour Dot, or Colour-Shape tasks.

Table 2.3a Multilevel Estimates from the Effects of HBPM Systolic Blood Pressure Variability and Effort on Cognitive Tasks

Variable	Symbol search Estimate (SE)	Dot Memory Estimate (SE)	Colour Dot Estimate (SE)	Colour-Shape Estimate (SE)	Stroop Estimate (SE)
Fixed Effects					
WP variables					
Intercept (γ_{00})	2.52 (0.07)***	10.53 (0.688)***	66.48 (4.39)***	0.51 (0.04)***	1634.53 (40.49)***
Linear time (γ_{10})	-0.01 (0.00)***	-0.08 (0.010)***	-0.40 (0.09)***	0.00 (0.00)***	-4.89 (0.69)***
Effort (γ_{20})	-0.00 (0.00)	-0.03 (0.024)	-0.26 (0.15)	-0.00 (0.00)	1.42 (0.68)*
Between-person variables					
sBPV (γ_{01})	0.07 (0.03)**	0.18 (0.26)	1.47 (1.27)	-0.02 (0.02)	29.78 (13.73)*
Effort (γ_{02})	0.01 (0.00)*	-0.04 (0.05)	-0.04 (0.16)	0.00 (0.00)*	1.35 (2.04)
Age (γ_{03})	0.01 (0.02)	0.18 (0.12)	0.32 (0.98)	-0.00 (0.01)	-8.17 (10.05)
Education (γ_{04})	-0.11 (0.05)*	-0.77 (0.38)*	-2.74 (1.51)	0.01 (0.02)	20.48 (24.63)
Sex (γ_{05})	0.11 (0.15)	-2.16 (1.20)	-3.33 (4.75)	-0.09 (0.06)	7.14 (92.60)
BP meds (γ_{06})	0.09 (0.51)	1.13 (0.97)	1.71 (4.32)	-0.07 (0.04)	10.15 (77.25)
Random effects					
WP (σ_e^2)	0.10 (0.01)***	31.52 (1.65)***	1297.03 (131.84)***	0.08 (0.01)***	26834.99 (2461.22)***
Between-person					
Intercept (σ_0^2)	0.17 (0.030)***	12.15 (2.425)***	226.29 (139.778)	0.03 (0.01)***	62694.05 (10873.70)***
Linear time (σ_1^2)	0.00 (0.00)**	0.00 (0.00)	0.01 (0.10)	0.00 (0.00)*	22.61 (8.28)**
Effort (σ_2^2)	0.00 (0.00)	0.00 (0.01)	0.14 (0.14)	0.00 (0.00)	1.49 (3.40)

Note. Results are based on up to 2112 twice-daily assessments ($N = 64$). Lower values indicate better performance on all cognitive tasks except Colour-Shape; HBPM= Home-Based Blood Pressure Monitoring; BPV= Blood pressure variability; sBPV = systolic BPV; WP= Within-person; BP meds= BP medications; Symbol Search= Symbol Search reaction time in seconds; Dot Memory= Dot Memory accuracy in grid units; Colour Dot= Colour Dot accuracy in grid

unit; Colour-Shape= Colour-Shape accuracy; Stroop= Stroop reaction time in milliseconds;
 Bolded values presented on **sBPV** (γ_{01}) row reflect estimates for Prediction 1; * $p < 0.05$;
 ** $p < 0.01$; *** $p < 0.001$

Table 2.3b Multilevel Estimates from the Effects of HBPM Diastolic Blood Pressure Variability and Effort on Cognitive Tasks

Variable	Symbol search Estimate (<i>SE</i>)	Dot Memory Estimate (<i>SE</i>)	Colour Dot Estimate (<i>SE</i>)	Colour-Shape Estimate (<i>SE</i>)	Stroop Estimate (<i>SE</i>)
Fixed Effects					
WP variables					
Intercept (γ_{00})	2.52 (0.07)***	10.52 (0.69)***	66.10 (4.21)***	0.51 (0.04)***	1637.31 (42.30)***
Linear time (γ_{10})	-0.01 (0.00)***	-0.08 (0.01)***	-0.40 (0.09)***	0.00 (0.00)***	-4.89 (0.69)***
Effort (γ_{20})	-0.00 (0.00)	-0.03 (0.02)	-0.26 (0.15)	-0.00 (0.00)	1.43 (0.68)*
Between-person variables					
dBPV (γ_{01})	0.06 (0.03)*	0.20 (0.24)	2.266 (1.36)	-0.016 (0.013)	22.96 (15.43)
Effort (γ_{02})	0.001 (0.01)	-0.04 (0.05)	-0.08 (0.15)	0.004 (0.001)*	0.26 (1.91)
Age (γ_{03})	0.02 (0.02)	0.20 (0.12)	0.41 (1.01)	-0.003 (0.01)	-4.73 (9.95)
Education (γ_{04})	-0.10 (0.05)*	-0.75 (0.38)	-2.71 (1.47)	0.01 (0.02)	25.73 (23.06)
Sex (γ_{05})	0.09 (0.16)	-2.19 (1.23)	-3.07 (4.79)	-0.09 (0.06)	-4.37 (97.62)
BP meds (γ_{06})	0.02 (0.14)	1.20 (1.00)	2.83 (4.533)	-0.07 (0.04)	13.56 (74.81)
Random effects					
WP (σ_e^2)	0.10 (0.01)***	31.52 (1.65)***	1297.45 (129.40)***	0.08 (0.004)***	26840.42 (2463.10)***
Between-person					
Intercept (σ_0^2)	0.18 (0.03)***	12.16 (2.43)***	218.51 (156.65)	0.03 (0.01)***	65001.74 (11141.57)***
Linear time (σ_1^2)	0.00 (0.00)**	0.00 (0.00)	0.00 (0.13)	0.00 (0.00)**	22.535 (8.23)**
Effort (σ_2^2)	0.00 (0.00)	0.00 (0.01)	0.14 (0.15)	0.00 (0.00)	1.429 (3.38)

Note. Results are based on up to 2112 twice-daily assessments ($N = 64$). Lower values indicate better performance on all cognitive tasks except Colour-Shape; HBPM= Home-Based Blood Pressure Monitoring; BPV= Blood pressure variability; dBPV = diastolic BPV; WP= Within-person; BP meds= BP medications; Symbol Search= Symbol Search reaction time in seconds; Dot Memory= Dot Memory accuracy in grid units; Colour Dot= Colour Dot accuracy in grid units; Colour-Shape= Colour-Shape accuracy; Stroop= Stroop reaction time in milliseconds; Bolded values presented on **dBPV** (γ_{01}) row reflect estimates for Prediction 1; * $p < 0.05$;
 ** $p < 0.01$; *** $p < 0.001$

Within-Person Associations for BP and Cognitive Functioning

To resolve convergence issues, Symbol search was rescaled to seconds, rather than milliseconds. At Level 1 (i.e., within-person; intraindividual), analyses did not reveal any significant coupled associations between BP and cognition when only adjusting for effort as a time-varying covariate (see Tables 2.4a and 2.4b). However, once physical activity was added to the model (see Tables 2.5a and 2.5b), the within-person coupled association between sBP and Colour Dot accuracy was marginally significant ($p = 0.052$), and when further adjusting for time-varying stressors (see Tables 2.5c and 2.5d), the coupled association was significant. These results suggest that when individuals have higher sBP compared to their personal average, they perform relatively worse on the Colour Dot task (on occasions when they engage in their average level of effort, physical activity and stressors). Mean sBP was also significant within these models, which suggests that the coupled, within-person relationship between sBP and Colour Dot accuracy is stronger for individuals with higher average sBP relative to individuals with lower average sBP.

The coupled association between Colour-Shape location accuracy and dBP was also marginally significant when adjusting for time-varying effort and physical activity ($p = 0.054$; see Table 2.5b), as well as when adjusting for time-varying effort, physical activity and stressors ($p = 0.059$; see Table 2.5d). These results suggest that when individuals have higher dBP compared to their person average, they are less accurate on the Colour-Shape task compared to their personal average (on occasions when they engage in their average level of effort, physical activity, and stressors). None of the residuals for the coupled association between cognitive functioning and BP were significant, so a cross-level interaction term was not added to the models.

Within-Person Associations for Cognitive Functioning and Covariates

At Level 1, there was a significant coupled association between self-reported effort and Stroop reaction time, for both the sBP (see Table 2.4a) and dBP models (see Table 2.4b). The positive coupled association between the constructs suggests that on occasions when individuals reported more effort compared to their personal average across occasions, their reaction time increased (i.e., they performed less well on the task). These results seem somewhat counterintuitive, but this may reflect care in accurate responding over speed of responding. Though participants correctly identified 12/12 trials in 70.3% of sessions, and at least 6/12 trials in 99.98% of sessions (i.e., the majority were mostly accurate), slowing down just enough to ensure responses were correct may account for this coupled association. Further, reaction time metrics do not account for error rate. Once time-varying physical activity minutes were added to the models (see Table 2.5a and 2.5b), the within-person coupled association was no longer significant in either the sBP or dBP models, suggesting that the significant variability in the model taken up by effort is mediated by that day's physical activity minutes. Analyses did not reveal any other significant coupled associations between effort and cognitive functioning.

One additional significant coupled association appeared between physical activity and Symbol Search reaction time, consistently across both the sBP and dBP models, and when stressors were added to the models (see Tables 2.5c and 2.5d). The association was positive, suggesting that on occasions when individuals engaged in more physical activity, their reaction time increased (i.e., they performed less well on the task). Again, this result is somewhat unexpected, as existing literature suggests that physical activity tends to improve cognitive performance. However, many studies in this literature do not examine daily physical activity, and/or examine the association based on clinical cognitive tests as opposed to mobile measures

of cognition in a daily context, and perhaps individuals who engage in several hours of physical activity (which was often the case within this sample) become fatigued and react more slowly.

Between-Person Associations for BP and Cognitive Functioning

At Level 2, analyses suggest that individuals with higher overall sBP and dBP relative to others were less accurate on the Colour Dot and Colour-Shape tasks, on average (see Tables 2.4a and 2.4b). These results suggest that participants with higher sBP and dBP on average were less accurate compared to individuals with lower sBP and dBP, adjusting for mean age and education, sex, and BP medications. These significant effects persisted for models adjusted for time-varying physical activity and stressors (see Table 2.5a-2.5c) except one; average dBP over time was no longer significantly associated with accuracy on the Colour Dot task when physical activity and stressors were added to the models (see Table 2.5d). Mean level of sBP and dBP were not associated with Stroop reaction time or Dot Memory accuracy.

Between-Person Associations for Cognitive Functioning and Covariates

Mean level of effort was a significant interindividual predictor of Symbol Search reaction time, adjusting for time-varying dBP, physical activity (see Table 2.5c), and stressors (see Table 2.5d). Specifically, individuals who report more effort on average, were also significantly slower on the symbol search task, on average, adjusting for dBP, physical activity, and stressors. Likewise, participants who reported more effort on average, were more accurate on the Dot Memory task, adjusting for time-varying dBP or sBP, physical activity (see Table 2.5a and 2.5b), and stressors (see Table 2.5c and 2.5d). Further, individuals who reported more effort on average performed less accurately on the Colour-Shape task (see Table 2.4a), though the between-person association was no longer significant after adding physical activity (see Table 2.5c) and stressors

(see Table 2.5d) to the sBP and dBP models. Between-person differences in effort were not associated with on Colour Dot location accuracy or Stroop reaction time.

Sex was a significant between-person covariate, but only for the models examining the coupled association between Dot Memory accuracy, BP (sBP and dBP), and effort (see Tables 2.4a and 2.4b). These results suggest that on average, men were more accurate on the Dot Memory task on average compared to women. Finally, education was a significant between-person covariate in the models examining the association between BPV and Symbol Search and BPV and Dot Memory, suggesting that individuals with more education performed better on the Symbol Search and Dot Memory (see Table 2.3a and 2.3b) tasks.

Table 2.4a Multilevel Estimates from the Effects of HBPM Systolic Blood Pressure and Effort on Cognitive Tasks

Variable	Symbol search Estimate (<i>SE</i>)	Dot Memory Estimate (<i>SE</i>)	Colour Dot Estimate (<i>SE</i>)	Colour-Shape Estimate (<i>SE</i>)	Stroop Estimate (<i>SE</i>)
Fixed Effects					
WP variables					
Intercept (γ_{00})	2.59 (0.07)***	10.66 (0.65)***	68.15 (4.66)***	0.51 (0.04)***	1662.83 (42.49)***
Linear time (γ_{10})	-0.01 (0.00)***	-0.08 (0.01)***	-0.38 (0.09)***	0.00 (0.00)***	-5.07 (0.74)***
sBP (γ_{20})	-0.00 (0.00)	-0.02 (0.02)	0.14 (0.11)	0.00 (0.00)	0.236 (0.53)
Effort (γ_{30})	-0.00 (0.00)	-0.03 (0.03)	-0.29 (0.20)	-0.00 (0.00)	1.50 (0.68)*
Between-person variables					
sBP (γ_{01})	0.01 (0.01)	0.03 (0.03)	0.52 (0.22)*	-0.01 (0.00)*	4.29 (2.54)
Effort (γ_{02})	0.01 (0.00)	-0.04 (0.05)	-0.01 (0.17)	0.00 (0.00)*	0.83 (1.98)
Age (γ_{03})	0.02 (0.02)	0.20 (0.12)	0.42 (1.32)	-0.00 (0.01)	-4.12 (10.46)
Education (γ_{04})	-0.09 (0.05)	-0.72 (0.37)	-2.43 (1.65)	0.01 (0.02)	31.84 (24.44)
Sex (γ_{05})	0.01 (0.16)	-2.56 (1.23)*	-8.23 (5.81)	-0.06 (0.06)	-36.65 (99.12)
BP meds (γ_{06})	0.00 (0.15)	0.86 (1.01)	-1.44 (5.01)	-0.03 (0.04)	-28.54 (78.45)
Random effects					
WP (σ_e^2)	0.10 (0.01)***	31.12 (1.73)***	1275.33 (157.56)***	0.08 (0.00)***	26380.27 (2413.29)***
Between-person					
Intercept (σ_0^2)	0.19 (0.03)***	12.30 (2.38)***	217.17 (365.59)	0.02 (0.01)***	67850.63 (11494.92)**
Linear time (σ_1^2)	0.00 (0.00)**	0.00 (0.00)	0.00 (0.32)	0.00 (0.00)**	24.64 (9.19)*
sBP (σ_2^2)	0.00 (0.00)	0.00 (0.00)	0.18 (0.23)	0.00 (0.00)	5.32 (3.69)
Effort (σ_3^2)	0.00 (0.00)	0.00 (0.01)	0.17 (0.15)	0.00 (0.00)	1.06 (2.78)

Note. Results are based on up to 2112 twice-daily assessments ($N = 64$). Lower values indicate better performance on all cognitive tasks except Colour-Shape; HBPM= Home-Based Blood Pressure Monitoring; BP= Blood pressure; sBP = systolic BP; WP= Within-person; BP meds= BP medications; Symbol Search= Symbol Search reaction time in seconds; Dot Memory= Dot Memory accuracy in grid units; Colour Dot= Colour Dot accuracy in grid unit; Colour-Shape= Colour-Shape accuracy; Stroop= Stroop reaction time in milliseconds; Bolded values presented on **sBP (γ_{01}) row** reflect estimates for Prediction 2; Bolded values presented on **sBP (γ_{20}) row** reflect estimates for Prediction 3; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 2.4b Multilevel Estimates from the Effects of HBPM Diastolic Blood Pressure and Effort on Cognitive Tasks

Variable	Symbol search Estimate (SE)	Dot Memory Estimate (SE)	Colour Dot Estimate (SE)	Colour-Shape Estimate (SE)	Stroop Estimate (SE)
Fixed Effects					
WP variables					
Intercept (γ_{00})	2.59 (0.07)***	10.62 (0.66)***	68.06 (4.61)***	0.51 (0.04)***	1656.79 (42.25)***
Linear time (γ_{10})	-0.01 (0.00)***	-0.08 (0.01)***	-0.39 (0.09)***	0.00 (0.00)***	-5.04 (0.73)***
dBP (γ_{20})	-0.00 (0.00)	-0.03 (0.02)	0.22 (0.17)	0.00 (0.00)	-0.42 (0.78)
Effort (γ_{30})	-0.00 (0.00)	-0.03 (0.03)	-0.27 (0.16)	-0.00 (0.00)	1.47 (0.67)*
Between-person variables					
dBP (γ_{01})	0.02 (0.01)*	0.03 (0.05)	0.71 (0.28)*	-0.01 (0.00)*	4.01 (3.87)
Effort (γ_{02})	0.01 (0.00)*	-0.04 (0.05)	-0.00 (0.16)	0.00 (0.00)*	0.58 (2.02)
Age (γ_{03})	0.02 (0.02)	0.21 (0.12)	0.61 (0.75)	-0.00 (0.01)	-2.52 (10.49)
Education (γ_{04})	-0.09 (0.05)	-0.71 (0.38)	-2.33 (1.69)	0.01 (0.02)	32.04 (24.36)
Sex (γ_{05})	-0.01 (0.16)	-2.54 (1.27)*	-9.06 (5.32)	-0.05 (0.06)	-33.34 (99.42)
BP meds (γ_{06})	0.02 (0.14)	0.95 (1.01)	-0.21 (4.69)	-0.04 (0.04)	-15.91 (77.00)
Random effects					
WP (σ_e^2)	0.10 (0.01)***	31.29 (1.74)***	1274.04 (139.03)***	0.08 (0.00)***	26576.70 (2404.27)***
Between-person					
Intercept (σ_0^2)	0.18 (0.03)***	12.38 (2.39)***	221.43 (46.28)***	0.02 (0.01)***	69027.32 (11414.88)***
Linear time (σ_1^2)	0.00 (0.00)**	0.00 (0.00)	0.00 (0.07)	0.00 (0.00)**	2.32 (8.96)**
dBP (σ_2^2)	0.00 (0.00)	0.00 (0.01)	0.42 (0.27)	0.00 (0.00)	8.17 (6.08)
Effort (σ_3^2)	0.00 (0.00)	0.00 (0.01)	0.17 (0.16)	0.00 (0.00)	1.00 (2.81)

Note. Results are based on up to 2112 twice-daily assessments ($N = 64$). Lower values indicate better performance on all cognitive tasks except Colour-Shape; HBPM= Home-Based Blood Pressure Monitoring; BP= Blood pressure; dBP = diastolic BP; WP= Within-person; BP meds= BP medications; Symbol Search= Symbol Search reaction time in seconds; Dot Memory= Dot Memory accuracy in grid units; Colour Dot= Colour Dot accuracy in grid unit; Colour-Shape= Colour-Shape accuracy; Stroop= Stroop reaction time in milliseconds; Bolded values presented on **dBP (γ_{01}) row** reflect estimates for Prediction 2; Bolded values presented on **dBP (γ_{20}) row** reflect estimates for Prediction 3; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 2.5a Multilevel Estimates from the Effects of HBPM Systolic Blood Pressure, Effort, and Physical Activity on Cognitive Tasks

Variable	Symbol search Estimate (<i>SE</i>)	Dot Memory Estimate (<i>SE</i>)	Colour Dot Estimate (<i>SE</i>)	Colour-Shape Estimate (<i>SE</i>)	Stroop Estimate (<i>SE</i>)
Fixed Effects					
WP variables					
Intercept (γ_{00})	2.62 (0.06)***	10.46 (0.90)***	62.05 (3.73)***	0.45 (0.03)***	1632.66 (49.98)***
Linear time (γ_{10})	-0.01 (0.00)***	-0.08 (0.02)***	-0.26 (0.09)**	0.00 (0.00)***	-4.72 (0.92)***
sBP (γ_{20})	0.00 (0.00)	-0.04 (0.03)	0.21 (0.11)	0.00 (0.00)	0.52 (0.88)
Effort (γ_{30})	0.00 (0.00)	-0.02 (0.05)	-0.43 (0.29)	-0.00 (0.00)	1.90 (1.57)
PA (γ_{40})	0.00 (0.00)*	0.011 (0.01)	0.02 (0.04)	0.00 (0.00)	0.10 (0.26)
Stressors (γ_{50})	--	--	--	--	--
Between-person variables					
sBP (γ_{01})	0.01 (0.01)	0.03 (0.06)	0.31 (0.15)*	-0.01 (0.00)*	3.47 (4.39)
Effort (γ_{02})	0.01 (0.00)	-0.07 (0.03)*	-0.13 (0.16)	0.00 (0.00)	0.83 (3.09)
PA (γ_{03})	-0.00 (0.00)	-0.01 (0.03)	0.03 (0.09)	0.00 (0.00)	1.15 (1.00)
Stressors (γ_{04})	--	--	--	--	--
Random effects					
WP (σ_e^2)	0.10 (0.01)***	29.24 (1.82)***	1192.60 (134.20)***	0.08 (0.01)***	24833.92 (1485.68)***
Between-person					
Intercept (σ_0^2)	0.18 (0.03)***	17.50 (5.15)**	145.07 (68.95)*	0.02 (0.01)*	69884.15 (14751.14)***
Linear time (σ_1^2)	0.00 (0.00)	0.00 (0.00)	0.01 (0.07)	0.00 (0.00)	17.79 (7.32)*
sBP (σ_2^2)	0.00 (0.00)	0.00 (0.01)	0.014 (0.72)	0.00 (0.00)	0.28 (6.10)
Effort (σ_3^2)	0.00 (0.00)	0.00 (0.01)	1.034 (1.29)	0.00 (0.00)	0.50 (14.49)
PA (σ_4^2)	0.00 (0.00)	0.00 (0.00)	0.023 (0.02)	0.00 (0.00)	0.04 (0.31)

Note. Results are based on up to 2112 twice-daily assessments ($N = 64$). Lower values indicate better performance on all cognitive tasks except Colour-Shape; HBPM= Home-Based Blood Pressure Monitoring; BP= Blood pressure; dBP = diastolic BP; WP= Within-person; BP meds= BP medications; PA= physical activity; Symbol Search= Symbol Search reaction time in seconds; Dot Memory= Dot Memory accuracy in grid units; Colour Dot= Colour Dot accuracy in grid unit; Colour-Shape= Colour-Shape accuracy; Stroop= Stroop reaction time in milliseconds; Bolded values presented on **sBP (γ_{01}) row** reflect estimates for Prediction 2; Bolded values presented on **sBP (γ_{20}) row** reflect estimates for Prediction 3; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 2.5b Multilevel Estimates from the Effects of HBPM Diastolic Blood Pressure, Effort and Physical Activity on Cognitive Tasks

Variable	Symbol search Estimate (SE)	Dot Memory Estimate (SE)	Colour Dot Estimate (SE)	Colour-Shape Estimate (SE)	Stroop Estimate (SE)
Fixed Effects					
WP variables					
Intercept (γ_{00})	2.60 (0.06)***	10.47 (0.92)***	62.17 (3.65)***	0.46 (0.03)***	1632.83 (49.41)***
Linear time (γ_{10})	-0.01 (0.00)***	-0.08 (0.02)***	-0.26 (0.09)**	0.00 (0.00)***	-4.723 (0.92)***
dBP (γ_{20})	-0.00 (0.00)	-0.02 (0.04)	0.25 (0.17)	0.00 (0.00)	0.611 (1.06)
Effort (γ_{30})	0.00 (0.00)	-0.02 (0.05)	-0.44 (0.30)	-0.00 (0.00)	1.859 (1.55)
PA (γ_{40})	0.00 (0.00)*	0.01 (0.01)	0.02 (0.04)	0.00 (0.00)	0.097 (0.27)
Stressors (γ_{50})	--	--	--	--	--
Between-person variables					
dBP (γ_{01})	0.01 (0.01)	0.03 (0.10)	0.40 (0.24)	-0.01 (0.00)*	3.385 (6.20)
Effort (γ_{02})	0.01 (0.00)	-0.08 (0.03)*	-0.13 (0.16)	0.00 (0.00)	0.647 (3.17)
PA (γ_{03})	-0.00 (0.00)	0.01 (0.03)	0.04 (0.09)	0.00 (0.00)	1.180 (1.03)
Stressors (γ_{04})	--	--	--	--	--
Random effects					
WP (σ_e^2)	0.10 (0.01)***	29.25 (1.82)***	1189.87 (138.41)***	0.08 (0.01)***	24687.83 (1646.61)***
Between-person					
Intercept (σ_0^2)	0.18 (0.03)***	17.48 (5.22)**	148.64 (51.26)**	0.02 (0.01)*	70660.71 (15180.88)**
Linear time (σ_1^2)	0.00 (0.00)	0.00 (0.00)	0.02 (0.06)	0.00 (0.00)	17.95 (6.90)
dBP (σ_2^2)	0.00 (0.00)	0.00 (0.01)	0.07 (0.26)	0.00 (0.00)	2.80 (8.86)
Effort (σ_3^2)	0.00 (0.00)	0.00 (0.01)	1.09 (1.34)	0.00 (0.00)	0.49 (14.88)
PA (σ_4^2)	0.00 (0.00)	0.00 (0.00)	0.02 (0.02)	0.00 (0.00)	0.04 (0.31)
Stressors (σ_5^2)	--	--	--	--	--

Note. Results are based on up to 2112 twice-daily assessments ($N = 64$). Lower values indicate better performance on all cognitive tasks except Colour-Shape; HBPM= Home-Based Blood Pressure Monitoring; BP= Blood pressure; dBP = diastolic BP; WP= Within-person; BP meds= BP medications; PA= physical activity; Symbol Search= Symbol Search reaction time in seconds; Dot Memory= Dot Memory accuracy in grid units; Colour Dot= Colour Dot accuracy in grid unit; Colour-Shape= Colour-Shape accuracy; Stroop= Stroop reaction time in milliseconds; Bolded values presented on **dBP (γ_{01}) row** reflect estimates for Prediction 2; Bolded values presented on **dBP (γ_{20}) row** reflect estimates for Prediction 3; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 2.5c Multilevel Estimates from the Effects of HBPM Systolic Blood Pressure, Effort, Physical Activity, and Stressors on Cognitive Tasks

Variable	Symbol search Estimate (SE)	Dot Memory Estimate (SE)	Colour Dot Estimate (SE)	Colour-Shape Estimate (SE)	Stroop Estimate (SE)
Fixed Effects					
WP variables					
Intercept (γ_{00})	2.60 (0.06)***	10.25 (0.98)***	61.74 (3.66)***	0.45 (0.03)***	1632.11 (59.95)***
Linear time (γ_{10})	-0.01 (0.00)***	-0.08 (0.02)***	-0.26 (0.09)**	0.00 (0.00)***	-4.71 (0.92)***
sBP (γ_{20})	0.00 (0.00)	-0.04 (0.03)	0.21 (0.10)*	0.00 (0.00)	0.50 (0.89)
Effort (γ_{30})	0.00 (0.00)	-0.02 (0.05)	-0.43 (0.29)	-0.00 (0.00)	1.81 (1.78)
PA (γ_{40})	0.00 (0.00)*	0.01 (0.01)	0.02 (0.05)	0.00 (0.00)	0.10 (0.27)
Stressors (γ_{50})	-0.01 (0.03)	0.28 (0.70)	-0.63 (3.37)	0.01 (0.03)	4.92 (20.40)
Between-person variables					
sBP (γ_{01})	0.01 (0.01)	0.04 (0.06)	0.32 (0.14)*	-0.01 (0.00)*	3.29 (4.50)
Effort (γ_{02})	0.01 (0.00)*	-0.07 (0.03)*	-0.13 (0.17)	0.00 (0.00)	0.91 (3.49)
PA (γ_{03})	-0.00 (0.00)	-0.01 (0.03)	0.03 (0.09)	-0.17 (0.11)	1.15 (1.16)
Stressors (γ_{04})	0.22 (0.23)	-0.36 (3.42)	-2.11 (8.78)	0.00 (0.00)	47.31 (187.08)
Random effects					
WP (σ_e^2)	0.10 (0.01)***	29.22 (1.88)***	1192.21 (131.69)***	0.08 (0.01)***	24822.64 (1566.82)***
Between-person					
Intercept (σ_0^2)	0.18 (0.03)***	17.50 (5.61)**	145.10 (68.39)*	0.02 (0.01)***	69605.90 (17933.05)*
Linear time (σ_1^2)	0.00 (0.00)	0.00 (0.00)	0.01 (0.07)	0.00 (0.00)	17.734 (7.483)
sBP (σ_2^2)	0.00 (0.00)	0.00 (0.01)	0.01 (0.71)	0.00 (0.00)	0.31 (6.57)
Effort (σ_3^2)	0.00 (0.00)	0.00 (0.02)	1.04 (1.33)	0.00 (0.00)	0.52 (14.94)
PA (σ_4^2)	0.00 (0.02)	0.00 (0.00)	0.02 (0.02)	0.00 (0.00)	0.05 (0.35)
Stressors (σ_5^2)	0.00 (0.00)	0.15 (4.25)	0.97 (140.94)	0.00 (0.01)	1.00 (3661.03)

Note. Results are based on up to 2112 twice-daily assessments ($N = 64$). Lower values indicate better performance on all cognitive tasks except Colour-Shape; HBPM= Home-Based Blood Pressure Monitoring; BP= Blood pressure; dBP = diastolic BP; WP= Within-person; BP meds= BP medications; PA= physical activity; Symbol Search= Symbol Search reaction time in seconds; Dot Memory= Dot Memory accuracy in grid units; Colour Dot= Colour Dot accuracy in grid unit; Colour-Shape= Colour-Shape accuracy; Stroop= Stroop reaction time in milliseconds; Bolded values presented on **sBP (γ_{01}) row** reflect estimates for Prediction 2; Bolded values presented on **sBP (γ_{20}) row** reflect estimates for Prediction 3; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 2.5d Multilevel Estimates from the Effects of HBPM Diastolic Blood Pressure, Effort, Physical Activity, and Stressors on Cognitive Tasks

Variable	Symbol search Estimate (SE)	Dot Memory Estimate (SE)	Colour Dot Estimate (SE)	Colour-Shape Estimate (SE)	Stroop Estimate (SE)
Fixed Effects					
WP variables					
Intercept (γ_{00})	2.60 (0.06)***	10.46 (0.97)***	62.19 (3.65)***	0.46 (0.03)***	1632.40 (57.89)***
Linear time (γ_{10})	-0.01 (0.00)***	-0.08 (0.02)***	-0.27 (0.09)**	0.00 (0.00)***	-4.716 (0.93)***
dBP (γ_{20})	-0.00 (0.00)	-0.02 (0.04)	0.25 (0.17)	0.00 (0.00)	0.60 (1.10)
Effort (γ_{30})	0.00 (0.00)	-0.02 (0.05)	-0.44 (0.30)	-0.00 (0.00)	1.868 (1.74)
PA (γ_{40})	0.00 (0.00)*	0.01 (0.01)	0.02 (0.05)	0.00 (0.00)	0.098 (0.27)
Stressors (γ_{50})	-0.01 (0.03)	0.27 (0.71)	0.02 (0.05)	0.01 (0.03)	4.940 (20.15)
Between-person variables					
dBP (γ_{01})	0.01 (0.01)	0.03 (0.10)	0.42 (0.233)	-0.01 (0.00)*	3.003 (6.44)
Effort (γ_{02})	0.01 (0.00)*	-0.08 (0.03)*	-0.14 (0.163)	0.00 (0.00)	0.729 (3.56)
PA	-0.00 (0.00)	0.01 (0.03)	0.04 (0.087)	0.00 (0.00)	1.168 (1.20)
Stressors	-0.22 (0.23)	-0.12 (3.24)	-2.53 (9.175)	-0.17 (0.11)	55.513 (187.37)
Random effects					
WP (σ_e^2)	0.10 (0.01)***	29.23 (1.87)***	1189.59 (137.22)***	0.079 (0.01)***	24671.14 (1721.43)***
Between-person					
Intercept (σ_0^2)	0.18 (0.03)***	17.49 (5.61)**	148.54 (50.37)**	0.019 (0.01)***	70408.45 (18186.18)***
Linear time (σ_1^2)	0.00 (0.00)	0.00 (0.00)	0.01 (0.06)	0.00 (0.00)	17.90 (7.02)*
dBP (σ_2^2)	0.00 (0.00)	0.00 (0.01)	0.07 (0.25)	0.00 (0.00)	2.979 (9.29)
Effort (σ_3^2)	0.00 (0.00)	0.00 (0.01)	1.10 (1.37)	0.00 (0.00)	0.515 (15.08)
PA (σ_4^2)	0.00 (0.00)	0.00 (0.00)	0.02 (0.02)	0.00 (0.00)	0.047 (0.35)
Stressors (σ_5^2)	0.00 (0.02)	0.15 (4.11)	0.98 (142.32)	0.00 (0.01)	1.00 (3507.22)

Note. Results are based on up to 2112 twice-daily assessments ($N = 64$). Lower values indicate better performance on all cognitive tasks except Colour-Shape; HBPM= Home-Based Blood Pressure Monitoring; BP= Blood pressure; dBP = diastolic BP; WP= Within-person; BP meds= BP medications; PA= physical activity; Symbol Search= Symbol Search reaction time in seconds; Dot Memory= Dot Memory accuracy in grid units; Colour Dot= Colour Dot accuracy in grid unit; Colour-Shape= Colour-Shape accuracy; Stroop= Stroop reaction time in milliseconds; Bolded values presented on **dBP (γ_{01}) row** reflect estimates for Prediction 2; Bolded values presented on **dBP (γ_{20}) row** reflect estimates for Prediction 3; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Discussion

This project investigated the extent to which BP and BPV, assessed via twice-daily HBPM recordings, are associated with cognitive functioning and variability in cognitive functioning, assessed by a battery of five cognitive tests in the context of day-to-day life. Within-person and between-person associations were considered through the application of partial correlation coefficients and a series of multilevel models, applied to data collected via an intensive measurement design. *Overall* results suggest a relatively consistent pattern of associations at both levels of analysis; that is, higher BP and BPV were associated with worse cognitive functioning at both the within-person and between-person levels. Further, results suggest a pattern of differences in the associations between BPV and BP. Specifically, in our sample, higher BPV appears to be associated with slower and more variable performance on the Symbol Search and Stroop tasks, whereas higher BP appears to be associated with poorer performance on the Colour Dot and Colour-Shape tasks. However, these analyses were relatively exploratory in nature and not well powered for between-person comparisons. Further, Type 1 error may be a factor given the multiplicity of analyses.

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Partial correlation coefficients revealed a significant positive association between dBPV and variability in Stroop reaction time, adjusting for the learning effect during the study protocol, as well as additional between-person covariates (sex, anti-hypertensive medications, and mean age, education, effort, physical activity minutes, and stress). This finding suggests that individuals who have higher dBPV are more variable in reaction time during the study protocol. Partial correlation coefficients did not reveal significant associations between sBPV or dBPV and variability in any of the other four cognitive outcomes. As such, the current project provides

relatively limited evidence that higher BPV is associated with more variability in cognitive functioning. However, these results may be more meaningful when considering the between-person estimates from the MLM analyses examining concurrent BPV and cognitive functioning during the study protocol. Specifically, the analyses suggested that sBPV was associated with Symbol Search and Stroop reaction time, and that dBPV was also associated with Symbol Search reaction time. In each of these cases, individuals with higher BPV on average were significantly slower on the reaction time cognitive tasks, on average.

Together, these results are partially consistent with prediction #1, that higher variability in BP, on average, would be associated with worse and more variable performance on the cognitive functioning tasks. Importantly, the significant partial correlation coefficient between dBPV and variability in Stroop reaction time helps to clarify the non-significant association between dBPV and Stroop reaction time within the MLMs: individuals with higher dBPV were not consistently *slower* on the Stroop task, but they were more *variable*. Importantly, analyses revealed a relatively consistent pattern of results across the two reaction time tasks (sBPV and dBPV were significantly associated with slower *or* more variable reaction time across both tasks), suggesting that variability in BP may be most closely associated with tasks that include a component of reaction time. Somewhat consistent with these findings, analyses suggest that sBPV and dBPV were not associated with either higher variability or lower accuracy on the Dot Memory, Colour Dot, or Colour-Shape cognitive tasks. However, both of these tasks, and especially Stroop, are more complex than simple in-lab reaction time tasks, as they include aspects of decision making and cognitive interference (i.e., executive functioning). As such, the consistent findings across these “reaction time” tasks may be a chance occurrence, rather than

reflective of an underlying mechanism causing individuals with high BPV to respond more slowly and more inconsistently.

There are, however, some potential mechanistic explanations linking variability in BP to slower and more variable response time. Namely, research finds an association between variability in response time and adverse cognitive outcomes in older adulthood (Grand et al., 2016; Halliday et al., 2017; Bielak et al., 2010), as well as reduced global white matter volume (Walhovd and Fjell, 2007). This research suggests that intraindividual variability in response time may be a sensitive metric reflecting the central nervous system and white matter integrity. Within this literature, response time inconsistency is typically assessed in-lab and at a single sitting (e.g., 100+ response time trials per participant). The current project did not assess response time inconsistency using this approach; however, we did administer Symbol Search and Stroop twice per day for two weeks ($N=12$ trials of each task per session). Responding slowly or more variably to these tasks across study protocol may reflect similar mechanisms as response time inconsistency. As noted, the Symbol Search and (especially) Stroop tasks include aspects of processing; however, both include a response time component. Participants are instructed to respond as quickly as possible to Symbol Search and Stroop, whereas participants are permitted to take their time for the Dot Memory, Colour Dot, and Colour-Shape tasks. The pressure to respond as quickly as possible may cause some individuals to activate in neural regions responsible for regulating emotional response, such as the amygdala, which is also implicated in regulation of BP. Since cumulative stress may damage the neural networks responsible for regulating BP, individuals who are more vulnerable to cumulative stressors may have higher BP and BPV on average, and may also have slower or more variable performance on cognitive tasks

that require fast responding due to the accumulation of dysregulation within neural networks responsible for processing stress.

Further, in the current sample, Symbol Search and Stroop tasks were characterized by more variability at the between-person level, suggesting that some individuals were faster relative to other individuals, on average (in contrast, the accuracy tasks, Colour Dot, Dot Memory and Colour-Shape, were characterized by more within-person variance). As noted, research suggests that variability in neural blood flow negatively affects brain circuitry (Liu et al., 2012) and contributes to brain atrophy (Goldstein et al., 2002) on a more global level (i.e., impacts the whole brain). The negative impact of high BPV on neural integrity may manifest as slower and/or more variable performance on the Symbol Search and Stroop tasks, particularly considering research suggesting that response time inconsistency may be a sensitive marker of neural integrity and is associated with reduced global white matter volume (Walhovd and Fjell, 2007).

These proposed neural underpinnings linking stress, BPV, and cognitive functioning are just possibilities. Unfortunately, correlational studies in the field are inconsistent regarding which cognitive domains may be most associated with BPV. Many studies in the ABPM- and HBPM-BPV literature assess cognition using the mini mental state examination (MMSE) (e.g., (Bellelli et al., 2001; Cicconetti et al., 2004; Liu et al., 2016; Matsumoto et al., 2014; Mossello et al., 2015; Sakakura et al., 2007; Tadic et al., 2019; Yamaguchi et al., 2014)). There are many limitations of relying on the MMSE to assess cognitive functioning, such a ceiling effect in healthy older adults (e.g., Cicconetti et al., 2004; see Chapter 1). Further, research suggests that the MMSE suffers from patterns of missingness, such that data are not Missing Completely at Random, as a result of systematic problems during administration (e.g., manual dexterity,

literacy, or visual impairment) (Godin et al., 2017). Many studies have administered a neuropsychological battery, but subsequently computed a global cognitive functioning score (e.g., Baranowski et al., 2018; Cho et al., 2018; Conway et al., 2015). While this approach may reduce the likelihood of Type 1 error, it limits the ability to isolate whether particular aspects of cognition are more sensitive to variability in BP. Not surprisingly, research that has reported associations between BPV and distinct cognitive tasks has not suggested a consistent pattern of results. For instance, a study examining psychomotor speed, verbal memory and executive functioning found that higher visit-to-visit BPV was associated with worse speed and memory, but not executive functioning (Yano et al., 2014). Additionally, research examining the association between three domains of cognitive functioning and a composite BPV index based on within-visit, 24-hour ABPM and 7-day HBPM BP recordings found that more variability in BP was associated with lower memory functioning, but not processing speed or executive functioning (Zhou et al., 2019). Further, research examining ABPM-BPV and six cognitive tests assessing various cognitive domains found that higher BPV was associated with worse performance on attention, working memory and short-term visual memory, but was not associated with psychomotor speed or verbal working memory (Goldstein et al., 2002). As such, there does not appear to be a consistent pattern between BPV and particular domains of cognitive functioning.

These studies, however, varied substantially in primary sample features and statistical approach. As such, distinguishing whether findings vary due to true differences in the association between BPV and particular cognitive domains or due to differences in sample characteristics or methodological approach is challenging. Future research that administers several tests for each cognitive domain may provide the opportunity to delineate whether (and which) domains of

cognitive functioning are most implicated by BPV. Moreover, coordinated analysis, in which identical models (to the extent possible) are fitted across several independent datasets, may help to elucidate a pattern of results, evaluate generalizability of findings, and protect against Type I and Type II errors (see Chapter 1, Multiplicity and Heterogeneity in Statistical Methodology).

It is important to note that the current project is the first to focus on the association between midterm BPV and *concurrent* cognitive functioning. Only a handful of studies have examined the association between midterm BPV, assessed via HBPM, and cognition; all four previous studies observed a significant association between higher BPV and cognitive decline (de Heus et al., 2019; Liu et al., 2016; Matsumoto et al., 2014), as well as all-cause dementia, vascular dementia, and Alzheimer's disease (Oishi et al., 2017). While a strength of their approach is the investigation of within-person change in cognitive functioning over time, the previous studies were not able to obtain information on all lifestyle and medication factors that may have changed during the period between HBPM and follow-up cognitive assessment spanning 1 – 7.8 years across studies. For instance, changes to blood pressure control during the study follow-up may limit accuracy of the findings. Relatedly, tests of cognitive functioning in clinical contexts may not capture the dynamic nature of cognition. Traditional approaches for assessment of cognition have typically relied on testing individuals in laboratory and clinical settings; however, clinical detection of cognitive impairment tends to occur quite late in the progression of non-normative cognitive change, often occurring up to 15 years after the onset of neurodegeneration. Likewise, research suggests that cognitive change points are occurring 6-10 years prior to clinical diagnosis of dementia (Thorvaldsson et al., 2011), which limits options for preventative and early treatments.

Similarly to the shortfalls of measuring BP in clinical contexts (e.g., BP phenotypes; natural variability in BP), cognitive testing in a single context by trained professionals can adversely affect the reliability and ecological validity of assessments (Allard et al., 2014; Timmers et al., 2014). That is, individuals may perform better or worse due to unmeasured circumstantial factors (e.g., anxiety elicited within a clinical or laboratory context; poor sleep quality the night prior to testing), which may limit inferences for cognitive outcomes based on a single testing session. Further, cognitive testing in clinical contexts is highly dissimilar to the context in which individuals perform cognitively demanding tasks in their daily lives, and limited research has examined the extent to which clinically assessed cognitive functioning translates to cognitive performance in the real world (Sliwinski et al., 2018).

To address these shortcomings, researchers have turned to repeated, ambulatory assessments of cognitive functioning in day-to-day life, facilitated by advances in mobile technology. This approach is posited to improve precision, reliability, and ecological validity of cognitive evaluation (Sliwinski et al., 2018). Indeed, research suggests that a battery of brief, ambulatory cognitive assessments purposely developed for unsupervised administration (and nearly identical to the cognitive assessments administered to our DASH sample), demonstrated high between-person reliability and construct validity, relative to in-lab assessments (Sliwinski et al., 2018). Researchers in this field are hopeful that the improved ecological validity and reliability of these ambulatory cognitive assessments will facilitate earlier detection of cognitive change (Dorsey et al., 2015).

Although our analyses examining the association between BPV and concurrent cognitive functioning, as well as the associations between BPV and variability in cognitive functioning, were exploratory and revealed relatively few significant associations, our small sample size

likely limited the power to detect between-person differences. Nonetheless, results from the current project suggest that higher BPV may be associated with slower or more variable performance on reaction time tasks at the interindividual level, and perhaps worse executive functioning performance, as the Stroop task is also a measure of executive functioning. The literature would benefit from future research applying an intensive measurement burst design in which a larger sample of older adults are rigorously assessed via HBPM and ambulatory cognitive assessments for several days or a few weeks (i.e., a burst) at repeated occasions (e.g., annually or biennially). In addition, the sample would ideally focus on both older adults and very old adults, including those with and without hypertension, as well as those who are treated and untreated for hypertension. Such an approach may permit a robust exploration of the association between BP, midterm and long-term BPV, cognitive functioning, and cognitive decline.

Blood Pressure and Cognitive Functioning

Interindividual Associations. At the between-person level (i.e., Level 2), MLMs suggested significant associations between dBP/sBP and accuracy on the Colour Dot and Colour-Shape tasks. In both cases, individuals with higher sBP and dBP on average compared to individuals with lower sBP and dBP responded less accurately, on average. These results are consistent with prediction #2, that BP and cognitive functioning would be inversely associated at the between-person level. This hypothesis was based on neurology and epidemiology research. Namely, research suggests that hypertension accelerates reduction in quantity of cerebral capillaries, and also contributes to fibrotic membranes, lower resting cerebral blood flow, and dysfunction in cerebral circulation regulation (Cordonnier et al., 2007; Gao et al., 2014; Gasecki et al., 2013). Additionally, extensive literature suggests many adverse effects of hypertension on cognition (Breteler et al., 1994; Cherbuin et al., 2009; Elias et al., 2003; Kilander et al., 1998;

Meng et al., 2014; Reitz et al., 2007). However, it is important to note that while both higher sBP and dBP were consistently associated with worse performance on accuracy tasks assessing visual short-term memory requiring temporary retention of the location and/or colour of objects, analyses did not indicate significant associations for Dot Memory accuracy, Symbol Search reaction time, or Stroop reaction time. This may have been due to our relatively limited power for interindividual analyses, or that the association between BP and cognition is dependent on cognitive domain.

Similarly to the BPV and cognition literature, a pattern of findings regarding particular cognitive domains that may be most affected by BP is yet to be established as many studies use the MMSE (e.g., (Peters et al., 2009)) or a composite score based on a battery of tests (e.g., (Lennon et al., 2021)). However, consistent with the current interindividual results examining BP and cognition, some studies suggest that high BP may implicate memory. For instance, De Vito et al. (2021) found that hypertension was associated with worse delayed memory, and that individuals with high BP significantly decreased on immediate memory over time, but that high BP was not associated with initial score or change in attention or visuospatial construction. Other research, however, suggests that high BP may impact reaction time rather than memory. Specifically, research comparing cognitive functioning in a sample of older adults ($N= 770$) suggested that individuals with hypertension, treated and untreated, were significantly slower on reaction time, processing speed, and motor speed tasks compared to normotensive older adults (Hudak et al., 2013). Likewise, Yeung and associates (2017) found that higher sBP was significantly associated with worse performance on general problem solving items and reaction speed. Further, very few studies have investigated the association between BP and cognitive

functioning using a repeated battery of brief cognitive assessments administered in daily contexts, which limits comparisons between the current findings and previous findings.

Returning to the underlying mechanisms initially discussed, research suggests that high cerebral BP may cause cumulative weakening and damage to vascular and microvascular structures by accelerating reduction in quantity of cerebral capillaries (Gasecki et al., 2013) and increasing risk of cerebral microbleeds (Cordonnier et al., 2007; Gao et al., 2014). Further, extensive research finds a significant association between hypertension and reduced brain volume (see systematic review, Beauchet et al., 2013). As such, we might expect that high BP contributes to cognitive impairment and decline on a more global scale. However, there is some evidence linking high BP with neural correlates that may also support particular aspects of cognitive functioning.

As mentioned, the cardiovascular system is regulated by a cortical network including the insular cortex, anterior cingulate gyrus, and amygdala, which is activated in response to stress (Kitamura et al., 2020). Cumulative stress may then damage this network, potentially leading to heightened BP and BPV over time. It is possible that the neural areas most affected by long-term excess pressure within vascular structures overlap with, or are spatially close to, the neural regions that support short-term memory. Indeed, existing research suggests that the anterior cingulate cortex is a neural correlate of short-term visual memory (Parra et al., 2014), particularly for spatial memories (Teixeira et al., 2006). For instance, animal studies have found increased activation in the anterior cingulate cortex when presented with familiarized objects (i.e., during object recognition) in novel locations (Weible et al., 2009). Importantly, a study examining the brain regions involved in encoding and maintenance of abstract shapes, colours, and colour-shape bindings found that the anterior cingulate cortex activated during maintenance

(as opposed to encoding of) feature-related activity (i.e., identifying the colour or shape of an object) (Parra et al., 2014). In other words, this research suggests that the anterior cingulate cortex, which is also thought to be implicated in hypertension, is activated during short-term visual memory of shapes and colours of objects. While the current project did not examine neural activation during cognitive testing, our findings, which suggest that higher dBp and sBP are associated with impaired accuracy on tasks requiring maintenance and identification of the shapes and colours of objects, are consistent with brain imaging studies. Akin to the future directions recommended for BPV and cognition, research administering several tests for each cognitive domain, as well as baseline MRI assessment, may provide the opportunity to delineate whether (and which) domains of cognitive functioning are most implicated by BP.

Intraindividual Associations. Multilevel modelling revealed a significant association between sBP and Colour Dot accuracy at the within-person level (i.e., Level 1), when accounting for the learning effect during the study protocol, as well as time-varying effort, physical activity, and stressors. These models also revealed that between-person sBP was a significant predictor of the association between sBP and Colour Dot accuracy. These findings suggest that the within-person coupling relationship between sBP and Colour Dot accuracy is stronger in magnitude for individuals higher in sBP, which is consistent with research investigating the cumulative impact of high BP on brain regions responsible for regulating the cardiovascular structures and short-term visual memory (just discussed). These findings are also consistent with research suggesting that individuals with a combination of high BP and high BPV have the strongest relationship to brain atrophy compared to either high BP or high BPV alone (Goldstein et al., 2002).

Analyses also revealed a marginally significant within-person association between dBp and Colour-Shape accuracy, adjusting for time-varying effort, physical activity and stressors

(Table 2.5b $p=0.054$; Table 2.5d $p=0.059$). Together, these findings provide some evidence, albeit rather limited, that is consistent with prediction #3, that BP and cognitive functioning would be inversely associated at the within-person level, such that on occasions when individuals have higher BP than their personal average, their cognitive performance would be lower compared to their own personal average. However, the within-person association between sBP and Colour Dot accuracy was *only* significant when time-varying stressors were added to the models, which is inconsistent with prediction 4, that the association between BP and cognitive functioning would be attenuated once time-varying daily stressors are added to the models. Yet, the within-person coupling association between BP and cognition found in the current project may still be a result of psychological stress or distractions, despite adjusting for occasion-specific effort and stressors.

Research suggests that compared to younger adults, older adults tend to report less interpersonal tension and stress, and are more likely to do nothing in response to tensions (Birditt et al., 2005). These findings are consistent with lifespan theories, which posit that people become better at regulating their responses to problems as they mature, and become more concerned with maintaining interpersonal relationships (Blanchard-Fields & Cooper, 2003; Carstensen et al., 1999). Given that the stress and coping paradigm views stress as a transactional process between a person and their environment, as opposed to a particular environmental stimulus (Cohen et al., 1995), the majority of research in this field examines self-reported stressors. However, self-reported assessment of stressors may disregard natural physiological responses to daily problems. That is, although older adults are less likely to appraise a situation as stressful, they may still experience some degree of physiological strain, such as heightened BP compared to their average BP. Those upward fluctuations in BP may occur concurrently with the downward

fluctuations in short-term memory, similarly to the underlying mechanisms linking BP and cognition at the between-person level. Likewise, while self-reported effort was modeled to account for occasions when individuals may have not been applying their full attention to the cognitive tasks for any number of reasons (including distractions), participants may have not considered distractions when responding to the item regarding effort. That is, an individual may aim to fully attend to the cognitive tasks despite several distractions, which may result in a context that increases BP.

Finally, comparisons with previous research is challenging, as only two previous studies have examined the coupled association between BP and cognitive functioning, and both administered a different battery of brief cognitive tests compared to the current project. Notably, the significant associations found by Gamaldo et al. (2008) and Kelly et al. (2015) were based on cognitive tests dissimilar to the cognitive tasks administered in the current project. That is, Gamaldo et al. found a positive association between sBP and inductive reasoning and that the coupled association between BP and cognition was stronger in individuals with higher BP on average, while Kelly et al. found an inverse association between dBP and delayed recall. As such, the results from the current project are consistent with Gamaldo et al. directionally, but not for cognitive-task specificity. Further, both studies administered the cognitive tasks according to a different protocol; Gamaldo et al. did not specify how their cognitive tasks were administered, while Kelly et al. administered the tests via an online survey system. Importantly, neither of their cognitive batteries were developed for unsupervised assessment, which may compromise the validity of the tasks (e.g., writing down the items from delayed recall list).

Strengths, Limitations and Future Directions

To my knowledge, the current project is the first to examine the association between BPV and day-to-day variability in cognitive functioning. Further, this project is the first to investigate the association between BPV, assessed via HBPM, and concurrent cognitive functioning. Further still, only two studies have previously examined the within-person associations between BP and cognitive functioning using a daily diary design, and neither utilized the convenience and objectivity of mobile devices for assessment of cognitive functioning and automated BP monitors that electronically track measurements. Finally, both existing studies were relatively smaller than the DASH sample (Gamaldo et al. $N= 36$; Kelly et al. $N= 27$) and neither adjusted for occasion-specific self-reported effort or physical activity. Together, this project contributes novelty to the field in a number of ways. In particular, the findings that BPV may be most related to reaction time tasks, including aspects of executive functioning, while day-to-day BP may be most related to accuracy tasks (at both the interindividual and intraindividual levels) adds incrementally to the field and illuminates avenues for future research.

At home, daily BP recordings and the monitors used for BP recordings were also strengths of the current project. Relative to ABPM and visit-to-visit BP recordings, HBPM is a robust approach for measurement precision in the assessment of resting BP (Bonafini & Fava, 2015). DASH study participants attended a two-hour intake session, which included extensive training in use of the iFORA automated BP monitors. After instruction, participants practiced recording their BP under direct supervision. Participants were also sent home with an instruction manual, including graphics, which reiterated how to use the BP monitors and mobile devices. Furthermore, the BP monitors automatically assess BP three times, and the average of the three recordings is saved automatically within the devices. Together, these characteristics contribute to

measurement precision of resting BP within the current project. Furthermore, twice-daily cognitive assessment via a battery of brief, ambulatory tests especially developed for unsupervised administration and completed in day-to-day context contributes to reliability and ecological validity of the measurement of cognitive functioning.

Although this project suggests some interesting findings, some limitations should be noted. First, the DASH sample was mostly female, well-educated, Caucasian older adults, which may limit the generalizability of results. Second, though the sample was substantially larger than existing studies investigating the intraindividual associations between BP and cognition, a larger sample would provide more power to test interindividual differences. Importantly, simulations for intensive measurement designs suggest that a minimum sample of 20 participants is required for intraindividual power of .80 in a 14-day study, however 130 individuals are required for similar power at the interindividual level (Rush, Rast & Hofer, 2014). As such, the between-person associations reported in the current project should be interpreted with caution. Third, this project included fitting an extensive number of models; this multiplicity of analyses may contribute to Type 1 error.

Furthermore, some research suggests that BPV is a stronger correlate of adverse outcomes compared to BP (Cho et al., 2018; Gosmanova et al., 2016; Lattanzi et al., 2018; Mehlum et al., 2018). This pattern was not noted in the current research: both BPV and BP were associated with lower cognitive functioning. For instance, higher sBPV and slower Symbol Search reaction time, as well as higher dBPV and more variability in Stroop reaction time, were significantly associated, adjusting for mean BP. However, the associations between sBPV and Stroop reaction time, as well as dBPV and Symbol Search reaction time did not remain significant after adjusting for mean BP, suggesting that BPV does not account for fluctuations in

these cognitive tasks beyond mean BP. Again, this was likely an issue of power for between-person comparisons, and future research with a larger, more diverse sample of older adults with and without hypertension would improve our understanding of the association between BP, BPV, and cognitive functioning.

Conclusion

Existing literature consistently documents an association between high BP and adverse cognitive outcomes, such as cognitive impairment, cognitive decline, and dementia diagnosis. As exemplified by Chapter 1, several independent studies have also concluded that higher BPV is associated with adverse cognitive outcomes, though not all of these studies adjust for mean BP or find an association between BPV and cognition beyond mean BP. The majority of the existing literature investigates these associations at the between-person level. To my knowledge, only two studies have examined the association at the intraindividual, daily level, and no research has investigated the association between BPV and concurrent cognition or variability in cognitive functioning. By systematically exploring the association between BP, BPV, cognitive functioning, and variability in cognitive functioning, the current project is unique in several ways. This project's findings warrant further investigation of the impact of intraindividual and interindividual differences in BP on several tests for each cognitive domain in larger samples, and ideally coordinated across multiple samples to assess the reliability of findings and protect against potential Type 1 and Type 2 error. Indeed, replication of the reported findings is essential to clarify the associations between BP, BPV, cognitive functioning, and variability in cognitive functioning.

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